Comparative Effectiveness Review Number 55

Drug Therapy for Rheumatoid Arthritis in Adults: An Update



Number 55

Drug Therapy for Rheumatoid Arthritis in Adults: An Update

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Prepared by:

RTI International—University of North Carolina Evidence-based Practice Center Research Triangle Park, NC

Investigators:

Katrina E. Donahue, M.D., M.P.H. Dan E. Jonas, M.D., M.P.H. Richard A. Hansen, Ph.D. Robert Roubey, M.D. Beth Jonas, M.D., M.P.H. Linda J. Lux, M.P.A. Gerald Gartlehner, M.D., M.P.H. Elizabeth Harden, M.P.H. Tania Wilkins, M.S.

Visali Peravali, M.S. Shrikant I. Bangdiwala, Ph.D. Andrea Yuen, B.S. Patricia Thieda, M.A. Laura C. Morgan, M.A. Karen Crotty, Ph.D. Rishi Desai, M.S. Megan Van Noord, M.S.I.S.

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Preface

The Agency for Healthcare Research and Quality (AHRQ) conducts the Effective Health Care Program as part of its mission to organize knowledge and make it available to inform decisions about health care. As part of the Medicare Prescription Drug, Improvement, and Modernization Act of 2003, Congress directed AHRQ to conduct and support research on the comparative outcomes, clinical effectiveness, and appropriateness of pharmaceuticals, devices, and health care services to meet the needs of Medicare, Medicaid, and the Children's Health Insurance Program (CHIP).

AHRQ has an established network of Evidence-based Practice Centers (EPCs) that produce Evidence Reports/Technology Assessments to assist public- and private-sector organizations in their efforts to improve the quality of health care. The EPCs now lend their expertise to the Effective Health Care Program by conducting Comparative Effectiveness Reviews (CERs) of medications, devices, and other relevant interventions, including strategies for how these items and services can best be organized, managed, and delivered.

Systematic reviews are the building blocks underlying evidence-based practice; they focus attention on the strength and limits of evidence from research studies about the effectiveness and safety of a clinical intervention. In the context of developing recommendations for practice, systematic reviews are useful because they define the strengths and limits of the evidence, clarifying whether assertions about the value of the intervention are based on strong evidence from clinical studies. For more information about systematic reviews, see http://effectivehealthcare.ahrq.gov/reference/purpose.cfm.

AHRQ expects that CERs will be helpful to health plans, providers, purchasers, government programs, and the health care system as a whole. In addition, AHRQ is committed to presenting information in different formats so that consumers who make decisions about their own and their family's health can benefit from the evidence.

Transparency and stakeholder input are essential to the Effective Health Care Program. Please visit the Web site (www.effectivehealthcare.ahrq.gov) to see draft research questions and reports or to join an email list to learn about new program products and opportunities for input. Comparative Effectiveness Reviews will be updated regularly.

We welcome comments on this CER. They may be sent by mail to the Task Order Officer named below at: Agency for Healthcare Research and Quality, 540 Gaither Road, Rockville, MD 20850, or by email to epc@ahrq.hhs.gov.

Carolyn M. Clancy, M.D. Director Agency for Healthcare Research and Quality

Stephanie Chang, M.D., M.P.H. Director, EPC Program Agency for Healthcare Research and Quality Jean Slutsky, P.A., M.S.P.H. Director, Centre for Outcomes and Evidence Agency for Healthcare Research and Quality

Carmen Kelly, Pharm.D., R.Ph. EPC Program Task Order Officer Agency for Healthcare Research and Quality

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Technical Expert Panel

Teresa J. Brady, Ph.D. Patient Representative

Jeffrey R. Curtis, M.D., M.P.H.
Assistant Professor
Division of Clinical Immunology and Rheumatology
Associate Director
Center for Education and Research on Therapeutics of MSK disorders
University of Alabama at Birmingham
Birmingham, AL

Marion McDonagh, Pharm.D. Assistant Professor Informatics and Clinical Epidemiology Oregon Health & Science University Portland, OR

Christopher T. Ritchlin, M.D., M.P.H. Internal Medicine, Rheumatology School of Medicine and Dentistry University of Rochester Rochester, NY

Peer Reviewers

Joan M. Bathon, M.D.
Professor of Medicine
Division of Rheumatology
Department of Medicine
Johns Hopkins University
Director, Johns Hopkins Arthritis Center
Co-Deputy Director, Division of Rheumatology
Bayview Medical Center
Baltimore, MD

Louis Bridges, Jr., M.D., Ph.D.
Professor of Medicine and Microbiology
Director of the Division of Clinical Immunology and Rheumatology
Deputy Director of the Comprehensive Arthritis, Musculoskeletal, and Autoimmunity Center
University of Alabama at Birmingham
Birmingham, AL

Marion McDonagh, Pharm.D. Assistant Professor Informatics and Clinical Epidemiology Oregon Health & Science University Portland, OR

James O'Dell, M.D.
Professor and Program Director
Department of Internal Medicine
University of Nebraska
Lincoln, NE

Nancy Olsen, M.D. McGee Foundation Distinguished Professor in Arthritis Research Internal Medicine – Rheumatic Diseases UT Southwestern Medical School Dallas, TX

Drug Therapy for Rheumatoid Arthritis in Adults: An Update

Structured Abstract

Objectives: Compare the benefits and harms of corticosteroids, oral and biologic disease-modifying antirheumatic drugs (DMARDs) for adults with rheumatoid arthritis.

Data Sources: English-language articles from 1980 to February 2011 identified through PubMed, Embase, Cochrane Library, and International Pharmaceutical Abstracts; unpublished literature including dossiers from pharmaceutical companies.

Methods: Two people independently selected relevant head-to-head trials of any sample size, prospective cohort studies with at least 100 participants, and relevant good- or fair-quality meta-analyses that compared benefits or harms of 14 drug therapies. Retrospective cohort studies were also included for harms. For biologic DMARDs, placebo-controlled, double-blind RCTs were also included. We required trials and cohort studies to have a study duration of at least 12 weeks. Literature was synthesized qualitatively within and between the two main drug classes (oral and biologic DMARDs). Network meta-analysis also was performed to examine the relative efficacy of biologic DMARDs and comparing withdrawal rates from placebo controlled trials.

Results: Head-to-head trials showed no clinically important differences in efficacy among oral DMARD comparisons (methotrexate, sulfasalazine, leflunomide). The only head-to-head trial comparing biologic DMARDs (abatacept vs. infliximab) found no clinically important differences. Combination therapy of biologic DMARDs plus methotrexate improved clinical response rates and functional capacity more than monotherapy with methotrexate. Network meta-analyses found higher odds of reaching ACR 50 response for etanercept compared with most other biologic DMARDs (abatacept, adalimumab, anakinra, infliximab, rituximab, tocilizumab) for methotrexate-resistant patients with active rheumatoid arthritis. Similar overall tolerability profiles were found among oral and biologic DMARDs, but short-term adverse events were more common with biologic DMARDs. Adjusted indirect comparisons of biologic DMARDs found that certolizumab had the most favorable overall withdrawal profile, followed by etanercept and rituximab. Certolizumab had lower relative withdrawal rates due to lack of efficacy than adalimumab, anakinra, and infliximab. Certolizumab and infliximab had more, while etanercept had fewer withdrawals due to adverse events than most other drugs. Evidence was insufficient to assess comparative risk of serious adverse events among biologic DMARDs. Combinations of biologic DMARDs have higher rates of serious adverse events than biologic DMARD monotherapy. Limited data existed for subgroups.

Conclusions: Limited head-to-head comparative evidence does not support one therapy over another for adults with rheumatoid arthritis. Network meta-analyses from placebo-controlled trials of biologics suggest some differences, including higher odds of reaching ACR 50 response, but strength of evidence was low.

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Executive Summary

Background

Rheumatoid arthritis (RA), which affects 1.3 million adult Americans, is an autoimmune disease that involves inflammation of the synovium (a thin layer of tissue lining a joint space) with progressive erosion of bone leading in most cases to misalignment of the joint, loss of function, and disability. The disease tends to affect the small joints of the hands and feet in a symmetric pattern, but other joint patterns are often seen. The diagnosis is based primarily on the clinical history and physical examination with support from selected laboratory tests. Treatment of patients with RA aims to control pain and inflammation and, ultimately, the goal is remission or at least low disease activity for all patients. Available therapies for RA include corticosteroids, oral disease-modifying antirheumatic drugs or DMARDs (hydroxychloroquine, leflunomide, methotrexate [MTX], and sulfasalazine), and biologic DMARDs (five anti-tumor necrosis factor drugs [anti-TNF]: adalimumab, certolizumab, etanercept, golimumab, infliximab; and others including abatacept, anakinra, rituximab, and tocilizumab).

Treatment strategies for RA continue to evolve. Early use of DMARDs is considered crucial to avoid persistent and erosive arthritis. Clinicians frequently start treatment regimens with oral DMARD monotherapies and adjust dosages as appropriate to achieve a low disease activity or remission. Clinical experience supports the use of MTX as the oral DMARD of choice unless there are contraindications (e.g., liver impairment, alcohol abuse, pregnancy, lung disease). Experts have not arrived at consensus about the comparative effectiveness of corticosteroids, oral DMARDs, and biologic DMARDs. More importantly, it is unclear how the effectiveness and safety of different types of combination therapy compare, for example, oral DMARDs with corticosteroids, oral DMARDs with biologic DMARDs, or a triple combination of corticosteroids, oral DMARDs, and biologic DMARDs. In addition, there is debate about how early in the disease process combination therapy should be initiated. Many questions remain about the risks of these agents across a spectrum of adverse events, from relatively minor side effects such as injection site reactions to severe and possibly life-threatening problems such as severe infections or infusion reactions. Finally, very little is known about the benefits or risks of these drugs in different patient subgroups, including ethnic minorities, the elderly, pregnant women, and patients with other comorbidities.

Objectives

This report summarizes the evidence on the comparative efficacy, effectiveness, and harms of corticosteroids, oral DMARDs, and biologic DMARDs in the treatment of patients with RA. This report updates a previous version published in 2007. The Key Questions (KQs) are as follows:

KQ1: For patients with RA, do drug therapies differ in their ability to reduce disease activity, to slow or limit the progression of radiographic joint damage, or to maintain remission?

KQ2: For patients with RA, do drug therapies differ in their ability to improve patient-reported symptoms, functional capacity, or quality of life?

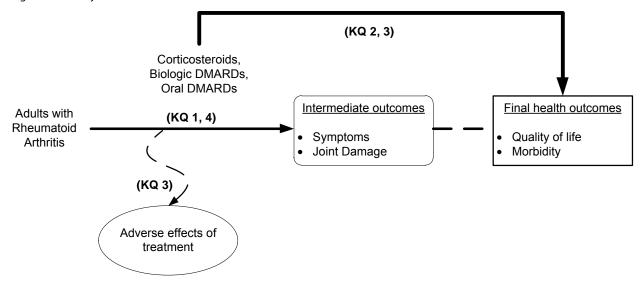
KQ3: For patients with RA, do drug therapies differ in harms, tolerability, patient adherence, or adverse effects?

KQ4: What are the comparative benefits and harms of drug therapies for RA in subgroups of patients based on stage of disease, prior therapy, demographics, concomitant therapies, or comorbidities?

Analytic Framework

Figure A depicts the analytic framework for rheumatoid arthritis.

Figure A. Analytic framework for treatment for rheumatoid arthritis



Methods

A Technical Expert Panel was employed for the finalization of the KQs and review of the planned analysis strategy. Our KQs and protocol were posted on the Agency for Healthcare Research and Quality Web site for public review and comment. Individuals who were experts in rheumatology and various stakeholder and user communities performed an external peer review of the report. The report was also posted for public review. We compiled all comments and addressed each one individually, revising the text as appropriate.

We searched MEDLINE®, Embase, the Cochrane Library, and the International Pharmaceutical Abstracts to identify relevant articles. We limited the electronic searches to "human" and "English language." For this update, the searches went up to January 2011. Hand searches were conducted on the Center for Drug Evaluation and Research (CDER) database of the U.S. Food and Drug Administration and unpublished literature including dossiers from pharmaceutical companies.

Study eligibility (inclusion and exclusion) criteria were designed in respect to study design or duration, patient population, interventions, outcomes, and comparisons for each KQ. For efficacy and effectiveness, we focused on head-to-head trials and prospective cohort studies comparing one drug with another. For biologic DMARDs, we also included placebo-controlled, double-blind randomized controlled trials (RCTs). For harms and tolerability, as well as for efficacy and effectiveness in subgroups, we included head-to-head trials, high-quality systematic reviews, and observational studies. We included studies with sample sizes of at least 100 and duration of at

least 3 months. We only included studies that used doses within the recommended dosing range or that used doses that could be considered equivalent to recommended doses.

Two individuals independently reviewed abstracts identified by searches. If both reviewers agreed that a study did not meet eligibility criteria, we excluded it. We obtained the full text of all remaining articles. Two individuals again independently reviewed the full text of all remaining articles to determine whether they should be included. We designed and used a structured data abstraction form to ensure consistency of appraisal for each included study. Trained reviewers abstracted data from each study. A senior evaluated the completeness of each data abstraction.

We rated the quality of individual studies using the predefined criteria based on those developed by the U.S. Preventive Services Task Force (ratings: good, fair, poor) and the National Health Service Centre for Reviews and Dissemination. Two independent reviewers assigned quality ratings. They resolved any disagreements by discussion and consensus or by consulting with a third reviewer. We gave a good-quality rating to studies that met all criteria. We gave a poor-quality rating to studies that had a fatal flaw (defined as a methodological shortcoming that leads to a very high risk of bias) in one or more categories and excluded them from our analyses. We graded the strength of evidence as high, moderate, low, or insufficient based on methods guidance for the Evidence-based Practice Program.^{3,4} We graded strength of evidence for the outcomes determined to be most important: measures of disease activity (e.g., American College of Rheumatology [ACR] 20/50/70, Disease Activity Score [DAS]), radiographic changes, functional capacity, quality of life, withdrawals due to adverse events, and specific adverse events if data were available (e.g., injection-site reactions, infections, malignancy). We generally synthesized the literature qualitatively, but we did conduct metaanalyses comparing the relative efficacy of biologic DMARDs and comparing withdrawal rates from placebo-controlled trials. To compare the relative efficacy of biologic DMARDs, we conducted a mixed treatment comparison (MTC) meta-analysis using WinBUGS Version 1.4.3, a Bayesian software package that uses Markov chain Monte Carlo (MCMC) techniques. The primary efficacy outcome of our MTC meta-analysis was the ACR 50.

Results

We identified 3,868 citations from our searches. We included 258 published articles reporting on 211 studies: 31 head-to-head RCTs, 1 head-to-head nonrandomized controlled trial, 44 placebo-controlled trials, 28 meta-analyses or systematic reviews, and 107 observational studies. We identified 30 studies for quantitative synthesis for KQ1 and 42 studies for quantitative syntheses for KQ3. Most studies were of fair quality.

Our major findings are presented in this section by type of drug comparison for benefits and harms (Table A). Subpopulation analyses are described after Table A because the evidence is very limited.

Key Comparisons	Efficacy Strength of Evidence	Harms Strength of Evidence
Oral DMARD vs. O	ral DMARD	
Leflunomide vs. MTX	No differences in ACR 20 or radiographic responses. Low	No consistent differences in tolerability and discontinuation rates.
	No clinically significant difference for functional capacity. Low	Mixed results for specific adverse events. Insufficient
	Greater improvement in health-related quality of life (SF-36 physical component) for leflunomide. Low	
Leflunomide vs. sulfasalazine	Mixed ACR response rates. Insufficient	No differences in tolerability and discontinuation rates. Low
	No differences in radiographic changes. Low	Mixed results for specific adverse events. Insufficient
	Greater improvement in functional capacity for leflunomide Low	
Sulfasalazine vs. MTX	No differences in ACR 20 response, disease activity scores and radiographic changes. ** Moderate*	No differences in tolerability; more patients stayed on MTX long term. Low
	No differences for functional capacity. [†] Moderate	Mixed results for specific adverse events. Insufficient
Oral DMARD Comb	oinations vs. Oral DMARD	
Sulfasalazine plus MTX vs. sulfasalazine or MTX monotherapy	In patients with early RA, no differences in ACR 20 response rates or radiographic changes. Moderate	Withdrawal rates attributable to adverse events higher with combination. Low
	No differences in functional capacity. Moderate	Insufficient evidence for specific adverse events. Insufficient

Table A. Summary of findings with strength of evidence (continued)

	Efficacy	Harms
Key Comparisons	Strength of Evidence	Strength of Evidence
Oral DMARD plus prednisone vs. oral DMARD	Mixed results for disease activity. Insufficient	No differences in discontinuation rates; addition of corticosteroid may increase time to discontinuation of treatment.
	Less radiographic progression in patients on DMARD plus prednisone.	Moderate
	Low	No differences in specific adverse events, except addition of corticosteroid may increase wound-
	In patients with early RA, significantly lower radiographic progression and fewer eroded. joints Low	healing complications. Low
	Greater improvement in functional capacity for one oral DMARD plus prednisolone than for oral DMARD monotherapy. Moderate	
	No difference in quality of life. Low	
Biologic DMARDs	vs. Biologic DMARDs	
Abatacept vs. Infliximab	Greater improvement in disease activity for abatacept, but no difference in remission or functional capacity. Statistically significant difference between groups for quality of life (SF-36 PCS) that did not reach the minimal clinically important difference. Low	Discontinuation rates and severe adverse events higher with infliximab. Low

Table A. Summary of findings with strength of evidence (continued)

Key Comparisons	Efficacy Strength of Evidence	Harms Strength of Evidence
Biologic vs. biologic (Mixed treatment comparisons)	No significant differences in disease activity (ACR 50) in MTC analyses between abatacept, adalimumab, golimumab, infliximab, rituximab, and tocilizumab in patients resistant to MTX. Low Less improvement in disease activity (ACR 50) for anakinra compared with etanercept and compared with adalimumab in MTC analyses in patients resistant to MTX. Comparisons with abatacept, golimumab, infliximab, rituximab, and tocilizumab did not reach statistical significance. Low	Adjusted indirect comparisons found a more favorable withdrawal profile for certolizumab pegol than other biologic DMARDs. Also, etanercept and rituximab had a more favorable overall withdrawal profile than some other biologic DMARDs. Certolizumab pegol had fewer withdrawals due to lack of efficacy than adalimumab, anakinra, and infliximab. All but adalimumab, golimumab, and infliximab had fewer withdrawals than anakinra due to lack of efficacy. Both certolizumab pegol and infliximab had more withdrawals due to adverse events than etanercept and rituximab. Low
Biologic vs. biologic (Mixed treatment comparisons) (continued)	Greater improvement in disease activity (ACR 50) for etanercept compared with abatacept, adalimumab, anakinra, infliximab, rituximab, and tocilizumab in MTC analyses. No significant differences when compared with golimumab. Low	Risk for injection site reactions apparently highest with anakinra. Low Mixed results for specific adverse events. Insufficient
Biologic DMARDs	vs. Oral DMARDs	
Anti-tumor necrosis factor drugs vs. MTX	In patients with early RA, no clinically significant differences in clinical response between adalimumab or etanercept and MTX; in patients on biologic DMARDs, better radiographic outcomes than in patients on oral DMARDs. Moderate	No differences in adverse events in efficacy studies. Low Insufficient evidence on differences in the risk for rare but severe adverse events. Insufficient
	No difference in functional capacity between adalimumab and MTX for MTX-naïve subjects with early RA; mixed results for etanercept vs. MTX. Low; Insufficient	
	Faster improvement in quality of life with etanercept than MTX. Low	

Table A. Summary of findings with strength of evidence (continued)

Key Comparisons	Efficacy Strength of Evidence	Harms Strength of Evidence
Biologic DMARD Co	ombinations	
Biologic DMARD plus biologic DMARD vs. biologic DMARD	No additional benefit in disease activity or functional capacity from combination of etanercept plus anakinra compared with etanercept monotherapy or combination of etanercept plus abatacept compared with abatacept monotherapy, but greater improvement in quality of life with etanercept plus abatacept vs. etanercept. Low	Substantially higher rates of serious adverse events from combination of two biologic DMARDs than from monotherapy. Moderate

Table A. Summary of findings with strength of evidence (continued)

Key Comparisons	Efficacy Strength of Evidence	Harms Strength of Evidence
Biologic DMARDs plus MTX vs. biologic DMARDs	Better improvements in disease activity from combination therapy of biologic DMARDs (adalimumab, etanercept, infliximab, rituximab) plus MTX than from monotherapy with biologics. Moderate In MTX-naive patients with early aggressive RA, better ACR 50 response, significantly greater clinical remission, and less radiographic progression in the combination therapy group. Low In MTX-naïve subjects or those not recently on MTX, greater improvement in functional capacity (Moderate) and quality of life (Low) with combination therapy. In subjects with active RA despite treatment with MTX, no difference in functional capacity or quality of life. Low	No differences in adverse events in efficacy studies. Low Insufficient evidence on differences in the risk for rare but severe adverse events. Insufficient
Biologic DMARDs plus oral DMARD other than MTX vs. biologic DMARDs	No difference in clinical response rates, functional capacity, and quality of life between etanercept plus sulfasalazine and etanercept monotherapy. Low	No differences in adverse events in efficacy studies. Low Insufficient evidence on differences in the risk for rare but severe adverse events Insufficient
Biologic DMARD plus MTX vs. MTX	Better clinical response rates, functional capacity, and quality of life from combination therapy of biologic DMARDs and MTX than from MTX monotherapy. High for clinical response and functional capacity, Moderate for quality of life	Better tolerability profile for MTX plus abatacept, adalimumab, certolizumab, etanercept, and rituximab than for MTX monotherapy from metanalysis. Low Mixed evidence on differences in the risk for rare but severe adverse events. Insufficient

Table A. Summary of findings with strength of evidence (continued)

Key Comparisons	Efficacy Strength of Evidence	Harms Strength of Evidence
Strategies in Early	RA	
Two oral DMARDs plus prednisone vs. oral DMARD	In patients on two oral DMARDs, improved ACR 50 response rates, disease activity scores, but no difference at 56 weeks. Low	No differences in discontinuation rates. Moderate
	In patients with early RA, significantly lower radiographic progression and fewer eroded joints at 56 weeks. Low	
	More rapid improvement in functional capacity by 28 weeks but no differences by 56 weeks. Low	
Three oral DMARDs plus prednisone vs. one oral DMARD	In patients on three oral DMARDs, improved ACR 50 response rates, disease activity scores, and less work disability. Low	No differences in discontinuation rates. Moderate
	In patients with early RA, significantly lower radiographic progression and fewer eroded joints Low	
Sequential monotherapy starting with MTX vs. step-up combination therapy vs. combination with tapered high-dose prednisone vs. combination with infliximab	Less radiographic progression, lower disease activity scores, and better functional ability and health-related quality of life from initial combination therapy of MTX, sulfasalazine, and tapered high-dose prednisone or initial combination therapy with infliximab plus MTX than from sequential DMARD monotherapy or step-up combination therapy. However no differences between groups for functional ability and quality of life by 2 years and no difference in remission at 4 years.	No differences in serious adverse events between groups. Low

† at MTX doses ranging from 7.5-25 mg per week
ACR = American College of Rheumatology; DMARD = disease-modifying antirheumatic drug; MTC = mixed treatment comparisons; MTX = methotrexate; RA = rheumatoid arthritis; vs = versus

Subpopulations. Limited good or fair evidence for benefits or harms of subpopulations exists; therefore, the strength of evidence was low and results should be interpreted cautiously. Patients with moderate RA had significant improvements and better overall functional status than those with severe RA, but those with severe RA had the greatest improvements from baseline in disease activity. For MTX, the odds for major clinical improvement dropped slightly as the age of clinical trial patients increased; age did not affect MTX efficacy or the rate of side effects. Biologics neither decreased nor increased cardiovascular risks in the elderly. Those taking anakinra and concomitant diabetic, antihypertensive, or statin medications did not have higher adverse events rates. Toxicity was more likely with MTX in patients with greater renal impairment. Those with high-risk comorbidities (cardiovascular events, diabetes, malignances, renal impairment) and taking anakinra did not experience an increase in serious adverse events or overall infectious events.

Discussion

Existing comparative evidence did not support the superiority of one oral DMARD over another. Limitations to these trials included the wide range of MTX dosing in the trials. Biologic DMARD comparisons are limited to mostly observational studies and findings from MTC meta-analyses. Our MTC meta-analyses, suggest some differences, such as etanercept having a higher probability of improvement in disease activity than most other biologic DMARDs, but are limited primarily to indirect evidence (low strength of evidence) and therefore should be interpreted with caution. The limited evidence precludes drawing firm conclusions about whether one combination strategy is better than another in early RA. Overall tolerability is similar among biologic and among oral DMARDs; however, several studies suggest that adverse events are more common with biologic DMARDs compared with oral DMARDs. Limited evidence does not suggest an increased risk of severe adverse events, including cardiovascular or cancer, with oral DMARDs. Most studies found no risk of cardiovascular events and malignancy with biologic DMARDs, except for cohort studies, which describe an increased risk of heart failure with adalimumab, etanercept, and infliximab compared with oral DMARDs.

Common problems for RA studies included the lack of effectiveness information, that is, studies and findings with a high level of applicability to community populations. Future investigations need to take into account factors such as varying adherence because of administration schedules, costs, and adverse events. Information is also needed about the performance of these drugs in subgroups of patients defined by health status, sociodemographic, or other variables.

To address problems with current literature, future studies should include using designs of longer duration and followup, enrolling patients representing key subgroups (or reporting on them when they are enrolled), and ensuring that quality of life (or other patient-centered outcomes) is measured, in addition to clinician-centered measures such as joint erosion. Ideally, studies need to mimic clinical decisionmaking, where if a patient is not doing well after a specified time, the protocol gives them something different. Important areas that will influence clinical decisionmaking include three critical topics: (1) specific head-to-head comparisons focusing on different combination strategies and different biologic DMARDs, (2) timing of initiation of therapies, and (3) applicability of combination strategies and biologic DMARD therapy in community practice. The results of the MTC meta-analyses suggested some differences. However, the strength of evidence was low for the MTC findings, and head-to-head

studies are needed to confirm or refute these results before any firm clinical recommendations can be made.

Analyses involving subpopulations, specifically those defined by age and coexisting conditions, will be beneficial, given that RA disease onset generally occurs in middle age, when the risk of comorbidities increases. Studies of longer duration and followup will be beneficial, given that RA is a progressive, chronic condition. Such studies will also help to clarify whether early initiation of any regimen can improve the long-term prognosis of RA and, particularly, whether early use of biologic DMARDs is helpful.

Abbreviations

ACR American College of Rheumatology Anti-TNF Anti-tumor necrosis factor drugs

CDER Center for Drug Evaluation and Research
DMARD Disease-modifying antirheumatic drug
MCMC Markov chain Monte Carlo techniques

MTC Mixed-treatment comparisons

MTX Methotrexate

RA Rheumatoid arthritis

RCT Randomized controlled trial

SF36 Short Form 36

References

- 1. Harris RP, Helfand M, Woolf SH, et al. Current methods of the U.S. Preventive Services Task Force: a review of the process. Am J Prev Med. 2001 Apr;20(3 Suppl):21-35.
- 2. Anonymous. Undertaking systematic reviews of research on effectiveness: CRD's guidance for those carrying out or commissioning reviews. CRD Report Number 4 (2nd edition). 2001.
- 3. Agency for Healthcare Research and Quality. Methods reference guide for effectiveness and comparative effectiveness reviews, version 1.0. Rockville, MD: Agency for Healthcare Research and Quality; October 2007 (draft). http://effectivehealthcare.ahrq.gov/repFiles/2007_10DraftMethodsGuide.pdf.
- 4. Owens DK, Lohr KN, Atkins D, et al. AHRQ series paper 5: grading the strength of a body of evidence when comparing medical interventions--Agency for Healthcare Research and Quality and the Effective Health Care Program. J Clin Epidemiol. 2010 May;63(5):513-23.

Introduction

Arthritis and other rheumatic conditions constitute the leading cause of disability among U.S. adults, with more than 46 million Americans reporting doctor-diagnosed arthritis. Noninflammatory arthritic conditions (e.g., osteoarthritis) are most common, but inflammatory arthritides such as spondyloarthropathies (e.g., ankylosing spondylitis, psoriatic arthritis [PsA]), and reactive arthritis) and rheumatoid arthritis (RA) can be equally or more disabling.

Among patients with RA, the burden of disease is evidenced by decreased quality of life,³⁻⁶ decreased employment rates,^{7,8} and increased direct and indirect costs.⁹⁻¹² In 2003, arthritis and other rheumatic conditions cost the United States \$127.8 billion (\$80.8 billion in medical care expenditures and \$47.0 billion in lost earnings).¹³ Annually, approximately 9 million physician office visits and more than 250,000 hospitalizations occur as the result of RA. The mean total annual direct cost to patients with RA is estimated to be \$9,519 per person,⁹ and most studies have reported indirect costs to be roughly twofold greater than direct costs.¹⁴

Causes and Diagnosis

RA is an autoimmune disease that affects 1.3 million adults in the United States.² Disease onset generally occurs between ages 30 and 50 years, and incidence is higher in women and older adults. RA presentations range from mild to severe. Some people are affected for as little as a few months, whereas others are affected for a lifetime and suffer severe joint damage and disability.

The hallmarks of the disease are inflammation of the synovium (a membrane that lines the joint capsule and produces lubricating fluid in the joint) with progressive erosion of bone leading to malalignment of the joint. As the inflamed synovium destroys the joint, the surrounding muscles and tendons become weak, leading to disability in most cases. Unlike osteoarthritis, RA can affect other areas in addition to joints. Most patients develop anemia. Some patients have dry eyes and mouth (sicca syndrome). Rarely, patients develop inflammation in the lining of the lung (pulmonary fibrosis), various layers of the eye wall (episcleritis and scleritis), small vessels (vasculitis), and the outer covering of the heart (pericarditis).

The exact etiology of RA is not completely understood, but genetic susceptibility plays an important role.^{15, 16} Studies have shown the importance of T cells, B cells, and cytokines in the pathogenesis of RA.^{17, 18} Cytokines of particular interest are tumor necrosis factor (TNF), interleukin (IL)-1, and IL-6.

TNF plays a central role in the pathobiology of RA. It is an important regulator of other proinflammatory molecules and stimulates the secretion of matrix metalloproteinases. It also exerts a direct effect on the multiple tissues inside the joint including chondrocytes, macrophages, synovial fibroblasts, and osteoclasts. Together, its action leads to inflammation and the formation of pannus, a mass of tissue that causes localized joint destruction. ¹⁸

The diagnosis of RA is primarily a clinical one, based on multiple patient symptoms. No single laboratory test confirms RA. Constitutional symptoms including low-grade fever, fatigue, or malaise are common before the onset of joint swelling and pain. Joint stiffness is almost always present and is frequently most severe after periods of prolonged rest. The disease tends to affect the small joints of the hands and feet first in a symmetric pattern, but other joint patterns are often seen. A serum rheumatoid factor is present in up to 75 percent of patients with RA but is frequently negative in early disease. A more specific marker, anticyclic citrullinated peptide

(CCP) antibody, has recently been described and may be a useful marker in patients with early disease. ^{19, 20} Table 1 presents the 1988 diagnostic criteria for RA developed by the American College of Rheumatology (ACR) and used by many of the studies in this review. ²¹ Patients are said to have RA if they meet four of the seven criteria in the table. ²¹ It should be noted that these criteria are relatively insensitive for early disease and efforts are underway to revise the criteria to address this issue. In 2010, a collaborative work group of the ACR and the European League Against Rheumatism (EULAR) released new classification criteria that are sensitive to the current treatment goals—remission or at least low disease activity in all patients. ²² (Further information on these criteria can be found at the end of Appendix).

Table 1. ACR criteria for the diagnosis of rheumatoid arthritis

Crite	ila
1.	Morning stiffness lasting greater than 1 hou

- Arthritis in three or more joint areas
- Arthritis of the hand joints (metacarpophalangeal [MCP], proximal interphalangeal [PIP], wrists)
- 4. Symmetric arthritis
- 5. Rheumatoid nodules
- Serum rheumatoid factor
- 7. Radiographic changes: erosions or unequivocal periarticular osteopenia

Source: Arnett et al., The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. Arthritis Rheum. 1988 Mar; 31(3):315-24. ²¹

Treatment of Rheumatoid Arthritis

Treatment of patients with RA aims to control pain and inflammation and, ultimately the goal is remission or at least low disease activity for all patients. This review focuses on treatments commonly used for RA in the United States.^a

Corticosteroids. Corticosteroids—sometimes referred to as glucocorticoids or steroids—are used for many inflammatory and autoimmune conditions. As a class, corticosteroids have been used since the discovery of cortisone in the 1940s. Commonly used oral corticosteroids include methylprednisolone, prednisone, and prednisolone.

Corticosteroids are a synthetic form of cortisol, a hormone produced by the adrenal glands. They produce their anti-inflammatory and immunosuppressive response by interacting with steroid-specific receptors in the cytoplasm of cells, thereby inhibiting the movement of inflammatory cells into the site of inflammation, inhibiting neutrophil function, and inhibiting prostaglandin production. They are widely prescribed as an oral treatment for RA because of their ability to reduce inflammation and subsequent joint pain and swelling.

Oral disease-modifying antirheumatic drugs (DMARDs). Oral DMARDs such as methotrexate (MTX), sulfasalazine, hydroxychloroquine, and leflunomide modify the course of inflammatory conditions, presumably through their effects on the immune system. Most of the oral DMARDs have been used in clinical practice for more than 20 years. MTX was developed in the 1940s as a treatment for leukemia but was not approved for the treatment of arthritis until 1988. Sulfasalazine also has been available since the 1940s; it is a combination salicylate (acetylsalicylic acid) and antibiotic (sulfapyearidine) that originally was used to treat patients with inflammatory bowel disease. Hydroxychloroquine, approved in the 1950s for the treatment of malaria, is believed to work in arthritis by interfering with antigen presentation and the activation of immune response by increasing the pH within macrophage phagolysosomes. Additionally, hydroxychloroquine possibly inhibits toll-like receptors that mediate

^a Minocycline, gold cyclosporine, and azathioprine are not included in this review.

proinflammatory cytokine production. Only leflunomide, an isoxazole immunomodulatory agent, was specifically developed for treating inflammatory arthritis; the U.S. Food and Drug Administration (FDA) approved its use in 1998.

Oral DMARDs are not members of a single drug family. They are classified together, however, because they all are slow acting with the aim of improving symptoms, reducing or preventing joint damage, and preserving structure and function in patients with inflammatory disease. All the oral DMARDs covered in this review can be given orally, although MTX can also be injected (subcutaneous [SQ] or intramuscular [IM]).

Biologic DMARDs. Biologic DMARDs—commonly referred to as biological response modifiers or simply biologics—are a relatively new injectable category of DMARDs that differ from oral DMARDs in that they target specific components of the immune system. The FDA approved the first of the biologics (infliximab) in 1998; this report covers eight additional agents approved since that time: etanercept (1998), anakinra (2001), adalimumab (2002), abatacept (2005), rituximab (2006), certolizumab pegol (2008), golimumab (2009), and tocilizumab (2010). Of the nine agents, all are currently FDA approved for treating RA.

The biologic DMARDs work by selectively blocking mechanisms involved in the inflammatory and immune response. Adalimumab, certolizumab pegol, etanercept, golimumab, and infliximab are known as TNF inhibitors (i.e., drugs that block specific proinflammatory mediators known as cytokines). They produce their primary effect by blocking TNF from interacting with cell surface TNF receptors. Adalimumab, infliximab, and golimumab are monoclonal antibodies. Adalimumab is a fully human monoclonal antibody that binds specifically to TNF, blocking its interaction with both the p55 and p75 cell surface TNF receptor. Golimumab is also a human monoclonal antibody that binds to TNF alpha with high affinity. Infliximab is a chimeric (i.e., made from human and mouse proteins) monoclonal antibody that binds specifically to human TNF alpha. Etanercept is not a monoclonal antibody, but rather a TNF-soluble receptor protein. More specifically, it is a soluble dimeric form of the p75 TNF receptor linked to the Fc portion of human immunoglobulin G1 (IgG1). Etanercept exerts its action by binding circulating TNF and preventing it from interacting with a cell surface receptor. It does not form neutralizing antibodies or mediate cell lysis in the presence or absence of complement. Certolizumab pegol is a pegylated humanized antibody fragment of TNF monoclonal antibody. The drug binds to the TNF alpha-receptor and blocks TNF alpha activity. It only possesses the Fab fragment and lacks the Fc region. Hence, it does not induce antibodydependant cell mediated apoptosis or toxicity.

IL-1, another naturally occurring cytokine, has both immune and proinflammatory actions. Anakinra, an IL-1 receptor antagonist, is a human recombinant protein that competitively blocks the IL-1 receptor, thus blocking various inflammatory and immunological responses.

The immunosuppressant agent abatacept produces its immune response by interfering with T lymphocyte activation. Abatacept is a soluble fusion protein that consists of the extracellular domain of human cytotoxic T lymphocyte-associated antigen (CTLA-4) and the modified Fc portion of IgG1.

Rituximab, a chimeric murine/human monoclonal antibody, works by binding to the CD20 antigen found on the surface of B lymphocytes. Thus, it removes circulating B cells from the pre-B cell stage through the activated B cells. B cells are believed to play a role in autoimmune and inflammatory processes, such as those involved in RA.

IL-6 is a naturally occurring cytokine involved in the regulation of immune responses and inflammation. Tocilizumab is a monoclonal antibody that inhibits interleukin-6 (IL-6) receptors,

blocking the action of IL-6, and leading to a reduction in cytokine and inflammatory response. Tables 2 through 4 provide detailed information (names, manufacturers, and available dosage forms) on agents used in the treatment of RA that we have included in this review. Also presented are routes of administration, labeled uses, and usual (recommended) adult doses and frequency for RA.

Table 2. Pharmaceutical treatments for rheumatoid arthritis: Corticosteroids

	Manufacturer U.S. Trade		
Generic Name		How Supplied	Usual Adult Dose
Cortico- steroids: Methyl- prednisolone	Multiple Medrol [®] , Depo-Medrol [®] , Solu-Medrol [®]	Acetate - Injectable IM—20, 40, and 80 mg/ml Sodium succinate - Injectable IM—40, 125, and 500 mg, 1 and 2	Acetate: IM—10 to 80 mg every 1 to 2 weeks Intra-articular, intralesional—4 to 80 mg every 1 to 5 weeks
		g vials Oral: Tabs—2, 4, 8, 16, and 32 mg	Sodium succinate: IM—10 to 80 mg daily IV—10 to 40 mg every 4 to 6 hours; up to 30 mg/kg every 4 to 6 hours
			Oral: 2 to 60 mg in 1 to 4 divided doses to start, followed by gradual reduction
Prednisone	Multiple Deltasone [®] , Sterapred [®] , LiquiPred	Oral Solution—1 and 5 mg/ml Tabs—1, 2.5, 5, 10, 20, and 50 mg	Use lowest effective dose. Usually ≤ 10 mg/day, but doses range from 5-60 mg/day
Prednisolone	Multiple Orapred®, Pediapred®, Prelone®, Delta-Cortef®, Econopred®	Oral Solution/Syrup—5, 15, and 20 mg/5 ml Oral Tabs—5 and 15 mg	Use lowest effective dose (5 to 7.5 mg/day), up to 60 mg/day

IM = intramuscular; IV = intravenous; kg = kilogram; mg = milligram; ml = milliliter

^{*}Listed trade names are limited to commonly prescribed U.S. products when multiple trade names are available.

Table 3. Pharmaceutical treatments for rheumatoid arthritis: Oral DMARDs

	Manufacturer U.S. Trade		
Generic Name	Name(s)*	How Supplied	Usual Adult Dose
Hydroxy- chloroquine	Multiple	Oral Tabs—200 mg	200 to 400 ^a mg/day in 1 or 2 divided doses
	Plaquenil [®]		
Leflunomide	Multiple	Oral Tabs—10 and 20 mg	10 to 20 mg/day in a single dose. May give loading dose of 100 mg/day for 3 days in
	Arava [®]		patients with low risk of hepatic or hematologic toxicity.
Methotrexate	Multiple	Injectable—25 mg/ml, 20 mg and 1 g vials	IM, SQ, oral—7.5 to 20 mg/week in a single dose
	Trexall [®] ,	Oral Tabs—2.5, 5, 7.5, 10, and 15	•
	Folex [®] ,	mg	
	Rheumatrex®		
Sulfasalazine	Multiple	Oral Suspension—250 mg/5 ml Oral Tabs—500 mg	500 to 3,000 mg/day in 2 to 4 divided doses
	Azulfidine [®] ,	Ç	
	EN-tabs [®] ,		
	Sulfazine [®]		

g = gram; IM = intramuscular; mg = milligram; ml = milliliter
*Listed trade names are limited to commonly prescribed U.S. products when multiple trade names are available.
and all the commonly prescribed U.S. products when multiple trade names are available.

Table 4. Pharmaceutical treatments for rheumatoid arthritis: Biologic DMARDs

	Manufacturer U.S. Trade	nents for medinatoid artifitis: i		
Generic Name		Injectable Supply	Usual Adult Dose	
Abatacept Brist	ol Myers Squibb	250 mg vial	IV—Dosed according to body weight (< 60 kg = 500 mg; 60-100 kg = 750 mg; > 100 kg = 1,000 mg); dose repeated at 2 weeks	
	Orencia [®]		and 4 weeks after initial dose, and every 4 weeks thereafter SQ—may give weight-based IV loading	
			dose, then 125 mg SQ once weekly	
Adalimumab Abbott		40 mg/0.8 ml, 20 mg/0.4 ml prefilled syringe	SQ—40 mg every other week; may increase to 40 mg per week in patients not	
	Humira [®]		taking concomitant MTX	
Anakinra	Amgen Kineret®	100 mg/0.67 ml syringe	SQ—100 mg/day; dose should be decreased to 100 mg every other day in	
Certolizumab	UCB	200 mg powder for reconstitution,	renal insufficiency SQ—Initial dose of 400 mg, (as 2 SQ	
Pegol	Cimzia [®]	200 mg/ml solution	injections of 200 mg), repeat dose 2 and 4 weeks after initial dose; maintenance dose is 200 mg every other week (may consider maintenance dose of 400 every 4 weeks)	
Etanercept Amo	Pfizer Immunex	50 mg/ml in 25 mg or 50 mg single use prefilled syringe	SQ—50 mg once weekly with or without MTX	
	Enbrel [®]			
Golimumab Centoc or Ortho Biotech		50 mg/0.5 ml syringe	SQ—50 mg once per month in combination with MTX	
	Simponi [®]			
Infliximab Cento	oc or Ortho Biotech	100 mg in a 20 ml vial	IV—3 mg/kg in combination with MTX at 0, 2, and 6 weeks followed by maintenance every 8 weeks thereafter; may increase to	
	Remicade [®]		maximum of 10 mg/kg or treat as often as every 4 weeks	
Rituximab	Biogen Idec / Genentech	100 mg/10 ml and 500 mg/50 ml vial	IV—1,000 mg IV infusion separated by 2 weeks (one course) every 24 weeks or based on clinical evaluation, but not	
	Rituxan [®]		sooner than every 16 weeks	
Tocilizumab	Genentech / Roche	80 mg/4 ml, 200 mg/10 ml, 400 mg/20 ml vial	IV—4 mg/kg every 4 weeks; increase to 8 mg/kg every 4 weeks based on clinical response	
	Actemra [®] , RoActemra [®]			

kg = kilogram; mg = milligram; ml = milliliter; MTX = methotrexate; IV = intravenously SQ = subcutaneously *Listed trade names are limited to commonly prescribed U.S. products when multiple trade names are available.

Treatment Strategies

In RA, nonsteroidal anti-inflammatory drugs (NSAIDs) are frequently used in early or mild disease, but they do not have any disease-modifying properties. The oral DMARD MTX is the cornerstone of treatment, as it has demonstrated good disease control. However, MTX toxicity may limit its use, and many patients do not adequately respond to MTX monotherapy. Leflunomide, hydroxychloroquine, and sulfasalazine are alternative oral DMARDs that can be given as monotherapy or in combination; recommendations for their use are largely based on disease duration, degree of disease activity, and prognostic features.²³

Combination therapies serve an important role because treatment with a single DMARD often does not adequately control symptoms. Low-dose systemic corticosteroids (prednisone 7.5-10 mg/day) or intra-articular corticosteroids are used as an adjunct to DMARDs. In patients with persistent disease despite aggressive management with standard agents, biologic agents, often in combination with MTX, are now considered the standard of care. Although combination therapies improve response rates in patients initially receiving monotherapy, available evidence does not predict which combination strategy will provide the best outcome.²⁴

There is debate about which types of combination therapy are preferred and how early in the disease process to initiate this intervention. No settled opinion exists as to whether treatment should proceed in a sequential step-up approach (progressing from single therapy to combination therapy) or in a step-down approach (beginning with combination therapy and stepping down treatment when symptoms are under control). Additional uncertainty remains regarding risks and benefits of therapies in patient subgroups.

Recent reports have examined treatment of RA, supporting the overall efficacy of treatments. ²⁵⁻²⁹ However, additional agents have since been introduced on the market, necessitating an update of the evidence. A further examination of the comparative efficacy and effectiveness of various treatments and treatment strategies, as well as long-term outcomes and subpopulations, is warranted.

Scope and Key Questions

The purpose of this review is to compare the efficacy, effectiveness, and harms of corticosteroids, oral DMARDs, and biologic DMARDs in the treatment of patients with RA. We address the following four Key Questions (KQs):

- KQ 1: For patients with RA, do drug therapies differ in their ability to reduce disease activity, to slow or limit the progression of radiographic joint damage, or to maintain remission?
- KQ 2: For patients with RA, do drug therapies differ in their ability to improve patient-reported symptoms, functional capacity, or quality of life?
- KQ 3: For patients with RA, do drug therapies differ in harms, tolerability, patient adherence, or adverse effects?
- KQ 4: What are the comparative benefits and harms of drug therapies for RA in subgroups of patients based on stage of disease, prior therapy, demographics, concomitant therapies, or comorbidities?

Organization of the Report

The remainder of this comparative effectiveness review describes our methods to review and synthesize this literature, presents our results by KQ, and discusses the implications of those results for clinical applications and future research. Appendix A describes our search strategy; Appendix B presents our review and abstraction forms; Appendix C lists our articles by database searched; Appendix D lists excluded studies and the reasons for exclusion; Appendix E contains our evidence tables; Appendix F presents the criteria for assessing the quality of individual studies; Appendix G describes clinical assessment scales commonly used in arthritis trials; Appendix H contains our Poor Quality studies; Appendix I, our Strength of Evidence tables; Appendix J, the sensitivity analysis methods for the Mixed Treatment Comparisons; and Appendix K, the ACR 20 and ACR 70 results for the Mixed Treatment Comparisons.

Methods

In this chapter, we document the procedures that the RTI International—University of North Carolina Evidence-based Practice Center (RTI–UNC EPC) used to develop this comparative effectiveness review (CER) on pharmacologic treatments for rheumatoid arthritis. We briefly describe the topic development process below. We then document our literature search and retrieval process and describe methods of abstracting relevant information from the eligible articles to generate evidence tables. We also document our criteria for rating the quality of individual studies and for grading the strength of the evidence as a whole.

Topic Development

This report is an update of a CER completed in 2007. ²⁶ The topic of the original report and the preliminary Key Questions (KQs) arose through a public process involving the public, the Scientific Resource Center (SRC, at www.effectivehealthcare.ahrq.gov/aboutUs/index.cfm#RC) for the Effective Health Care program of the Agency for Healthcare Research and Quality (AHRQ) (www.effectivehealthcare.ahrq.gov), and various stakeholder groups (www.effectivehealthcare.ahrq.gov/aboutUs/index.cfm#SG). Investigators from the RTI-UNC EPC then refined the original questions into the KQs used for the original report, in consultation with AHRQ, the SRC, and the Technical Expert Panel (TEP) during multiple conference calls. For this update, the original KOs were again refined into the final set of KOs cited in the introduction. No substantive changes to the KQs were made for this update other than adding new medications that have been approved since the previous report. The protocol for the project was posted on the AHRQ Web site (www.effectivehealthcare.ahrq.gov). The original report included both rheumatoid arthritis (RA) and psoriatic arthritis (PsA). When updating the material, the decision was made to divide into the material into two separate reports, one for RA and one for PsA. This report includes only the information related to patients with RA. This report is intended to replace the original report; it includes the information from the original report as well as the new information we identified.

Literature Search

To identify articles relevant to each KQ, we searched MEDLINE®, Embase, the Cochrane Library, and the International Pharmaceutical Abstracts. The full search strategy is presented in Appendix A. We conducted this review at the same time as a review on PsA; the literature searches and review processes were conducted in parallel, shown in Appendix A. We used either Medical Subject Headings (MeSH or MH) as search terms when available or key words when appropriate. We combined terms for selected indications (RA, PsA), drug interactions, and adverse events with a list of included medications. We included the following medications: corticosteroids (methylprednisolone, prednisone, and prednisolone), four oral disease-modifying antirheumatic drugs (DMARDs) (methotrexate [MTX], leflunomide, sulfasalazine, and hydroxychloroquine), and nine biologic DMARDs (abatacept, adalimumab, anakinra, certolizumab pegol, etanercept, golimumab, infliximab, rituximab and tocilizumab). We limited the electronic searches to "human" and "English language." For the original report, sources were searched from 1990 to September 2006. For this update, sources were searched from June 2006 to January 2011. We overlapped the update search with the original search to account for delays in indexing. We used the National Library of Medicine publication type tags to identify reviews,

randomized controlled trials (RCTs), and meta-analyses. We manually searched reference lists of pertinent review articles and letters to the editor to supplement searches for the original report. We used the ScopusTM abstract and citation database to supplement searches for this update. We imported all citations into an electronic database (EndNote X.0.2). Additionally, we handsearched the Center for Drug Evaluation and Research (CDER) database to identify unpublished research submitted to the U.S. Food and Drug Administration (FDA). The SRC contacted pharmaceutical manufacturers and invited them to submit dossiers, including citations. We received dossiers from five pharmaceutical companies (Abbott, Amgen, Bristol-Myers Squibb, Centocor, and Genentech) for the original report. We received dossiers from six pharmaceutical companies (Abbott, Amgen, Centocor, Horizon, Genentech, and UCB) for this update. The SRC also searched the following for potentially relevant unpublished and ongoing literature: FDA Web site; Health Canada; Authorized Medicines for EU; ClinicalTrial.gov; Current Controlled Trials, Clinical Study Results, WHO Clinical Trials, Conference Papers Index; Scopus; NIH RePORTER; HSRPROJ; Hayes, Inc. Health Technology Assessment; and the New York Academy of Medicine's Grey Literature Index.

Study Selection

We developed eligibility (inclusion and exclusion) criteria with respect to study design or duration, patient population, interventions, outcomes, and comparisons for each KQ, as described in Table 5. For efficacy and effectiveness, we focused on head-to-head trials and prospective cohort studies comparing one drug with another. For biologic DMARDs, we also included placebo-controlled, double-blind RCTs. For harms and tolerability, as well as for efficacy and effectiveness in subgroups, we included head-to-head trials, high-quality systematic reviews, and observational studies.

For this review, results from well-conducted, valid head-to-head trials provide the strongest evidence to compare drugs with respect to efficacy, effectiveness, and harms. We defined head-to-head trials as those comparing one drug of interest with another. RCTs or prospective cohort studies of at least 3 months' duration were eligible for inclusion. Because multiple large RCTs had been conducted on this topic, we adopted a minimum sample size requirement ($N \ge 100$) to focus on the best available evidence. However, we did not use a sample size cutoff for our meta-analyses (RCTs of any sample size were eligible for our mixed treatment comparisons). For harms (i.e., evidence pertaining to tolerability, adverse effects, and adverse events), we examined data from both experimental and observational studies. We included RCTs and observational studies with sample sizes of at least 100 patients that last at least 3 months, and that reported an outcome of interest.

As equipotency among the reviewed drugs is not well established, we assumed that comparisons made within the recommended dosing ranges in the Introduction chapter are appropriate. Dose comparisons made outside the recommended daily dosing range are not in our report. Doses that that could be considered equivalent to the recommended doses, but were not identical to recommended doses are included in the report. For example, 40 mg every other week is a recommended dose for adalimumab and some studies used a 20 mg weekly dosing (not a recommended dose). We considered the 20 mg weekly dose to be equivalent to 40 mg every other week and included studies using the 20 mg every week dose.

Table 5. Outcome	measures	and study	eligibility	criteria
Table J. Outcome	iiicasuics	and Study	CHAINIIII	CHILEHIA

Key Questions, Outcomes of Interest,	Study Eligibility Criteria
and Specific Measures KQ 1/KQ 2: ^a	Study Design
Efficacy/effectiveness	Head-to-head double-blind RCTs
KQ 1:	
 Disease activity^b 	Systematic reviews Prespective controlled cohort studies
Radiographic joint damage	 Prospective, controlled cohort studies Minimum Study Duration
Remission	RCT—3 months
Remission	Observational—3 months
KQ 2:	Study Population
Functional capacity	Ages 19 or older
Quality of life	Patients with RA
Patient-reported symptoms	Sample Size
T dilont reported symptoms	• RCT N ≥100
	Observational N ≥100
KQ 3:	Study Design
Harms, tolerability, adherence, adverse	Head-to-head double-blind RCTs
effects	Systematic reviews
	Observational studies, prospective and retrospective
	Minimum Study Duration
	RCT—3 months
	Observational—3 months
	Study Population
	Ages 19 or older
	Patients with RA
	Sample Size
	• RCT N ≥100
	Observational N ≥100
KQ 4:	Study Design
Benefits and harms in subgroups based	Head-to-head double-blind RCTs
on stage, history of prior therapy,	Systematic reviews
demographics, concomitant therapies,	Observational studies
comorbidities	Minimum Study Duration
	RCT—3 months
	Observational—3 months
	Study Population
	Ages 19 or older
	Patients with RA
	Sample Size
	• RCT N ≥100
	Observational N ≥100
KO - Key Question: N - number of subjects and	rolled (i.e. sample size): RA = rheumatoid arthritis: RCT = randomized controlled

 $KQ = Key\ Question;\ N = number\ of\ subjects\ enrolled\ (i.e.\ sample\ size);\ RA = rheumatoid\ arthritis;\ RCT = randomized\ controlled\ trial$

Two individuals independently reviewed abstracts (Appendix B contains review criteria for title/abstract stage). If both reviewers agreed that a study did not meet eligibility criteria, we excluded it. We obtained the full text of all remaining articles and used the same eligibility

^a We divided the assessment of efficacy/effectiveness into two KQs based on two groups of outcomes: those addressing disease activity, radiographic measures, and remission (KQ 1) and those addressing functional capacity, quality of life, and other patient reported symptoms (KQ 2). We did this to group measures that are based on more objective measures under KQ 1 and those that are based more on subjective patient reported outcomes under KQ 2.

^b Disease activity reflects the overall RA activity. Measures of disease activity, such as the American College of Rheumatology 20 percent response (ACR 20), 50 percent response (ACR 50), 70 percent response (ACR 70), and the Disease Activity Score (DAS), include assessment of some or all of the following: the number of swollen and tender joints, the patient's global assessment of his/her disease activity, the physician's global assessment of the patient's disease activity, patient's pain score, patient's physical function score, and acute phase reactants (C-reactive protein). Appendix provides additional details about these measures.

criteria (Appendix B) to determine which, if any, to exclude at this stage. Appendix C lists our full bibliography and their source database. Appendix D summarizes reasons for excluding studies that were reviewed as full-text articles but did not meet eligibility criteria. We did not include studies that met eligibility criteria but were reported as an abstract only.

We reviewed studies that reported health outcomes for efficacy or effectiveness. For example, these outcomes included clinical response to treatment, remission, functional capacity, and quality of life. In addition, we included radiographic outcomes as intermediate outcome measures. For harms, we looked for both total adverse events and specific adverse events ranging in severity (e.g., serious infections, malignancies, hepatotoxicity, hematological adverse events, infusion and injection reactions, and nausea), withdrawals attributable to adverse events, and drug interactions. We included systematic reviews and meta-analyses in our evidence report if we found them to be relevant for a KQ and of good or fair methodological quality. We did not abstract individual studies if they had been used in an included systematic review or meta-analysis of good quality. However, we reviewed them to determine whether any other outcomes of interest were reported.

Data Extraction

We designed and used a structured data abstraction form to ensure consistency of appraisal for each study. Trained reviewers abstracted data from each study. A senior reviewer read each abstracted article and evaluated the completeness of the data abstraction.

We abstracted the following data from included articles: study design, eligibility criteria, intervention (drugs, dose, and duration), additional medications allowed, methods of outcome assessment, population characteristics (such as age, sex, race or ethnicity, or mean disease duration), sample size, loss to followup, withdrawals because of adverse events, results, and adverse events reported. We recorded intention-to-treat (ITT) results if available. All data abstraction employed SRS 4.0, Mobius AnalyticsTM. Evidence tables containing all abstracted data of included studies are presented in Appendix E.

Quality Assessment

To assess the quality (internal validity) of trials, we used predefined criteria based on those developed by the U.S. Preventive Services Task Force (ratings: good, fair, poor)³⁰ and the National Health Service Centre for Reviews and Dissemination.³¹ Elements of quality assessment included randomization and allocation concealment, similarity of compared groups at baseline, use of ITT analysis (i.e., all patients were analyzed as randomized), adequacy of blinding, and overall and differential loss to followup.

In general terms, a "good" study has a low risk of bias and results are considered to be valid. A "fair" study is susceptible to some risk of bias but probably not sufficient to invalidate its results. The fair-quality category is likely to be broad, so studies with this rating will vary in their strengths and weaknesses. A "poor" rating indicates significant risk of bias (stemming from, e.g., serious errors in design, analysis reporting large amounts of missing information, or discrepancies in reporting) that may invalidate the study's results.

To assess the quality of observational studies, we used criteria outlined by Deeks et al.³² Items assessed included selection of cases or cohorts and controls, adjustment for confounders, methods of outcomes assessment, length of followup, and statistical analysis. To assess the quality of systematic reviews and meta-analyses, we assessed the following: whether the review was based on a clear question, clear reporting of inclusion criteria, methods used for identifying

literature (the search strategy), whether two reviewers independently reviewed publications to determine eligibility, whether authors used a standard method of critical appraisal (or quality rating or validity assessment), assessment of heterogeneity, assessment of publication bias, and statistical analysis. Systematic reviews were categorized as good when all criteria were met.

Two independent reviewers assigned quality ratings. They resolved any disagreements by discussion and consensus or by consulting with a third reviewer. Appendix F details the predefined criteria used for evaluating the quality of all included studies. We gave a good-quality rating to studies that met all criteria. We gave a poor-quality rating to studies that had a fatal flaw (defined as a methodological shortcoming that leads to a very high risk of bias) in one or more categories and excluded them from our analyses. Poor-quality studies and reasons for that rating are presented in Appendix .

Applicability Assessment

We used the parameters for evaluation on guidance provided by AHRQ's Methods Guide for Comparative Effectiveness Reviews,³³ to evaluate the applicability of the included studies. Applicability is similar to generalizability or external validity of the studies included in the evidence base. We evaluated applicability using a qualitative assessment of the population, intervention/treatment, comparator, outcomes measured, timing of followup, and setting. We specifically considered whether populations enrolled in these trials or studies differed from target populations as laid out in the Introduction, whether studied interventions are comparable with those in routine use, whether comparators reflect best alternatives, whether measured outcomes reflect the most important clinical outcomes, whether followup was sufficient, and whether study settings were representative of most settings.

Grading Strength of Evidence

We evaluated the strength of evidence based on methods guidance for the EPC program. ^{33, 34} For this report, we graded the strength of evidence for the outcomes determined to be most important: measures of disease activity (e.g., ACR 20/50/70, DAS), radiographic changes, functional capacity, quality of life, withdrawals due to adverse events, and specific adverse events if data were available (e.g., injection-site reactions, infections, malignancy). The strength of evidence for each outcome or comparison that we graded incorporates scores on four domains (Table 5): risk of bias, consistency, directness, and precision; it can also reflect ratings for other domains that can be factored in when relevant (e.g., dose-response relationships).

As described in Owens et al., the evaluation of risk of bias includes assessment of study design and aggregate quality of studies.³⁴ We judged good-quality studies to result in evidence with low risk of bias. We graded evidence as consistent when effect sizes across studies were in the same direction. When the evidence linked the interventions directly to health outcomes, we graded the evidence as being direct. We graded evidence as being precise when results had a low degree of uncertainty. A precise estimate is an estimate that would allow a clinically useful conclusion. An imprecise estimate is one for which the confidence interval is wide enough to include clinically distinct conclusions.³⁴

We dually evaluated the overall strength of evidence for each major outcome based on a qualitative assessment of strength of evidence for each domain and reconciled all disagreements. The levels of strength of evidence are shown in Table 6.

Table 6. Strength of evidence grades and their definitions³⁴

Grade	Definition
High	High confidence that the evidence reflects the true effect. Further research is very unlikely to
•	change our confidence in the estimate of effect.
Moderate	Moderate confidence that the evidence reflects the true effect. Further research may change
	our confidence in the estimate of effect and may change the estimate.
Low	Low confidence that the evidence reflects the true effect. Further research is likely to change
	our confidence in the estimate of effect and is likely to change the estimate.
Insufficient	Evidence either is unavailable or does not permit estimation of an effect.

Data Synthesis

A direct comparative effectiveness assessment of two treatments was available if a comparative study of the two treatments has been conducted. Ideally, this would be a randomized controlled trial that directly compares the two treatments. However, many competing treatments have not been compared directly. In such cases, indirect methods that utilize data from common comparators (e.g., placebo) were available. There were very few head-to-head studies of biologic DMARDS, but there were numerous placebo-controlled studies. Using MTC meta-analysis allowed us to incorporate both direct evidence (from head-to-head studies) and indirect evidence (from placebo-controlled studies) to determine how biologic DMARDs compare with each other."

Throughout this CER, we generally synthesized the literature qualitatively. The exceptions are the meta-analysis comparing the relative efficacy of biologic DMARDs and the meta-analyses comparing withdrawal rates from placebo-controlled trials. Comparisons of the drugs that were not quantitatively analyzed in any of the included meta-analyses were either limited to fewer than three good or fair RCTs or had heterogeneous/noncomparable study populations. Therefore, we did not attempt any quantitative analyses of such comparisons.

To compare the relative efficacy of biologic DMARDs, we used a mixed treatment comparison (MTC) meta-analysis. MTC is a generalization of standard pairwise meta-analysis that allows for simultaneous pairwise comparisons based on a network of evidence. To one advantage of MTC using a Bayesian framework is that it allows for the combination of both direct head-to-head evidence and indirect evidence (e.g., different treatments with a common comparator) in a way that preserves randomization and minimizes bias. Another advantage is that the Bayesian framework allows for a ranking of treatments based on the probability of which treatment is best. To

We conducted the MTC meta-analysis using the methods developed by the Multi-Parameter Evidence Synthesis (MPES) Research Group at the University of Bristol. ^{35, 36, 38} We used a random effects logistic regression model that adjusted for correlations between arms within each study. The analysis was performed using WinBUGS Version 1.4.3, a Bayesian software package that uses Markov chain Monte Carlo (MCMC) techniques. ³⁹ We used WinBUGS code developed by the MPES Research Group, which is available from their program Web site. ⁴⁰ For our analysis, study effect and treatment effect parameters were modeled by noninformative (flat) prior distributions that were normal (0, 10,000). For the heterogeneity of the random-effects model, we used a uniform prior distribution centered at zero with sufficiently large variance. The first 20,000 simulations were discarded to allow for model convergence, and then an additional 80,000 simulations were used in estimating the posterior probabilities. Satisfactory convergence was verified by trace plots and calculation of the Monte Carlo error for each parameter.

In conducting any meta-analysis, it is important to consider various sources of heterogeneity and bias. Valid inferences are based on the assumption of studies of similar design, similar patient populations, and a network of evidence with a common comparator. Evidence suggests that adjusted indirect comparisons agree with head-to-head trials if component studies are similar and treatment effects are expected to be consistent in patients included in different trials. 41-43

For the MTC meta-analyses for efficacy, we included studies with a good or fair quality rating that compared biologic DMARDs to a placebo- or active-control in patients with active RA despite MTX therapy. Patients could be on a background dose of MTX, but both treatment and placebo arms needed to be on comparable doses. Only studies with durations greater than 3 months were considered. For MTC meta-analyses for efficacy, we excluded trials enrolling either (1) patients who were MTX-naïve, or (2) patients who previously failed treatment with biologic DMARDs. This population reflects a clinically relevant subset, because in general, biologics are prescribed when patients are resistant to MTX and many of the studies were conducted in MTX-resistant patients who are new to biologic therapy. In addition, patients who are MTX-naïve or who have previously failed treatment with biologic DMARDs may have different response to treatments. We felt that an inadequate number of studies examined other populations, such as MTX-naïve patients, to allow us to conduct MTC meta-analyses for efficacy for other populations.

For MTC meta-analyses of withdrawals, we did not exclude studies enrolling patients who were MTX-naïve or patients who previously failed treatment with biologic DMARDs because we did not consider these factors to be significant in evaluating tolerability profiles. Unlike efficacy, we believe that tolerability is more likely to be a function of the specific treatment regimen than it is to be related to how patients previously have responded to other treatments (i.e., MTX naïve and anti-TNF failure).

Our outcome measures of choice were American College of Rheumatology (ACR) response rates and withdrawals (overall, due to lack of efficacy, and due to adverse events). ⁴⁴ The primary efficacy outcome of our MTC meta-analysis is the ACR 50; results are reported in the Results chapter. The results from the analysis of ACR 20 and ACR 70 are presented in Appendix . We present the relative efficacies of biologic DMARDs as odds ratios and 95 percent Credible Intervals (CrI).

A total of 34 studies were identified for potential inclusion in the MTC meta-analysis of ACR response rates, and were further reviewed to explore sources of heterogeneity before conducting the MTC. We excluded four studies from the main analysis because of heterogeneity due to study design, whereas other sources of heterogeneity were explored through sensitivity analyses (Appendix K). The four excluded studies had early escape designs, a large number of crossovers from placebo to active treatment, and no ACR outcomes reported prior to the crossover. All potentially eligible studies of certolizumab were among these four studies. A total of 30 studies were included in the final MTC meta-analysis for efficacy, evaluating eight biologic DMARDs: abatacept, adalimumab, anakinra, etanercept, golimumab, infliximab, rituximab, and tocilizumab. Detailed information on the included studies for the efficacy analysis can be found in the Results chapter.

The meta-analysis comparing withdrawal rates from placebo-controlled trials used a random effects model to calculate pooled odds ratios of treatment withdrawals for each biologic DMARD relative to placebo. In these analyses, certolizumab pegol was included (because outcomes were reported prior to, or at the time of, crossover) in addition to the eight biologic DMARDs listed above. The outcomes of interest were rates of overall withdrawals, withdrawals

due to lack of efficacy, and withdrawals due to adverse events. For each analysis, we conducted a test of heterogeneity (I² statistic) and assessed publication bias with funnel plots. These analyses were performed using Stata 10. Additional meta-analyses comparing withdrawal rates between the biologic DMARDs were performed using an MTC meta-analysis.

Peer Review

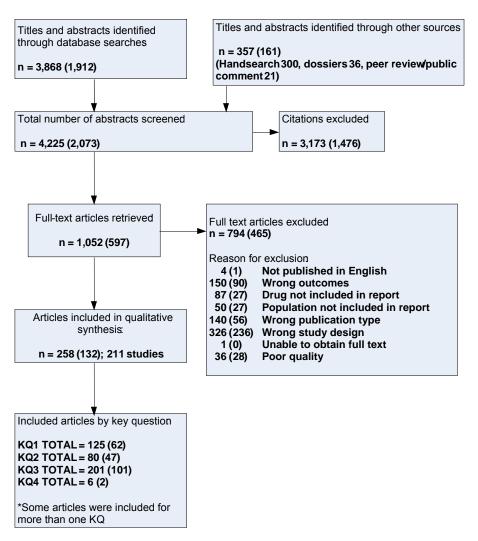
Individuals who were experts in rheumatology and various stakeholder and user communities (listed in the front matter) performed an external peer review on this CER. The SRC oversaw the peer review process. Peer reviewers were charged with commenting on the content, structure, and format of the evidence report, providing additional relevant citations, and pointing out issues related to how we had conceptualized and defined the topic and KQs. Our peer reviewers (listed in the front matter) gave us permission to acknowledge their review of the draft. We compiled all comments and addressed each one individually, revising the text as appropriate. AHRQ and the SRC also requested review from its own staff. In addition, the SRC placed the draft report on the AHRQ Web site (http://effectivehealthcare.ahrq.gov) and compiled the comments for our review.

Results

Introduction

Figure 1 depicts the disposition of identified articles. We included 258 published articles reporting on 211 studies: 31 head-to-head randomized controlled trials (RCTs), 1 head-to-head nonrandomized controlled trial, 44 placebo-controlled trials, 28 meta-analyses or systematic reviews, and 107 observational studies. Our findings include studies rated good or fair for internal validity, unless a particular study rated poor provides some unique information that we judged to be of interest. Most studies were of fair quality; we designate in the text only those of good or poor quality. Evidence tables for included studies, by Key Question (KQ), can be found in Appendix E.

Figure 1. Disposition of articles (PRISMA figure)



KQ, key question n, number of studies PRIMSA Preferred Reporting Items for Systematic Reviews and Meta Analyses

^{*}The first number listed includes all references identified in both the original and update reports

Of the 211 included studies, 104 (49 percent) were supported by pharmaceutical companies; 42 (20 percent) were funded by governmental or independent funds; and 20 (10 percent) were supported by a combination of pharmaceutical and government funding. We could not determine the source of support for 45 (21 percent) studies.

This chapter is organized by Key Question. We then present findings in order by class of drugs and combinations of drugs as appropriate to the particular key question. Generally, the chapter is organized using the following categories: individual oral disease-modifying antirheumatic drug (DMARD) versus oral DMARD, oral DMARD combinations (with or without corticosteroids) versus oral DMARD combinations, biologic versus biologic, biologic versus oral DMARD, biologics plus oral DMARD versus biologic, biologic plus oral DMARD versus oral DMARD, and early RA strategies. For purposes of this review, we defined strategies as studies where drug regimens were not fixed, but rather when a clinician made dose adjustments or drug changes according to patient response.

Across all Key Questions, we included head-to-head studies, observational studies, and systematic reviews. When comparative evidence is available, we discuss it before presenting indirect analyses of placebo-controlled trials.

Table 7 gives the numbers of trials for drug class comparisons reported only from head-to-head studies; when some groupings have important subcomparisons, we note these as well. Additionally, we included 107 observational studies in the report.

Table 7. Number of head-to-head trials by drug comparison for rheumatoid arthritis

Drug Comparison	Number of Trials; [†] Quality Rating
Oral DMARDs vs. oral DMARDs	8 fair; 1 good
Oral DMARD combinations	3 fair; 3 good
Biologic DMARDs vs. biologic DMARDs	1 fair
Biologic DMARDs vs. oral DMARDs	4 fair; 1 good
Biologic DMARD+oral DMARD combinations	9 fair; 3 good
Early RA Strategies	1 fair; 3 good

DMARD = disease modifying anti-rheumatic drug

Table 8 lists abbreviations and full names of diagnostic scales and health status or quality-of-life instruments encountered in these studies, as well information about clinical significance when available. For further details about such instruments and scales, see Appendix .

[†] Trials may fall into more than one drug comparison category, depending on the treatment arms discussed in the report.

Table 8. Disease activity, radiographic progression, functional capacity, and quality-of-life measures

Abbreviated Name	Complete Name of Measure or Instrument	Range of Scores	Improvement Denoted by	Clinically Significant Improvement
ACR-N	American College of Rheumatology percent improvement from baseline to endpoint	0 to 100 percent	Increase	
ACR 20/50/70*	American College of Rheumatology response scores based on 20, 50, or 70 percent criteria for improvement	0 to 100 percent	Increase	ACR 20 is 20% minimal improvement; ACR 50/70 considered more clinically significant ⁴⁵
ASHI	Arthritis-Specific Health Index (Medical Outcomes Study Short Form SF-36 Arthritis-specific Health Index)	0 to 100	Increase	
DAS*	Disease Activity Score	0 to 10	Decrease	DAS <1.6 correlates with remission ^{45, 46}
DAS 28	Disease Activity Score Short Form	0 to10	Decrease	DAS28 <2.6 correlates with remission 45,47
DLQI	Dermatology Life Quality Index	0 to 30	Decrease	
EQ-5D*	EuroQol EQ-5D Quality of Life Questionnaire	0 to 1	Increase	
EULAR response	European League Against Rheumatism response	N/A	N/A	
HAQ [*] (D-HAQ)	Health Assessment Questionnaire (Dutch Version)	0 to 3	Decrease	HAQ >= 0.22 change ⁴⁸
HAQ-DI	Disability Index of the Heath Assessment Questionnaire	0 to 3	Decrease	
SF-36*	Medical Outcomes Study Short Form 36 Health Survey	0 to 100	Increase	SF36 physical or mental component two standard error of the mean (SEM) ⁴⁹⁻⁵²
SHS*	Sharp/van der Heijde Method (SHS) for Scoring Radiographs (SHS is frequently modified by individual authors to meet study requirements and needs; there is no standard modified SHS)	Erosion: 0 to 160 for hands; 0 to 120 for feet Joint space narrowing: 0 to 168 Total: 0 to 448	Decrease	Changes in joint damage around the level of 5 units of the Sharp/van der Heijde method as minimally clinically important ⁵³

These key scales are defined in Appendix

Key Question 1: Reductions in Disease Activity, Limitations of Disease Progression, and Maintenance of Remission

This Key Question concerned three main topics. Specifically, for patients with rheumatoid arthritis (RA), do drug therapies differ in their ability to reduce disease activity, to slow or limit progression of radiographic joint damage, or to maintain remission? Evidence Tables in Appendix E document details about all these studies.

⁻⁻⁼ less commonly used measures for which there is little or no research regarding what constitutes a clinically significant improvement

Overview

Individual study details are found in the Evidence Tables, Appendix E. The main drug classes that we compared include oral disease-modifying antirheumatic drug (DMARDs), biologic DMARDs (also referred to simply as biologics), and various combined therapies.

Overall strength of evidence by disease activity and radiographic changes, when available, is listed in Table 9. Table 10 provides information on comparisons made, symptom response, and quality ratings. Table 11 provides information on radiographic joint damage, indicating whether the study populations included patients with early RA. When possible, we describe whether treatment effects reach minimal clinically important differences (MCIDs). In this section, achieving at least an American College of Rheumatology 20% improvement criteria (ACR), a disease activity score (DAS)<1.6, a DAS28<2.6, or a Sharp/van de Heijde change in joint damage of 5.0 are considered minimally clinically important (Table 9).

Oral DMARD versus oral DMARD. One trial found no statistically significant difference by ACR 20 between budesonide and prednisolone for disease activity outcomes.⁵⁴ The strength of evidence is low.

Two trials found no statistically significant difference by ACR 20 between methotrexate (MTX) and leflunomide for disease activity outcomes at 2 years or radiographic changes. These results are limited by the use of lower doses of MTX. ^{55, 56} The strength of evidence is low.

Three trials did not find a significant difference by ACR 20 between MTX and sulfasalazine for disease activity outcomes. These results are limited by the lower doses of MTX used in the earlier studies⁵⁷⁻⁵⁹ The strength of evidence is low.

One trial found that leflunomide lessens disease activity outcomes by ACR 20 at 2 years compared to sulfasalazine but did not detect differences in radiographic changes. The strength of evidence is insufficient for disease activity and low for radiographic changes.

No fair or good evidence exists for comparing hydroxychloroquine monotherapy with other oral DMARD monotherapy.

Oral DMARD combinations. Combination therapy with sulfasalazine and MTX compared to monotherapy provides different results depending on the population. Two trials and one cohort of DMARD naïve patients with early RA showed no difference in ACR 20 response between combination sulfasalazine and MTX versus monotherapy. The strength of evidence is moderate. The one trial in those without early RA (up to 10 years duration) supported combination therapy with sulfasalazine and MTX versus monotherapy with either drug; the changes in DAS scores were greater for combination therapy than for monotherapy, but MCID was not reached by ACR 20 response. The strength of evidence is low

The strength of evidence is low for suggesting that sulfasalazine and MTX compared with monotherapy alone limit progression of radiographic joint damage.

The strength of evidence is moderate for suggesting that combinations of MTX, sulfasalazine, and hydroxychloroquine lessen disease activity by ACR 20 resonse compared to one or two drugs. ^{61, 62}

Low doses of glucocorticoids taken with an oral DMARD (generally MTX or sulfasalazine) reduce x-ray progression over 1-2 years. The strength of evidence is low. However, the evidence is conflicting for change in DAS over 2 years; one study found significant change and one did not. The strength of evidence is insufficient.

Biologic DMARDs. We found one head-to-head randomized controlled trial (RCT) that compared one biologic DMARD with another ⁶⁶ providing low strength of evidence that abatacept lessens disease activity at 1 year compared with infliximab. However, remission by DAS did not

reach significance at 1 year. Other existing direct head-to-head evidence is limited to a nonrandomized, open-label effectiveness trial⁶⁷ and six prospective cohort studies.⁶⁸⁻⁷³ Because of the methodological limitations of observational studies, findings of these studies must be interpreted cautiously. The studies that compared etanercept with infliximab reported a faster onset of response for etanercept during the first months of therapy but no differences in efficacy by ACR 20 and ACR 50 thereafter.^{67-71, 73} The faster onset of etanercept might be attributable partly to necessary dose adjustments for patients treated with infliximab. The strength of evidence is low.

Adalimumab lessens disease activity over 1 year compared with infliximab by DAS28, but MCID can not be determined.^{71,73} Evidence is limited to two cohort studies. There were no differences in achievement of ACR 70 for adalimumab compared with etancercept.⁷³ The strength of evidence is low for both of these comparisons.

A cohort of patients who had failed at least one anti-tumor necrosis factor (TNF) drug were subsequently treated with rituximab, and their outcomes were compared with those of patients treated with other anti-TNF agents. The results indicated that the patients treated with rituximab had a greater reduction in disease activity at 6 months than the patients treated with the other anti-TNF agents. The MCID can not be determined. The strength of evidence is low.

Mixed treatment comparisons performed in this report suggest higher efficacy for improving disease activity (ACR 50) for etanercept compared with individual biologics including abatacept, adalimumab, anakinra, infliximab, rituximab, and tocilizumab; nonsignificant differences with golimumab were reported. The strength of evidence is low and should be interpreted cautiously given the indirectness of the evidence.

Anakinra appears to have lower efficacy based on our mixed treatment comparisons. However, ACR 50 was significant only for for adalimumab and etanercept. Prior indirect comparisons have found similar results. The strength of evidence is low and should be interpreted cautiously given the indirectness of the evidence.

Mixed treatment comparisons found no significant differences in disease activity with abatacept, adalimumab, golimumab, infliximab, rituximab, and tocilizumab. The strength of evidence is low and should be interpreted cautiously given the indirectness of the evidence.

Biologic DMARD versus oral DMARD. Population-based, observational evidence from prospective cohort studies and RCTs of individual drugs indicated that biologic DMARDs as a class (adalimumab, anakinra, etanercept, infliximab) were more efficacious by ACR 20, 50 and remission by DAS28 than oral DMARDs as a class (MTX, leflunomide). ^{67, 68, 76-78} The strength of evidence for available comparisons is moderate.

Radiographic outcomes were significantly better in patients treated with biologic DMARDs adalimumab and etanercept than in patients treated with MTX. How such intermediate outcomes translate to the long-term clinical progression of the disease remains unclear. The strength of the evidence for the available comparisons is low.

Individual trials of adalimumab and etanercept favor approved doses of biologic versus MTX. The strength of evidence for these comparisons is low.

Biologic DMARD combinations. There are no synergistic effects of a combination treatment of etanercept and anakinra⁷⁹ or etanercept and abatacept by ACR/20/50 response⁸⁰ compared with etanercept monotherapy. The strength of evidence is low.

Overall, moderate evidence suggests that some benefit in ACRresponse to biologic DMARD combinations over monotherapy, at least in relation to combining MTX with adalimumab, infliximab, or rituximab. A combination of MTX with either adalimumab, or infliximab, 68, 81-83

or rituximab⁸⁴ led to statistically significantly greater improvements in ACRresponse and radiographic progression than with biologic DMARD monotherapy. A combination of etanercept with MTX trended toward greater improvements in disease activity and radiographic outcomes than with monotherapy but not all studies reached statistical significance.^{68, 81, 85-88} A combination of etanercept with sulfasalazine did not achieve better outcomes than etanercept monotherapy at 1 year.⁸⁵ All RCTs were funded by the makers of the biologic DMARDs. Except for the PREMIER study on adalimumab,⁷⁶ none of these trials was conducted in patients with early RA. The strength of evidence is low for the individual comparisons. No evidence is available on abatacept, anakinra, certolizumab pegol, golimumab, tocilizumab, and combinations with oral DMARDs.

Overall, the evidence is high for combination of biologic DMARDs with oral DMARDs versus oral DMARDs. A combination of MTX with abatacept, ⁸⁹ adalimumab, ⁷⁶ etanercept, ^{86, 90, 91} golimumab, ⁹² or infliximab ⁸² led to significantly greater improvements in disease activity by ACR 20/50 response than MTX alone.

Evidence from two prospective cohorts for anti-TNF drugs with MTX compared to anti-TNF with leflunomide note similar efficacy. ^{93, 94} Anti-TNF drugs included anakinra, etanercept, and adalimumab. The strength of evidence is low.

None of the RCTs can be considered an effectiveness study. Of four population-based prospective cohort studies, only one was conducted in the United States. The generalizability of results to the average population of community rheumatology patients, therefore, remains unclear. All RCTs were funded by the makers of the biologic DMARDs.

Strategies limited to early RA. Combination therapy, which included two oral DMARDs (MTX and sulfasalazine) plus a stepped-down prednisolone treatment, demonstrated less radiographic progression by modified Sharp/van der Heijde score (5.6 vs. 8.6; P=0.001) than sulfasalazine alone. ^{95, 96} The strength of evidence is low.

Combination of three oral DMARDs (MTX, sulfasalazine, and hydroxychloroquine) plus prednisolone led to less radiographic change than one oral DMARD (sulfasalazine, which could be changed to MTX). ^{97, 98} The MCID can not be determined. The strength of evidence is low.

Evidence from one trial found that in patients not responding to methotrexate in DAS response-driven treatment, combination of three oral DMARDs (MTX, sulfasalazine, and hydroxychloroquine) resulted in less response by European League Against Rheumatism (EULAR) criteria compared to infliximab plus MTX. The MCID cannot be determined. The strength of evidence is low.

A strategy of either (1) MTX, sulfasalazine, and tapered high-dose prednisone, or (2) MTX and infliximab resulted in less radiographic change over 12 months than (3) sequential DMARD therapy or (4) stepped-up combination therapy. At 4 years, the remission by DAS among groups was similar. The strength of evidence is low.

Rheumatoid Arthritis: Detailed Analysis

Oral DMARD versus oral DMARD. Table 9 presents disease activity and remission and Table 10 presents radiographic joint damage results in these comparisons.

Corticosteroids versus corticosteroids. We found one head-to-head RCT (N=143) comparing two corticosteroids (Table 9).⁵⁴ It examined the efficacy of low-dose budesonide (3 mg/day), high-dose budesonide (9 mg/day), and prednisolone (7.5 mg/day) over 12 weeks. Mean disease duration of RA was 9 years. When comparing drugs, the percentage achieving ACR 20 response criteria for high-dose budesonide (9 mg) was significantly greater than that for lower- dose

budesonide (3 mg) (42 percent vs. 22 percent; P<0.001), but the percentages for high-dose budesonide and prednisolone did not differ significantly (42 percent vs. 56 percent; P=0.11). Similarly, high-dose budesonide and prednisolone did not differ significantly for tender joint count, swollen joint count, and the DAS.

Leflunomide versus MTX. We found two trials comparing leflunomide (20 mg/day) with MTX (studies ranging from 7.5 mg/week to 15 mg/week) and two systematic reviews with meta-analysis of leflunomide. We describe these two studies in detail here first. One trial randomized 482 patients to leflunomide (n=182) or MTX (n=182) over 12 months. Hean disease duration of RA across these groups was 6.5 years to 7 years. The proportion of patients meeting ACR 20 response criteria at 12 months was higher for leflunomide than MTX but not statistically significantly so (52 percent vs. 46 percent; P=NR). Proportions meeting ACR 50 and ACR 70 criteria also did not differ significantly. Leflunomide had less disease progression by Sharp score than MTX (respectively, 0.53 vs. 0.88; P=0.05) (Table 10).

A continuation study followed the same cohort for 2 years (leflunomide, n=98; MTX, n=101). At 2 years, leflunomide was associated with a higher proportion of patients meeting ACR 20 response criteria than MTX (79 percent vs. 67 percent; P=0.049). The percentage of patients meeting either ACR 50 or ACR 70 criteria at 2 years did not differ significantly, and the change in total Sharp score also did not differ significantly at 2 years (1.6 vs. 1.2; P=0.659).

These 2-year follow-up results are limited by the 45 percent attrition rate from the initial study.

The other trial comparing leflunomide to MTX examined 999 patients for 12 months with an optional second year (leflunomide, n=501; MTX, n=498). Mean disease duration across the groups was 3.5 to 3.8 years. At 12 months, the proportion of patients meeting ACR 20 response criteria was lower for leflunomide than for MTX (50.5 percent vs. 64.8 percent; P<0.001), but differences were not significant at 2 years (64.3 percent vs. 71.7 percent; P=not significant [NS], not reported [NR]). Radiological outcomes at 12 months using Larsen Scale scores for joint narrowing were statistically equivalent (0.03 increase in both groups). After 2 years, no further increase in joint damage occurred in patients treated with leflunomide; patients taking MTX had a small improvement (data NR). The overall result was a small significant difference in Larsen Scale scores favoring MTX after 2 years (data NR).

In the systematic review that included two trials comparing leflumonide with MTX (n=1,348), there were no differences in achieving an ACR 20 response at12 months (odds ratio [OR], 1.08; 95% CI, 0.75 to 1.55) or at 2 years (OR, 1.05; 95% CI, 0.81 to 1.37). Patients receiving leflunomide and MTX did not differ in ACR 50 and ACR 70 responses, and the two drugs also did not differ in delaying bone erosions or joint damage assessed by total Sharp score. This systematic review was limited by the small number of studies that the authors could use for the individual comparisons in the meta-analysis. Similarly, the second systematic review examined the efficacy and safety of oral DMARDs in adults with RA to inform the EULAR recommendations. In the four studies included comparing leflunomide with MTX (N=1,889), there were no differences in ACR 20 response (MTX, OR, 1.04; 95% CI, 0.60 to 1.79). It should be noted that the mean dose of MTX was 12.5 mg/week. MTX could be increased to ≥15 mg/week in all studies, but dosing was not as high as currently recommended in most studies.

Table 9. Disease activity and remission for oral DMARD versus oral DMARD studies

	Study Design	and remission for oi			Ovality
Study	N Duration	Study Population	Comparison (dose)	Results	Quality Rating
Corticoste	eroid vs. Corticost	eroid			
Kirwan et al., 2004 ⁵⁴	RCT	Population-based; active RA; mean	BUD (3 mg/day) vs. BUD (9 mg/day) vs.	No significant difference between 9 mg BUD and PNL	Fair
,	143 12 weeks	disease duration 9 years	PNL (7.5 mg/day)	for ACR 20, DAS (ACR 20: 42% vs. 56%; P=0.11) at 12 weeks	
Leflunomi	de vs. MTX			·	
Emery et	RCT	Mean disease	LEF (20 mg/day) vs.	Lower ACR 20 responses at	Fair
al., 2000 ¹⁰⁵	999	duration 3.5 to 3.8 years	MTX (10 to 15 mg/week)	12 months (50.5% vs. 64.8%; <i>P</i> <0.001); no significant	
	1 year with optional 2nd year			differences in ACR at 2 years (64.3% vs. 71.7%; <i>P</i> =NS, NR)	
Strand et	RCT	Mean disease	LEF (20 mg/day) vs.	At 1 year, ACR 20 numerically	Fair
al., 1999 ^{56,}	482	duration 6.5 to 7 years	MTX (7.5 to 15 mg/week)	higher for LEF but not significant (52% vs. 46%;	
	12 months (1 year continuation)			P=NR); at 2 years, ACR 20 difference not significant (79% vs. 67%; P=0.049)	
Leflunomi	de vs. Sulfasalazir	ne		· · · · · · · · · · · · · · · · · · ·	
Smolen et	RCT	Mean disease	LEF (20 mg/day) vs.	Similar ACR 20 response	Fair
al., 1999; ¹⁰⁷	358	duration 5.7 to 7.6 years	SSZ (2 g/day)	rates (48% vs. 44%; <i>P</i> =NR)	
Smolen, 1999; ¹⁰⁸	24 weeks (12- and 24-month				
Larsen et al., 2001 ⁶⁰	followup)				
Sulfasalaz	ine vs. MTX				
Capell et	RCT	Scotland; multicenter;	SSZ (≤4 g/day) vs.	At 18 months, no significant	Fair
al., 2006 ⁵⁹	165 (Phase 1 run- in: 687)	active RA; mean disease duration 1.6 to 1.8 years	MTX (≤25 mg/week)	difference in DAS for SSZ vs. MTX (-0.30 vs0.26; <i>P</i> =0.79); no significant	
	6 months (18	to 1.0 youro		difference in any ACR	
	months for those with DAS ≥2.4 at 6 months)			responses	
Dougados		Multinational; DMARD	SSZ (2 to 3 g/day) vs.	No significant difference in	Fair
et al., 1999 ⁵⁷	209 (146)	naive; mean disease duration 2.3 to 3.4	MTX (7.5 to 15 mg/week)	DAS between SSZ vs. MTX (-1.15 vs0.87; <i>P</i> =NS, NR);	
	52 weeks (5-year followup)	months	3 44 /	no significant difference in ACR 20 responses; P=NR	
Haagsma	RCT	Netherlands academic			Fair
et al., 1997 ⁵⁸	105	and peripheral clinics; DMARD naive; mean	MTX (7.5 to 15 mg/week	DAS for SSZ vs. MTX (-1.6 vs1.7; <i>P</i> =NS, NR)	
	52 weeks	disease duration 2.6 to 3.1 months	Ŭ	· , ,	

ACR = American College of Rheumatology; BUD = budesonide; CI = confidence interval; DAS = disease activity score; DMARD = disease-modifying antirheumatic drug; g = gram; LEF = leflunomide; MTX = methotrexate; mg = milligram; NR = not reported; NS = not significant; PNL = prednisolone; PRED = prednisone; RA = rheumatoid arthritis; RCT = randomized controlled trial; SSZ = sulfasalazine; vs. = versus

Table 10. Radiographic joint damage in oral DMARD versus oral DMARD

Table 10.			I DMARD versus oral DMA	AND .	
Study	Study Design N Duration	Population with Early RA (<3 years)	Comparison (dose)	Radiographic Outcomes	
Leflunomic	le vs. MTX				
Emery et al., 2000 ¹⁰⁵	RCT 999	No	LEF (20 mg/day) vs. MTX (10 to 15 mg/week)	Larsen score change at 1 year: 0.3 vs. 0.3; <i>P</i> =NS	
	1 year with optional 2nd year			Larsen score change at 2 years: 1.27 vs. 1.31; <i>P</i> =NS, NR	
Strand et	RCT	No	LEF (20 mg/day) vs. MTX	Total Sharp score change at 1	
al., 1999 ¹⁰⁴	482		(7.5 to 10 mg/week)	year: 0.53 vs. 0.88; <i>P</i> =0.05 Total Sharp score at 2 years:	
	12 months (1 year continuation)			1.6 vs. 1.2; <i>P</i> =0.659	
Leflunomic	le vs. Sulfasalazine				
Smolen et al., 1999; ¹⁰⁷ Larsen, et.		No	LEF (20 mg/day) vs. SSZ (2 g/day)	Larsen score change at 24 weeks: 0.01 vs. 0.01; P=NS Larsen score change at 1 year:	
al., 2001; ⁶⁰ Sharp et al., 2000 ¹⁰⁹	24 weeks (12- and 24-month followup)			0.02 vs. 0.02; <i>P</i> =NS Larsen score change at 2 years: -0.07 vs0.03; <i>P</i> =NR	
Sulfasalazi	ne vs. MTX				
Capell et	RCT	Yes (70% 1 year	SSZ (≤4 g/day) vs. MTX (≤25 mg/week)	No significant difference in total	
al., 2006 ⁵⁹	165 (Phase 1 run- in: 687)	or less)		modified Sharp/van der Heijde score change (data NR)	
	6 months (18 months for those with DAS ≥2.4 at 6 months)				
Dougados	RCT	Yes	SSZ (2 to 3 g/day) vs.	Total modified Sharp/van der	
et al., 1999 ⁵⁷	209 (146)		MTX (7.5 to 15 mg/week)	Heijde score change: 4.64 vs. 4.50 vs. 3.36; <i>P</i> =NS,NR; change at 5 years: 8.5 vs. 7.5; <i>P</i> =0.7	
	52 weeks (5 years)				

DMARD = disease-modifying antirheumatic drug; g = gram; LEF = leflunomide; mg = milligram; MTX = methotrexate; NR = not reported; NS = not significant; RCT = randomized controlled trial; SSZ = sulfasalazine; vs. = versus

Leflunomide versus sulfasalazine. One study¹⁰⁷ with a 2-year followup⁶⁰ compared leflunomide with sulfasalazine (Tables 9 and 10). In addition, one systematic review did a meta-analysis of leflunomide against sulfasalazine.⁵⁵ Given that the systematic review included only one trial with this comparison, we describe it in detail first.^{107, 108} This study was a 24-week, double-blind, multinational RCT of 358 patients on 20 mg/day leflunomide (n=133) or 2 g/day sulfasalazine (n=133).¹⁰⁷ Mean disease duration across groups was 5.7 to 7.6 years. ACR 20 response at 24 weeks was similar for leflunomide and sulfasalazine (48 percent vs. 44 percent; *P*=NR). The percentage achieving ACR 50 response criteria was also similar in the two groups (33 percent leflunomide, 30 percent sulfasalazine). Larsen Scale scores were also similar for leflunomide and sulfasalazine, and the Larsen Scale change score at endpoint was 0.01 for both drugs (Table 10). In the followup study, patients who completed the first study could opt to continue on the 12- and 24-month double-blind extension.⁶⁰ At 12 months (leflunomide, n=80; sulfasalazine, n=76), ACR 20 response was similar for leflunomide and sulfasalazine (77 percent

vs. 73 percent; P=NR). At 24 months (leflunomide, n=28; sulfasalazine, n=27), ACR 20 response was significantly greater for leflunomide than for sulfasalazine (82 percent vs. 60 percent; P=0.0085). Changes in Larsen Scale scores were also similar for leflunomide and sulfasalazine (mean change: 0.02 vs. 0.02 at 12 months, -0.07 vs. -0.03 at 24 months; P=NR). Changes in Sharp scores were also not significantly different (mean change: 0.97 vs. 1.38; P=0.685). However, these long-term results are significantly limited by the attrition rates of 65 percent to 70 percent.

The systematic review with a meta-analysis compared leflunomide (10 to 20 mg/day) with sulfasalazine (2 g/day). The analysis included the study described above. Response to the two drugs did not differ as measured by either ACR 20 or ACR 50 criteria at 6 months and 12 months. However, leflunomide was more efficacious at 24 months (ACR 20: OR, 0.73; 95% CI, 0.57 to 0.93; P=0.012; ACR 50: OR, 0.48; 95% CI, 0.28 to 0.80; P=0.0048). The groups did not differ in the ACR 70 at 6, 12, or 24 months. Leflunomide and sulfasalazine also did not differ in delaying bone erosions or joint damage by Sharp score or Larsen Scale score at 6, 12, or 24 months. Again, these results are significantly limited because they include only the one study. Sulfasalazine versus MTX. Three RCTs. 75-59 and one systematic review examined the

Sulfasalazine versus MTX. Three RCTs. ⁵⁷⁻⁵⁹ and one systematic review ¹⁰⁶ examined the efficacy of sulfasalazine and MTX (Tables 9 and 10). Overall, findings from these studies showed similar improvement rates between sulfasalazine and MTX for any ACR, DAS, and radiological outcomes. Two of the trials included patients with disease burden of less than 1 year and used a lower dose of weekly MTX (7.5 mg) than the doses generally used in the United States. ^{57, 58} These trials also included a combination therapy arm, which we describe below (in the section on *Oral DMARD combinations versus oral DMARD combinations or oral DMARD monotherapy*).

One trial randomized 209 patients to receive 2 g/day to 3 g/day sulfasalazine (n=68), 7.5 mg/week to 15 mg/week MTX (n=69), or a combination of sulfasalazine and MTX (n=68) for 52 weeks. ⁵⁷ Mean disease duration for the groups ranged from 2.3 months to 3.4 months. The trial did not detect any differences between the MTX and sulfasalazine groups in improvement as measured on the ACR 20 (59 percent sulfasalazine; 59 percent MTX; *P*=NR). The DAS change score favored sulfasalazine therapy (-1.15, sulfasalazine; -0.87, MTX; *P*=NR), but the statistical analysis examined only the comparison with combination therapy (reported under *Oral DMARD combinations versus oral DMARD combinations or oral DMARD monotherapy*). The mean total modified Sharp/van der Heijde scores of 8.5 for sulfasalazine and 7.5 for MTX indicated that the radiological scores at 5 years did not differ significantly (*P*=0.7).

Another RCT, lasting 52 weeks (N=105), also demonstrated similar ACR 20 and DAS results for sulfasalazine and MTX.⁵⁸ This trial compared 1 g/day to 3 g/day sulfasalazine (n=34) with 7.5 mg/week to 15 mg/week MTX (n=35) and with a combination (discussed later in this chapter); mean disease duration was 2.6 to 3.1 months. The mean change in DAS over 52 weeks was -1.6 in the sulfasalazine group and -1.7 in the MTX group (*P*=NS). The percentage of patients achieving improvement on the ACR 20 was 25 percent for sulfasalazine and 25 percent for MTX.

Finally, one trial included a population with disease duration of up to 10 years. ⁵⁹ The investigators gave 687 patients sulfasalazine (up to 4 g/day) for 6 months. Those with DAS \geq 2.4 were offered inclusion into a Phase II study and randomized to (1) sulfasalazine (n=55), (2) MTX (n=54) (maximum dose, 25 mg/week), and (3) sulfasalazine plus MTX (n=56). At 18 months, the DAS change was similar for sulfasalazine and MTX alone (-0.30 vs. -0.26; P=0.79). The ACR 20, 50, and 70 responses were also similar (ACR 20, 18 percent vs. 15

percent; ACR 50, 6 percent vs. 7 percent; ACR 70, 2 percent vs. 2 percent; *P*=NR). The groups also did not differ in modified Sharp/van der Heijde score, total erosions, and joint space narrowing (data NR) (Table 9). However, 18 months is a short period for observing radiological outcomes, and this study was not powered to detect radiological progression.

Similarly, a systematic review that examined the efficacy and safety of oral DMARDs in adults with RA to inform the EULAR recommendations. ¹⁰⁶ In the two studies (N=193), there were no differences in ACR 50 response (MTX, OR, 1.57; 95% CI, 0.82 to 3.00). The mean dose of MTX was 14.2 mg/week, which is lower than currently recommended.

Oral DMARD combinations versus oral DMARD combinations or oral DMARD monotherapy, with or without corticosteroids. Table 11 presents disease activity and remission and Table 12 provides radiographic joint damage results for these comparisons.

Sulfasalazine plus MTX versus sulfasalazine or MTX. Three RCTs, ⁵⁷⁻⁵⁹ one systematic review and one observational cohort ¹¹⁰ compared the efficacy of sulfasalazine and MTX versus that of either sulfasalazine or MTX alone (Tables 11 and 12). Findings from two of these randomized trials consistently reported no significant differences in ACR, DAS, or radiological outcomes. ^{57, 58} They included patients with disease duration of less than 1 year and again used a lower dose of weekly MTX (7.5 mg) than the doses generally used in the United States. ^{57, 58} The third trial included patients with RA duration of up to 10 years, and their DAS results favored the sulfasalazine-MTX combination therapy over monotherapy. ⁵⁹

Table 11. Disease activity and remission for oral DMARD combinations versus monotherapy or combinations with or without corticosteroid studies

Study	Study Design N Duration	Study Population	Comparison (dose)	Results	Quality Rating
		asalazine or MTX m		- Instante	9
Capell et al., 2006 ⁵⁹	RCT 165 (Phase 1 run-in: 687)	Scotland, 8 NHS sites; active RA; mean disease duration 1.6 to 1.8	SSZ (≤4 g/day)+MTX (≤25 mg/week) vs. SSZ (≤4 g/day) vs. MTX (≤25 mg/week)	Combination therapy better than monotherapy MTX or SSZ for DAS (-0.67, -0.30, -0.26; <i>P</i> =0.039 for SSZ+MTX vs.	Fair SZ
	6 months (18 months for those	years		SSZ; P = 0.023 for SSZ+MTX vs. MTX)	
	with DAS ≥2.4 at 6 months)			No significant difference in ACR responses	
Dougados	RCT	Multinational;	SSZ (2 to 3	No significant difference in	Fair
et al., 1999 ⁵⁷ Maillefert et al., 2003 ¹¹¹	209 (146)	DMARD naive; mean disease	g/day)+MTX (7.5 to 15 mg/week) vs. SSZ (2 to 3 g/day) vs. MTX (7.5 to 15 mg/week)		
	52 weeks (5- year followup)	duration 2.3 to 3.4 months		DAS change (-1.26 vs1.15 vs0.87; <i>P</i> =0.019)	
				DAS change NS at year 5	

Table 11. Disease activity and remission for oral DMARD combinations versus monotherapy or combinations with or without corticosteroid studies (continued)

	Study Design N				Quality
Study Haagsma et al., 1997 ⁵⁸	RCT 105 52 weeks	Netherlands academic and peripheral clinics; DMARD naive; mean disease duration 2.6 to 3.1 months	SSZ (2 to 3 g/day)+MTX (7.5 to 15 mg/week) vs. SSZ (1 to 3 g/day) vs. MTX (7.5 to 15 mg/week)	No significant difference in ACR or DAS responses	Fair
*Schipper et al., 2008 ¹¹⁰	Prospective cohort 230 52 weeks (primary outcome at 6 months)	Netherlands;early RA;sulfasalazine resistant; mean disease duration 3 months-1 year	SSZ (750 to 3g/day)+MTX (7.5-30 mg/week) vs. MTX (7.5-30 mg/week)	No significant difference for DAS responses DAS28 change (-0.8 vs0.9; <i>P</i> 0.737)	Fair
MTX+Hydr	oxychloroquine-	⊦Sulfasalazine vs. on	e or two oral DMARDs		
O'Dell et al., 2002 ⁶¹	RCT 171 2 years	Mean disease duration 5.8 to 7.9 years	1: MTX (7.5 titrated to 17.5 mg/week)+SSZ (2 g/day)+HCQ (400 mg/day) vs. 2: MTX+HCQ vs. 3: MTX+SSZ	ACR 20: 78%, 60%, 49% 1 vs. 2: <i>P</i> =0.05 1 vs. 3: <i>P</i> =0.002	Good
O'Dell et al., 1996 ⁶²	RCT 102 2 years	Poor response to at least 1 DMARD; mean disease duration 6 to 10 years	1: MTX (7.5 to 17.5 mg/week)+SSZ (1 g/day)+HCQ (400 mg/day) vs. 2: MTX vs. 3: SSZ (+ HCQ	50% improvement (defined by authors): 77%, 40%, 33% 1 vs. 3: <i>P</i> <0.001 1 vs. 2: <i>P</i> =0.003	Good
Oral DMA	RD+Corticostero	id vs. Oral DMARD			
*Choy, et al., 2008 ⁶⁴	RCT 467 2 years	England/Wales, Multicenter: early RA; mean disease duration 2.7-5.1 months	MTX (≤15 mg/week)+PNL (60 mg/day stepped down and stopped at 34 weeks) vs. MTX	No significant differences for DAS (-1.37 vs1.42; <i>P</i> =0.19); DAS 28 remission 20% vs. 18%; <i>P</i> =NR	Good
Svensson et al., 2005 ⁶⁵	Open-label trial 250 2 years	Population-based; active RA; early RA	DMARD (SSZ or MTX, dosages NR)+PNL (7.5 mg/day) vs. DMARD	More patients in DMARD+PNL combination group achieve remission (DAS<2.6) than DMARD-only group (55.5% vs. 43.8%; <i>P</i> =0.0005)	Fair

^{*} New study added since last review

ACR = American College of Rheumatology; DAS = disease activity score, DMARD = disease-modifying antirheumatic drug; g = gram; HQC = hydroxychloroquine; MTX = methotrexate; mg = milligram; NHS = National Health Service; NR = not reported; NS = not significant; PNL = prednisolone; RA = rheumatoid arthritis; RCT = randomized controlled trial; SSZ = sulfasalazine; vs. = versus

Table 12. Radiographic joint damage in oral DMARD combinations versus monotherapy combinations with or without corticosteroid studies

Study	Study Design N Duration	Population with Early RA (< 3 years)	Comparison (dose)	Radiographic Outcomes	
Sulfasalazi	ne+MTX vs. Sulfasa	alazine or MTX			
Capell et al., 2006 ⁵⁹	RCT	Yes		No significant difference in total	
ai., 2000	165 (Phase 1 run- in: 687)	(70% 1 year or less)	mg/week) vs. SSZ (≤4 g/day) vs. MTX (≤25 mg/week)	Sharp score (data NR)	
	6 months (18 months for those with DAS ≥2.4 at 6 months)				
Dougados	RCT	Yes	MTX (7.5 to 15 mg/week)	5-year mean modified Sharp/van der Heijde score change: 8.5 vs. 7.5; <i>P</i> =0.7	
et al., 1999; ⁵⁷	209 (146)				
Maillefert et al., 2003 ¹¹¹	52 weeks (5-year followup)		MTX (7.5 to 15 mg/week)		
Oral DMAR	D+Corticosteroid v	s. Oral DMaRD			
*Choy, et	RCT	Yes		Larsen score change 7.41 vs.	
al., 2008 ⁶⁴	467			4.70; <i>P</i> =0.008	
	2 years		MTX		
Svensson et al.,	Open-label RCT trial	Yes	DMARD (SSZ or MTX, dosages NR)+PNL (7.5	Median modified Sharp/van der Heijde score change: 1.8 vs. 3.5;	
2005 ⁶⁵	250		mg/day) vs. DMARD	<i>P</i> =0.019 Erosion score median change:	
	2 years			0.5 vs. 1.25; <i>P</i> =0.007 Joint space narrowing score median change: 1.0 vs. 2.0; <i>P</i> =0.08	

^{*}New study added since last review.

ACR = American College of Rheumatology; DAS = disease activity score, DMARD = disease-modifying antirheumatic drug; g = gram; HQC = hydroxychloroquine; LEF = leflunomide; MTX = methotrexate; mg = milligram; NR = not reported; NS = not significant; PRED = prednisone; RA = rheumatoid arthritis; RCT = randomized controlled trial; SSZ = sulfasalazine; vs. = versus

Biologic DMARDs versus biologic DMARDs. We identified one head-to-head RCT,⁶⁶ one nonrandomized, open-label effectiveness trial,⁶⁷ and six prospective cohort studies (Table 13);⁶⁸⁻⁷³ all but three studies ^{66,71,72} compared etanercept with infliximab. Other comparisons included adalimumab with infliximab,^{71,73} adalimumab with etanercept,⁷³ abatacept with infliximab ⁶⁶ and rituximab compared with other anti-TNF agents.⁷² All studies had minimal exclusion criteria, enrolling patients who were starting treatments with biologic DMARDs. Mean disease durations ranged from 7.3 years to 14.5 years, indicating that most patients suffered from advanced RA; the proportion of patients with early RA in these studies remains unclear. One study contained a multinational patient population, ⁶⁶ one was conducted in the United States; ⁶⁸ the other six were carried out in Sweden, ^{67,69,72} Denmark, ⁷³ the Netherlands, ⁷¹ and Spain. ⁷⁰

Table 13. Disease activity and remission for biologic DMARD versus biologic DMARD studies

Otrodo	Study Design N	Otrada Damalada	O(1)	Decodes	Quality
Study	Duration	Study Population	Comparison (dose)	Kesuits	Rating
	vs. Infliximab				
*Schiff, et al., 2008 ⁶⁶ ATTEST study	RCT 431 1 year	Patients who have failed MTX; active RA; mean disease duration 7.3-8.4	ABA (~10 mg/kg every 4 weeks) vs. INF (3 mg/kg every 8 weeks)	Greater decrease in DAS28 for ABA vs. INF at 1 year (estimate of difference -0.62 95% CI, -0.96 to -0.29).	Fair
		years		Trend toward greater remission for ABA vs. INF at 1 year (estimate of difference 6.5%; 95% CI, -2.2 to 15.2, <i>P</i> =NS, NR)	
*Hetland et al., 2010 ⁷³ DANBIO	Prospective cohort 2,326	Patients with RA initiating therapy with biologic DMARDs	ADA (mean: 40 mg) wks) vs. ETN (mean 45 mg) vs. INF (mean 3.5	Higher achievement of ACR 70 response after 6 months for ADA than INF (OR 2.05, 95% CI, 1.52 to 2.76, <i>P</i> =NR)	Fair
B/ ((1B))	6 months (48 months)		mg/kg)		
*Kievit et al., 2008 ⁷¹	Prospective cohort	Population-based, Netherlands, Anti-	(dosages NR)	Greater decrease in DAS28 for ADA vs. INF at 1 year (ADA - 1.8, INF -1.2; <i>P</i> <0.05)	Fair
	707	TNF naïve patients, failed at least 2			
	1 year	DMARDs; mean disease duration 6- 7.7 years			
Adalimum	ab vs. Etanercept				
*Hetland et al., 2010 ⁷³	Prospective cohort	Patients with RA initiating therapy	mg) wks) vs. ETN (mean 45 mg) vs.	No difference in achievement of ACR 70 response after 6 months for ADA vs. ETN (OR 1.15, 95% CI, 0.82 to 1.60,	Fair
	2,326	with biologic DMARDs			
DANBIO	6 monhs (48 months)		mg/kg)	P=NR)	
Etanercep	t vs. Infliximab				
Geborek et al., 2002 ⁶⁷	Nonrandomized, open-label trial	Population-based; active RA; had failed at least 2 DMARDs;	ETN (25 mg twice weekly) vs. INF (3 mg/kg or higher)	Higher ACR 20 responses for ETN at 3 (data NR; <i>P</i> <0.02) and 6 months (data NR; <i>P</i> <0.05); no	Fair
	369 1 year	mean disease duration 14.5 years		significant differences in ACR response rates at 1 year (data NR)	
*Fernande z-Nebro et al., 2007 ⁷⁰	Prospective cohort 161 6 years	Tertiary care center, Spain; Anti-TNF naïve patients; mean disease duration 9.5 -9.9 years	ETN vs. INF (dosages NR)	Significantly greater decrease t in DAS28 at 6 months for ETN vs. INF (-1.7 vs1.3; <i>P</i> =0.03); No difference in EULAR responses between ETN vs. INF at 6 months	Fair

Table 13. Disease activity and remission for biologic DMARD versus biologic DMARD studies (continued)

Study	Study Design N Duration	Study Population	Comparison (dose)	Results	Quality Rating
*Hetland et al., 2010 ⁷³ DANBIO	Prospective cohort 2,326	Patients with RA initiating therapy with biologic	wks) vs. ETN (mean	Higher achievement of ACR 70 response after 6 months for ETN vs. INF (OR 1.78, 95%	Fair
	6 monhs (48 months)	DMARDs	3.5 mg/kg)	CI, 1.28 to 2.50, <i>P</i> =NR)	
*Kievit et al., 2008 ⁷¹	Prospective cohort 707 1 year	Population-based, Netherlands, Anti- TNF naïve patients, failed at least 2 DMARDs; mean disease duration 6- 7.7 years	ETN vs. INF (dosages NR)	Greater decrease in DAS28 for ETN vs. INF at 1 year (ETN - 1.8, INF -1.2; <i>P</i> <0.05)	Fair
Kristensen et al., 2002 ⁶⁹	Prospective cohort 949 3 years	Population-based, Inadequate response to at least 2 DMARDs	ETN (25 mg twice weekly) vs. INF (3 mg/kg or higher)	No difference in ACR 50 response at 3 years (data NR)	Fair
Weaver et al., 2006 ⁶⁸	Prospective cohort 1,371 1 year	Population-based; patients with active RA who required change in therapy; mean disease duration 9.3 years	ETN (25 mg twice weekly) vs. INF (3.8 mg/kg or higher)	Higher ACR 20 response rates for ETN than INF at 1 year (41% vs. 26%; <i>P</i> =NR)	Fair
Rituximab	vs. Anti-tumor N	ecrosis Factor Therap	oies		
*Finckh et al., 2007 ⁷²	Prospective cohort 116 6 months	Population-based, Switzerland; Patients who have failed at least 1 Anti- TNF treatment; mean disease duration 9-10 yrs	agent (INF, ETN or	Greater reduction in DAS28 at 6 months for RTX vs. Anti-TNF (-1.6 vs0.98; <i>P</i> =0.01)	Fair

^{*} New study added since last review.

ACR = American College of Rheumatology; ADA = adalimumab; ATTEST = Abatacept or infliximab vs. placebo, a trial for tolerability, efficacy, and safety in treating rheumatoid arthritis; CI = confidence interval; DAS = disease activity score; DMARD = disease modifying antirheumatic drug; ETN = etanercept; INF = infliximab; mg/kg = milligram/kilogram; mACR = modified American College of Rheumatology; NR = not reported; NS = not significant; PCS = physical component score; RA = rheumatoid arthritis; TNF = tumor necrosis factor; US = United States; vs. = versus

Abatacept versus infliximab. One head-to-head multinational RCT (N=431) examined the effectiveness of abatacept (10 mg/kg every 4 weeks) and infliximab (3 mg/kg every 8 weeks) over 1 year. ⁶⁶ All participants had active RA, were MTX-resistant, and continued on background MTX for the study. At 1 year abatacept had a greater reduction in DAS28 than infliximab (-2.88 vs. -2.25; estimate of difference -0.62; 95% CI, -0.96 to -0.29). There was also a nonsignificant trend in DAS, ESR (erythrocyte sedimentation rate) defined, remission (18.7% vs. 12.2%; estimate of difference 6.5; 95% CI, -2.2 to 15.2). Additionally, ACR 20 response was significantly higher for abatacept than infliximab (72.4 percent vs. 55.8 percent, estimate of difference 16.7 percent; 95% CI, 5.5 to 27.8) but ACR 50 and ACR 70 did not reach statistical significance. This study is limited by the fixed dosing of infliximab, which may be lower than

generally used in practice. Additionally, the study was powered only to detect differences between the biologics with placebo at 197 days.

Adalimumab versus etanercept. One 52-week prospective observational study used the nationwide Danish DANBIO registry to examine TNF inhibitors adalimumab, etanercept, and infliximab in patients (n=2,326) with RA in whom the first biologic treatment was initiated. Twenty-nine percent received adalimumab (mean: 40 mg), 22 percent received etanercept (mean: 45 mg), and 49 percent received infliximab (mean: 3.5 mg/kg). After correction for differences in sex, age, disease duration, seropositivity, DAS28, concomitant MTX and prednisolone treatment, number of previous DMARDs, Health Assessment Questionnaire (HAQ) at baseline, the odds of achieving an ACR 70 at 6 months was not significant for adalimumab compared with etanercept (OR 1.15; 95% CI, 0.82 to 1.60). However, achieving a good EULAR response was higher for adalimumab (OR 1.49; 95% CI, 1.13 to 1.96). Results were similar at 12 months (data NR). This study is limited by the lack of blinding to treatment

Etanercept versus infliximab. The nonrandomized, open-label effectiveness study (N=369) assessed the effectiveness and safety of etanercept (25 mg twice weekly) and infliximab (3 mg/kg or higher every 8 weeks). Study duration was 12 months. Comparisons of etanercept and infliximab with the leflunomide arm are reported in the section below comparing oral DMARDs with biologic DMARDs. Etanercept had significantly greater improvement on the ACR 20 at 3 months (P<0.02; data NR) and 6 months (P<0.05; data NR) and on the ACR 50 at 3 months (P<0.005; data NR) than infliximab. The authors attributed these differences partly to a high need of dose adjustments (57 percent) in the infliximab group during the first months of the study. No significant differences between the therapy groups could be detected after 6 months.

Three prospective cohort studies provide similar results, initially favoring etanercept, but with differences lessening over longer time periods. $^{69-71}$ The first prospective cohort study (N=161) in anti-TNF naïve patients found a higher change in DAS28 at 6 months for etanercept than infliximab (-1.7 vs. -1.3; P=0.03), but no differences in EULAR responses. 70 The second prospective cohort (N=707) in anti-TNF naïve patients found a higher change in DAS28 at 12 months for etanercept than infliximab (-1.8 vs. -1.2, P<0.05). A prospective cohort (N=949) with longer followup found that etanercept treatments led to greater improvement on the ACR 50 than infliximab during the first months of treatment, but no differences were noted thereafter for up to 36 months. 69 The authors of this study created an index called the LUNDEX (an index of drug efficacy in clinical practice developed at Lund University in Sweden, calculated as the proportion of starters still on the drug at time T times the proportion responding at time T), which takes adherence and efficacy together into consideration. Patients on etanercept achieved higher LUNDEX scores than patients on infliximab, which reflected a significantly lower level of adherence of patients on infliximab compared with those on etanercept (data NR; P<0.001).

Findings from the U.S. prospective cohort study, which was based on the RADIUS (Rheumatoid Arthritis DMARD Intervention and Utilization Study) program and funded by the maker of etanercept, reported similar results. Etanercept-treated patients had greater responses than infliximab-treated patients on the modified ACR 20 (mACR 20, which omits ESR and C-reactive protein [CRP] values because they are infrequently measured in clinical practice); percentage improvement rates were 43 percent for etanercept plus MTX, 41 percent for etanercept monotherapy, 35 percent for infliximab plus MTX, and 26 percent for infliximab monotherapy (*P*=NR). Similarly a Danish cohort (described above in adalimumab vs. etanercept) found a higher odds of achieving an ACR 70 and a good EULAR response at 6 months for

etanercept compared with infliximab (good EULAR for etanercept: OR, 1.41; 95% CI, 1.09 to 1.84).⁷³

Adalimumab versus infliximab. In addition to examining the effects of etanercept, two prospective cohort studies examined adalimumab with infliximab. The first (N=116) examined adalimumab with infliximab in anti-TNF naïve patients as part of the Dutch Rheumatoid Arthritis Monitoring (DREAM) register. Adalimumab-treated patients had a greater decrease in DAS28 than infliximab-treated patients at 1 year (- 1.8 vs. -1.2, P<0.05). Similarly, the Danish cohort (described above in adalimumab vs. etanercept) found a higher odds of achieving an ACR 70 and good EULAR response at 6 months for adalimub compared with infliximab (good EULAR for adalimumab: OR 2.10; 95% CI 1.66 to 2.66).

Rituximab versus anti-TNF. One cohort study (N=116) examined the effectiveness of rituximab (1,000 mg x 2 with concomitant IV glucocorticoids) compared to other anti-TNF agents in patients who had inadequate response to previous ant-TNF therapy. The population included Swiss patients receiving anti-TNF therapy in 2003. Patients included in this analyses had an inadequate response to at least one anti-TNF agent (infliximab, etanercept, or adalimumab) and initiated a second or third anti-TNF or rituximab. At 6 months, rituximab-treated patients had a greater decrease in DAS28 than patients treated with an alternative anti-TNF agent (-1.6 vs. -0.98, P=0.01).

Indirect head-to-head comparisons of biologic DMARDs. Multiple placebo-controlled RCTs and meta-analyses^{25, 29, 112} provide evidence on the efficacy of abatacept, ^{66, 113-117} adalimumab, ¹¹⁸⁻¹²⁷ anakinra, ^{75, 128-134} etanercept, ^{86, 126, 135-145} infliximab, ^{66, 126, 135, 146-156}, rituximab, ^{84, 157-163} certolizumab pegol, ¹⁶⁴⁻¹⁶⁸ golimumab, ^{166, 169-171} and tocilizumab. ^{164, 172-178} Most of these studies were conducted in patients who previously failed oral DMARD treatment.

Using information from these placebo-controlled trials, several research groups did meta-analyses to produce adjusted indirect comparisons of biologic DMARDs. ^{28, 74, 75, 179, 180} The underlying assumption for adjusted indirect comparisons to be valid is that the relative efficacy of an intervention is consistent across included studies. ¹⁸¹ In the more recent analysis, findings suggested that efficacy does not differ substantially for adalimumab, etanercept, and infliximab, abatacept, and rituximab. ^{27, 74, 180} However, given the wide confidence intervals, clinically significant differences cannot be excluded with certainty. Compared with anakinra, point estimates favored adalimumab, etanercept, and infliximab, but the results were not all statistically significantly different. ^{74, 180} Adjusted indirect comparisons of anti-TNF drugs as a class with anakinra showed a statistically significantly greater efficacy of the anti-TNF drugs on ACR 20 but not on ACR 50. ⁷⁴

Mixed treatment comparisons. Our team conducted mixed treatment comparisons (MTC) meta-analyses using Bayesian methods for ACR 20/50/70 that included RCTs of abatacept, adalimumab, anakinra, etanercept, golimumab, infliximab, rituximab, and tocilizumab in MTX-resistant patients. A summary of the studies included and network diagram are described in Table 14 and Figure 2. In the analysis of ACR 50, the data show that etanercept has the highest mean treatment response and anakinra the lowest mean response. Point estimates favor other biologics over anakinra; but the differences were only statistically significant for comparisons with adalimumab and etanercept for ACR 50. In addition, point estimates for etanercept are

Table 14. Summary of the 30 studies included in mixed treatment comparison meta-analysis

Abatacept k	Author and Year Kremer, 2006 ¹¹⁶	Study Name	(weeks)	NI .
•	Kremer, 2006 ¹¹⁶		(in conto)	N
ŀ		AIM	24	652
	Kremer, 2003 ¹¹³	NR	24	234
	Schiff, 2008 ^{a66}	ATTEST	28	266
Adalimumab V	Weinblatt, 2003 ¹²³	ARMADA	24	129
F	Furst, 2003 ¹²¹	STAR	24	636
ŀ	Keystone, 2004 ¹²⁰	NR	52	619
V	van de Putte, 2004 ¹²²	NR	26	438
V	van de Putte, 2003 ¹¹⁹	NR	12	212
ŀ	Kim, 2007 ¹²⁷	NR	24	128
(Chen, 2008 ¹⁸²	NR	12	47
Anakinra (Cohen, 2002 ¹³¹	NR	24	153
(Cohen, 2004 ¹³³	NR	24	506
E	Bresnihan, 1998 ¹²⁸	NR	24	353
Etanercept N	Moreland, 1999 ¹⁴⁰	NR	26	158
V	Weinblatt, 1999 ¹⁴²	NR	24	89
L	_an, 2004 ¹⁴³	NR	12	58
N	Moreland, 1997 ¹⁴⁴	NR	12	88
Golimumab k	Keystone, 2009 ¹⁶⁹	GO-FORWARD	14	222
ŀ	Kay, 2008 ¹⁶⁶	NR	16	70
Infliximab A	Abe, 2006 ¹⁵³	NR	14	147
ŀ	Kavanaugh, 2000 ¹⁵⁴	NR	12	21
Z	Zhang, 2006 ¹⁵⁶	NR	18	173
N	Maini, 1999 ¹⁴⁸	ATTRACT	30	428
V	Westhovens, 2006 ¹⁵⁵	START	22	1,084
9	Schiff, 2008 ^{a,66}	ATTEST	28	275
Rituximab E	Edwards, 2004 ⁸⁴	NR	24	80
E	Emery, 2010 ¹⁶²	SERENE	24	512
Tocilizumab k	Kremer, 2010 ¹⁷⁸	LITHE	24	1,196
9	Smolen, 2008 ¹⁶⁴	OPTION	24	623
(Genovese, 2008 ¹⁷⁶	TOWARD	24	1,220
N	Maini, 2006 ¹⁷⁴	CHARISMA	16	148

NR = not reported

^a Schiff 2008 (ATTEST) is listed twice as the study included comparisons with both abatacept and infliximab.

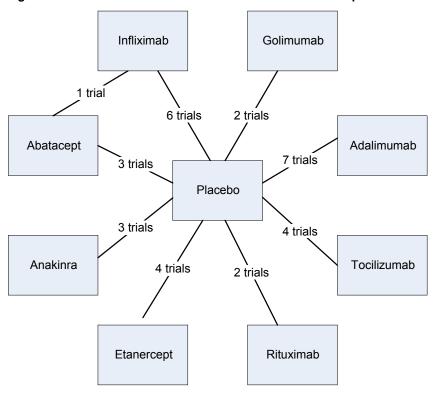


Figure 2. Evidence network for ACR 50 mixed treatment comparisons

Note: The total number of trials does not appear to equal 30 (the total number of studies included in the analysis) because some trials have multiple arms that were included.

favored over the other included biologics (ACR 50 OR range for etanercept 2.39-5.20). The differences showed statistically significant improvements in disease activity with etanercept than with abatacept, adalimumab, anakinra, infliximab, rituximab, or tocilizumab, but no statistically significant differences between etanercept and golimumab.

As described in Appendix four sensitivity analyses were conducted to examine various sources of potential heterogeneity. The four analyses are described below and results are presented in Table 15.

- Sensitivity Analysis 1: Four trials with early escape designs were removed in the main MTC analysis because a large number of crossovers (from placebo to active treatment) in these studies might have led to inaccurate calculations of treatment effects. These four studies were included in a sensitivity analysis to gauge potential impact on overall results.
- Sensitivity Analysis 2: Some trials included in the MTC did not have patients in the relevant arms on a background dose of MTX. To separate the effects that combination therapy may have on the relative treatment effects, monotherapy trials were removed in a sensitivity analysis.
- Sensitivity Analysis 3: To evaluate whether study duration influenced our findings, and to compare with other analyses that have used a 6-month cutoff, the ACR 50 analysis was rerun with studies of durations of 22 weeks or longer.
- Sensitivity Analysis 4: Two trials with etanercept, Lan 2004¹⁴³ and Moreland 1997,¹⁴⁴ had both a high ACR 50 response and low placebo response. Due to the relatively large differences between treatment and placebo response, we removed these two trials in a sensitivity analysis.

Table 15. Expected (mean) ACR 50 treatment response of biologic DMARDs

			Scenario		
Treatment	ACR 50	Sensitivity Analysis 1	Sensitivity Analysis 2	Sensitivity Analysis 3	Sensitivity Analysis 4
Placebo	0.0943	0.0874	0.1029	0.0922	0.0964
Abatacept	0.2767	0.2603	0.2972	0.2762	0.2818
Adalimumab	0.3591	0.3381	0.3734	0.3377	0.3824
Anakinra	0.2220	0.2076	0.2663	0.2171	0.2283
Certolizumab	NA	0.4837	NA	NA	NA
Etanercept	0.6353	0.6129	0.6844	0.6088	0.7129
Golimumab	0.3909	0.3691	0.4173	NA	0.3986
Infliximab	0.2810	0.2643	0.3017	0.2960	0.2861
Rituximab	0.2957	0.2770	0.3179	0.2911	0.3041
Tocilizumab	0.3118	0.2948	0.3300	0.3324	0.3153

NA = not applicable

In the analysis of ACR 50, the data show that etanercept has the highest mean treatment response and anakinra the lowest mean response. Under each scenario, this trend was maintained. Ranking of the other biologics show that golimumab and adalimumab have the second and third highest response in the ACR 50 analysis and Sensitivity Analyses 2 and 4. In Sensitivity Analysis 3, which included studies with durations of 22 weeks or more, adalimumab and tocilizumab rank behind etanercept, respectively (there are no longer any studies of golimumab included in this analysis). In the sensitivity analysis including all 34 potential studies (Sensitivity Analysis 1), certolizumab pegol has the second highest response, but this relative ranking may be due to the difference in study design, with the required early escape biasing results in favor of active treatment. The results from the sensitivity analyses show the model to be fairly robust.

These findings are consistent with a good-quality German retrospective cohort study based on the RABBIT (German acronym for Rheumatoid Arthritis – Observation of Biologic Therapy) database, which reports higher discontinuation rates due to lack of efficacy for patients on anakinra than for patients on either etanercept or infliximab after 12 months of treatment (30 percent vs. 20 percent vs. 20 percent; P=NR). In addition, they are consistent with several cohort studies reporting greater improvements in disease activity with etanercept than with infliximab. Similarly, one meta-analysis of short-term (12-30 week) treatment of etanercept, adalimumab, and infliximab found higher risk ratios for reaching ACR 50 for etanercept than adalimumab and infliximab (ACR 50 for etanercept 5.28, 95% CI, 3.12 to 8.92; adalimumab 3.50, 95% CI, 2.75 to 4.44, infliximab 2.68, 95% CI, 1.79 to 3.99. Is 3.99.

Comparisons with other MTC meta-analyses of biologic DMARDs. We compared our analysis with four other reviews using MTC meta-analyses that compared biologic DMARDs (Nixon 2007, ¹⁸⁴ Devine 2011, ¹⁸⁵ Bergman 2010, ¹⁸⁶ and CADTH 2010¹⁸⁷). All the meta-analyses present arm-based random effects logistic regression models within a Bayesian framework. Two of the MTC analyses, Devine 2011 and Nixon 2007, use meta-regression to adjust for study-level covariables. Some differences exist between the inclusion/exclusion criteria of our analysis compared with the others, shown in Table 16.

Table 16. Exclusion criteria of MTC meta-analyses

	Exclusions						
Study	6-Month Duration	MTX Naïve	Monotherapy	Biologic Failure	Low-Dose MTX		
Devine, 2011	Х			х			
Bergman, 2010	Х	X					
CADTH, 2010	X	Х	Х	х	Х		
Nixon, 2007	Х		Х				
RTI-UNC EPC Limited to 6-month duration In sensitivity analysis		Х	Removed these studies in a sensitivity analysis	Х			

These differences in criteria led to a different set of studies included in the MTC. Studies included in the other meta-analyses, including our MTC meta-analysis, are listed in Table 14. Reasons for exclusion from our MTC are listed beside trial name. Figure 3 illustrates the relative treatment effect for ACR response.

Biologic DMARD versus oral DMARD. Four RCTs, a nonrandomized trial, and a prospective cohort study determined the comparative efficacy and safety of various biologic and oral DMARDs with approved doses. The RCTs compared adalimumab, ⁷⁶ etanercept, ^{77, 86} and tocilizumab with MTX; the nonrandomized trial compared etanercept and infliximab with leflunomide; ⁶⁷ and the cohort study assessed differences in class effects (Table 17). ⁷⁸ No evidence exists on abatacept, anakinra, and rituximab, certolizumab, golimumab, or on oral DMARDs other than MTX and leflunomide. Disease activity and remission results are presented in Table 17 and radiographic damage in Table 18.

Biologic DMARDs as a class versus oral DMARDs as a class. A prospective cohort study examined differences in clinical and functional remission between biologics as a class (adalimumab, anakinra, etanercept, infliximab (n=818) and oral DMARDs as a class (n=265) in patients who had failed two previous DMARD treatments. This study was population-based and part of RABBIT, a German long-term, prospective cohort study of RA patients who had required a change in therapy in daily rheumatologic care. Patients on biologics were younger and had a significantly more active disease at baseline. In a multivariate logistic regression, adjusting for baseline confounders, the investigators determined that patients on biologics had a statistically significantly greater chance of remission (DAS<2.6) after 12 months of treatment (OR, 1.95; 95% CI, 1.20 to 3.19). Likewise, patients treated with biologics had an almost four times higher likelihood of achieving functional independence than patients treated with oral DMARDs (OR, 3.88; 95% CI, 1.71 to 8.79). Nevertheless, both groups had a substantial risk of relapse during the treatment period. Approximately one-half of the patients who were in remission at 6 months achieved a sustained remission until 12 months (biologics, 55 percent; oral DMARDs, 58 percent).

Adalimumab versus MTX. The PREMIER study was conducted in MTX-naive patients with early (disease duration<3 years), aggressive RA. This multinational study randomized 799 patients with early RA to a combination of adalimumab (40 mg every other week) and MTX (20 mg/week), adalimumab monotherapy (40 mg every other week), or MTX monotherapy (20 mg/week). Two treatment arms of this 2-year study assessed differences in the efficacy of adalimumab monotherapy (40 mg every other week) and MTX monotherapy (20 mg/week). After 2 years, the proportion of patients who met ACR 50 criteria was lower for those on

Figure 3. Relative treatment effect for ACR 50 response for biologics

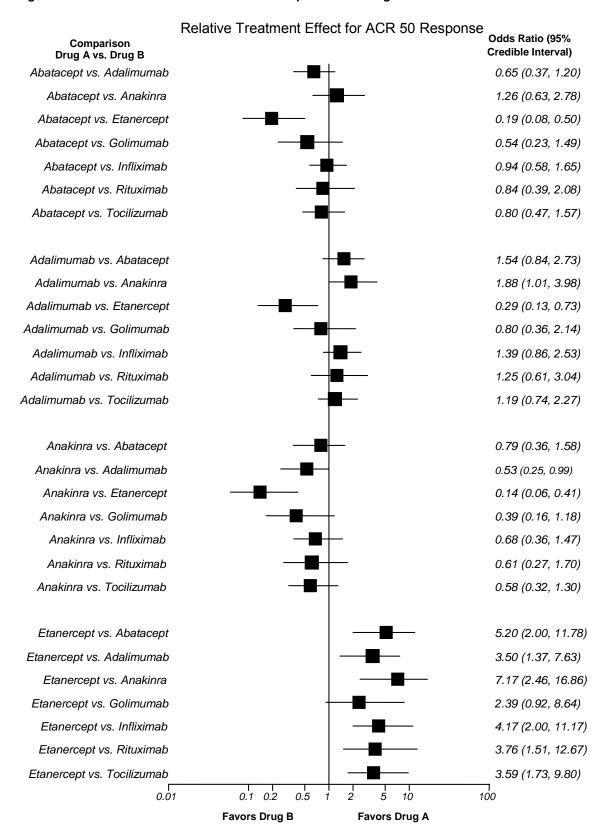


Figure 3. Relative treatment effect for ACR 50 response for biologics (continued)

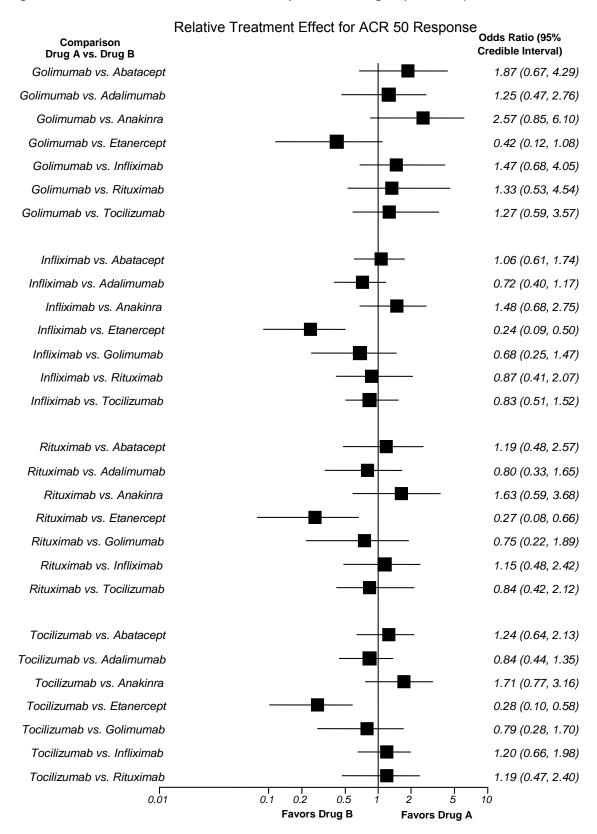


Table 17. Disease activity and remission for biologic DMARD versus oral DMARD

N			Comparison		Quality
Duration	Study Populati	on	(dose)	Results	Rating
s. Oral DMARD					
	(D	MARD n	aïve)		
			ADA (40 mg	Lower ACR 50 response rates for ADA than MTX	Fair
, 799				(37% vs. 43%; <i>P</i> =NR)	
2 years	years)				
Oral DMARD					
	(D	MARD n	aive)		
RCT se			ETN (10 or 25 mg twice weekly) vs.	Similar ACR 20 at 12 months for ETN vs. MTX	Fair
	disease duration		MTX (20 mg/week)	(72% vs. 65%; <i>P</i> =0.16)	
year open-lab					
extension)	/Prior	DIMADE) failura)		
DCT	,			Higher area under ourse	Foir
					ган
÷I '	than MTX; mea	n	(7.5 titrated to 20	MTX(14.7%-years vs.	
		disease duration 6.6			
	years			•	
weeks)				(76% vs. 75%, <i>P</i> =NR)	
				Higher ACR 20/50	Fair
·	least 2 DMARD	s; mean	n mg/kg or higher) vs. LEF (20	INF vs. LEF at 3 months (data NR; P<0.05) and for	
		า 14.5			•
12 months	years		mg/day)	(data NR; P<0.05); results	;
. MTX					
	(D	MARD n	aïve)		
., RCT	,		•	Higher ACR 20 response	Fair
			weeks) vs. MTX (8	for TCZ than MTX (80.3%	
			mg/week)	vs. 25.0%; <i>P</i> <0.001)	
				O. 15	
Prospective cohort	based; patients	(ADA, A	ANA, ETN, INF;	of remission for biologics	Fair
1,083				than oral DMARDs (OR,	
12 months		as a cla			
	therapy; mean			,	
	disease duration				
	N Duration S. Oral DMARD RCT 799 2 years Oral DMARD RCT 632 (512) 12 months (1 year open-labe extension) RCT et 686 (503 for 2 year results) et 52 weeks (2 years, 100 weeks) Nonrandomize open-label tria 369 12 months S. MTX RCT 1 127 24 weeks Prospective cohort 1,083	Duration Study Population S. Oral DMARD (D) RCT Early, aggressive MTX-naive; mean disease duration years) Prospective Cohort RCT Active RA; haddease duration years RCT Active RA; inaddease duration years	N Duration Study Population S. Oral DMARD (DMARD notes as duration NR (<2) 2 years years) Oral DMARD (DMARD notes as duration NR (<2) 2 years years) Oral DMARD (DMARD notes as duration NR (<2) 2 years years) Oral DMARD (DMARD notes as duration 11.7 months (Prior DMARD (Pr	Study Population Study Population (DMARD naïve) RCT Farly, aggressive RA; ADA (40 mg biweekly) vs. MTX disease duration NR (<3 (20 mg/week) years) (DMARD naive) RCT Se 632 (512) Farly, aggressive RA; ADA (40 mg biweekly) vs. MTX disease duration NR (<3 (20 mg/week) years) (DMARD naive) RCT Farly, aggressive RA; BTN (10 or 25 mg twice weekly) vs. MTX (20 mg/week) months (Prior DMARD failure) RCT Farly, aggressive RA; BTN (10 or 25 mg twice weekly) vs. MTX (20 mg/week) months (Prior DMARD failure) RCT Farly, aggressive RA; BTN (10 or 25 mg twice weekly) vs. MTX (20 mg/week) months (Prior DMARD failure) RCT Farly, aggressive RA; BTN (10 or 25 mg twice weekly) vs. MTX (20 mg/week) months (Prior DMARD failure) RCT Farly, aggressive RA; BTN (10 or 25 mg twice weekly) vs. MTX (20 mg/week) months (Prior DMARD failure) RCT Farly, aggressive RA; ADA (40 mg biweekly) vs. MTX (20 mg/week) months (Prior DMARD failure) (Pri	Norrandomized open-label trial 369 Norrandomized open-label trial 27 Norrandomized open-label trial 369 Norrandomized open-label trial 369 Norrandomized open-label trial 369 Norrandomized open-label trial 27 Norrandomized open-label trial 369 Norrandomized open

^{*} New study added since last review.

ACR = American College of Rheumatology; ADA = adalimumab; ANA = anakinra; CI = confidence interval; DAS = disease activity score; DMARD = disease modifying antirheumatic drug; ERA = early rheumatoid arthritis; ETN = etanercept; INF = infliximab; LEF = leflunomide; mg = milligram; MTX = methotrexate; NR = not reported; OR = odds ratio; RA = rheumatoid arthritis; RCT = randomized controlled trial; TCZ = tocilizumab; vs. = versus

Table 18. Radiographic joint damage in biologic DMARDs versus oral DMARD studies

Study	Study Design N Duration	Population With Early RA (<3 years)	Comparison (dose)	Radiographic Outcomes
Adalimumab v	s. Oral DMARD			
Breedveld et al., 2006 ⁷⁶ ,	RCT 799	Yes; MTX-naive patients with early, aggressive RA	ADA (40 mg biweekly) vs. MTX (20 mg/week)	Total modified Sharp score change: 5.5 vs. 10.4; <i>P</i> <0.001
*Hoff et al., 2009 ¹⁹⁰ PREMIER	2 years			Erosion score change: 3.0 vs. 6.4; <i>P</i> <0.001
study				Joint space narrowing score change: 2.6 vs. 4.0; <i>P</i> <0.001
Etanercept vs.	. Oral DMARD			
Bathon et al., 2000; ⁷⁷	RCT	Yes; MTX-naive patients with	ETN (10 or 25 mg twice weekly) vs. MTX (20	Total Sharp score change: 1.0 vs. 1.59; <i>P</i> = 9,111
Genovese et al., 2002; ¹⁸⁸ Genovese et al., 2005 ¹⁸⁹ ERA study	632 (512) 12 months (1 year open-label extension)	early, aggressive RA	mg/week)	Erosion score change: 0.47 vs. 1.03; P=0.006
Klareskog et	RCT	No	ETN (25 mg twice	At 1 year:
al., 2004 ⁸⁶ van der Heijde et al., 2006 ¹³⁶	686 (503 for 2- year results)		weekly) vs. MTX (7.5 titrated to 20 mg/week)	Total modified Sharp score change: 0.52 vs. 2.80; <i>P</i> =0.047
van der Heijde et al., 2006 ¹³⁸ TEMPO study	52 weeks (2 years, 100			Erosion score change: 0.21 vs. 1.68; <i>P</i> <0.008
	weeks)			Joint space narrowing score change: 0.32 vs. 1.12; <i>P</i> =NR (NS)

^{*} New study added since last review.

ADA = adalimumab; DMARD = disease modifying antirheumatic drug; ERA = early rheumatoid arthritis; ETN = etanercept; INF = infliximab; LEF = leflunomide; mg = milligram; MTX = methotrexate; NR = not reported; P=NR (NS), p value not reported but authors stated it was not significant; RA = rheumatoid arthritis; RCT = randomized controlled trial; TCZ = tocilizumab; TEMPO = Trial of etanercept and Methotrexate with radiographic patient outcomes; vs. = versus

adalimumab than for those on MTX monotherapy (37 percent vs. 43 percent; P=NR). In contrast, radiographic progression was statistically significantly lower in patients treated with adalimumab than with MTX (5.5 vs. 10.4 Sharp units; P<0.001) (Table 18). No difference was apparent in clinical remission (DAS 28<2.6) between the two treatment groups (both 25 percent); discontinuation rates due to lack of efficacy were similar in the adalimumab and MTX groups (19.0 percent vs. 17.9 percent; P=NR). We report on results of the other comparisons of the PREMIER study in the respective sections (below) on $Biologic\ DMARD\ plus\ oral\ DMARD\ versus\ oral\ DMARD$.

Etanercept versus MTX. Two trials (in six publications) compared etanercept (10 mg or 25 mg twice weekly) with MTX (20 mg/week) over 52 weeks. Tr, 86, 136, 138, 188, 189 The ERA (Early Rheumatoid Arthritis) study (N=632) was conducted in patients with early RA who were MTX-naive. The TEMPO (Trial of Etanercept and Methotrexate with Radiographic Patient Outcomes) trial randomized 686 patients to etanercept plus MTX (25 mg twice weekly plus up to 20 mg/week MTX), etanercept monotherapy (25 mg twice weekly), and MTX monotherapy (up to 20 mg/week). Patients had active RA and had failed at least one DMARD other than MTX. About 57 percent of the study population was MTX naive. Patients

who had either failed prior MTX treatment or experienced toxic effects were excluded from this study.

Both studies failed to show statistically significant differences between etanercept and MTX in clinical and health outcome measures (SF-36, the Health Assessment Questionnaire [HAQ], the Arthritis-Specific Health Index [ASHI]), and ACR 20/50/70 responses at study endpoints (52 weeks). By contrast, radiographic outcomes were significantly better in patients on etanercept than in those on MTX. For example, in the ERA trial, 72 percent of patients on etanercept and 60 percent on MTX had no radiographic progression of disease (P=0.007). Improved radiographic outcomes were maintained during an open-label extension of the ERA study to 2 years and 5 years. ¹⁸⁹

Etanercept or infliximab versus leflunomide. No RCT compared biologic DMARDs to leflunomide. The only head-to-head evidence came from a nonrandomized, open-label study (N=369) that accessed the efficacy and safety of etanercept (25 mg twice weekly), infliximab (3 mg/kg or higher every 8 weeks), and leflunomide (20 mg/day). This study has been described in greater detail in the section (above) on Biologic DMARD versus biologic DMARD. At 3 months and 6 months, a greater percentage of patients on etanercept met ACR 20 and ACR 50 criteria than those on leflunomide (data NR; P<0.05). A greater percentage of patients on infliximab achieved ACR 20 and ACR 50 criteria at 3 months than those on leflunomide (data NR; P<0.05). The authors did not report 12-month data. Both etanercept and infliximab led to significant reductions in prednisolone dosage; by contrast, the investigators did not find any reduction in prednisolone dosage with leflunomide. These findings must be viewed cautiously. Baseline characteristics of patients differed substantially between the leflunomide group and the biologic groups. Leflunomide patients were older and had significantly more joint damage than patients on etanercept or infliximab. Such differences can potentially confound results, introducing bias that would support differences in results among these treatment groups.

Golimumab versus MTX. Two RCTs compared unapproved doses of golimumab (100 mg) with MTX. 92, 169 These two studies are referenced in other sections of this report for study arms using approved doses (e.g., golimumab 50 mg plus MTX compared with MTX section), but we do not include them in Table 17 and 18, the overview, our conclusions, or in strength of evidence tables due to the use of unapproved doses in the golimumab plus placebo arms, because it is difficult to draw conclusions about the comparative effectiveness of the approved use of golimumab (50 mg every 4 weeks) with MTX.

The GO-FORWARD study was a phase III, multicenter 52-week trial that randomized subjects (assigned in a 3:3:2:2 ratio) to receive placebo injections plus MTX, golimumab 100 mg injections plus placebo, golimumab 50 mg injections plus MTX, or golimumab 50 mg injections plus MTX 52. At week 16, patients in the first three groups who had less than 20% improvement in tender and swollen joints were allowed to enter an early escape The trial found no difference in the ACR 20 response between those treated with golimumab 100 mg and those treated with MTX at 52 weeks (ACR 20 45 percent vs. 44 percent, *P*=NS, NR).

The GO-BEFORE study was a phase III, multicenter trial that randomized subjects to subcutaneous placebo injections plus MTX, golimumab 100 mg injections plus placebo, golimumab 50 mg injections plus MTX, or golimumab 100 mg injections plus MTX capsules. ⁹² At week 24, there were no differences in ACR 20, 50, or 70 between those treated with golimumab 100 mg and those treated with MTX (ACR 50: 32.7 percent vs. 29.4 percent, *P*=NR) data NR).

Tocilizumab versus MTX. The SATORI study, a multisite RCT in Japan, examined 127 patients with active RA and an inadequate response to MTX. Subjects were randomized to MTX (8 mg/week) plus placebo or to tocilizumab (8 mg/kg every 4 weeks) plus placebo. After 24 weeks, those treated with tocilizumab had significantly higher ACR 20 response than those treated with MTX (80.3 percent vs. 25.0 percent, *P*<0.001). The study findings are limited by a high withdrawal rate; 48% of patients in the MTX group, compared with 11% in the tocilizumab group withdrew during the study, mostly due to unsatisfactory response. Additionally, the dose of MTX used in this study is below the dose usually considered therapeutic. Mulitnational evidence-based recommendations suggest starting MTX at 10-15 mg/week, with the escalation of 5 mg every 2-4 weeks up to 20-30 mg week. Thus, this study does not provide evidence that is relevant to determine how tocilizumab compares with MTX as it is generally used in clinical practice.

Biologic combinations: Biologic DMARD plus biologic DMARD versus biologic DMARD. A 24-week RCT did not detect any synergistic effects of a combination treatment of etanercept (25 mg/week or 50 mg/week) and anakinra (100 mg/day) compared with etanercept monotherapy (Table 19). Overall, 242 patients who were on stable doses of MTX treatment were enrolled. At endpoint, combination treatment did not lead to greater efficacy than etanercept only. Furthermore, the frequency of serious adverse events was substantially higher in the combination groups (14.8 percent for 50 mg etanercept plus anakinra, 4.9 percent for 25 mg etanercept plus anakinra, and 2.5 percent for etanercept only; P=NR). Likewise, withdrawals because of adverse events were higher in the combination groups than in the etanercept group (8.6 percent vs. 7.4 percent; P=NR).

Table 19. Disease activity and remission for biologic DMARD+biologic DMARD versus biologic DMARD studies

Study	Study Design N Duration	Study Population	Comparison (dose)	Results	Quality Rating
ETN+AKA vs	s. ETN				
Genovese et	RCT	Inadequate control	ETN (25 mg twice	Higher ACR 50 response	Fair
al., 2004 ⁷⁹	242	of disease with MTX: mean disease	weekly)+ANK (100 mg/day) vs. ETN (25 mg/week)	rates for ETN monotherapy (31% vs. 41%; <i>P</i> =0.914)	
	24 weeks	duration 9.9 years			
ETN+ABA vs	s. ETN				
*Weinblatt,	RCT	Patients on ETN; mean disease duration 12.8-13 yrs	ETN (25 mg twice	No difference in mACR	Fair
et al., 2007 ⁸⁰	121		weekly)+ABA 2g/kg increased to 10 mg/kg	20/50/70 response rates at 1 year	
	1 year		after 1 year) vs. ETN (25		
	2-year long-term extension		mg twice weekly)		

^{*} New study added since last review.

ABA = abatacept; ACR = American College of Rheumatology; ANK = anakinra; ETN = etanercept; kilogram = kg; mACR = modified American College of Rheumatology; milligram = mg; RCT = randomized controlled trial; vs. = versus; yr = year

Similarly, a 1-year RCT (N=121) followed by a 2-year open-label long-term extension (N=80) found no significant differences in modified ACR 20 at 1 year or at 2 and 3 years in the long-term extension for patients treated with abatacept (2 mg/kg for RCT, 10 mg in long-term extension) combined with etanercept (25 mg twice weekly) compared to etanercept only (Table 19). Although the initial RCT dosing of abatacept was lower than currently used clinically, the

frequency of serious adverse events was higher in the abatacept combined with etanercept-treated patients than in the etanercept-only treated patients.

Biologic DMARD plus oral DMARD versus biologic DMARD. The majority of trials assessed a combination of a biologic DMARD and MTX against a monotherapy of the respective biologic DMARD. ^{68, 76, 81, 84, 86, 87, 126} Only one trial used sulfasalazine as a oral DMARD in combination with a biologic DMARD. ⁸⁵ No evidence is available on combination treatments of abatacept or anakinra. Disease activity and remission results are presented in Table 20 and radiographic joint damage in Table 21.

Adalimumab plus MTX versus adalimumab. The PREMIER study was conducted in MTX-naive patients with early (disease duration<3 years), aggressive RA. To Details of this study are reported above in *Biologic DMARD versus oral DMARD*. After 2 years, significantly more patients on the combination therapy achieved response criteria on ACR 50 than patients on adalimumab monotherapy (59 percent vs. 37 percent; P < 0.001); in addition, they had statistically significantly less progression on a modified Sharp/van der Heijde score (1.9 vs. 5.5 Sharp units; P < 0.001). After 2 years of treatment, 49 percent of patients on the combination therapy and 23 percent on adalimumab monotherapy achieved remission (DAS 28<2.6; P < 0.001). Discontinuation rates because of lack of efficacy were lower in the combination group than in the monotherapy group (4.2 percent vs. 19.0 percent; P = NR). We report on results of the other comparisons of the PREMIER study in the respective sections on *Biologic DMARD versus oral DMARD* and *Biologic DMARD plus oral DMARD versus oral DMARD*.

Etanercept plus MTX versus etanercept. Two RCTs (in four publications)^{86, 87, 136, 138} and two prospective cohort studies^{68, 81} assessed differences in efficacy between an etanercept-MTX combination and etanercept monotherapy in patients with active, DMARD-resistant disease. Findings of these studies consistently supported greater efficacy for the combination therapy than for the etanercept monotherapy.

The TEMPO trial (described above in *Biologic DMARD versus oral DMARD*) enrolled a mixed population of MTX-naive patients (about 57 percent) and patients who had been on prior MTX treatment (about 43 percent). Patients who had either failed prior MTX treatment or experienced toxic effects were excluded from this study. Results of the etanercept-MTX combination (25 mg twice weekly plus up to 20 mg/week) and the etanercept monotherapy (25 mg twice weekly) arms showed that the combination treatment was significantly more efficacious than etanercept alone. After 52 weeks, 69 percent in the combination group and 48 percent in the etanercept group achieved ACR 50 response criteria (*P*<0.0001). Likewise, a statistically significantly higher proportion of patients in the combination than in the monotherapy group met ACR 20 and ACR 70 response criteria. The proportion of patients achieving remission (DAS<1.6) was 35 percent in the combination group and 16 percent in the monotherapy group (*P*<0.0001). In addition, the combination regimen led to significantly better radiographic outcomes (changes in total Sharp score: -0.54 vs. 0.52; *P*<0.0001) than the etanercept monotherapy. ¹³⁶

Table 20. Disease activity and remission for biologic DMARD+oral DMARD versus biologic DMARD studies

	Study Design N				Quality
Study	Duration	Study Population	Comparison (dose)	Results	Rating
Adalimumab+l	MTX vs. Adalimi	umab			
Breedveld et al., 2006 ⁷⁶ PREMIER	RCT 799	Early, aggressive RA; MTX-naive; mean disease	ADA (40 mg biweekly)+MTX (20 mg/week) vs. ADA (40 mg		Fair
study	2 years	duration NR (<3 years)	biweekly)	(59% vs. 37%; <i>P</i> <0.001)	
Etanercept+vs	. Etanercept				
Combe et al.,	RCT	Active RA despite	Z treatment; weekly)+SSZ (2, 2.5, or 3 rates between ETN+SSZ		Fair
200685	260	SSZ treatment; mean disease			
	24 weeks	duration 6.6 years	twice weekly)	P=NR)	
Klareskog et	RCT	Active RA; had	ETN (25 mg twice	Significantly higher area	Fair
al., 2004; ⁸⁶ van der Heijde et al., 2006; ¹³⁶	686 (503 for 2 year results)	failed at least 1 DMARD other than MTX; mean disease	weekly)+MTX (7.5 titrated to 20 mg/week) vs. MTX (7.5 titrated to 20	under curve of ACR-N for ETN+MTX than ETN (18.3%-years vs. 14.7%-	
van der Heijde et al., 2006; ¹³⁸ *Kavanaugh et al., 2008 ¹⁹² TEMPO study	52 weeks (2 years, 100 weeks)	duration 6.6 years	mg/week)	years; <i>P</i> <0.0001) at 24 weeks	
Van Riel et al., 2006 ⁸⁷	Open-label RCT	of disease with MTX; mean disease	disease with weekly)+MTX (>12.5 X; mean disease mg/week) vs. ETN (25 mg	Similar proportions of patients achieved an improvement of >1.2 units of DAS 28 (75% vs. 73%; <i>P</i> =0.66)	Fair
	315				
	16 weeks	•	• ,		
Hyrich et al., 2006 ⁸¹	Prospective cohort	Population-based; patients with active	ETN (25 mg twice weekly)+MTX (dose NR) vs. ETN (25 mg twice weekly)+other DMARD	Significantly higher EULAR response rates for ETN+MTX than ETN (OR,	Good
	2,711	RA who required change in therapy;			
	6 months	mean disease duration 14.3 years	(dose NR) vs. ETN (25 mg twice weekly)	1.98; 95% CI, 1.45-2.71)	
Weaver et al., 2006 ⁶⁸	Prospective cohort	Population-based; patients with active	ETN (25 mg twice weekly)+MTX (dose NR)	Similar mACR 20 response rates for ETN+MTX and ETN (43% vs. 41%; <i>P</i> =NR)	Fair
	3,034	RA who required change in therapy;	vs. ETN (25 mg twice weekly)		
	12 months	mean disease duration 8.3 years		,	
Zink et al., 2005 ⁸⁸	Retrospective cohort	Patients with RA who had a change	ETN+MTX vs. ETN (dosages NR)	Discontinuation due to lack of efficacy:	Good
	1,523	in treatment regimen		Greater in ETN monotherap vs. combination (ETN+MTX 16.9%; ETN: 19.9%; <i>P</i> =NR)	:

Table 20. Disease activity and remission for biologic DMARD+oral DMARD versus biologic DMARD studies (continued)

Study	Study Design N Duration	Study Population	Comparison (dose)	Results	Quality Rating
Infliximab+MT	X vs. Infliximab				
Zink et al., 2005 ⁸⁸	Retrospective cohort	Patients with RA who had a change	hange (dosages NR) than combination	Greater in INF monotherapy than combination	
	1,523	in treatment regimen		(INF+MTX: 17.9%, INF: 45%)	
	1 year				
Hyrich et al., 2006 ⁸¹	Prospective cohort	Population-based; patients with active RA who required change in therapy;	INF (3 mg/kg)+MTX (dose NR) vs. INF (3	rates for INF+MTX than INF	Good
	2,711		mg/kg)+other DMARD (dose NR) vs. INF (3	(OR, 1.35; 0.92-2.00)	
	6 months	mean disease duration 14.3 years	mg/kg)		
Rituximab+MT	X vs. MTX				
Edwards et al.,	RCT	Active RA despite	RTX (1,000 mg/days 1 & Higher ACR 50 response rates for the RTX+MTX vs. RTX (1,000 mg/days 1 combination than for RTX monotherapy (43% vs. 33%; <i>P</i> =NR)		Fair
2004 ⁸⁴	161	MTX treatment; mean disease			
	24 weeks	duration 10.4 years			

^{*} New study added since last review.

ACR = American College of Rheumatology; ACR-N = American College of Rheumatology percent improvement from baseline to endpoint; ADA = adalimumab; CI = confidence interval; ETN = etanercept; ETN+ABA = etanercept plus abatacept; ETN+AKA = etanercept plus anakinra; EULAR = European League Against Rheumatism response; INF = infliximab; kg = kilogram; mg = milligram; MTX = methotrexate; NR = not reported; NS = not significant; OR = odds ratio; RA = rheumatoid arthritis; RCT = randomized controlled trial; RTX = rituximab; SSZ = sulfasalazine; vs. = versus

Table 21. Radiographic joint damage biologic DMARD+oral DMARD versus biologic DMARD studies

Study	Study Design N Duration	Population with Early RA (<3 years)	Comparison (dose)	Radiographic Outcomes
Adalimumab-	⊦MTX vs. Adalimu	mab		
Breedveld et al., 2006; ⁷⁶ *Hoff et al., 2009 ¹⁹⁰ PREMIER study	RCT 799 2 years	Yes; MTX-naive patients with early, aggressive RA	ADA (40 mg biweekly)+MTX (20 mg/week) vs. ADA (40 mg biweekly)	Total modified Sharp score change: 1.9 vs. 5.5; <i>P</i> <0.001 Erosion score change: 1.0 vs. 3.0; <i>P</i> <0.001 Joint space narrowing score change: 0.9 vs. 2.6; <i>P</i> <0.001
Etanercept+N	ITX vs. Etanercep	t		
Klareskog et al., 2004; 86 van der Heijde et al., 2006; 136 van der Heijde et al., 2021; 138	RCT 686 52 weeks	No	ETN (25 mg twice weekly)+MTX (20 mg/week) vs. ETN (25 mg twice weekly)	Total modified Sharp score change: -0.54 vs. 0.52; <i>P</i> =0.0006
2006 ¹³⁸ TEMPO study				At 2 years: Total modified Sharp score change: -0.56 vs. 1.10; <i>P</i> <0.05 Erosion score change: -0.76 vs. 0.36; <i>P</i> <0.05 Joint space narrowing score change: 0.20 vs. 0.74; <i>P</i> =NR (NS)

^{*} New study added since last review.

ADA = adalimumab; CI = confidence interval; ETN = etanercept; mg = milligram; MTX = methotrexate; NR = not reported; NS = not significant; P=NR (NS) = p value not reported but authors stated it was not significant; RA = rheumatoid arthritis; RCT = randomized controlled trial; vs. = versus

A German retrospective cohort study based on the RABBIT database did not find differences in discontinuation rates due to lack of efficacy between patients on etanercept monotherapy and those on an etanercept-MTX combination (19.9 percent vs. 16.9 percent; P=NR). 88

Results of year 2 of the TEMPO trial confirmed the long-term sustainability of findings from efficacy RCTs. ¹³⁸ ACR response criteria, DAS remission rates, quality-of-life measures, and radiographic progression were statistically significantly better in the combination group than in the etanercept monotherapy group. Attrition was 39 percent after 2 years and could compromise the internal validity of the long-term results.

The other three studies included a 16-week, open-label RCT (N=315),⁸⁷ a 12-month prospective cohort study,⁶⁸ and a 6-month prospective cohort study.⁸¹ Their results were generally consistent with findings from the TEMPO trial. Both prospective cohort studies were population-based, one in the United States⁶⁸ and the other in the United Kingdom,⁸¹ and both have a high generalizabilty.

The UK study also compared the effectiveness of the etanercept-MTX combination and a combination of etanercept and other DMARDs (leflunomide, azathioprine, sulfasalazine, hydroxychloroquine, cyclosporine A, penicillamine, gold, minocycline) as a class. After adjusting for potential confounders, the investigators reported statistically significantly higher response rates for MTX as a cotherapy than for other DMARDs (OR, 1.66; 95% CI, 1.14 to 2.42).

Etanercept plus sulfasalazine versus etanercept. A 24-week RCT assessed the comparative efficacy of etanercept and sulfasalazine combination therapy (respectively, 25 mg twice weekly plus 2, 2.5, or 3 g/day), etanercept monotherapy (25 mg twice weekly), and sulfasalazine monotherapy (2, 2.5, or 3 g/day) in patients with active RA who had failed previous sulfasalazine treatment. Because sulfasalazine monotherapy resembles a placebo treatment (patients had to have failed it to be eligible), we focus on results from the combination (n=101) and etanercept monotherapy (n=103) arms. After 24 weeks, both groups had similar clinical responses on multiple outcome measures (ACR 20/50/70, DAS28). On ACR 20, the primary efficacy variable, 74 percent of patients in both groups met the relevant response criteria. Likewise, results on patient-reported measures of quality of life (HAQ, EuroQOL, general health VAS) were similar for patients on the combination and monotherapy interventions.

Golimumab plus MTX versus golimumab. Two RCTs compared golimumab plus MTX with unapproved does of golimumab (100 mg). 92, 169 These two studies are referenced in other sections of this report for study arms using approved doses (e.g., golimumab 50 mg plus MTX compared with MTX section), but we do not include them in Table 20 and 21 the overview, our conclusions, because it is difficult to draw conclusions about the comparative effectiveness of the approved use of golimumab (50 mg every 4 weeks) plus MTX.

The GO-BEFORE study was a phase III, multicenter trial that randomized subjects to subcutaneous placebo injections plus MTX, golimumab 100 mg injections plus placebo, golimumab 50 mg injections plus MTX, or golimumab 100 mg injections plus MTX capsules. The GO-FORWARD study was a phase III, multicenter 52-week trial that randomized subjects (assigned in a 3:3:2:2 ratio) to receive placebo injections plus MTX, golimumab 100 mg injections plus placebo, golimumab 50 mg injections plus MTX, or golimumab 50 mg injections plus MTX 52. For both trials, the golimumab plus placebo arm of the trial used an unapproved dose of golimumab, thus it is difficult to draw conclusions about the comparative effectiveness of the approved use of golimumab (50 mg every 4 weeks and combination therapy with golimumab plus MTX.

Infliximab plus MTX versus infliximab. No RCT examined the comparative efficacy and effectiveness of a combination of infliximab and MTX against infliximab monotherapy in patients with RA. Of note, infliximab is not FDA approved for use as monotherapy. The only comparative evidence includes one U.S. and one U.K. prospective cohort study (already described). Both studies indicated that EULAR and modified ACR response criteria were greater for patients in the studies' infliximab combination groups. Remission rates, however, were similar in both studies for the two regimens. At 6 months, U.K. patients in the combination group had higher EULAR response rates than those in the monotherapy group (OR, 1.35; 95% CI, 0.92 to 2.00). At 12 months, mACR 20 responses were similar for U.S. patients in the combination and the monotherapy groups (OR, 0.96; 95% CI, 0.76 to 1.21; P=0.72). 68

A German retrospective cohort study assessing discontinuation rates in clinical practice reported findings similar to those noted above. Discontinuation rates because of lack of efficacy were higher among patients on an infliximab monotherapy than among those on an infliximab-MTX combination regimen (45 percent vs. 18 percent; P=NR). Overall discontinuation rates, however, were statistically significantly higher in the monotherapy than in the combination group (56 percent vs. 34 percent; hazard ratio, 1.9; 95% CI, 1.1 to 3.1).

Rituximab plus MTX versus rituximab. One RCT enrolled patients with highly active, long-standing, DMARD-resistant RA to compare the efficacy of rituximab and MTX (1,000 mg on day 1 and day 15 plus MTX 10 mg or more/week), rituximab monotherapy (1,000 mg on day 1

and day 15), rituximab and cyclophosphamide, and MTX monotherapy. ⁸⁴ Because cyclophosphamide is not a drug of interest for this report and because MTX monotherapy resembles a placebo treatment (patients had to have failed MTX treatment to be eligible), we focus on results of the rituximab-MTX combination (n=40) and the rituximab monotherapy (n=40) arms. After 24 weeks, patients on the combination intervention experienced changes in DAS outcomes similar to those for patients on rituximab monotherapy (-2.6 vs. -2.2; *P*=NR). A similar proportion of patients in both treatment groups achieved a good or moderate EULAR response (83 percent vs. 85 percent; *P*=NR). However, the proportion of patients meeting all three ACR response criteria was higher for patients treated with the rituximab combination treatment than for patients on rituximab monotherapy (ACR 20, 73 percent vs. 65 percent; ACR 50, 43 percent vs. 33 percent; ACR 70, 23 percent vs. 15 percent; *P*=NR). Higher ACR response rates for the combination treatment were maintained during a 48-week, double-blinded followup. After 48 weeks, 35 percent of patients on the combination regimen and 15 percent of patients on rituximab monotherapy met the ACR 50 response criteria.

Biologic combinations: Biologic DMARD plus oral DMARD versus oral DMARD. The evidence is limited to six studies and one systematic review ¹⁹³ comparing a combination regimen of abatacept plus MTX⁸⁹ adalimumab plus MTX⁷⁶ or a combination of etanercept plus MTX^{86, 90} or a combination regimen of infliximab plus MTX⁸² with MTX monotherapy. One study examined etanercept plus sulfasalazine versus sulfasalazine monotherapy. ⁸⁵ Four studies and a systematic review ¹⁹³ were conducted in patients with early, aggressive RA. ^{76, 82, 89, 90} Table 22 presents disease activity and remission results, followed by radiographic joint damage in Table 23.

Table 22. Disease activity and remission for biologic DMARD+oral DMARD versus oral DMARD

	Study Design				Quality
Study	N Duration	Study Population	Comparison (dose)	Results	Quality Rating
Abatacept+M	TX vs. MTX				
*Westhovens	RCT	Early RA, MTX-	Abatacept (~10	Significantly higher ACR 50	Good
et al., 2009 ⁸⁹	509	naïve or previous MTX ≤10 mg/week	mg/kg)+MTX vs. MTX	response rates for ABA+MTX than MTX (57.4% vs. 42.3%;	
	2 year (1 year	for 3 weeks or less,		P<0.001)	
	reported)	with none for prior 3 months		Higher remission rates for ABA+MTX than MTX (41.4% vs. 23.3%; <i>P</i> <0.001)	
Adalimumab-	MTX vs. MTX				
Breedveld et	RCT	Early, aggressive	ADA (40 mg	Significantly higher ACR 50	Fair
al., 2006 ⁷⁶ PREMIER	799	RA; MTX-naive; mean disease duration NR (<3 years)		response rates for ADA+MTX than MTX (59% vs. 43%; P<0.001)	
study	2 years				
Etanercept+M	ITX vs. MTX				
*Emery et al.,	RCT	MTX-naïve patients;	•	Higher ACR 20 response rates	Fair
2008 ⁹⁰ ; Emery et al., 2010 ⁹¹	542	Early RA, mean disease duration 9	mg/week)+MTX 7.5 mg vs. MTX	between ETN+MTX vs. MTX (86%, 67%, <i>P</i> <0.001)	
COMET study	52 weeks [†]	months	-	Higher remission between	
	2 years ⁹¹			ETN+MTX vs. MTX (50%, 28%, <i>P</i> <0.001)	

Table 22. Disease activity and remission for biologic DMARD+oral DMARD versus oral DMARD (continued)

	Study Design				Quality
Study	Duration	Study Population	Comparison (dose)	Results	Rating
Klareskog et al., 2004; ⁸⁶ van der Heijde et al., 2006; ¹³⁶ van der Heijde et al., 2006, ¹³⁸ *Kavanaugh et al., 2008 ¹⁹² TEMPO study	RCT 686 (503 for 2 year results) 52 weeks (2 years, 100 weeks)	Active RA; had failed at least 1 DMARD other than MTX; mean disease duration 6.6 years	ETN (25 mg twice weekly)+MTX (7.5 titrated to 20 mg/week) vs. MTX (7.5 titrated to 20 mg/week)	Significantly higher area under curve of ACR-N for ETN+MTX than MTX (18.3%-years vs. 12.2%-years; <i>P</i> <0.0001) at 24 weeks	Fair
Etanercept+S	ulfasalazine vs	s. Sulfasalazine			
Combe et al., 2006 ⁸⁵ *Combe et al.,	260	Active RA despite SSZ treatment; mean disease	weekly)+SSZ (2, 2.5,	Higher ACR 20 response rates between ETN+SSZ and SSZ (74% vs. 28%; <i>P</i> =NR)	Fair
2009 ¹⁴⁵	24 weeks 2 years	duration 6.6 years	2.5, or 3 g/day)	Higher remission at 2 years ETN+SSZ than SSZ (DAS <2.5; 57% vs.4.0%; P<0.01)	
Golimumab+l	MTX vs. MTX				
*Emery et al., 2009 ⁹² GO- BEFORE	RCT 637 24 weeks	MTX-naïve patient with active RA	GOL (50 mg)+MTX vs. MTX	Higher ACR 50 response rates between GOL+MTX and MTX (40.3% vs. 29.4%; <i>P</i> =0.042)	Fair
Infliximab+M	ΓX vs. MTX				
St Clair et al., 2004; ⁸² Smolen et al., 2006; ⁸³ *Smolen et al., 2009 ¹⁹⁴ ASPIRE study	1,049 54 weeks	Early, aggressive RA; MTX-naive; mean disease duration 0.9 years	INF (3 mg/kg/8 weeks)+MTX (20 mg/week) vs. INF (6 mg/kg/8 weeks)+MTX (20 mg/week) vs. MTX (20 mg/week)	Significantly greater improvement of ACR-N for INF 3 mg+MTX and INF 6 mg+MTX than MTX (38.9% vs. 46.7% vs. 26.4%; <i>P</i> <0.001) Higher remission in INF+MTX vs. MTX (DAS28-ESR<2.6; 21.3%, 12.3%; <i>P</i> <0.001)	Fair

^{*} New study added since last review.

[†]In COMET, subjects were randomized to one of four treatment groups: (1) ETN+MTX for year 1 followed by the same treatment for year 2, (2) ETN+MTX for year 1 followed by ETN alone for year 2, (3) MTX for year 1 followed by ETN+MTX for year 2, or (4) MTX for year 1 followed by continued MTX for year 2. Thus, all subjects were treated with ETN+MTX or MTX for 1 year and we present the 52-week outcomes in this table

ADA = adalimumab; ETN = etanercept; mg = milligram; MTX = methotrexate; RA = rheumatoid arthritis; RCT = randomized controlled trial; TEMPO = Trial of etanercept and Methotrexate with radiographic patient outcomes; vs. = versus

Table 23. Radiographic joint damage of biologic DMARD+oral DMARD versus oral DMARD

Study	Study Design N Duration	Study Population	Comparison (dose)	Results
Abatacept+N	NTX vs. MTX			
*Westhovens	RCT	Early RA, MTX-	Abatacept (~10 mg/kg)+MTX	
et al., 2009 ⁸⁹	509	naïve or pervious MTX ≤10	vs. MTX	score mean change 0.63 vs. 1.06; <i>P</i> <0.040
	2 year (1 year reported)	mg/week for 3 weeks or less, with none for prior 3 months		,
Adalimumab	+MTX vs. MTX			
Breedveld et al., 2006, ⁷⁶	RCT 799	Yes; MTX-naive patients with	ADA (40 mg biweekly)+MTX (20 mg/week) vs. MTX (20 mg/week) vs. ADA (40 mg biweekly)	Total modified Sharp score change: 1.9 vs. 10.4; <i>P</i> <0.001
*Hoff et al., 2009 ¹⁹⁰ PREMIER	2 years	early, aggressive RA		Erosion score change: 1.0 vs. 6.4; <i>P</i> <0.001
study				Joint space narrowing score change: 0.9 vs. 4.0; <i>P</i> <0.001
Etanercept+l	MTX vs. MTX			
*Emery et	RCT	MTX-naïve	ETN (50 mg/week)+MTX 7.5	Lower radiographic progression
al., 2008; ⁹⁰ Emery et al.,	542	patients; early RA, mean	mg vs. MTX	between ETN+MTX vs. MTX (mTSS -2.44, -0.27 <i>P</i> <0.001)
2010 ⁹¹	52 weeks [†]	disease duration		,
COMET study	2 years ⁹¹	9 months		

^{*} New study added since last review.

ADA = adalimumab; ETN = etanercept; mg = milligram; MTX = methotrexate; RA = rheumatoid arthritis; RCT = randomized controlled trial; TEMPO = Trial of etanercept and Methotrexate with radiographic patient outcomes; vs. = versus

Abatacept plus MTX versus MTX. One multinational RCT randomized 509 subjects with early RA to receive abatacept plus MTX or placebo plus MTX. ⁸⁹ The trial enrolled subjects with early agressive RA who were MTX-naïve and seropositive for rheumatoid factor, anti-cyclic citrullinated protein type 2, or both, and had radiographic evidence of joint erosions. At 1 year, subjects treated with abatacept plus MTX had statistically significantly greater improvement in ACR 50 measures, remission defined by DAS28 less than 2.6 (41.4 percent vs. 23.3 percent; P<0.001) and less radiographic progression (mean change TS 0.63 vs. 1.06; P 0.040).

Adalimumab plus MTX versus MTX. The PREMIER study was conducted in MTX-naive patients with early (disease duration <3 years), aggressive RA⁷⁶ (see *Biologic DMARD plus oral DMARD versus biologic DMARD*). Two treatment arms of this 2-year study assessed differences in efficacy between a combination of adalimumab (40 mg every other week) and MTX (20 mg/week) and MTX monotherapy (20 mg/week).⁷⁶ After 2 years, statistically significantly more patients on the combination therapy met ACR 50 response criteria than patients on MTX monotherapy (59 percent vs. 43 percent; P<0.001); in addition, they had statistically significantly less progression on the modified SHS score (changes in total Sharp score: 5.5 vs. 10.4; P<0.001). After 2 years of treatment, 49 percent of patients on the combination therapy

[†]In COMET, subjects were randomized to one of four treatment groups: (1) ETN+MTX for year 1 followed by the same treatment for year 2, (2) ETN+MTX for year 1 followed by ETN alone for year 2, (3) MTX for year 1 followed by ETN+MTX for year 2, or (4) MTX for year 1 followed by continued MTX for year 2. Thus, all subjects were treated with ETN+MTX or MTX for 1 year and we present the 52-week outcomes in this table.

and 25 percent on MTX monotherapy achieved remission (DAS28<2.6; P<0.001). Discontinuation rates because of lack of efficacy were lower in the combination than in the MTX group (4.2 percent vs. 17.9 percent; P=NR).

Etanercept plus MTX versus MTX. Two trials (in six publications) compared etanercept (10 mg or 25 mg twice weekly or 50 mg weekly) with MTX (20 mg/week) over 52 weeks. 86, 136, 138, ¹⁹² The COMET (Combination of Methotrexate and Etanercept in Active Early Rheumatoid Arthritis) study (N=542) was conducted in patients with early RA who were MTX-naïve. 90 The TEMPO trial, 86, 136, 138, 192 described above in the section, Biologic DMARD versus biologic DMARD randomized 686 patients to etanercept plus MTX (25 mg twice weekly plus up to 20 mg/week), etanercept monotherapy (25 mg twice weekly), and MTX monotherapy (up to 20 mg/week). 86, 136, 138 The COMET trial 90 compared 542 early RA patients with etanercept (50 mg weekly) plus MTX (7.5 mg weekly) versus MTX in year 1. However, subjects were actually randomized to one of four treatment groups: (1) etanercept plus MTX for year 1 and year 2 (EM/EM), (2) etanercept plus MTX for year 1 followed by etanercept alone for year 2 (EM/E), (3) MTX for year 1 followed by year 2 (M/EM), or (4) MTX for year 1 followed by continued MTX for year 2 (M/M). 91. Both studies showed statistically significant differences between etanercept plus MTX versus MTX in achieving ACR 20 response criteria at 24 weeks⁸⁶ and 52 weeks. 90 In the COMET study, patients treated with etanercept plus MTX had a higher remission (50 percent vs. 28 percent, P<0.001) and less radiographic progression than MTX only. ⁹⁰ After 2 years, remission remained higher for patients in the EM/EM group compared with the M/M group (57 percent vs. 35 percent, P=0.002) and radiographic progression was also less (10 percent vs. 33 percent, P = 0.009). 91

Golimumab plus MTX versus MTX. The GO-BEFORE study was a phase III, multicenter RCT in MTX-naïve patients with active RA that randomized subjects to subcutaneous placebo injections plus MTX capsules, golimumab 100 mg injections plus placebo capsules, golimumab 50 mg injections plus MTX capsules, or golimumab 100 mg injections plus MTX capsules. The trial reported a higher ACR 50 response at week 24 for golimumab 50 mg plus MTX than MTX only (ACR 50: 40.3 percent vs. 29.4 percent; P=0.042).

Infliximab plus MTX versus MTX. The ASPIRE (Active-controlled Study of Patients Receiving Infliximab for the Treatment of Rheumatoid Arthritis of Early Onset) trial enrolled 1,049 patients with early RA (disease duration <3 years) who were MTX-naive. ⁸² This study compared the benefits of initiating treatment with MTX (20 mg/week) alone or of using two different combinations of MTX and infliximab (3 mg/kg or 6 mg/kg) over 54 weeks. At endpoint, patients in the combination groups had significantly higher ACR-N (ACR-N is the percentage of ACR improvement from baseline to endpoint) scores than patients on MTX monotherapy (38.9 percent [3 mg infliximab plus MTX] versus 46.7 percent [6 mg infliximab plus MTX] versus 26.4 percent [MTX]; P<0.001); remission rates were 31 percent, 21 percent, and 15 percent, respectively. The patients treated with infliximab plus MTX also had higher remission rates than patients treated with MTX alone (DAS28 ESR <2.6; 21.3 percent vs. 12.3 percent, P<0.001). ¹⁹⁴

Biologic plus MTX versus MTX. One systematic review with meta-analysis of seven trials (N=2,763 patients) examined four combinations of biologics with MTX, including infliximab, adalimumab, etanercept, and abatacept, compared to MTX only. ¹⁹³ Overall, clinical remission was higher for the compination therapy as compared with MTX only (RR, 1.74; 95% CI, 1.54 to 1.98). Radiographic nonprogression was also higher for combination therapy (RR, 1.30; 95% CI,

1.01 to 1.68). These results are limited by the heterogeneity in the definity of clinical remission and radiographic nonprogression. None of the included trials lasted more than 1 year.

Biologic combinations: Biologic DMARD plus oral DMARD versus biologic DMARD plus oral DMARD. Three prospective cohorts compared patients taking an anti-TNF plus oral DMARD to patients taking another anti-TNF plus oral DMARD. Each compared a different anti-TNF-oral DMARD combination and followup ranged from 6 months to 17 months. Comparisons included anakinra plus MTX versus anakinra plus LEF, and 'anti-TNF' (infliximab, etanercept or adalimumab) plus MTX versus anti-TNF plus MTX. Overall, all three studies found similar disease activity responses (measured by ACR 20, EULAR and DAS28) for patients on anti-TNF plus oral DMARD compared to patients taking another anti-TNF plus oral DMARD. Similarly, radiographic progression was similar among anti-TNF+MTX groups. Table 24 presents disease activity and remission while Table 25 presents radiographic joint damage.

Table 24. Disease activity and remission for biologic DMARD+oral DMARD versus biologic DMARD+oral DMARD

	Study Design N				Quality
Study	Duration	Study Population	Comparison (dose)	Results	Rating
Anakinra+MT	X vs. Anakinra+	Leflunomide			
*Karanikolas, et al., 2008 ⁹³	Prospective cohort	Patients failed oral DMARD	ANK (100 mg/day)+MTX (25	No significant difference in ACR 20 response between	Fair
	128		mg/week) vs. ANK+LEF (20	ANK +MTX and ANK+LEF (65%, 81%; <i>P</i> =NS, NR)	
	48 weeks		mg/week) `		
Etanercept+C	Dral DMARD vs.	Infliximab+Oral DMA	IRD		
*Hyrich, et al., 2006 ¹⁹⁵	Prospective cohort	Population-based, UK; patients failed	ETN (dose NR) vs. INF (NR) ; (98% also received MTX)	Similar good EULAR response between ETN and INF (17.3%	Fair
	2,879	at least 2 DMARDs; mean disease		vs. 18.7%; <i>P</i> =NR	
	6 months	duration 14 years	,		
Anti-TNF+MT	X vs. Anti-TNF+	Leflunomide			
*Finckh et al., 2009 ⁹⁴	Cohort	Population-based: treatment with INF,	Anti-TNF(INF or ETN or ADA)(dose	Similar DAS 28 improvement at 1 yr for anti-TNF+MTX and	Fair
SCQM cohort	1,218	ETN or ADA; mean disease duration	NR)+MTX (NR) vs. anti- TNF (INF or ETN	anti-TNF+LEF (0.74; 95% CI, 0.63 to 0.84 vs. 0.63; 95% CI,	
	17 months (mean)	8.4-8.9 years	or ADA) (NR)+LEF	0.45 to 0.82, <i>P</i> =NR)	

^{*} New study added since last review.

ACR = American College of Rheumatology; ADA = adalimumab; ANK = anakinra; CI = confidence interval; DMARD = disease modifying anti-rheumatic drug; ETN = etanercept; EULAR = European League Against Rheumatism response; INF = infliximab; LEF = leflunomide; mg = milligram; NR = not reported; NS = not significant; SCQM = Swiss Clinical Quality Management; TNF = tumor necrosis factor; vs. = versus

Table 25. Radiographic joint damage for biologic DMARD+oral DMARD versus biologic DMARD+oral DMARD

Study	Study Design N Duration	Study Population	Comparison (dose)	Results	Quality Rating
Anti-TNF+N	ITX vs. Anti-TNI	F+Leflunomide			
*Finckh et al., 2009 ⁹⁴ SCQM cohort	Prospective cohort 1,218	treatment with INF, ETN or ADA; mean disease	Anti-TNF(INF or ETN or ADA)(NR)+MTX (NR) vs. anti-TNF (INF or ADA)	Similar nonsignificant radiographic progression for anti-TNF +MTX and anti-TNF+LEF (0.91%; 95% CI,	Fair
	17 months (mean)	duration 8.4-8.9 years	(NR)+LEF	0.54 to 1.27 vs. 0.74%; 95% CI, 0.21 to 1.27, <i>P</i> =NS, NR)	

^{*} New study added since last review.

ADA = adalimumab; ASPIRE = Active-Controlled Study of Patients Receiving Infliximab for Treatment of Rheumatoid Arthritis of Early Onset; SCQM = Swiss Clinical Quality Management; INF = infliximab; kg = kilogram; LEF = leflunomide; mg = milligram; NR = not reported; NS = not reported; RA = rheumatoid arthritis; RCT = randomized controlled trial; TNF = tumor necrosis factor; vs. = versus

Treatment strategies. Treatment strategies are guided by clinical response and may involve drug combinations. Disease activity and remission are presented in Table 26 and radiographic joint damage in Table 27. Available treatment strategy studies focus on early RA patients.

Two oral DMARDs plus corticosteroid versus oral DMARD. One multicenter RCT, known as COBRA (Combinatietherapie Bij Reumatoide Artritis), assessed differences in efficacy between a combination of stepped-down prednisolone, MTX, and sulfasalazine and sulfasalazine only. 95 The investigators randomized 155 Dutch patients with early RA for 56 weeks. Patients with active RA were included if they had had symptoms for fewer than 2 years and had not used DMARDs in the past. Patients were then followed indefinitely in an open-label prospective cohort (5-year follow-up data reported). 96 Combination therapy included a stepped-down prednisolone treatment (60 mg/day tapered over 28 weeks), MTX (7.5 mg/week stopped after 40 weeks), and sulfasalazine (2 g/day). Mean duration of RA was 4 months. The authors applied a pooled index, which yielded a weighted change score of five disease activity measures: tender joint count, grip strength, erythrocyte sedimentation rate (ESR), assessor's global assessment by visual analog scale (VAS), and the McMaster Toronto arthritis questionnaire (MACTAR) (score range not given). At 28 weeks, patients on combination therapy had an improved change score in this index (mean change 1.4 vs. 0.8; P<0.0001). At 52 weeks, however, the change results on the pooled index were no longer significant (mean change 1.1 vs. 0.9; P=0.20). In terms of radiographic progression, patients on combination therapy had statistically significantly less progression than the monotherapy patients on the modified Sharp/van der Heijde score at 28 weeks (1 vs. 4; P < 0.0001), 56 weeks (2 vs. 6; P < 0.004), and 80 weeks (4 vs. 12; P < 0.01). Over 5 years, the modified Sharp/van der Heijde change score per year was lower for combination therapy than for monotherapy (5.6 vs. 8.6; P=0.001).

Table 26. Disease activity and remission for early RA DMARD strategies

	Study Desig				
Study	N Duration	Study Population	Comparison (dose)		Quality Rating
Two Oral DMAF	RDs+Corticos	teroid vs. Oral DI	MARD		
Boers et al., 1997; ⁹⁵ Landewe et al., 2002 ⁹⁶ COBRA Study	RCT 155 (148) 56 weeks (5-year followup)	Multicenter; early RA; mean disease duration 4 months	SSZ (2 g/day)+MTX (7.5 mg/day stopped after 40 weeks)+PNL (60 mg/day tapered over 28 weeks) vs. SSZ	Pooled disease index: mean change better in combo group than SSZ alone at 28 weeks (1.4 vs. 0.8; <i>P</i> <0.0001) vs. no longer significant at 52 weeks (1.1 vs. 0.9; <i>P</i> =0.20)	Good
				(Pooled index included tender joint count, grip strength, ESR, VAS, MACTAR questionnaire)	
Three Oral DMA	ARDs+Cortico	steroid vs. Oral [DMARDs		
Mottonen et al., 1999; ⁹⁷ Korpela et al., 2004 ⁹⁸ FIN-RACo study	RCT 199 24 months (5-year follow-up)	Multicenter; early RA; mean disease duration 7.3-8.6 months	MTX (7.5 to 10 mg/week)+HCQ (300 mg/day)+SSZ (2 g/day)+PNL (5 to 10 mg/day) vs. DMARD (SSZ could be changed to MTX or 3rd line) ± PNL	Remission (defined by ACR preliminary criteria modified by authors) higher in combination group (37.9% vs. 18.4%; P =0.011); ACR 50 higher in combination group (71% vs. 58% P =0.058); (5-year remission, NS, 28% vs.	Fair ;
Three Oral DMA	ARDs vs. Biol	ogic+Oral DMARI	D	22%; <i>P=</i> NS)	
Van Vollenhoven et alo., 2009 ⁹⁹ Swefot trial	RCT 258 12 months	Swedish, multicenter; early RA; mean disease duration 6.2-6.3 months	DAS-driven treatment; MTX up to 20mg /wk for 3-4 months, if DAS >3.2 randomized to MTX (up to 20 mg/week) +SSZ (1,000 mg twice/day)+HCQ (400 mg/day vs. MTX (up to 20 mg/week)+INF (3 mg/kg)	EULAR good response lower in combination oral DMARD group (25% vs. 39%; <i>P</i> =0.0160	Fair
Other Combina	tion Strategie	es			
Goekoop- Ruiterman et al., 2005; ¹⁰⁰ *Allaart et al., 2006; ¹⁰¹ *Goekoop-	12 months	Multicenter; early RA; median duration between diagnosis and	DAS-driven treatment; 1: sequential monotherapy starting with MTX (15 mg/week) vs. 2: stepped-up combination therapy (MTX,	DAS ≤2.4: 53%, 64%, 71%, 74% P=0.004 for 1 vs. 3; P=0.001 for 1 vs. 4; P=NS for other comparisons Shorter time to DAS<2.4 for initia	
Ruiterman et al., 2007; ¹⁰² *van der Kooij, et al., 2009; ¹⁰³ *van der Kooij et al., 2009; ¹⁹⁶ *van	4 years	inclusion 2 weeks (IQR 1 to 5); median duration of symptoms 23 weeks (IQR 14	then SSZ, then HCQ, then PRED) vs. 3: combination with tapered high-dose PRED (60 mg/d to 7.5 mg/day) vs. 4: combination (MTX 25 to 30 mg/week)	combination therapy groups (groups 3 and 4) than monotherapy groups (groups 1 and 2) (Median months; 3,3,9,9 P <0.001)	ı
der Kooij et al., 2008 ¹⁹⁷ BeSt study		to 53)	with INF (3 mg/kg every 8 weeks, per DAS, could be titrated to 10 mg/kg)	Similar remission among groups at 4 years (DAS<1.6; 50%, 41%, 38%, 42%; <i>P</i> =0.40)	

^{*} New study added since last review.

BeST = Dutch acronym for Behandel Sstrategieen; COBRA = Combinatietherapie Bij Reumatoide Artritis; DAS = disease activity score; DMARD = disease modifying antirheumatic drug; ERA = early rheumatoid arthritis; ESR = erythrocyte sedimentation rate; ETN = etanercept; g = gram; HCQ = hydroxychloroquine; INF = infliximab; IQR = interquartile range; kilogram = kg; MACTAR = McMaster Toronto Arthritis Questionnaire mg = milligram; MTX = methotrexate; NR = not reported; NS = not significant; PNL = prednisolone; PRED = prednisone; RA = rheumatoid arthritis; RCT = randomized controlled trial; SSZ = sulfasalazine; VAS = visual analog scale; vs. = versus

Table 27. Radiographic joint damage in early RA strategy studies

Study	Study Design N Duration	Population with Early RA (<3 years)	Comparison (dose)	Radiographic Outcomes
Two Oral DMA	RDs+Corticostero	id vs. Oral DMARD)	
Boers et al., 1997; ⁹⁵ Landewe et al.,	RCT 155 (148)	Yes	SSZ (2 g/day)+MTX (7.5 mg/day stopped after 40 weeks)+PNL (60 mg/day	56 week Modified Sharp/van der Heijde
2002 ⁹⁶ COBRA Study	56 weeks (5-year followup)		tapered over 28 weeks) vs. SSZ	5.6 vs. 8.6; <i>P</i> =0.001
Two Oral DMA	RDs+Corticostero	id vs. Oral DMARD)	
Mottonen et al., 1999; ⁹⁷ Korpela		Yes	MTX (7.5 to 10 mg/week)+HCQ (300	2-year Larsen score change: 2 vs. 10; <i>P</i> =0.002
et al., 2004 ⁹⁸ FIN-RACo study	24 months (5 years)		mg/day),+SSZ (2 g/day)+PNL (5 to 10 mg/day) vs. DMARD (SSZ could be	2-year erosion score change: 2 vs. 3; <i>P</i> =0.006
	youroy		changed to MTX or 3rd line) ± PNL	5-year median Larsen score: 11 vs. 24; <i>P</i> =0.001
Other combina	tion strategies			
Goekoop- Ruiterman, 2005 ¹⁰⁰ *Allaart et al., 2006; ¹⁰¹	RCT 508 12 months (2 years, 4 years)	Yes	DAS-driven treatment: 1: sequential monotherapy starting with MTX (15 mg/week) vs. 2: stepped-up combination therapy (MTX,	Median modified Sharp/van der Heijde score change: 2.0, 2.5, 1.0, 0.5; <i>P</i> =0.003 for 1 vs. 3, <i>P</i> <0.001 for 1 vs. 4; <i>P</i> =0.007 for 2 vs. 3; <i>P</i> <0.001 for 2 vs. 4
*Goekoop- Ruiterman et al., 2007; ¹⁰² *van der Kooij, et al., 2009; ¹⁰³ *van der Kooij,			then SSZ, then HCQ, then PRED) vs. 3: combination with tapered high-dose PRED (60 mg/day-7.5 mg/day) vs. 4: combination (MTX 25 to 30 mg/week) with	In year 2, less joint damage in groups 3 and 4 (median modified Sharp/van der Heijde score change: 2.0, 2.0, 1.0, 1.0; P =0.004)
et al., 2009; ¹⁹⁶ *van der Kooij et al., 2008 ¹⁹⁷ BeST study			INF (3 mg/kg every 8 weeks, per DAS, could be titrated to 10 mg/kg)	In year 4, less joint damage in groups 3 and 4 (median modified Sharp/van der Heijde score change: 5.0, 5.5, 3.0, 2.5; <i>P</i> <0.05 for 1 and 2 vs. 4)

^{*} New study added since last review.

BeST = Dutch acronym for Behandel Sstrategieen; COBRA = Combinatietherapie Bij Reumatoide Artritis; DAS = disease activity score; DMARD = disease modifying antirheumatic drug; ETN = etanercept; FIN-RACo = Finnish Rheumatoid Arthritis Combination Therapy; g = gram; HCQ = hydroxychloroquine; INF = infliximab; kg = kilogram; mg = milligram; MTX = methotrexate; NR = not reported; NS = not significant; PNL = prednisolone; PRED = prednisone; RA = rheumatoid arthritis; RCT = randomized controlled trial; SSZ = sulfasalazine; vs. = versus

Three oral DMARDs plus corticosteroid versus oral DMARD. The FIN-RACo (Finnish Rheumatoid Arthritis Combination Therapy) RCT assessed the efficacy of a complex combination of prednisolone (5 to 10 mg/day), MTX (7.5 to 10 mg/week), sulfasalazine (2 g/day), and hydroxychloroquine (300 mg/day) against that of monotherapy with a DMARD with or without prednisolone. The investigators randomized 199 patients with early RA to either combination therapy or monotherapy. Patients on monotherapy were initially started on sulfasalazine (2 to 3 g/day) but could be changed to MTX (7.5 to 15 mg/week), then changed to a third DMARD if needed (azathioprine, auranofin, hydroxychloroquine, injectable gold, penicillamine, or podophyllotoxin). If patients reached remission in the first year, they could be tapered and prednisolone and MTX could be discontinued at 9 months and 18 months, respectively. Adding prednisolone (up to 10 mg/day) in the monotherapy group was left up to the

treating physician and allowed in patients with continuously active disease. After 2 years, remission (judged by the authors using modified ACR 20) was higher in the combination group than in the monotherapy group (37.9 percent vs. 18.4 percent; P=0.011); the proportion achieving ACR 50 response criteria was higher in the combination group than in monotherapy group but did not reach statistical significance (71 percent vs. 58 percent; P=0.058). Larsen Scale radiographic scores had also improved at 2 years in the combination group as compared with the monotherapy group (Larsen Scale score increase 2 vs. 10; P=0.002). Subsequently, patients in this trial were followed for 5 years. ⁹⁸ Those in the monotherapy group were allowed to be treated with combinations of DMARDs if their response was insufficient. At 5 years, the median Larsen Scale score remained lower in the combination therapy group than in the monotherapy group (11 vs. 24; P=0.001). This trial can be considered an effectiveness trial given the flexibility of dosing in an effort to follow clinical practice.

Three oral DMARDs versus biologic plus oral DMARD. One multicenter RCT in Sweden examined the efficacy of an oral DMARD combination versus a biologic plus oral DMARD. ⁹⁹ A total of 487 patients with early RA were initially treated MTX (up to 20 mg/wk) and if they did not respond after 3-4 months, they were randomized to MTX (up to 20 mg/wk) plus sulfasalazine (1000 mg twice/day) plus hydroxychloroquine (400 mg/day) versus MTX (up to 20 mg/wk) plus infliximab (3 mg/kg at week 0, 2, 6 and then every 2 months). Of the 487 patients enrolled, 29.8% (n=145) responded to MTX monotherapy and 258 were randomized to the combination oral DMARD arm versus the infliximab plus MTX arm. At 1 year, significantly more patients in the infliximab plus MTX arm achieved a good EULAR response, defined as a decrease of DAS28 score by at least 1.2 after randomization and a resulting DAS28 of 3.2 or lower (RR: 1.59, 95% CI 1.10 to 2.30). ACR 20 and 50 responses were also significantly higher for the infliximab plus MTX arm (ACR 50: 25% vs. 15%; *P* = 0.0424).

Other combination strategies. One good-quality RCT examined four different treatment strategies over 12 months. 100 The BeSt Study (Dutch acronym for Behandel Strategieen, "treatment strategies") randomized 508 patients with early RA to one of four groups: (1) sequential DMARD, starting with MTX (15 mg/week), (2) stepped-up combination therapy with MTX (15 to 30 mg/week) followed by sulfasalazine (2 g/day), hydroxychloroquine, and prednisone, (3) initial combination therapy of MTX, sulfasalazine, and tapered high-dose prednisone 60 mg/day to 7.5 mg/day in 7 weeks, and (4) initial combination therapy with MTX 25 to 30 mg/week and infliximab 3 mg/kg every 8 weeks (dose titrated up to 10 mg/kg dependent upon DAS 44>2.4). This design called for frequent changes in treatment strategy; the DAS (i.e., DAS in 44 joints) was calculated every 3 months and if it was greater than 2.4, the therapeutic strategies were adjusted. At 12 months, more patients in group 3 (MTX, sulfasalazine, tapered high-dose prednisone) and in group 4 (MTX with infliximab) reached a DAS of 2.4 or less. Respectively, these proportions were 53 percent, 64 percent, 71 percent, and 74 percent (P=0.004 for group 1 vs. group 3; P=0.001 for group 1 vs. group 4; P=NS for other comparisons). Additionally, the median change in modified Sharp/van der Heijde score was lower for groups 3 and 4 than for groups 1 and 2 (2.0, 2.5, 1.0, and 0.5, respectively; P=0.003 for group 1 vs. group 3; P<0.001 for group 1 vs. group 4; P=0.007 for group 2 vs. group 3; P<0.001 for group 2 vs. group 4). Interestingly, at four years, the remission rates were similar among the groups (DAS<1.6; 50 percent, 41 percent, 38 percent, 42 percent, P=0.40).

Key Question 2: Functional Capacity and Quality of Life

This question specifically examined the issue of whether drug therapies differed in their ability to improve functional capacity or quality of life for patients with RA. Findings are organized as for KQ 1. Table 8 (above) lists the abbreviated and full names of all instruments and scales referred to in this section. For the purposes of this report we divided outcomes into functional capacity and health-related quality of life. *Functional capacity, functional status, and functional ability* are three concepts often used interchangeably to refer to similar capabilities. We use these terms to refer to condition-specific measures, such as the Health Assessment Questionnaire (HAQ), developed to assess function in patients with RA or other rheumatic diseases. Quality of life is a far broader construct comprising physical health, mental or emotional health, a variety of symptom states (e.g., pain, fatigue), and coping, spiritual and other domains. We use the term *quality of life* when referring to generic measures, such as the Medical Outcomes Study Short Form 36 Health Survey (SF-36), that have been developed to assess health-related quality of life in both healthy persons and those with different conditions. Outcomes for functional capacity and health-related quality of life were often secondary outcomes in these studies.

Overview

Details of the individual studies are found in the Evidence Tables in Appendix E. Many of the studies in this section are described in more detail in the corresponding KQ 1 sections. For each comparison, tables in Appendix I provide the strength of evidence for functional capacity and quality-of-life outcomes.

Small differences in outcome measures may be statistically significant, yet clinically unimportant. Therefore, in the text below, we consider whether treatment effects reach minimal clinically important differences (MCIDs) for the HAQ and SF-36, the two most commonly reported outcome measures in this section. When we describe "no difference" between two treatments, we use this to indicate that the available evidence did not support a statistically or clinically significant difference between the two treatments. When we describe greater improvements with one treatment compared with another, the difference was both statistically significant and reached the threshold for a MCID. For the HAQ, we considered a difference of ≥0.22 to be a MCID. For the SF-36, some have suggested an improvement of 3 to 5 for the MCID. Data from clinical trials of rheumatoid arthritis patients suggest slightly lower values, with ranges of 2.6-4.4 for the physical component score (PCS) and 2.2-4.7 for the mental component score (MCS). We used these lower ranges to take a conservative approach on what might be a MCID.

Oral disease-modifying antirheumatic drugs (DMARDs) versus oral DMARD. One head-to-head RCT found that patients treated with prednisolone (7.5 mg/d) had greater improvements in functional capacity and quality of life than those treated with budesonide (3 or 9 mg/d) (low strength of evidence). The differences reached thresholds for MCIDs (difference in improvement in mean HAQ: 0.28 to 0.39 units, P<0.01; difference in improvement in SF-36 PCS: 3.7 to 5.4 units, P<0.05).

The evidence from two RCTs^{56, 104, 105, 199} does not support a clinically significant difference between leflunomide and methotrexate (MTX) for improvement in functional capacity (low strength of evidence), although some results reached statistically significant differences favoring leflunomide (mean improvement in HAQ-DI at 12 months: -0.45 vs. -0.26, $P \le 0.01$). Evidence

from one study found greater improvement in quality of life with leflunomide than with MTX (SF-36 PCS mean improvement at 12 months of 7.6 vs. 4.6, *P*<0.01, low strength of evidence).

One RCT¹⁰⁷ with a 2-year followup²⁰⁰ provides low strength of evidence that leflunomide yields greater improvements in functional capacity at 24 weeks, 6 months, and 24 months than sulfasalazine (improvement in HAQ at 24 months: -0.65 vs. -0.36, P<0.01).

Evidence from three RCTs⁵⁷⁻⁵⁹ provides moderate strength of evidence that there is no difference in functional capacity between patients treated with sulfasalazine and MTX.

Oral DMARD combinations. Three RCTs compared a combination of two oral DMARDs (sulfasalazine plus MTX) to monotherapy with either drug and provide moderate strength of evidence that there is no statistically significant difference in functional capacity (between-group differences for change in HAQ ranged from 0.03 to 0.25, all *P* values=NS). ⁵⁷⁻⁵⁹

Two RCTs provide moderate strength of evidence that using corticosteroids and one oral DMARD results in greater improvements in functional capacity than using oral DMARD monotherapy (difference in mean change in HAQ -0.28, *P*=0.02).^{64, 65} One RCT provides low strength of evidence supporting no difference in quality-of-life outcomes for the same comparison.⁶⁴

Biologic DMARD versus biologic DMARD. We found one head-to-head RCT and three prospective cohort studies that compared one biologic DMARD with another.^{66, 68, 70, 71} The head-to-head RCT⁶⁶ provides low strength of evidence that there is no difference in functional capacity between those treated with abatacept and infliximab; the difference for quality-of-life outcomes was statistically significant, but the difference did not reach the MCID (difference in SF-36 PCS at 1 year 1.93, 95% CI, 0.02 to 3.84).

Data from the three prospective cohort studies do not provide any convincing evidence of a difference between biologic treatments. Overall, the strength of evidence (Appendix I) for all comparisons of biologic DMARDs from these studies was low or insufficient and does not suggest a significant difference between etanercept, infliximab, and adalimumab. Some individual studies reported statistically significant differences favoring etanercept over infliximab for functional capacity (one of three studies) or for quality of life (one study), or adalimumab over infliximab for functional capacity and quality of life (one study), but differences did not reach MCIDs or data were not reported. We rated the risk of bias moderate to high for this body of evidence. Because of the methodological limitations of observational studies, findings of these studies should be interpreted cautiously.

Biologic DMARD versus oral DMARD. We found four RCTs^{76, 77, 86, 173} and one prospective cohort study⁷⁸ that included comparisons of monotherapy with a biologic DMARD to monotherapy with an oral DMARD. We found no evidence on approved doses of biologic DMARDs other than etanercept, adalimumab, and tocilizumab and no studies comparing biologics with oral DMARDs other than MTX. The evidence from these studies is mixed. Overall, the strength of the evidence is insufficient for biologics as a class compared to oral DMARDs as a class. Two of the RCTs found no differences when comparing either adalimumab⁷⁶ or etanercept⁸⁶ with MTX. One RCT⁷⁷ found that etanercept resulted in better improvement of function and quality of life during the first 12 weeks of treatment, and that a greater percentage of patients treated with etanercept 25 mg or etanercept 10 mg had significant improvements in functional capacity compared with MTX at 24 months (\geq 0.5 unit improvement in HAQ-DI: 55 percent vs. 43 percent vs. 37 percent, P=0.021 and<0.001, respectively). One RCT found subjects treated with tocilizumab had significantly greater improvements in functional capacity than those treated with MTX, but this trial used a dose of MTX below the

dose usually considered therapeutic; thus, it does not provide evidence to determine how tocilizumab compares with MTX as it is generally used in clinical practice. ¹⁷³ All RCTs were funded by the makers of the biologic DMARDs. Population-based, observational evidence from the cohort study indicated that biologic DMARDs as a class resulted in better functional capacity than oral DMARDs as a class in patients with active RA who required a change in therapy. ⁷⁸

Biologic DMARD combinations. One RCT provides low strength of evidence that there is no difference in functional capacity between a combination of etanercept plus abatacept compared with etanercept alone. ⁸⁰ The same RCT provides low strength of evidence that the combination results in statistically significantly greater improvement in physical, but not mental, health-related quality of life (as measured by the SF-36 PCS and MCS, respectively). Of note, the study concluded that abatacept in combination with etanercept should not be used for patients with RA due to limited efficacy findings and safety concerns (more serious adverse events).

For studies comparing a biologic DMARD plus an oral DMARD versus a biologic DMARD, we stratified by population. Based on results of two RCTs, we conclude that biologic DMARDs plus MTX result in greater improvements in functional capacity (difference in improvement in HAQ-DI at 1 year -0.3, $P \le 0.002$, moderate strength of evidence) and quality of life (low strength of evidence) than biologic DMARDs alone for MTX naïve subjects or those not recently on MTX. ^{76,86} However, for subjects with active RA despite treatment with the same oral DMARD used in the combination therapy, we conclude that there is no difference in improvements in functional capacity or quality of life (moderate strength of evidence) between a biologic DMARD plus an oral DMARD and biologic DMARD monotherapy. ^{68,85,201} For most individual medications in these comparisons, the evidence is limited to a single study. All RCTs were funded by the makers of the biologic DMARDs. No evidence (for biologic DMARD plus oral DMARD vs. biologic DMARD) was available for approved doses of biologic DMARDs other than adalimumab, etanercept, or infliximab and combinations with oral DMARDs other than MTX and sulfasalazine.

Results from seven RCTs and one prospective cohort study suggest greater improvement in functional capacity with combination treatment with a biologic DMARD plus an oral DMARD than with oral DMARD monotherapy (high strength of evidence). ^{68, 76, 82, 85, 86, 89, 90, 92, 136, 138, 145} Five of the RCTs enrolled all or a majority of subjects with early RA; ^{76, 82, 89, 90, 92} Effect sizes for studies finding a clinically important and statistically significant difference between groups ranged from 0.3 to 0.35 for difference in improvement in HAQ-DI and from 9 percent to 38 percent for difference in percentage of subjects with clinically significant improvement in HAQ. All but two of the trials reported results that reached MCIDs; for the two that did not, point estimates were in the direction favoring combination therapy. ^{89, 92} Four of the RCTs also reported quality-of-life outcomes, finding greater improvement in the biologic DMARD plus oral DMARD combination therapy group (moderate strength of evidence). ^{82, 86, 89, 90, 136, 138} The specific comparisons in these studies were a combination regimen of abatacept plus MTX, ⁸⁹ adalimumab plus MTX, ⁷⁶ golimumab plus MTX, ⁹² infliximab plus MTX, ^{68, 82} or etanercept plus MTX adalimumab plus MTX monotherapy; and a combination of etanercept plus sulfasalzine with sulfasalazine monotherapy. ^{85, 145}

Treatment strategies for early RA. Based on the results of two RCTs (three publications), $^{95, 97, 98, 202}$ we concluded that combination strategies using corticosteroids plus multiple oral DMARDs result in more rapid improvement in functional capacity (difference in mean change in HAQ at 28 weeks -0.5, P<0.0001) and less work disability (median 12.4 days

per patient-observation year vs. 32.2 days, *P*<0.008) than oral DMARD monotherapy (low strength of evidence for each outcome).

One RCT (the BeSt study) in patients with early RA found that patients treated with initial combination therapy with prednisone (study group 3) or initial combination therapy with infliximab (group 4) had more rapid improvement in functional ability than those treated with sequential DMARD monotherapy (group 1) or with step-up combination therapy (group 2) (statistically significantly greater improvements at 3, 6, 9, and 12 months). By 2 years, improvement was maintained in all groups, but there were no statistically significant differences between groups (low strength of evidence).

Detailed Analysis

Oral DMARD versus oral DMARD. Functional capacity and health-related quality-of-life outcomes are presented in Table 28.

Corticosteroids versus corticosteroids. One 12-week head-to-head RCT (N=143) compared budesonide (3 mg/day or 9 mg/day; n=37 and 36, respectively) and prednisolone (7.5 mg/day; n=39). Mean disease duration of RA was 9 years. Overall, prednisolone produced greater improvement in functional capacity and health-related quality of life than either dose of budesonide. At 12 weeks, those treated with prednisolone had better improvement in mean HAQ scores than budesonide (Table 28). Those treated with prednisolone also had better improvement in health-related quality of life as measured by the physical subscale of the SF-36. Improvement on the mental subscale of the SF-36 was not statistically significantly different between groups. Of note, functional capacity and health-related quality of life were secondary outcome measures; the study had not been designed to compare differences in either the HAQ or the SF-36.

Leflunomide versus MTX. We found two RCTs^{104, 105} comparing leflunomide (20 mg/day) with MTX (7.5 mg/week to 15 mg/week)^{104, 105} and two systematic reviews.^{55, 106} We describe the individual studies first.

The first trial randomized 482 patients to leflunomide (n=182) or MTX (n=182) over 12 months. $^{104, 199}$ Patients receiving leflunomide reported greater mean improvement in the HAQ-DI that was statistically significant (Table 28), but the difference between groups did not reach the MCID. Those receiving leflunomide had greater improvement on the SF-36 physical component than those receiving MTX at 12 months that was statistically significant and reached the MCID. At 12 months, the two groups did not differ significantly in improvement in the SF-36 mental summary score or in work productivity. A 2-year followup of 235 patients (leflunomide, n=98; MTX, n=101) found greater mean improvement in the HAQ-DI (-0.60 vs. -0.37; P=0.005) and MHAQ scores (-0.43 vs. -0.28; P ≤0.05) with leflunomide than with MTX. The groups did not differ significantly in mean improvement in the SF-36 physical or mental summary scores at 24 months. These 2-year results are limited by the high attrition rate (45 percent) from the initial study.

A 1-year multinational RCT (N=999) comparing leflunomide and MTX with an optional second year enrolled RA subjects with a mean disease duration of 3.5 years to 3.8 years. ¹⁰⁵ At 12 months, a statistically significant but minimal quantitative difference (number not reported, shown in bar graph) ¹⁰⁵ for change in the HAQ (P<0.05) was reported between the two groups; at 24 months, however, the groups did not differ significantly.

Table 28. Oral DMARD versus oral DMARD studies: Functional capacity and health-related quality-of-life outcomes

Study	Study Design N Duration	Study Population	Comparison (dose)	Functional Capacity	Health-Related Quality of Life	Quality Rating
	roid vs. Cortico					
Kirwan et al., 2004 ⁵⁴	RCT 143 12 weeks	Population- based; active RA; mean disease duration 9 years	BUD (3 mg/day) vs. BUD (9 mg/day) vs. PNL (7.5 mg/day)	Improvement in mean HAQ scores: PNL 0.393 units better than BUD 3 mg; P<0.001 PNL 0.276 units better than BUD 9 mg; P<0.01	Improvement in SF-36 physical component: mean change 5.4 units better for PNL than BUD 3 mg, <i>P</i> <0.01; 3.7 units better than BUD 9 mg, <i>P</i> <0.05	Fair
Leflunomi	de vs. MTX					
Emery et al., 2000 ¹⁰⁵	RCT 999 1 year with optional second year	Mean disease duration 3.5 to 3.8 years	mg/day) vs.	Change in HAQ at 12 months, minimal quantitative (data NR) but significant (<i>P</i> <0.05); at 24 months, difference NS	NR	Fair
Strand, et al., 1999 ¹⁰⁴ Cohen et al., 2001 ⁵⁶ ,	RCT 482 12 months (1- year continuation)	Mean disease duration 6.5 to 7 years		Mean improvement in HAQ-DI greater in LEF than MTX at 12 months (-0.45 vs0.26; $P \le 0.01$) and MHAQ (-0.29 vs0.15; $P < 0.01$)	Mean improvement in SF-36 physical greater in LEF than MTX at 12 months (7.6 vs. 4.6; <i>P</i> <0.01) but not mental component (1.5 vs. 0.9; <i>P</i> =NS)	Fair
Leflunomi	de vs. Sulfasala	zine				
Smolen et al., 1999 ¹⁰⁷ Scott et al., 2001 ²⁰⁰	RCT 358 (146) 24 weeks (12- and 24-month followup)	Mean disease duration 5.7 to 7.6 years		Improvement in HAQ scores at 24 weeks greater in LEF than SSZ (-0.50 vs0.29; P <0.03) and continued in 2-year followup group at 6 and 24 months (-0.50 vs0.29; -0.65 vs0.36; both P <0.01)	NR	Fair
Sulfasalaz	ine vs. MTX					
Capell et al., 2007 ⁵⁹	RCT 165 (Phase 1 run-in: 687) 6 months (18 months for those with DAS ≥2.4 at 6 months)	Scotland; 8 NHS sites; active RA; mean disease duration 1.6 to 1.8 years	SSZ (≤4 g/day) vs. MTX (≤25 mg/week)	No significant difference between groups in change from baseline HAQ (SSZ: -0.25; MTX: -0.19; <i>P</i> =0.99)	NR	Fair

Table 28. Oral DMARD versus Oral DMARD studies: functional capacity and health-related quality-of-life outcomes (continued)

Study	Study Design N Duration	Study Population	Comparison (dose)	Functional Capacity	Health-Related Quality of Life	Quality Rating
Dougados et al.,	RCT 209 (146)	Multinational; DMARD	SSZ (2 to 3 g/day) vs.	No statistically significant difference in change from	NR Fair	
1999 ⁵⁷	52 weeks (5 year followup)	naive; mean disease duration 2.3 to 3.4 months	MTX (7.5 to 15 mg/week) vs. SSZ (2 to 3 g/day)+MTX (7.5 to 15 mg/week)	baseline HAQ to 1 year (SSZ -0.74 vs. MTX -0.73; <i>P</i> =NS)		
Haagsma et al., 1997 ⁵⁸	RCT 105 52 weeks	Netherlands academic and peripheral clinics; DMARD naive; mean disease duration 2.6 to 3.1 months	SSZ (1 to 3 g/day) vs. MTX (7.5 to 15 mg/week)	Difference in change from baseline HAQ to 52 weeks not significant (SSZ -0.32; 95% CI, -0.53 to -0.10, MTX -0.46; 95% CI, -0.68 to -0.25; <i>P</i> =NR)		

BUD = budesonide; combo = combination therapy; DAS = disease activity score; DMARD = disease modifying antirheumatic drug; ETN = etanercept; HAQ = Health Assessment Questionnaire; HAQ-DI = Health Assessment Questionnaire - Disability Index; HCQ = hydroxychloroquine; INF = infliximab; LEF = leflunomide; mg = milligram; MTX = methotrexate; NHS = National Health Service; NR = not reported; NS = not significant; PNL = prednisolone; PRED = prednisone; RCT = randomized controlled trial; SF-36 = Medical Outcomes Test, Short Form 36; SOFI = Signals of Functional Impairment Scale; SSZ = sulfasalazine

One systematic review with meta-analysis included 33 trials comparing leflunomide, either as monotherapy or combined with another medication, with placebo or other oral DMARDs in patients with active RA. MHAQ scores improved significantly more in patients treated with leflunomide than in those treated with MTX at 6, 12, and 24 months. The leflunomide group and the MTX group did not differ in improvement on the HAQ index at either 12 months or 24 months. Work productivity did not improve significantly in the leflunomide group when compared with the MTX group (weighted mean difference [WMD], -2.3 points; 95% CI, -6.37 to 1.77). When comparing leflunomide with MTX, changes in SF-36 scores showed better improvement in the physical summary score with leflunomide (WMD, -3.0 points; 95% CI, -5.41 to -0.59) but not the mental summary score (WMD, -0.6 points; 95% CI, -3.01 to 1.81). The only study that contributed to this outcome (SF-36 physical summary score) was the RCT (N=482) described above in this section. This systematic review was limited by the number of studies included for meta-analysis; only one study was available for each individual functional capacity or quality-of-life outcome measure except for change in HAQ scores.

The second systematic review aimed to assess the efficacy and safety of oral DMARDs in adults with RA to inform the European League Against Rheumatism (EULAR) recommendations. ¹⁰⁶ The review included a total of 97 RCTs (14,159 patients) covering a variety of comparisons. The results were not significantly different for leflunomide and MTX for pain (four studies, 1,475 patients, SRM -0.04, 95% CI, -0.33 to 0.26) or for disability (four studies, 1,465 patients, SRM -0.09, 95% CI, -0.30 to 0.11). The mean dose of MTX, reported in three studies, was 12.5 mg/week. MTX could be increased to ≥15 mg/week in all studies, but dosing was not as high as currently recommended in most studies.

Leflunomide versus sulfasalazine. One RCT¹⁰⁷ with a 2-year followup²⁰⁰ compared leflunomide (20 mg/day) with sulfasalazine (2 g/day) and placebo; one systematic review included a meta-analysis of leflunomide.⁵⁵ The RCT was a multinational, multicenter study of 358 patients (leflunomide, n=133; sulfasalazine, n=133; placebo, n=92).¹⁰⁷ Baseline HAQ scores were similar for all groups. The leflunomide group had significantly greater improvement in HAQ scores at 24 weeks, 6 months, and 24 months compared with the sulfasalzine group (Table 28).²⁰⁰ Subjects completing the first 6 months were given the option to continue. Those in the placebo group were switched to sulfasalazine if they continued in the study. The study was limited by only including 146 (leflunomide, n=60; sulfasalazine, n=60; placebo then sulfasalzine, n=26) of the original 358 subjects and having a 21 percent attrition rate (116 completed the study).

One systematic review with meta-analysis compared leflunomide (10 to 20 mg/day) with other DMARDs in patients with active RA.⁵⁵ For the comparison of leflunomide and sulfasalazine, the meta-analysis included one study (N=229) with changes in HAQ at 6, 12, and 24 months.²⁰⁰ At 6 and 24 months, the leflunomide group had greater improvements in the HAQ-DI than the sulfasalazine group (WMD -0.25 point; 95% CI, -0.42 to -0.08; WMD -0.29 point; 95% CI, -0.57 to -0.01, respectively). This evidence is limited because the meta-analysis included only one study for this outcome; they did not pool data from multiple studies. *Sulfasalazine versus MTX*. Three RCTs⁵⁷⁻⁵⁹ and one systematic review¹⁰⁶ compared

Sulfasalazine versus MTX. Three RCTs⁵⁷⁻⁵⁹ and one systematic review¹⁰⁶ compared sulfasalazine with MTX. Their findings are consistent and do not support a difference in functional capacity between the groups (Table 28). These included a multinational 52-week RCT of 209 DMARD-naive subjects,⁵⁷ a 52-week RCT of 105 DMARD-naive subjects in academic and peripheral clinics in the Netherlands,⁵⁸ and an 18-month RCT of 165 subjects at eight sites in Scotland.⁵⁹

The systematic review aimed to assess the efficacy and safety of oral DMARDs to inform the EULAR recommendations and included a variety of comparisons. ¹⁰⁶ The results were not significantly different for sulfasalazine versus MTX for disability (two studies, 208 patients, SRM 0.62, 95% CI, -0.86 to 2.10).

Oral DMARD combinations: MTX plus sulfasalazine versus monotherapy with MTX or sulfasalazine. Three RCTs (four publications) compared MTX plus sulfasalazine to either drug alone. ^{57-59, 111} Two of the RCTs included patients with disease duration of less than 1 year; ^{57, 58} the third included patients with RA of up to 10 years. ⁵⁹ Findings of these studies do not support a difference in functional capacity between combination therapy and either monotherapy. Study data are presented in Table 29.

Table 29. Oral DMARD combination studies: Functional capacity and health-related quality-of-life outcomes

Study	Study Design N Duration	Study Population	Comparison (dose)	Functional Capacity	Health-Related Quality of Life	Quality Rating
Sulfasalaz	ine+MTX versus	Sulfasalazine	e or MTX Monotherapy			
Capell et al., 2007 ⁵⁹	RCT 165 (Phase 1 run-in: 687) 6 months (18 months for those with DAS ≥2.4 at 6 months)	Scotland; 8 NHS sites; active RA; mean disease duration 1.6 to 1.8 years	SSZ (≤4 g/day)+MTX (≤25 mg/week) vs. SSZ (≤4 g/day) vs. MTX (≤25 mg/week)	Change from baseline HAQ: no significant difference between groups (SSZ+MTX - 0.50 vs. SSZ - 0.25; P=0.51), (SSZ+MTX -0.50 vs. MTX -0.19; P=0.57)	NR	Fair
Dougados et al., 1999 ⁵⁷ Maillefert et al., 2003 ¹¹¹	RCT 209 (146) 52 weeks (5- year followup)	Multinational; DMARD naive; mean disease duration 2.3 to 3.4 months	SSZ (2 to 3 g/day) vs. MTX (7.5 to 15 mg/week) vs. SSZ (2 to 3 g/day) plus MTX (7.5 to 15 mg/week)	No statistically significant difference in change from baseline HAQ to 1 year (SSZ+MTX -0.70 vs. SSZ -0.74 vs. MTX -0.73; P= NS) or in mean HAQ at 5 years (combination 0.6 vs. either single therapy 0.6; P=0.9)	NR	Fair
Haagsma et al., 1997 ⁵⁸	RCT 105 52 weeks	Netherlands academic and peripheral clinics; DMARD naive; mean disease duration 2.6 to 3.1 months	SSZ (1 to 3 g/day) vs. MTX (7.5 to 15 mg/week) vs. SSZ (2 to 3 g/day)+MTX (7.5 to 15 mg/week)	Difference in change from baseline HAQ to 52 weeks NS (SSZ+MTX -0.51: 95% CI, -0.76 to -0.26 vs. SSZ -0.32: 95% CI, -0.53 to -0.10 vs. MTX -0.46: 95% CI, -0.68 to -0.25; P=NR)	NR	Fair

Table 29. Oral DMARD combination studies: functional capacity and health-related quality-of-life outcomes (continued)

Study	Study Design N Duration	Study Population	Comparison (dose)	Functional Capacity	Health-Related Quality of Life	Quality Rating
Oral DMAF	RD+Corticostero	oid vs. Oral DN	MARD			
*Choy et al., 2008 ⁶⁴	RCT 467 2 years	England/Wal es, Multicenter: early RA; mean disease duration 2.7 to 5.1 months	MTX (≤15 mg/week)+PNL (60 mg/day stepped down and stopped at 34 weeks) vs. MTX	Difference in mean change in HAQ: -0.28 with additional PNL compared to MTX alone (<i>P</i> =0.02)	difference	Good
Svensson et al., 2005 ⁶⁵	Open-label trial 250 2 years	•	DMARD (SSZ or MTX, dosages NR)+PNL (7.5 mg/day) vs. DMARD	Greater improvement in DMARD+PNL group than DMARD-only group (from mean HAQ of 1.0 to 0.4 at 1 year and 0.5 at 2 years vs. 1.0, 0.6, and 0.7; <i>P</i> =NR)	NR	Fair
				Mean SOFI index decreased from 8 at baseline to 4 at 1 year and 4 at 2 years vs. 9, 6, and 7 respectively; <i>P</i> =NR)		

^{*} New study added since last review.

CI = confidence interval; DAS = disease activity score; DMARD = disease modifying antirheumatic drug; g = gram; HAQ = Health Assessment Questionnaire; mg = milligram; MTX = methotrexate; NHS = National Health Service; NR = not reported; NS = not significant; PCS = physical component score; PNL = prednisolone; RA = rheumatoid arthritis; RCT = randomized controlled trial; SF-36 = Medical Outcomes Test, Short Form 36; SOFI = Signals of Functional Impairment Scale; SSZ = sulfasalazine; vs. = versus; yrs = years

A multinational RCT of 209 DMARD-naive subjects compared sulfasalazine (n=68), MTX (n=69), and the sulfasalazine-MTX combination (n=68) for 52 weeks. No statistically significant difference in changes in HAQ scores occurred from baseline to 1 year.⁵⁷ A long-term followup comparing the combination therapy to monotherapy (combining the two monotherapy groups) did not find a significant difference in mean HAQ scores at 5 years (combination 0.6; monotherapy 0.6; P=0.9).¹¹¹

A 52-week RCT of 105 DMARD-naive subjects in Dutch academic and peripheral clinics reported a change in HAQ scores between baseline and 52 weeks of -0.51 (95% CI, -0.76 to -0.26) for the MTX-sulfasalazine combination therapy, a change of -0.32 (95% CI, -0.53 to -0.10; *P*=NR) for sulfasalazine, and a change of -0.46 (95% CI, -0.68 to -0.25; *P*=NR) for MTX.⁵⁸ The HAQ was a secondary outcome in this study; the authors did not attempt to explain these results or compare the values, but the differences between groups did not reach thresholds for MCIDs and the 95% CIs overlap between all groups.

The third study was an 18-month RCT of 165 subjects at eight sites in Scotland. The investigators found no significant difference between the combination therapy and the monotherapy groups in changes from baseline HAQ scores.⁵⁹

Oral DMARD plus corticosteroid versus oral DMARD. We found two RCTs; both found that corticosteroids and one oral DMARD results in greater improvements in functional capacity than using oral DMARD monotherapy (Table 29). The first was a 2-year RCT (N=467) comparing MTX plus prednisolone (60 mg/day stepped down and stopped at 34 weeks) with MTX monotherapy in subjects with early RA. The study reported greater improvements in functional capacity for subjects treated with MTX plus prednisolone than subjects treated with MTX alone, but found no difference in quality of life between groups.

One open-label RCT compared oral DMARD use with and without prednisolone in patients with active RA for 1 year or less. ⁶⁵ This 2-year study compared prednisolone (7.5 mg/day) added to an initial DMARD (chosen by the treating physician) with an oral DMARD only in patients with early RA. The authors reported greater improvement in functional capacity for the prednisolone group than the nonprednisolone group. The DMARD plus prednisolone group also had greater improvement in the mean Signals of Functional Impairment (SOFI) index. Scores on the HAQ and the SOFI index were not statistically compared for the two groups; the clinical relevance of these results is uncertain. In addition, the results should be interpreted cautiously, given the open-label design and potential for bias.

Biologic DMARD versus biologic DMARD. We identified one head-to-head RCT and three prospective cohort studies meeting our inclusion criteria (Table 30). ^{66, 68, 70, 71} Three of these included comparisons of etanercept with infliximab; ^{68, 70, 71} one study compared each of the following: adalimumab versus etanercept, ⁷¹ abatacept versus infliximab, ⁶⁶ and adalimumab versus infliximab. ⁷¹ Mean disease durations ranged from 6 years to 9.9 years; the proportion of patients with early RA in these studies remains unclear. One study was conducted in the United States; ⁶⁸ the others were carried out in the Netherlands, ⁷¹ Spain, ⁷⁰ or were multinational. ⁶⁶

Abatacept versus infliximab. One head-to-head multinational RCT (N=431) conducted in subjects with active RA who had an inadequate response to MTX did not find a difference in functional capacity between those treated with abatacept and infliximab. It found greater improvement in health-related quality of life for those treated with abatacept that reached statistical significance, but did not reach the threshold for a MCID (SF-36 PCS: difference of 1.93 at 1 year, 95% CI, 0.02 to 3.84).

Etanercept versus infliximab. Two of the three cohort studies comparing etanercept with infliximab reported no difference in functional capacity outcomes; one reported greater improvement with etanercept.⁶⁸ Only one of the three studies reported a quality-of-life outcome, finding greater improvement in the SF-36 PCS with etanercept than with infliximab.⁷¹

The first cohort study (N=161) was conducted in anti-tumor necrosis factor (TNF) na 70 The patients and found no difference in functional capacity between etanercept than infliximab. The second cohort study (N=707) was conducted in anti-TNF na 70 repatients that had failed at least two DMARDs and also found no difference in functional capacity between etanercept than infliximab, but reported statistically significantly greater improvement in health-related quality of life for those treated with etanercept, but the actual data were not reported.

Table 30. Biologic DMARD versus biologic DMARD studies: Functional capacity and health-related quality-of-life outcomes

Study	Study Design N Duration	Study Population	Comparison (dose)	Functional Capacity	Health- Related Quality of Life	Quality Rating
Abatacept v	s. Infliximab					
*Schiff et al., 2008 ⁶⁶ ATTEST	RCT 431 1 year	Multinational; Active RA with inadequate response to MTX	ABA (~10 mg/kg every 4 weeks) vs. INF (3 mg/kg every 8 weeks) Study also had a third arm (placebo)	Percentage of patients with improvement in HAQ-DI at 1 year: 57.7% vs. 52.7%; estimate of difference (95% CI, 5.0 (-6.5 to16.5)	SF-36 PCS: between group difference at 1 year favoring ABA of 1.93, 95% CI, 0.02 to 3.84	Fair
					SF-36 MCS: difference of 1.92, 95% CI, -0.30 to 4.15	
Etanercept v	/s. Infliximab					
*Fernandez- Nebro et al., 2007 ⁷⁰		Tertiary care center, Spain; Anti-TNF naïve patients; mean disease duration 9.5 to 9.9 years	ETN vs. INF (dosages NR)	Mean change in HAQ at 6 months: -0.46 vs0.32; P=0.218	NR	Fair
*Kievit et al., 2008 ⁷¹ DREAM register	Prospective cohort study 707 1 year	Population- based, Netherlands, Anti-TNF naïve patients, failed at least 2 DMARDs; mean disease duration 6 to 7.7 years	ETN vs. INF (dosages NR)	Mean change in HAQ at 12 months: -0.35 vs0.26; P=NS	SF-36 PCS: ADA and ETN patients had greater improvement than INF; P=0.001 (data NR, in Figure only)	Fair
Weaver et al., 2006 ⁶⁸	Prospective cohort study 1,371 12 months	Population- based, US; patients with active RA who required change in therapy; mean disease duration 9.3 years	ETN (25 mg twice weekly) vs. INF (3.8 mg/kg or higher)	Mean percentage improvements in HAQ at 12 months: 17% vs. 1%; <i>P</i> =NR	NR	Fair

Table 30. Biologic DMARD versus biologic DMARD studies: functional capacity and health-related quality-of-life outcomes (continued)

Study	Study Design N Duration	Study Population	Comparison (dose)	Functional Capacity	Health- Related Quality of Life	Quality Rating
Adalimumab	vs. Etanerce	pt				
*Kievit et al., 2008 ⁷¹ DREAM register	Prospective cohort study 707 1 year	Population- based, Netherlands, Anti-TNF naïve patients, failed at least 2 DMARDs; mean disease duration 6 to 7.7 years	ADA vs. ETN (dosages NR)	Mean change in HAQ at 12 months: - 0.42 vs0.35; <i>P</i> =NS	SF-36 PCS: ADA and ETN patients had greater improvement than INF; P=0.001 (data NR, in Figure only)	Fair
Adalimumak	vs. Inflixima	b				
*Kievit et al., 2008 ⁷¹ DREAM register	Prospective cohort study 707 1 year	Population- based, Netherlands, Anti-TNF naïve patients, failed at least 2 DMARDs; mean disease duration 6 to	ADA vs. INF (dosages NR)	Mean change in HAQ at 12 months: - 0.42 vs0.26; <i>P</i> <0.05)	SF-36 PCS: ADA and ETN patients had greater improvement than INF; <i>P</i> =0.001 (data NR, in Figure only)	Fair

^{*} New study added since last review.

7.7 years

ADA = adalimumab; CI = confidence interval; DMARD = disease modifying antirheumatic drug; ETN = etanercept; HAQ = Health Assessment Questionnaire; HAQ-DI = Health Assessment Questionnaire – Disability Index; INF = infliximab; MCS = mental component score; mg/kg = milligram/kilogram; NR = not reported; NS = not significant; PCS = physical component score; RA = rheumatoid arthritis; SF-36 = Medical Outcomes Test, Short Form 36; TNF = tumor necrosis factor; US = United States; vs. = versus

The third cohort study comparing etanercept with infliximab was based on the RADIUS (Rheumatoid Arthritis DMARD Intervention and Utilization Study) program. RADIUS was a primary care-based U.S. study that enrolled patients who were initiating any new DMARD at study entry. ⁶⁸ Mean disease duration was 9.3 years, indicating that most patients suffered from advanced RA. The percentage of patients with early RA was not reported. Patients treated with etanercept had a greater mean percentage improvement on the HAQ at 12 months than patients treated with infliximab (17 percent vs. 1 percent; *P*=NR). Among patients older than 65 years, after adjusting for baseline covariates, the authors reported that the etanercept-treated patients had a greater mean percentage improvement in the HAQ at 12 months than infliximab-treated patients (22 percent vs. 4 percent; *P*=NR). However, the authors did not describe direct statistical comparisons between etanercept and infliximab. The study was designed to compare combinations of etanercept or infliximab with MTX to monotherapy with etanercept, infliximab, or MTX.

Adalimumab versus etanercept. One cohort study (N=707) conducted in anti-TNF naïve patients that had failed at least two DMARDs reported no difference in functional capacity or health-related quality of life between adalimumab and etanercept.⁷¹

Adalimumab versus infliximab. One cohort study (N=707) conducted in anti-TNF naïve patients that had failed at least two DMARDs reported greater improvement in functional capacity that reached statistical significance but did not reach the MCID (mean change in HAQ at 12 months: -0.42 vs. -0.26, P<0.05). It also reported greater improvement in health-related quality of life (data NR, P=0.001) for subjects treated with adalimumab than for those treated with infliximab.⁷¹

Placebo-controlled studies. Multiple placebo-controlled RCTs and systematic reviews of placebo-controlled trials provide evidence on the efficacy of abatacept, ^{66, 113, 116, 203-207} adalimumab, ¹¹⁹⁻¹²⁵ anakinra, ^{75, 128, 129, 131-134} etanercept, ^{86, 136-145} infliximab, ^{66, 135, 148-156} rituximab, ^{84, 158-161, 208} certolizumab pegol, ^{164, 165, 168, 209} golimumab, ^{166, 169, 170, 210} and tocilizumab. ^{164, 172, 174-178} Most of these studies were conducted in patients who had failed oral DMARD treatment.

Biologic DMARD versus oral DMARD. We found four RCTs and one prospective cohort study that included comparisons of approved doses of biologic DMARD monotherapy with oral DMARD monotherapy (Table 31). The RCTs compared etanercept with MTX, ^{77, 86} adalimumab with MTX, ⁷⁶ and tocilizumab with MTX; ¹⁷³ the cohort study assessed differences in class effects. ⁷⁸ No head-to-head evidence exists for the other biologic DMARDs or for oral DMARDs other than MTX (although anakinra and infliximab were included in the prospective cohort study comparing biologics as a class to oral DMARDs as a class).

Table 31. Biologic DMARD versus oral DMARD studies: functional capacity and health-related quality-of-life outcomes

Study	Study Design N Duration	Study Population	Comparison (dose)	Functional Capacity	Health- Related Quality of Life	Quality Rating
Adalimumab	vs. MTX					
Breedveld et al., 2006 ⁷⁶ PREMIER study	RCT 799 2 years	Early, aggressive RA; MTX-naive; mean disease duration NR (<3 years)	ADA (40 mg biweekly) vs. MTX (20 mg/week)	At 1 year, ADA and MTX monotherapy groups had similar improvement in HAQ-DI (-0.8 vs0.8; <i>P</i> =NR). Improvements remained similar after 2 years	NR	Fair
Etanercept v	rs. MTX					
Bathon et al., 2000; ⁷⁷ Genovese et al., 2002; ¹⁸⁸ Genovese et al., 2005; ¹⁸⁹ Kosinski et al., 2002 ²¹¹ ERA study	RCT 632 (512) 12 months (1 year open-label extension)	Early, aggressive RA; MTX-naive; mean disease duration 11.7 months	ETN (10 or 25 mg twice weekly) vs. MTX (20 mg/week)	Better improvement in HAQ early in treatment (first 12 weeks) for ETN than MTX (<i>P</i> <0.0001). No significant difference in HAQ scores during weeks 16 to 52 Significantly greater percentage of patients with at least a 0.5 unit improvement in HAQ-DI at 24 months for ETN 25 mg than for either ETN 10 mg or MTX (55% vs. 43% vs. 37%; <i>P</i> =0.021 and <i>P</i> <0.001, respectively)	Better improvement in SF-36 physical summary and SF-36 arthritis-specific health index for ETN group than the MTX group during first 12 weeks (<i>P</i> <0.0001) No significant difference in weeks 16 to 52	Fair

Table 31. Biologic DMARD versus oral DMARD studies: functional capacity and health-related quality-of-life outcomes (continued)

Study	Study Design N Duration	Study Population	Comparison (dose)	Functional Capacity	Health- Related Quality of Life	Quality Rating
Klareskog et al., 2004; ⁸⁶ van der Heijde et al., 2006; ¹³⁶ van der Heijde et al., 2006 ¹³⁸ TEMPO study	686 (503 for 2-year results)	Active RA; had failed at least 2 DMARDs; mean disease duration 6.6 years	ETN (25 mg twice weekly) vs. MTX (20 mg/week)	Similar improvement in mean HAQ scores for MTX and ETN (scores fell from 1.7 to 1.1 and 1.7 to 1.0; <i>P</i> =0.3751)	NR	Good
Tocilizumab	vs. MTX					
*Nishimoto et al., 2009 ¹⁷³ SATORI	RCT 127 24 weeks	Active RA with inadequate response to MTX	TCZ (8 mg every 4 weeks) +placebo vs. MTX (8 mg/week)+plac	Percentage of patients with a decrease of at least 0.22 units in MHAQ at last observation: 67% vs. 34% (<i>P</i> <0.001)	NR	Fair
			ebo			
Biologic Cla	ss vs. Oral DMA	RD Class				
Listing et al., 2006 ⁷⁸	Prospective cohort study	Population- based; patients with	Biologics as a class (ADA, ANA, ETN, INF;	Severely disabled patients (≤50% of full function) in biologic group more likely to achieve physical	NR	Fair
	1,083	active RA	dose NR) vs.			
	12 months	who required	DMARDs as a class (dose NR)	independence (≥67% of full function, Hanover Functional Status Questionnaire) than DMARD group (OR, 3.88; 95% CI, 1.7 to 8.8)		
		years		Functional remission (≥83% of full function) more often achieved in biologic group than in DMARD group (OR, 2.18; 95% CI,		

^{*} New study added since last review.

ADA = adalimumab; ANA = anakinra; CI = confidence interval; DMARD = disease modifying antirheumatic drug; ERA = early rheumatoid arthritis; ETN = etanercept; GOL = Golimumab; HAQ = Health Assessment Questionnaire; HAQ-DI = Health Assessment Questionnaire - Disability Index; INF = infliximab; mg = milligram; MHAQ = modified Health Assessment Questionnaire; MTX = methotrexate; NR = not reported; OR = odds ratio; RA = rheumatoid arthritis; RCT = randomized controlled trial; SF-36 = Medical Outcomes Test, Short Form 36; TCZ = tocilizumab

1.04 to 4.6)

Adalimumab versus MTX. The only data come from the PREMIER study, a multinational 2-year RCT of 799 patients with early, aggressive RA who had not previously received MTX. Two treatment arms of this 2-year study were adalimumab monotherapy and MTX monotherapy. After 1 year, the adalimumab and MTX monotherapy groups had no difference in improvements in functional status measured using the HAQ-DI. Improvements remained similar after 2 years (-0.9 vs. -0.9; P=NR). After 2 years, 19 percent of patients in both monotherapy groups had HAQ-DI scores of zero.

Etanercept versus MTX. Two trials (seven publications) compared etanercept with MTX over 52 weeks. ^{77, 86, 136, 138, 188, 189, 211} ERA was a 52-week multicenter RCT of 632 patients with early

RA in the United States that compared etanercept with MTX. $^{77, 188, 189, 211}$ The treatment groups were similar at baseline. Most patients were female, white, and rheumatoid factor positive and had had RA for fewer than 18 months. Patients treated with etanercept had better early responses for functional status and health-related quality of life. Compared with patients treated with MTX, patients treated with etanercept showed better improvement early in treatment (during the first 12 weeks) on the HAQ (P<0.0001), the SF-36 physical subscale (P<0.0001), and the SF-36 arthritis-specific health index (ASHI) (P<0.0001). From weeks 16 to 52, these measures did not differ significantly; both groups showed similar improvement. These results may be attributed to an earlier response to etanercept than to MTX and the fact that patients were increased to the maximum MTX dose over 2 months. After 12 months, approximately 55 percent of patients in both the MTX and the 25- mg etanercept groups had at least a 0.5 unit improvement in the HAQ-DI. At 24 months, 55 percent of the 25- mg etanercept group had this level of improvement, as did 37 percent of the MTX group (P<0.001) and 43 percent of the 10- mg etanercept group (P=0.021).

TEMPO was a 52-week RCT of RA patients who had failed previous DMARD therapy that compared etanercept with MTX and with combination therapy with both drugs. ⁸⁶ Baseline HAQ scores were similar for all three groups. At 52 weeks, improvement of functional status did not differ significantly between the MTX group and the etanercept group.

Golimumab versus MTX. Two RCTs compared unapproved doses of golimumab (100 mg) with MTX. ^{92, 169} These two studies are referenced in other sections of this report for study arms using approved doses (e.g., golimumab 50 mg plus MTX compared with MTX section), but we do not include them in Table 31, the overview, our conclusions, or in strength of evidence tables due to the use of unapproved doses in the golimumab plus placebo arms, because it is difficult to draw conclusions about the comparative effectiveness of the approved use of golimumab (50 mg every 4 weeks) with MTX.

The GO-FORWARD study was a phase III, multicenter trial that randomized subjects (assigned in a 3:3:2:2 ratio) to receive placebo injections plus MTX, golimumab 100 mg injections plus placebo capsules, golimumab 50 mg injections plus MTX capsules, or golimumab 50 mg injections plus MTX capsules. ¹⁶⁹ The trial found no difference in the improvement in functional capacity (change in median HAQ-DI) between those treated with golimumab 100 mg and those treated with MTX at 24 weeks.

The GO-BEFORE study was a phase III, multicenter trial that randomized subjects to subcutaneous placebo injections plus MTX capsules, golimumab 100 mg injections plus placebo capsules, golimumab 50 mg injections plus MTX capsules, or golimumab 100 mg injections plus MTX capsules. ⁹² The trial reported a median percent improvement in HAQ-DI of 36.95 for the MTX group compared with 31.05 for the golimumab 100 mg plus placebo group (*P*=NR).

Tocilizumab versus MTX. The only data come from the Study of Active controlled TOcilizumab monotherapy for Rheumatoid arthritis patients with an Inadequate response to methotrexate (SATORI), a 24-week RCT of 127 patients with active RA and an inadequate response to MTX conducted at 25 sites in Japan. The Subjects were randomized to MTX monotherapy (8 mg/week) plus tocilizumab placebo or to tocilizumab plus MTX placebo. After 24 weeks, those treated with tocilizumab had significantly greater improvements in the percentage of subjects achieving at least a 0.22 unit improvement in MHAQ scores, which was considered significant clinical improvement and the MCID. Of note, the dose of MTX used in this study is below the dose usually considered therapeutic. Multinational evidence-based recommendations suggest starting MTX at 10-15 mg/week, with escalation of 5 mg every 2-4

weeks up to 20-30 mg/week.¹⁹¹ Thus, this study does not provide evidence that is relevant to determine how tocilizumab compares with MTX as it is generally used in clinical practice.

Biologic DMARD as a class versus oral DMARD as a class. One prospective cohort study examined differences in clinical and functional remission between biologics as a class (adalimumab, anakinra, etanercept, infliximab; n=818) and oral DMARDs as a class (n=265) in patients who had failed two previous oral or biologic DMARD treatments. This study was population-based and part of the RABBIT study, a German long-term, prospective cohort study of RA patients who required a change in therapy in daily rheumatologic care. Patients on biologics were younger and had a significantly more active disease at baseline. Severely disabled patients receiving biologic therapies were more likely to achieve physical independence than controls on conventional oral DMARD therapy (Table 31). Functional remission was more often achieved in patients receiving biologics than in controls.

Biologic combinations: biologic DMARD plus biologic DMARD versus biologic DMARD. We found a single 1-year RCT (N=121) followed by a 2-year open label long-term extension (N=80) that reported no significant differences in functional capacity for patients treated with abatacept combined with etanercept compared with etanercept only (Table 32). The study reported greater improvement in quality of life measured by the physical component summary of the SF-36 (data NR), but not the mental component summary. Although the initial RCT dosing of abatacept was lower than currently used clinically, the frequency of serious adverse events was higher in the abatacept combined with etanercept treated patients than the etanercept-only treated patients. The study concluded that abatacept in combination with etanercept should not be used for patients with RA due to limited efficacy findings and safety concerns (more abatacept and etanercept-treated patients experienced serious adverse events).

Table 32. Biologic DMARD plus biologic DMARD versus biologic DMARD studies: functional capacity and health-related quality-of-life outcomes

Study	Study Design N Duration	Study Population	Comparison (dose)	Functional Capacity	Health-Related Quality of Life	Quality Rating
Etanercept+	Abatacept vs. I	Etanercept				
*Weinblatt et al., 2006 ⁸⁰	RCT 121 1-year double-blind phase 2-year long term-extension	Patients with active RA despite ETN; mean disease duration 12.8 to 13 years	ETN (25 mg twice weekly)+ABA 2g/kg increased to 10 mg/kg after 1 year) vs. ETN (25 mg twice weekly)	Mean change in mHAQ at 12 months: -0.3 vs 0.2; <i>P</i> =NR Mean change in mHAQ from 1 year to 2 years: -0.1 vs. 0; <i>P</i> =NR)	Greater improvement in the SF-36 PCS for ETN+ABA group (data NR) Mean change in SF-36 MCS: 3.9 vs.1.06; P=NS	Fair

^{*}New studies since last review.

ABA = abatacept; ETN = etanercept; g/kg = gram/kilogram; mg = milligram; mg/kg = milligram/kilogram; mHAQ = modified health assessment questionnaire; NR = not reported; NS = not significant; PCS = physical component score; RA = rheumatoid arthritis; RCT = randomized controlled trial; SF-36 = Medical Outcomes Test, Short Form 36; vs. = versus; yr = year

Biologic combinations: biologic DMARD plus oral DMARD versus biologic DMARD. We found five studies, four RCTs^{76, 85, 86, 201} and one prospective cohort study, ⁶⁸ comparing the combination of a biologic DMARD plus an oral DMARD with approved doses of biologic DMARD monotherapy (Table 33). The majority of these studies compared a combination of a biologic DMARD and MTX with monotherapy of the same biologic DMARD. ^{68, 76, 86, 201} One trial used sulfasalazine as a oral DMARD in combination with a biologic DMARD. ⁸⁵ Three of

the studies found no difference between combination therapy and biologic DMARD monotherapy; two reported greater improvement with combination therapy. The two RCTs finding that combination therapy resulted in greater improvement in functional capacity or quality of life enrolled subjects that were MTX-naïve⁷⁶ or had not been on MTX for at least 6 months prior to enrollment.⁸⁶ The studies finding no difference enrolled subjects with active RA despite treatment with the same oral DMARD that was used in the combination therapy arm of the trial.

Table 33. Biologic DMARD plus oral DMARD versus biologic DMARD studies: functional capacity and health-related quality-of-life outcomes

Study	Study Design N Duration	Study Population	Comparison (dose)	Functional Capacity	Health-Related Quality of Life	Quality Rating
Breedveld et	RCT	Early,	ADA (40 mg	At 1 year, ADA+MTX group	NR	Fair
al., 2006 ⁷⁶ PREMIER study	799 2 years	aggressive RA; MTX- naive; mean disease duration NR (<3 years)	biweekly)+MT X (20 mg/week) vs. ADA (40 mg biweekly)	had greater improvements in HAQ-DI than ADA alone (mean, -1.1 units vs0.8; <i>P</i> =0.002). After 2 years, there was no difference (-1.0 vs0.9; <i>P</i> =0.058)		· u
				After 2 years, more ADA+MTX patients had improvement of ≥0.22 in HAQ-DI than ADA patients (72% vs. 58%; <i>P</i> <0.05); had a greater percentage with HAQ-DI scores of 0 (33% vs. 19%; <i>P</i> <0.001)		
Etanercept+	Oral DMARD vs	s. Etanercept				
Combe et al., 2006 ⁸⁵ *Combe et al., 2009 ¹⁴⁵	RCT 260 24 weeks 2 years	Europe multicenter; active RA despite SSZ treatment; mean disease duration 6.6 years	ETN (25 mg twice weekly)+SSZ (2, 2.5, or 3g/day) vs. ETN (25 mg twice weekly)	Mean percentage improvements in HAQ were similar for ETN+SSZ and ETN alone at 24 weeks (40.2% vs. 35.3%, <i>P</i> =NS). At 2 years, clinically significant improvement in HAQ was seen for 78% vs. 76% (<i>P</i> =NS)	Mean percentage improvements in EuroQOL VAS were similar for ETN+SSZ and ETN alone at 24 weeks (67.6% vs. 64.6%; P=NS)	Fair
Klareskog et al., 2004; ⁸⁶ van der Heijde et al., 2006; ¹³⁶ van der Heijde et al., 2006 ¹³⁷ . TEMPO study	686 (503 for 2- year results)	Europe multinational, multicenter; active RA; had failed at least 2 DMARDs; mean disease duration 6.6 years	ETN (25 mg twice weekly)+MTX (20 mg/week) vs. ETN (25 mg twice weekly)	At 52 weeks ETN+MTX was more likely to attain HAQ-DI scores similar to population norms (<0.5) than ETN alone (<i>P</i> <0.05). Combination group had greater improvement in mean HAQ scores (mean fall from 1.8 to 0.8 vs. 1.7 to 1.0; <i>P</i> <0.001; mean improvement from baseline HAQ 1.0 vs. 0.7; <i>P</i> <0.01)	ETN+MTX patients reported better quality of life than ETN-only patients (mean EQ-5D VAS 72.7 vs. 66.8; <i>P</i> <0.05)	Good

Table 33. Biologic DMARD plus oral DMARD versus biologic DMARD studies: functional capacity and health-related quality-of-life outcomes (continued)

Study	Study Design N Duration	Study Population	Comparison (dose)	Functional Capacity	Health-Related Quality of Life	Quality Rating
*Van Riel et al., 2008 ²⁰¹	Open-label RCT	Inadequate control of	ETN (25 mg twice	Mean change in HAQ DI at 16 weeks: -0.59 vs0.59;	Mean change in EQ-5D VAS:	Fair
ADORE trial	315 16 weeks	disease with MTX; mean disease duration 10.9 years	weekly)+MTX (>12.5 mg/week) vs. ETN (25 mg twice weekly)	difference between groups 0.029 (95% CI, -0.115 to 0.172)	21.00 vs. 19.76; difference between groups -2.593 (95% CI, -7.667 to -2.482)	
Weaver et al., 2006 ⁶⁸	Prospective cohort study	Population- based;	ETN (25 mg twice	Patients treated with ETN+MTX had similar	NR Fair	
	3,034	patients with active RA	weekly)+MTX (dose NR) vs.	improvements in functional capacity to those treated		
	12 months	who required change in therapy; mean disease duration 8.3 years	ETN (25 mg twice weekly)	with ETN only (mean percentage improvements in HAQ at 12 months: 17% vs. 17%; <i>P</i> =NR)		

^{*} New study added since last review.

ADA = adalimumab; CI = confidence interval; EQ-5D VAS = European Quality of Life-5 Dimensions Visual Analogue Scale; EuroQOL VAS = European Quality of Life Health Status Visual Analogue Scale; ETN = etanercept; HAQ = Health Assessment Questionnaire; HAQ-DI = Health Assessment Questionnaire – Disability Index; MTX = methotrexate; NR = not reported; NS = not significant; RA = rheumatoid arthritis; RCT = randomized controlled trial; SSZ = sulfasalazine; vs. = versus

Adalimumab plus MTX versus adalimumab. The PREMIER study was conducted in MTX-naive patients with early (<3 years), aggressive RA. This 2-year multinational study randomized 799 patients to a combination of adalimumab and MTX, adalimumab monotherapy, or MTX monotherapy. After 1 year, the combination group had greater improvements in HAQ-DI scores than the adalimumab group. After 2 years, the combination group and the adalimumab-only group did not differ significantly for improvements in the HAQ-DI. After 2 years, more patients in the combination group had achieved improvement of \ge 0.22 (the clinically relevant threshold) in HAQ-DI than the adalimumab group. In addition, 33 percent of patients in the combination group and 19 percent of those in the adalimumab group had HAQ-DI scores of zero (P<0.001).

Etanercept plus MTX versus etanercept. Two RCTs (four publications)^{86, 136, 138, 201} and one prospective cohort study⁶⁸ assessed differences in efficacy between a combination of etanercept and MTX and etanercept monotherapy. One RCT showed greater improvements for functional capacity and quality of life for combination therapy; one RCT found no difference; the cohort study found no difference. The study showing greater improvements for combination therapy enrolled subjects who had not taken MTX during the prior 6 months. The studies that found no difference enrolled subjects with active RA despite current MTX use.

The first RCT, the 52-week TEMPO trial, involved 686 patients with active RA who had failed previous DMARD therapy. $^{86, 136-138}$ Subjects were included only if they had not taken MTX for the 6 months prior to enrollment. Baseline HAQ scores were similar. At 52 weeks, patients in the combination group were significantly more likely to attain HAQ-DI scores similar to population norms (<0.5) than patients in the monotherapy group (P<0.05) and had greater

improvement in HAQ scores. In addition, those receiving combination therapy achieved better quality-of-life scores than etanercept monotherapy. Results of year 2 of the TEMPO trial confirmed the long-term sustainability of these findings. Improvement in disability (based on HAQ) remained significantly better in the combination group than in the etanercept monotherapy group (P<0.01). However, attrition was 39 percent for year 2, which could compromise the validity of the long-term results.

The second RCT, the ADORE trial,²⁰¹ randomized subjects (N=315) with active RA despite MTX treatment to 16 weeks of etanercept plus MTX or to etanercept monotherapy. The study reported no difference in change in functional capacity or quality of life between groups. Unlike the TEMPO trial described above, that enrolled subjects who had not been on MTX for the prior 6 months, the ADORE trial enrolled patients with active RA despite MTX use.

The prospective cohort study was based on the RADIUS program⁶⁸ (see Biologic DMARD versus biologic DMARD above). Mean percentage improvements in HAQ at 12 months did not differ between patients treated with etanercept plus MTX and those treated with etanercept monotherapy.

Etanercept plus sulfasalazine versus etanercept. A 24-week multicenter RCT in Europe assessed the comparative efficacy of etanercept monotherapy, sulfasalazine monotherapy, and an etanercept-sulfasalazine combination in patients with active RA who had failed previous sulfasalazine treatment. Two-year outcomes were also published for the trial. Results on patient-reported measures of functional status and quality of life (HAQ, EuroQOL VAS) were similar at baseline for patients in the two groups. The mean percentage improvement for HAQ was similar for the combination group and the etanercept group (P=NS). The mean percentage improvement for health-related quality of life measured by the EuroQOL VAS was also similar. After 2 years, a clinically significant improvement in functional capacity (HAQ improvement of \geq 0.22) was similar for both groups (Table 34).

Table 34. Biologic DMARD plus oral DMARD versus oral DMARD studies: Functional capacity and health-related quality-of-life outcomes

Study	Study Design N Duration	Study Population	Comparison (dose)	Functional Capacity	Health-Related Quality of Life	Quality Rating
Abatacept+M	TX vs. MTX					
*Westhovens et al., 2009 ⁸⁹	RCT 509 2 years	Early RA, MTX-naïve or pervious MTX ≤10 mg/week for 3 weeks	mg/kg)+MTX	Adjusted mean change from baseline in HAQ-DI: -0.96 vs0.76, between group difference -0.20, 95% CI -0.31 to -0.08	Adjusted mean change from baseline in SF-36 PCS: 11.68 vs. 9.18, P=0.005	Good
		or less, with none for prior 3 months			For SF-36 MCS: 8.15 vs. 6.34, <i>P</i> =0.046	

Table 34. Biologic DMARD plus oral DMARD versus oral DMARD studies: functional capacity and health-related quality-of-life outcomes (continued)

Study	Study Design N Duration	Study Population	Comparison (dose)	Functional Capacity	Health-Related Quality of Life	Quality Rating
Adalimumab Breedveld et al., 2006 ⁷⁶ PREMIER study	RCT 799 2 years	Early, aggressive RA; MTX- naive; mean disease duration <1 year	ADA (40 mg biweekly)+MT X (20 mg/week) vs. MTX (20 mg/week)	At 1 year, mean improvement in HAQ-DI: - 1.1 units vs0.8; P<0.001. After 2 years: -1.0 vs0.9; P<0.058 After 2 years, percentage of subjects with improvement of ≥0.22 in HAQ-DI: 72% vs. 63%; P<0.05 Percentage with HAQ-DI scores of 0: 33% vs. 19%; P<0.001	NR	Fair
Etanercept+l	MTX vs. MTX			F<0.001		
*Emery et al., 2008; ⁹⁰ Kekow, 2010 ²¹² Emery, 2010 ⁹¹ COMET study		MTX naïve patients; Early RA, mean disease duration 9 months	ETN (50 mg/week)+MT X (7.5-20 mg/week) vs. MTX (7.5 to 20 mg/ week)	Percent improvement in HAQ DI: 61% vs. 44%; P <0.0001 Mean improvement in HAQ: -1.02 vs0.72; P <0.001 Percent of subjects achieving normal HAQ-DI (score<0.5): 55% vs. 39%; P =0.0004	Mean improvement in SF-36 PCS: 13.7 vs. 10.7, P=0.003 Mean improvement in SF-36 MCS: 6.8 vs. 6.1, P=NS Mean improvement in EQ-5D VAS: 26.6 vs. 21.7, P=0.003	Fair
Klareskog et al., 2004; ³⁶ van der Heijde et al., 2006; ¹³⁶ van der Heijde et al., 2006 ^{137, 13} TEMPO study	⁸ vears. 100	Europe multinational, multicenter; active RA; had failed at least 2 DMARDs; mean disease duration 6.6 years	ETN (25 mg twice weekly)+MTX (20 mg/week) vs. MTX (20 mg/week)	Combination group had greater improvement in mean HAQ scores (mean improvement from baseline HAQ 1.0 vs. 0.65; <i>P</i> <0.01)	ETN+MTX patients reported better quality of life than MTX- only patients (mean EQ-5D VAS 72.7 vs. 63.7; P<0.01)	Good
Weaver et al., 2006 ⁶⁸	Prospective cohort study 3,034 12 months	Population- based; patients with active RA who required change in therapy; mean disease duration 8.3 years	ETN (25 mg twice weekly)+MTX (dose NR) vs. MTX	Greater mean percentage improvements in HAQ at 12 months for ETN+MTX than MTX (17% vs. 7%; P<0.01) Similar mean percentage improvements in HAQ at 12 months for INF+MTX and MTX (3% vs. 7%; P=NS)	NR	Fair

Table 34. Biologic DMARD plus oral DMARD versus oral DMARD studies: functional capacity and health-related quality-of-life outcomes (continued)

Study	Study Design N Duration	Study Population	Comparison (dose)	Functional Capacity	Health-Related Quality of Life	Quality Rating
Etanercept+	SSZ vs. SSZ					
Combe et al., 2006 ⁸⁵ , *Combe et al., 2009 ¹⁴⁵	RCT 260 24 weeks 2 years	Active RA despite SSZ treatment; mean disease duration 6.6 years	ETN (25 mg twice weekly)+SSZ (2, 2.5, or 3g/day) vs. SSZ (2, 2.5, or 3g/day)	Percentage of patients who achieved a clinically significant improvement in HAQ at 2 years: 78% vs. 40%; <i>P</i> <0,01	NR Fair	
Golimumab-	+MTX vs. MTX					
*Emery et al., 2009 ⁹² GO- BEFORE	RCT 637 24 weeks	patients with active RA	GOL (50 mg)+MTX vs. GOL (100 mg)+MTX vs. MTX vs. GOL (100 mg)	Median % improvement from baseline in HAQ-DI: 43.65 vs. 48.55 vs. 36.95 vs. 31.05 (<i>P</i> =0.141 for GOL 50+MTX vs. MTX) [‡]	NR Fair	
Infliximab+N	MTX vs. MTX					
St Clair et al., 2004; ⁸² Smolen et al., 2006 ⁸³ ASPIRE study	RCT 1,049 54 weeks	Early, aggressive RA; MTX- naive; mean disease duration 0.9 years	INF (3 mg/kg/8 weeks)+MTX (20 mg/week) vs. INF (6 mg/kg/8 weeks)+MTX (20 mg/week) vs. MTX (20 mg/week)	Median decrease in HAQ: $0.78 \text{ vs. } 0.79 \text{ vs. } 0.75$; P = $0.03 \text{ for INF } 3+\text{MTX } \text{ vs.}$ MTX and P < $0.001 \text{ for INF } 6+\text{MTX } \text{ vs.}$ MTX. Combination therapy was more effective for improving HAQ by at least $0.22 \text{ units } (76.0\% \text{ and } 75.5\% \text{ vs. } 65.2\%; P$ = $0.003; P$ = $0.004)$	Significantly greater improvement in SF-36 PCS for INF 6 mg+MTX vs. MTX (13.2 vs. 10.1; <i>P</i> =0.003) but not for INF 3 mg+MTX vs. MTX (11.7 vs. 10.1; <i>P</i> =0.10)	Fair

^{*} New study added since last review.

ADA = adalimumab; ETN = etanercept; EQ-5D VAS = European Quality of Life-5 Dimensions Visual Analogue Scale; GOL = golimumab; HAQ = Health Assessment Questionnaire; HAQ-DI = Health Assessment Questionnaire – Disability Index; INF = infliximab; MTX = methotrexate; NR = not reported; NS = not significant; RA = rheumatoid arthritis; RCT = randomized controlled trial; SF-36 PCS = Medical Outcomes Test, Short Form 36, physical component score; SSZ = sulfasalazine

Golimumab plus MTX versus golimumab. Two RCTs compared golimumab plus MTX with unapproved doses of golimumab (100 mg). These two studies are referenced in other sections of this report for study arms using approved doses (e.g., golimumab 50 mg plus MTX compared with MTX section), but we do not include them in Table 34, the overview, our conclusions, or in strength of evidence tables due to the use of unapproved doses in the golimumab plus placebo arms, because it is difficult to draw conclusions about the comparative effectiveness of golimumab plus MTX with the approved use of golimumab (50 mg every 4 weeks).

The GO-BEFORE study was a phase III, multicenter RCT that randomized subjects to subcutaneous placebo injections plus MTX capsules, golimumab 100 mg injections plus placebo

[†]In COMET, subjects were randomized to one of four treatment groups: (1) ETN+MTX for year 1 followed by the same treatment for year 2, (2) ETN+MTX for year 1 followed by ETN alone for year 2, (3) MTX for year 1 followed by ETN+MTX for year 2, or (4) MTX for year 1 followed by continued MTX for year 2. Thus, all subjects were treated with ETN+MTX or MTX for 1 year and we present the 52 week outcomes in this table.

 $^{^{\}ddagger}P$ =0.006 for GOL 100+MTX vs. MTX, but GOL 100 mg is an unapproved dose.

capsules, golimumab 50 mg injections plus MTX capsules, or golimumab 100 mg injections plus MTX capsules. ⁹² The trial reported a median percent improvement in HAQ-DI of 43.65 for golimumab 50 mg plus MTX compared with 48.55 for golimumab 100 mg plus MTX compared with 31.05 for the golimumab 100 mg plus placebo group (*P*=NR for golimumab plus MTX compared with golimumab).

The GO-FORWARD study was a phase III, multicenter trial that randomized subjects (assigned in a 3:3:2:2 ratio) to receive placebo injections plus MTX, golimumab 100 mg injections plus placebo capsules, golimumab 50 mg injections plus MTX capsules, or golimumab 50 mg injections plus MTX capsules. The golimumab plus placebo arm of the trial used an unapproved dose of golimumab; thus, it is difficult to draw conclusions about the comparative effectiveness of the approved use of golimumab (50 mg every 4 weeks) and combination therapy with golimumab plus MTX.

Infliximab plus MTX versus infliximab. No RCT compared the infliximab-MTX combination to infliximab monotherapy. The only comparative evidence comes from a cohort study from the RADIUS program (see *Etanercept plus MTX versus etanercept*). The mean percentage improvements in the HAQ at 12 months were similar for patients treated with the infliximab-MTX combination and those treated with infliximab monotherapy (3 percent vs. 1 percent; P=NR).

Biologic combinations: biologic DMARD plus oral DMARD versus oral DMARD. We included seven studies comparing a biologic DMARD plus an oral DMARD with oral DMARD monotherapy (Table 34). We found five RCTs^{76, 82, 89, 90, 92} and one prospective cohort study⁶⁸ comparing a combination regimen of abatacept plus MTX,⁸⁹ adalimumab plus MTX,⁷⁶ golimumab plus MTX,⁹² infliximab plus MTX,^{68, 82} or etanercept plus MTX^{68, 90} with MTX monotherapy. We found one RCT comparing a combination of etanercept plus sulfasalzine with sulfasalazine monotherapy.^{85, 145} Four RCTs were conducted in subjects with early RA;^{76, 82, 89, 90} another enrolled a majority of subjects with early RA (about 70 percent of subjects had RA for 3 years or less).⁹² All of the RCTs found greater improvement in functional capacity with combination therapies than with monotherapy, although findings in two of the studies did not reach both clinical and statistical significance.

Abatacept plus MTX versus MTX. One multinational RCT randomized 509 subjects with early RA to receive abatacept plus MTX or placebo plus MTX. The trial enrolled subjects with early RA who were MTX naïve and seropositive for rheumatoid factor, anti-cyclic citrullinated protein type 2, or both, and had radiographic evidence of joint erosions. At 1 year, subjects treated with abatacept plus MTX had statistically significantly greater improvement in measures of functional capacity (HAQ-DI) and quality of life (SF-36 PCS), but neither difference reached the threshold for MCID (Table 34).

Adalimumab plus MTX versus MTX. The PREMIER study was a multinational 2-year RCT of 799 patients with early, aggressive RA who had not previously received MTX; it compared adalimumab monotherapy, MTX monotherapy, and the combination of adalimumab plus MTX⁷⁶ (see KQ 1 section on *Biologic DMARD plus oral DMARD versus biologic DMARD*). After 1 year, the combination group had greater improvements in HAQ-DI scores than the MTX group. After 2 years, the combination was superior to MTX. More patients in the combination group had achieved improvement of \geq 0.22 in the HAQ-DI than the MTX group. In addition, 33 percent of patients in the combination group and 19 percent of those in the MTX group had HAQ-DI scores of zero (P<0.001).

Etanercept plus MTX versus MTX. The COMET study randomized 542 subjects with active, early, moderate to severe early RA to 52 weeks of MTX monotherapy or a combination of MTX and etanercept. Subjects in the combination therapy group had greater improvements in functional capacity and quality of life (Table 34). In addition, among subjects that were working full- or part-time at baseline, fewer patients needed to stop work for at least 1 week in the combination therapy group (9 percent vs. 24 percent, *P*=0.004). In COMET, although year 1 of the study compared combination therapy with etanercept and MTX with MTX alone, subjects were actually randomized to one of four treatment groups at the outset: (1) etanercept plus MTX for year 1 followed by the same treatment for year 2 (EM/EM), (2) etanercept plus MTX for year 1 followed by etanercept plus MTX for year 2 (EM/E), (3) MTX for year 1 followed by etanercept plus MTX for year 2 (M/EM), or (4) MTX for year 1 followed by continued MTX for year 2 (M/M). After 2 years, a greater proportion of subjects had normal HAQ DI scores in the EM/EM group compared with the M/M group (62 percent vs. 44 percent, *P*<0.011).

The 52-week TEMPO trial involved 686 patients with active RA who had failed previous DMARD therapy. 86, 136-138 Subjects were included only if they had not taken MTX for the 6 months prior to enrollment. We focus here on results of the etanercept-MTX combination and the MTX monotherapy arms; their baseline HAQ scores were similar. The combination therapy group had better improvement in functional status than the MTX monotherapy group. At 52 weeks, the combination group had greater improvement in functional capacity than the monotherapy group. In addition, those receiving combination therapy achieved better quality-of-life scores than MTX monotherapy (EQ 5-D VAS). Results of year 2 of the TEMPO trial confirmed the long-term sustainability of these findings. Improvement in disability (based on HAQ) remained significantly better in the combination group. However, attrition was 39 percent for year 2, which could compromise the validity of the long-term results.

A prospective cohort study from the RADIUS program showed that patients treated with the etanercept-MTX combination had statistically significantly greater mean percentage improvements in HAQ scores at 12 months than those treated with MTX alone.⁶⁸

Etanercept plus sulfasalazine versus sulfasalazine. A 2-year multicenter RCT in Europe assessed the comparative efficacy of etanercept monotherapy, sulfasalazine monotherapy, and an etanercept-sulfasalazine combination in patients with active RA who had failed previous sulfasalazine treatment. Two-year outcomes were also published for the trial. Results on patient-reported measures of functional status and quality of life (HAQ, EuroQOL VAS) were similar at baseline for patients in the two groups. A greater percentage of subjects treated with combination therapy achieved a clinically significant improvement in functional capacity (HAQ improvement of ≥0.22) at 2 years. ¹⁴⁵

Golimumab plus MTX versus MTX. The GO-BEFORE study was a phase III, multicenter RCT that randomized subjects to subcutaneous placebo injections plus MTX capsules, golimumab 100 mg injections plus placebo capsules, golimumab 50 mg injections plus MTX capsules, or golimumab 100 mg injections plus MTX capsules. ⁹² The trial reported a median percent improvement in HAQ-DI of 43.65 for golimumab 50 mg plus MTX compared with 48.55 for golimumab 100 mg plus MTX compared with 36.95 for the MTX group. Although the difference was statistically significant for the 100 mg dose of golimumab plus MTX compared with MTX, the difference was not statistically significantly for the approved dose of golimumab (50 mg) plus MTX compared with MTX (*P*=0.141 for GOL 50+MTX vs. MTX; *P*=0.006 for golimumab 100 mg plus MTX compared with MTX).

Infliximab plus MTX versus MTX. The ASPIRE trial enrolled 1,049 patients with early RA (disease duration<3 years) who were MTX-naive. This study compared the benefits of initiating treatment with MTX alone or with a combination of MTX and infliximab over 52 weeks. HAQ and SF-36 scores improved significantly more in the combination groups than in the MTX-only group. The median decrease in the HAQ score was greater for the combination groups than for the MTX-only group (Table 34). In addition, more patients in the combination groups improved their HAQ scores by at least 0.22 units than in the MTX-only group. The mean increases in SF-36 physical component summary scores were 11.7 and 13.2 for the combination groups and 10.1 for the MTX-only group (P=0.10 and P=0.003, respectively). Patients on the combination treatment also had a higher probability of maintaining their employability than did those on MTX alone (P<0.001).

One prospective cohort study from the RADIUS program in the United States (described above in the *Etanercept plus MTX versus etanercept section*) involved patients who were initiating any new DMARD.⁶⁸ The mean percentage improvements in the HAQ at 12 months were not significantly different between patients treated with the infliximab-MTX combination and those treated with MTX monotherapy.

Biologic combinations: biologic DMARD plus oral DMARD versus biologic DMARD plus oral DMARD. One prospective cohort compared patients taking an anti-TNF plus oral DMARD to patients taking another anti-TNF plus oral DMARD (Table 35). ⁹⁴ The study compared anti-TNF (infliximab, etanercept or adalimumab) plus MTX versus anti-TNF plus leflunomide. ⁹⁴ The study reported no difference in functional capacity between groups (mean improvement in HAQ at 1 year). ⁹⁴

Table 35. Biologic DMARD plus oral DMARD versus biologic DMARD plus oral DMARD studies: Functional capacity and health-related quality-of-life outcomes

Study	Study Design N Duration	Study Population	Comparison (dose)	Functional Capacity	Health-Related Quality of Life	Quality Rating
Anti-TNF+N	ITX vs. Anti-TNF	+LEF				
*Finckh et al., 2008 ⁹⁴ SCQM cohort	Prospective Cohort 1,218 17 months (mean)	Population- based: Treatment with INF, ETN or ADA; mean disease duration 8.4 to 8.9 years	Anti-TNF (INF or ETN or ADA) (NR)+MTX (NR) vs. Anti- TNF (INF or ETN or ADA) (NR)+LEF	Mean improvement in HAQ at 1 year: 0.12 vs. 0.14; <i>P</i> =0.09	NR	Fair

^{*} New study added since last review.

ADA = adalimumab; ETN = etanercept; HAQ = Health Assessment Questionnaire; INF = infliximab; LEF = leflunomide; NR = not reported; SCQM = Swiss Clinical Quality Management; TNF = tumor necrosis factor

Strategies in early RA. Functional capacity and health related quality-of-life outcomes are presented in Table 36.

Table 36. Early RA strategies: Functional capacity and health-related quality-of-life outcomes

	Study Design		, ,	·					
Study	N Duration	Study Population	Comparison (dose)	Functional Capacity	Health-Related Quality of Life	Quality Rating			
Two Oral D	Two Oral DMARD+Corticosteroid vs. Oral DMARD								
Boers et al., 1997; ⁹⁵ Landewe et al., 2002 ⁹⁶ , COBRA study	RCT 155 (148) 56 weeks (5- year followup)	Multicenter; early RA; mean disease duration 4 months	(2g/day)+MTX (7.5 mg/day stopped after 40 weeks)+PNL (60 mg/day tapered	Mean change in HAQ: SSZ+MTX combination had greater improvements in functional capacity at 28 weeks (mean change in HAQ -1.1 vs0.6; P<0.0001) but difference not significant at 56 weeks (-0.8 vs0.6; P<0.06)	NR	Good			
Two Oral D	MARD+Cortico	steroid vs. O	ral DMARD						
Mottonen et al., 1999; ⁹⁷ Korpela et al., 2004; ⁹⁸ Puolakka et al., 2004 ²⁰² , FIN-RACo study	RCT 199 24 months (5- year followup)	Multicenter; early RA; mean disease duration 7.3 to 8.6 months	mg/week)+HCQ (300 mg/day)+SSZ	Less work disability for combination group than monotherapy group (median 12.4 days per patient-observation year vs. 32.2; <i>P</i> =0.008)	NR	Fair			
Other Com	bination Strate	gies							
Goekoop-Ruiterman et al., 2005; 100 *Allaart et al., 2006; 101 Goekoop-Ruiterman et al., 2007; 102 van der Kooij et al., 2009; 103 van der Kooij et al., 2009 et al., 2009 beSt study	RCT 508 12 months 2 years 4 years	Multicenter; early RA; median duration between diagnosis and inclusion 2	DAS-driven treatment; 1: sequential monotherapy starting with MTX (15 mg/week) vs. 2: step-up combination therapy (MTX, then SSZ, then HCQ, then PRED) vs. 3: combination with tapered high-dose PRED (60 mg/d to 7.5 mg/d) vs. 4: combination (MTX 25 to 30 mg/week) with INF (3 mg/kg every 8 weeks, per DAS, could be titrated to 10 mg/kg)	All groups improved; greater improvement for groups 3 and 4 than groups 1 or 2 at 3 months (improvement in D-HAQ for strategies 1 through 4: 0.4 vs. 0.4 vs. 0.8 vs. 0.8); better functional ability after 12 months for patients in group 3 or 4 than in group 1 (improvement in mean D-HAQ scores for strategies 1 through 4 were 0.7, 0.7, 0.9, and 0.9, respectively; <i>P</i> <0.05 for 1 vs. 3 and 4, NS for other comparisons); No difference between groups at 24 months (0.7, 0.8, 0.9, and 0.9; <i>P</i> =0.26); improvements were maintained at 4 years, with no significant differences between groups (0.8, 0.7, 0.8, 0.8; <i>P</i> =0.64)	improvement at 3 months and 6 months for groups 3 and 4 than groups 1 and 2 (<i>P</i> <0.001); no difference at 1 and 2 years (<i>P</i> =0.10 and 0.95, respectively) difference SF-36 MCS: No differences between groups at 3 months, 6 months, 1 year, or 2 years	Good			

^{*} New study added since last review.

BeST = Dutch acronym for Behandel Sstrategieen; COBRA = Combinatietherapie Bij Reumatoide Artritis; DAS = disease activity score; D-HAQ = Health Assessment Questionnaire – Disability Index; DMARD = disease modifying antirheumatic drug; ERA = early rheumatoid arthritis; FIN-RACo = Finnish Rheumatoid Arthritis Combination Therapy; g/day = gram per day; HAQ = Health Assessment Questionnaire; HCQ = hydroxychloroquine; INF = infliximab; MCS = mental component score; mg/d = milligram per day; MTX = methotrexate; NR = not reported; NS = not significant; PCS = physical component score; PNL = prednisolone; PRED = prednisone; RA = rheumatoid arthritis; RCT = randomized controlled trial; SF-36 = Medical Outcomes Test, Short Form 36; SSZ = sulfasalazine

Two oral DMARDs plus corticosteroid versus oral DMARD. The COBRA study assessed differences in efficacy between a combination of sulfasalazine, MTX, and prednisolone and sulfasalazine only. ^{95, 96} This RCT evaluated 155 patients with early RA over 56 weeks. Combination therapy included sulfasalazine, MTX, and prednisolone treatment. Compared with patients treated with sulfasalazine alone, patients treated with combination therapy had greater improvements in functional capacity at 28 weeks. The difference was no longer statistically significant at 56 weeks.

Three oral DMARDs plus corticosteroid versus oral DMARD. The FIN-RACo RCT assessed the efficacy of a combination of MTX, sulfasalazine, hydroxychloroquine, and prednisolone against monotherapy with a DMARD with or without prednisolone. This study randomized 199 patients with early RA to combination therapy or monotherapy. Combination therapy included sulfasalazine, MTX, hydroxychloroquine, and prednisolone. Patients on monotherapy were initially started on sulfasalazine (2 g/day to 3 g/day), but they could be changed to MTX (7.5 mg/week to 15 mg/week) or to a third DMARD if needed. The study is described further in the KQ 1 section titled *Three oral DMARDs plus corticosteroid versus oral DMARD*. The initial publication reported no functional capacity or quality of life outcomes at 2 years. A 5-year follow-up trial reported that patients in the combination therapy group had significantly less work disability than patients in the monotherapy group. After 2 years, the drug treatment strategy was no longer restricted and was left to the discretion of individual physicians.

Other combination strategies. The BeSt RCT examined four different treatment strategies over 12 months. 100-103, 196 Patients (N=508) with early RA were randomized to one of four strategies: (1) sequential DMARD starting with MTX (15 mg/week); (2) step-up combination therapy of MTX (15 to 30 mg/week) followed by sulfasalazine (2g/day), hydroxychloroquine, and prednisone; (3) initial combination therapy of MTX, and sulfasalazine with tapered highdose prednisone (60 mg/day to 7.5 mg/day in 7 weeks); and (4) initial combination therapy with infliximab (3 mg/kg) and MTX (25 to 30 mg/week). Adjustments were made in each strategy when the DAS 44 (disease activity score in 44 joints) was greater than 2.4. All groups had similar D-HAQ (Dutch version of the HAQ) scores at baseline (1.4 \pm 0.7 or 1.4 \pm 0.6). Functional ability, measured by the D-HAQ, was a primary end point. Subjects in groups 3 and 4 had more rapid improvement in functional ability (statistically significant greater improvements at 3, 6, 9, and 12 months). After 12 months of treatment, patients treated with strategy 3 or 4 had statistically significant better functional ability than those treated with strategy 1. By 2 years, improvement was maintained in all groups, but there were no statistically significant differences between groups. Improvements were maintained at 4 years, with no significant differences between groups. Subjects in groups 3 and 4 had more rapid improvement in physical healthrelated quality of life; with greater improvement at 3 months and 6 months for groups 3 and 4 than groups 1 and 2 on the SF-36 PCS (P<0.001); but all groups had similar improvement by the end of 1 and 2 years (P=0.10 and 0.95, respectively). There were no differences at any point in mental health-related quality of life as measured by the SF-36 MCS.

Key Question 3: Harms, Tolerability, Adverse Effects, or Adherence

This key question examines whether drug therapies differ in harms, tolerability, or adverse effects in patients with RA. We describe overall tolerability, then specific adverse events for each drug class, followed by studies reporting on adherence. Evidence Tables in Appendix E describe details about these studies, some of which were described for efficacy in KQ 1, above.

Overview

A total of 66 randomized controlled trials (RCTs), one nonrandomized controlled trial, 99 observational studies, and 18 systematic reviews reported on tolerability, harms, and adherence (see Evidence Tables in Appendix E).

As with earlier KQs, the main drug classes examined are corticosteroids, oral disease-modifying antirheumatic drugs (DMARDs), and biologic DMARDs. Studies often defined comparator groups that were not specific to a particular agent, but instead encompassed any agent in a family of treatments (e.g., an oral DMARD). In cases of biologic DMARDs, studies often required all patients to already be on an oral DMARD such as methotrexate (MTX). In RCTs where the biologic DMARD plus MTX is compared with MTX monotherapy, we discuss these as placebo-controlled trials since the MTX is given to all patients. We differentiate this issue in the text when study designs may not otherwise be clear.

Most studies that examined the comparative efficacy of our drugs of interest also determined their harms. Methods of adverse events assessment, however, differed greatly. Few studies used objective scales such as the UKU-SES (Utvalg for Kliniske Undersogelser Side Effect Scale) or the adverse reaction terminology from the World Health Organization (WHO). Most studies combined patient-reported adverse events with a regular clinical examination by an investigator. Often, determining whether assessment methods were unbiased and adequate was difficult. Rarely were adverse events prespecified and defined. Short study durations and small sample sizes additionally limited the validity of adverse events assessment with respect to rare but serious adverse events.

Because few studies used the term *serious adverse events* as defined by the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use,²¹³ we describe serious adverse events as the individual studies identified and reported them.

Rheumatoid Arthritis: Key Points

Tolerability and adverse events. *Corticosteroids.* Comparative tolerability and overall adverse events between corticosteroids were similar but comparative data were limited to one 3-month trial. ⁵⁴ The strength of evidence is low (Appendix I).

Mixed results from one RCT and four observational studies suggest that corticosteroids may increase risk of cardiovascular events. One study showed a protective effect against cardiovascular morbidity with corticosteroids. The strength of the evidence is low.

Corticosteroid use significantly predicted the risk of serious infections, with increased risk of infection demonstrated in nine observational studies. ²¹⁸⁻²²⁶ The strength of evidence for risk of infection with corticosteroids is moderate.

Low strength evidence suggests that corticosteroid treatment is associated with an increased risk of septic (infectious) arthritis²²⁷ and interstitial lung disease. ²²⁸

Oral DMARDs and combinations. Three efficacy trials and one meta-analysis indicated similar tolerability and discontinuation rates of leflunomide, MTX, and sulfasalazine in data up to 2 years. ^{55, 56, 104, 105, 107, 108} A retrospective cohort study found improved tolerability with leflunomide. ²²⁹ In another meta-analysis, the proportion of patients who stayed on MTX was higher than the proportion remaining on sulfasalazine at 5 years based on analysis of 71 RCTs and 88 observational studies (36 percent vs. 22 percent, *P*=NR [not reported]). ²³⁰ The strength of evidence for comparisons of monotherapy with oral DMARDs is low (Appendix I).

Seven studies and two meta-analyses involving combinations of two or three DMARDs, including sulfasalazine, MTX, hydroxychloroquine, and etanercept (a biologic DMARD) versus one or two DMARDs have similar withdrawal rates attributable to adverse events. ^{29, 57-59, 61, 62, 95, 110, 231, 232} Although discontinuation rates were similar for these pharmaceuticals, the number of patients with adverse events (nausea, erythema, elevated transaminases) were higher in two studies of sulfasalazine plus MTX than in monotherapy with either drug. ^{57, 58} The strength of evidence comparing combinations of DMARDs with DMARD monotherapy is low.

Three studies of combinations including prednisone with one or more DMARD indicated similar discontinuation rates between groups. The BeST study compared various strategies of combining corticosteroids with oral and biologic DMARDs and found similar rates of serious adverse events. A retrospective cohort study of 154 patients found that addition of a glucocorticoid to hydroxychloroquine or MTX increased the mean time until withdrawal of DMARD therapy due to adverse events by approximately 6 months (P<0.05). The level of evidence is moderate.

Four observational studies assessed cardiovascular or cerebrovascular outcomes with monotherapy or combinations of oral DMARD treatment. ^{214, 215, 234, 235} All found either a decrease or no difference in risk of these events for patients treated with oral DMARDs. The reduction in risk was largest for leflunomide based on two studies. ^{215, 234} The strength of the evidence is low.

Hepatic events appeared to be similar among patients treated with MTX, leflunomide, hydroxychloroquine, sulfasalazine, infliximab, and etanercept in two retrospective studies over 2 years to 3 years. ^{229, 236} Longer-term evidence is lacking. The level of evidence is low.

Mixed evidence from 12 studies suggests that oral DMARDs do not significantly affect risk of infections. ^{218, 220, 221, 223, 224, 226, 229, 237-240} Evidence is inconclusive for comparing among oral DMARDs. One good-rated nested case-control study showed a lower rate of infection with MTX and hydroxychloroquine. Four other observational studies found no difference in risk with oral DMARDs, ^{218, 220, 221, 239} while five fair-rated observational studies suggest that risk of infection was increased with oral DMARDs. Because of these inconsistencies, the level of evidence is low.

In one 5-year retrospective cohort, interstitial lung disease appeared to be significantly higher with leflunomide use than with use of other DMARDs (relative risk [RR], 1.9; 95% CI, 1.1 to 3.6) but not significantly higher with use of either MTX (RR, 1.4; 95% CI, 0.8 to 2.3) or biologic DMARDs (RR, 0.8; 95% CI, 0.4 to 1.5).²¹⁷ Overall, the rate of hospitalizations because of interstitial lung disease in the entire cohort was 8.1 per 10,000 patient years. In a second study, the risk of interstitial lung disease was similar for leflunomide and other oral DMARDs. The level of evidence is insufficient.

Estimates of cancer risk were limited to retrospective cohort studies. No risk of lymphoma was found for MTX or sulfasalazine in a 30-year retrospective cohort. For the comparison of oral DMARDs, the strength of the evidence is low. Among RA patients, the development of nonmelanoma skin cancer was associated with use of prednisone (hazard ratio [HR], 1.28; P=0.014).

Additional studies suggest that oral DMARDs increase risk of septic (infectious) arthritis, ²²⁷ and that leflunomide increases risk of wound healing complications compared with MTX, ²⁴³ but hydroxychloroquine, leflunomide, MTX, and sulfasalazine do not increase risk of sinus problems ²⁴⁴ A good-rated RCT found that combination DMARD therapy did not increase risk of renal failure. ²⁴⁵ Evidence is insufficient regarding risks for fertility, pregnancy, and lactation. ²⁴⁶

The strength of this evidence is low because only a single study addresses each of these questions.

Biologic DMARDs. Meta-analysis of withdrawal rates from placebo-controlled trials indicate that fewer patients randomized to a biologic DMARD discontinue treatment compared with patients randomized to placebo or MTX monotherapy (oddsratio [OR] of discontinuation, 0.51; 95% CI, 0.40 to 0.65). This difference is largely driven by withdrawals because of lack of efficacy. In a meta-analysis of withdrawals because of lack of efficacy, the patients treated with a biologic DMARD were much less likely to withdraw than placebo- or MTX-treated patients (OR, 0.21; 95% CI, 0.17 to 0.27). Withdrawals because of adverse events were higher among patients treated with a biologic DMARD compared with placebo- or MTX-treated patients (OR, 1.43; 95% CI, 1.18 to 1.74). Because the *overall* withdrawals rates favored biologic DMARDs over placebo, we concluded that efficacy had a stronger influence on the likelihood of treatment continuation than adverse events. Adjusted indirect comparisons based on the same efficacy trials found no difference in overall withdrawals, with the exception of a more favorable withdrawal profile for certolizumab pegol. Also, etanercept and rituximab had a more favorable overall withdrawal profile than some other biologic DMARDs. Certolizumab pegol had fewer withdrawals due to lack of efficacy than adalimumab, anakinra, and infliximab. All but adalimumab, golimumab, and infliximab had fewer withdrawals than anakinra due to lack of efficacy. Both certolizumab pegol and infliximab had more withdrawals due to adverse events than etanercept and rituximab. These results should be interpreted cautiously because of the relatively small number of contributing studies and the corresponding wide confidence intervals.

Strength of evidence is presented in Appendix I; overall the strength of evidence is low.

Overall tolerability: studies on discontinuation rates not otherwise covered in quantitative analyses. Studies that assessed overall tolerability but were not eligible for inclusion in quantitative analyses are summarized in Table 38. One good-quality RCT compared etanercept with the combination of etanercept and abatacapt. Withdrawals due to adverse events occurred more in the combination group (11.8 percent) than in the monotherapy etanercept group (2.8 percent). Additional evidence on comparative discontinuation rates is provided by observational studies. While some studies did not find clinically or statistically significant differences in drug discontinuation rates, others did, generally suggesting higher discontinuation rates with infliximab, adalimumab, and anakinra. Ask, 210, 248, 250-252 One good-rated meta-analysis reported an elevated risk of withdrawals due to adverse events for infliximab, and another good-rated meta-analysis reported higher withdrawals due to adverse events or adalimumab, anakinra, and infliximab compared with etanercept. Ask, 27, 180

Two studies compared adverse event rates and serious adverse events with biologic DMARDs; one randomized controlled trial⁶⁶ and one retrospective cohort study.²⁵³ Both studies found more serious adverse events among patients treated with infliximab compared with abatacept, adalimumab, and etanercept. No other studies directly compared one biologic DMARD with another biologic DMARD with regard to tolerability or serious adverse events. The strength of this evidence is low.

Indirect evidence from additional efficacy trials, cohort studies, and meta-analyses suggests that the overall tolerability profiles are similar among biologic and oral DMARDs, or combinations of biologic and oral DMARDs. ^{67, 70, 76, 84, 86, 87, 89, 90, 116, 121, 127, 136, 138, 156, 170, 175, 177, 178, 183, 210, 254-256} However, several studies suggested that adverse events were more common with biologic DMARDs, given alone or in combination with an oral DMARD. ^{120, 145, 164-167, 173} One good-rated ¹²⁶ and one fair-rated ¹⁸³ systematic review and meta-analysis provide indirect evidence

that adverse event rates may be more common with infliximab than with adalimumab or etanercept. One prospective cohort study found a slightly lower rate of serious adverse events among patients who had an oral DMARD added to adalimumab, compared with patients who only received adalimumab (5.3 percent vs. 7.3 percent, respectively; P=NR). In contrast, in an RCT of MTX-naïve patients that compared golimumab monotherapy, MTX monotherapy, and golimumab plus MTX, serious adverse events were least common among the golimumab monotherapy group (3.2 percent vs. 6.9 percent vs. 6.3 percent, respectively; P=NR). Four RCTs were designed to assess adverse events as primary outcomes. 121, 155, 258, 259

Four RCTs were designed to assess adverse events as primary outcomes. ^{121, 155, 258, 259} Overall, adverse event rates were similar for abatacept, ²⁵⁸ adalimumab, ¹²¹ anakinra, ²⁵⁹ or infliximab ¹⁵⁵ and placebo. Other efficacy trials suggested that overall adverse events are higher with biologic DMARDs than with placebo.

Two trials indicated that a combination treatment of two biologic DMARDs can lead to substantially higher rates of severe adverse events than biologic DMARD monotherapy. The evidence, however, is limited to combinations of anakinra with etanercept, and abatacept with anakinra, adalimumab, etanercept, or infliximab. The strength of the evidence is moderate.

Five long-term extension studies of adalimumab, ¹²⁴ anakinra, ¹²⁹ etanercept, ²⁶⁰ and infliximab ^{149, 261} indicated that the rate of adverse events does not increase over time. The strength of the evidence is moderate. No evidence is available on the long-term tolerability of abatacept and rituximab.

Specific adverse events. The risk for long-term, rare but serious adverse events such as serious infections, malignancies, congestive heart failure, or autoimmunity is a cause of concern for all biologic DMARDs. We could not, however, reliably assess the *comparative* risk among biologic DMARDs for most serious adverse events because of insufficient evidence. A summary of studies assessing specific events can be found below later on in Table 39.

Cardiovascular and cerebrovascular events. No studies compared the risk of cardiovascular or cerebrovascular events with one biologic DMARD to another. Studies assessing class effects or individual biologic DMARDs provide mixed results. For example, one observational study reported lower rates of congestive heart failure.²⁶² for RA patients on anti-tumor necrosis factor (TNF) therapy than for those on conventional RA therapies. This study is contrasted by three other cohort studies that found an increased risk of heart failure with adalimumab, etanercept, and infliximab compared with no treatment or oral DMARD.²⁶³⁻²⁶⁵ Three observational studies assessed the risk of broadly defined cardiovascular events.^{215, 216, 266} One study found no statistically significant association between use of biologic DMARDs and cardiovascular events, while two studies reported a decreased risk of cardiovascular events with biologic DMARDs.^{215, 266} One nested case-control study found a slight decrease in the risk of stroke with adalimumab, etanercept, and infliximab (OR, 0.79; 95% CI, 0.34 to 1.82; *P*=NS),²¹⁴ and two cohort studies found no statistically significant differences in the risk of myocardial infarction (MI) (although results trended towards an increased risk of MI for these biologic DMARDs).^{234, 267}

Infection. The best comparative evidence for risk of infection stems from an RCT⁶⁶ and two prospective cohort studies. ^{268, 269} The trial abatacept plus MTX with infliximab plus MTX and reported that serious infections were more common in the infliximab group than the abatacept group (*P*=NR). ⁶⁶ One prospective cohort study suggested that risks do not differ for adalimumab, etanercept, and infliximab. ²⁶⁸ A second cohort study conducted in the British Society for Rheumatology Biologics Register (BSRBR) reported that anti-TNF drugs as a class increased risk of serious infections (HR, 1.2; 95% CI, 1.1 to1.5). ²⁶⁹ No statistically significant difference in

the incidence rate was observed comparing across the individual drugs. Six systematic reviews and meta-analyses have assessed serious adverse events with biologic DMARDs, with some showing elevated risk of infection for biologic DMARDs. ^{126, 183, 255, 270-272} Some of these analyses provide drug-specific effect size estimates that trended to be higher than for some drugs, although none of these analyses provide adjusted indirect comparisons or mixed treatment comparisons to adequately compare risk of infection among biologic DMARDs. Long-term observational studies generally support an increased risk of infection with biologic DMARDs, although not in across all studies. ^{158, 218, 222, 223, 226, 240, 273-279} Numerous studies suggest that biologic DMARDs have increased risk of tuberculosis (TB) or granulomatous infections, ^{219, 279-287} with one study indicating the risk may be higher for adalimumab and infliximab compared with etanercept. ²⁷⁹ Two studies indicated that the general risk of biologic DMARDs for serious infections is dose dependent. The evidence, however, is limited to adalimumab²⁷¹ and infliximab. ¹⁵⁵ The strength of comparative evidence is low, and the strength of general evidence of infection is moderate.

Infusion and injection site reactions. In efficacy studies, infusion reactions (abatacept, infliximab, rituximab, tocilizumab) and injection site reactions (adalimumab, anakinra, certolizumab, etanercept, golimumab) were the two most commonly and consistently reported adverse events. Overall, 0.5 percent of patients treated with infliximab had severe acute reactions that resembled acute anaphylactic conditions or led to convulsions. Fatal infusion reactions have also occurred with rituximab. Of existing comparative evidence, reactions with infliximab were reported more commonly than with other biologic DMARDs in an RCT comparing abatacept and infliximab, and in a retrospective cohort study comparing adalimumab, etanercept, and infliximab. A systematic review reported that the mean, crude incidence rates of injection site reactions in RCTs and observational studies were 17.5 percent (95% CI, 7.1 to 27.9) for adalimumab, 22.4 percent (95% CI, 8.5 to 36.3) for etanercept, and 67.2 percent (95% CI, 38.7 to 95.7) for anakinra.

Interstitial lung disease. Only one study assessed the risk of interstitial lung disease with biologic DMARDs. This prospective cohort study found that current treatment with etanercept and infliximab was not associated with hospitalization for interstitial lung disease. However, past treatment with etanercept (HR, 1.7; 95% CI, 1.0 to 3.0; P=0.056) and infliximab (HR, 2.1; 95% CI, 1.1 to 3.8; P=0.019) was associated with hospitalization for interstitial lung disease. P=0.019

Malignancies. Data from controlled trials do not provide sufficient evidence concerning an increase in the risk of cancer attributable to the use of either biologic DMARDs or a combination of biologic and oral DMARDs. In a large prospective cohort study the risk of lymphoma was higher for patients on anti-TNF therapies than for those on oral DMARDs, although not statistically significantly so (standardized incidence ratio: MTX, 1.7 (95% CI, 0.9 to 3.2); infliximab, 2.6 (95% CI, 1.4 to 4.5); and etanercept, 3.8 (95% CI, 1.9 to 7.5). ²⁸⁹ An update of this analysis with additional patients and follow-up time confirmed that the risk of lymphoma was not increased among patients taking adalimumab, etanercept, and infliximab. ²⁹⁰ Similarly, three retrospective cohort studies did not detect any differences in the risks of lymphoma between patients on anti-TNF treatment and those on oral DMARDs. ²⁹¹⁻²⁹³ The largest study included 4,160 patients treated with anti-TNF drugs. ²⁹² Results yielded an adjusted relative risk of 1.1 (95% CI, 0.6 to 2.1) for anti-TNF patients relative to patients on oral DMARDs. Four metanalyses have evaluated risk of overall malignancy with anti-TNF drugs. ^{183, 255, 271, 294} Effect size estimates were not statistically significant in three of these analyses, but one fair-rated metanalysis reported a pooled odds ratio for malignancies of 3.3 (95% CI, 1.2 to 9.1). Five large

cohort studies do not suggest a statistically significant increase in risk of malignancy. ^{276, 293, 295-297} The strength of the evidence is low.

Other adverse events. Evidence from randomized trials and observational studies is insufficient to draw conclusions regarding the comparative risk of rare but serious adverse events such as demyelination, autoimmunity, pancytopenia, and hepatotoxicity. Reports based on data from the FDA's Adverse Events Reporting System (AERS) indicated that adalimumab, etanercept, and infliximab might be associated with demyelination. Similar cases have been seen in regulatory trials of adalimumab. Reports of autoimmunity have not been confirmed in controlled trials and observational studies. However, case reports suggest an association between infliximab and drug-induced lupus and other autoimmune diseases. Lupus-like syndromes have also been reported for adalimumab.

Hepatotoxicity has been reported for infliximab.³⁰¹ One study also reported elevated liver enzymes in patients treated with tocilizumab.¹⁷⁴

A prospective cohort study indicated that patients on anti-TNF treatments were more likely to develop dermatological conditions (skin infections, eczema, drug-related eruptions). Another retrospective cohort study found no overall association of anti-TNF drugs with risk of psoriasis. Among the three biologic DMARDs included, adalimumab had a significantly increased risk of psoriasis compared with those treated with etanercept (incidence rate ratio [IRR], 4.6; 95% CI, 1.7 to 12.1) and infliximab (IRR, 3.5; 95% CI, 1.3 to 9.3).

One cross-sectional analysis of data from 7,243 patients reported a small elevated risk of sinus problems with etanercept (OR, 1.21; 95% CI, 1.02 to 1.42). No statistically significant increased risk of sinus problems was observed with adalimumab (OR, 1.09; 95% CI, 0.79 to 1.51) or infliximab (OR, 1.00; 95% CI, 0.88 to 1.15).

Adherence. Few efficacy studies reported rates of adherence. Results of efficacy trials do not indicate any differences in adherence among drug therapies used to treat RA. However, the quality of reporting and assessment of adherence was limited.

Findings from highly controlled efficacy studies may have limited generalizability to "real world" practice, especially because of the overall short duration of these trials. The evidence is insufficient to draw any conclusions about adherence from effectiveness studies.

For the comparison of one biologic DMARD with another, five observational studies provided mixed results. A review of a large, managed care database suggested that infliximab might have greater adherence than etanercept or MTX. This finding is supported by a second analysis that found greater adherence with infliximab compared with etanercept and anakinra. In contrast, two prospective cohort studies found that etanercept had better adherence than infliximab. One of these studies suggested that etanercept had a better response rate than infliximab attributable to greater adherence. Another prospective cohort study failed to find any differences in adherence between etanercept and infliximab. Overall strength of evidence is low or insufficient for adherence.

Detailed Analysis

Tables 37 to 56 provide information on harms, divided into separate sections for the three main categories of drugs covered in this review. In each section, we cover overall tolerability and then specific adverse events. When sufficient data are available, we break out specific events by type (e.g., hepatic, infection, etc). The overall tolerability section for biologic DMARDs is divided further to present results of quantitative analyses.

Corticosteroids: overall tolerability. Corticosteroids are associated with several well-known side effects (noted already in Tables 38 to 40). The prescription information for long-term use of corticosteroids highlights precautions including osteoporosis with secondary fractures, infection, glucose intolerance, peptic ulcer disease, gastrointestinal bleeding, cataracts, and glaucoma. ³⁰⁸⁻³¹²

Comparatively, the tolerability for corticosteroids appears to be similar among different corticosteroids, although the information is limited by short study duration and the fact that only one comparative study is available (Table 37). This head-to-head RCT, described more in detail for KQ 1, compared budesonide (3 mg/day), high-dose budesonide (9 mg/day), prednisolone (7.5 mg/day), and placebo over 12 weeks. Overall rates of adverse events were similar among groups (89 percent, 3 mg/day budesonide; 94 percent, 9 mg/day budesonide; 85 percent, prednisone; 90 percent, placebo; P=NR). Few adverse events caused patients to discontinue the drug; gastrointestinal symptoms, heart symptoms, and mood swings or insomnia were similar in all patient groups (P=NR).

Table 37. Overall tolerability in patients with rheumatoid arthritis treated with corticosteroids

Study	Study Design N Duration	Study Population	Drug	Results	Quality Rating
Kirwan et	RCT	Active RA	BUD	Similar in all groups	Fair
al., 2004 ⁵⁴	143		PNL		
	12 weeks				
Saag et al., 1994 ³¹³	Retrospective cohort	RA patients on low-dose	PRED No PRED	PRED 10 mg to 15 mg/day most related to development of AE (OR,	Fair
	224	PRED (15 mg/day or		32.3; 95% CI, 4.6 to 220)	
	≥1 year	less)		PRED 5 mg to 10 mg/day (OR, 4.5; 95% CI, 2.1 to 9.6)	
				No increase in AE for PRED<5 mg/day	
				Fracture: OR, 3.9 (95% CI, 0.8 to 18.1; <i>P</i> <0.09)	
				First infection: OR, 8.0 (95% CI, 1.0 to 64.0; <i>P</i> <0.05)	
				First GI event: OR, 3.3 (95% CI, 0.9 to 12.1; <i>P</i> <0.07)	

AE = adverse event; BUD = budesonide; CI = confidence interval; DMARD = disease-modifying antirheumatic drugs; GI = gastrointestinal; mg = milligram; HR = hazard ratio; OR = odds ratio; PNL = prednisolone; PRED = prednisone; RA = rheumatoid arthritis; RCT = randomized controlled trial

One retrospective cohort study of 224 RA patients directly assessed the toxicity of low-dose, long-term corticosteroid therapy (mean 4.9 years). In three outpatient rheumatology clinics, 112 patients on low-dose prednisone (<15 mg/day) for more than 1 year were matched with 112 patients not using prednisone. Investigators abstracted records from the date of prednisone initiation to the date of a predetermined adverse event (fracture, avascular necrosis of bone, new onset diabetes or diabetes out of control, infection requiring hospital or surgical intervention, herpes zoster, MI, cerebrovascular event, gastrointestinal (GI) bleeding or peptic ulcer disease, cataracts, glaucoma, and death). Low-dose and high-dose long-term prednisone use (>5 mg/day) was correlated with dose-dependent specific adverse events (adverse event at 10 to 15 mg/day):

OR, 32.3; 95% CI, 4.6 to 220; P=0.0004; adverse event at 5 to 10 mg/day: OR, 4.5; 95% CI, 2.1 to 9.6; P=0.0001; and adverse event at 0 to 4 mg/day: OR, 1.9; 95% CI, 0.8 to 4.7; P=0.15). Patients on long-term prednisone (any dose) were at higher risk for fracture (OR, 3.9; 95% CI, 0.8 to 18.1; P<0.09), infection (OR, 8.0; 95% CI, 1.0 to 64; P<0.09) and GI event (OR, 3.3; 95% CI, 0.9 to 12.1; P<0.07) than were those on shorter-term prednisone use.

Corticosteroids—specific adverse events. We found no comparative study of corticosteroids directly assessing specific serious adverse events. Sixteen studies assessed single agents or class effects of corticosteroids, and these studies are highlighted here for cardiovascular and cerebrovascular events (Table 38), infection (Table 39), and other specific events (Table 40).

Cardiovascular and cerebrovascular events. Four observational studies 214-216, 234 and one RCT⁶⁴ provide mixed evidence that corticosteroid treatment in patients with RA increases risk of cardiovascular events, and possibly cerebrovascular events (Table 38). Of the studies of cardiovascular outcomes, one fair-rated cross-sectional analysis of 4,363 patients with RA sampled from 15 countries reported a small reduction in risk of cardiovascular morbidity (HR, 0.95; 95% CI, 0.92 to 0.98). ²¹⁵ Three studies reported an increased risk of cardiovascular events. 64, 216, 234 A fair-rated RCT of patients with early RA reported that prednisolone was associated with an increased risk of developing hypertension (OR, 2.16; 95% CI, 1.07 to 4.36).⁶⁴ A fair-rated nested-case control study of Pennsylvania Medicare enrollees with RA found a glucocorticoid-related increased risk of cardiovascular events (OR, 1.5; 95% CI, 1.1 to 2.1), 216 and a fair-rated retrospective cohort study of U.S. commercially insured patients found that glucocorticoid use was associated with small increased risk of acute MI (RR, 1.32; 95% CI, 1.02 to 1.72). ²³⁴ Only one study assessed cerebrovascular outcomes; this nested case-control study from the National Data Bank for Rheumatic Diseases (NDB) study found a statistically nonsignificant increased risk of ischemic stroke with prednisolone treatment (OR, 1.75; 95% CI, 0.87 to 3.53).

Infection. Nine observational studies (Table 39) provide consistent evidence that corticosteroid use in patients with RA is associated with an increased risk of infection, including infections like TB and herpes zoster. These studies represent large treated populations with RA, varying in setting from U.S. commercially insured populations, Medicare patients in a single U.S. state, a U.S. registry, and populations in the UK and Canada. A risk of serious bacterial infection was shown in five fair-quality studies and one good-quality study. One fair-224 and one good-rated study demonstrated an increased risk of herpes zoster infection with corticosteroids, and one fair-rated study demonstrated an increased risk of TB with corticosteroids. Across all of these studies of patients with RA (regardless of type of infection), the risk of infection increased by approximately 50 percent to 150 percent with use of corticosteroids.

Table 38. Cardiovascular and cerebrovascular events in patients with rheumatoid arthritis treated with corticosteroids

Study	Study Design N Duration	Study Population	Drug	Results	Quality Rating
Cardiovascula	r and Cerebrovascul	lar Events			
*Choy et al.,	RCT	Pts with	MTX+PNL	The number need to harm (NNH) with	Fair
2008 ⁶⁴ CARDERA	467	early, active RA		added PNL for any adverse event leading to withdrawal was 14 (95% CI, 6 to 65).	
trial	2 years			PNL use associated with hypertension (OR, 2.16; 95% CI, 1.07 to 4.36).	
*Nadareishvili	Nested case-control		PRED	Association of PRED therapy with	Fair
et al., 2008 ²¹⁴	269 cases among 7,045 patients	National Data Bank for		ischemic stroke: OR,1.75; 95% CI, 0.87 to 3.53; <i>P</i> =0.114)	
	8 years	Rheumatic Diseases			
	Cross-sectional	Sample of	Glucocortic oids	Glucocorticoids associated with reduced risk for CV morbidity (HR, 0.95; 95% CI, 0.92 to 0.98).	Fair
2008 ²¹⁵	4,363	RA pts across 15			
	Clinician and patient recall	countries		,	
*Solomon et al., 2006 ²¹⁶	Nested case-control study	Medicare	Glucocortic oids	Glucocorticoid monotherapy associated with increased risk for cardiovascular	Fair
	3,501	enrollees with RA		events (OR, 1.5; 95% CI, 1.1 to 2.1).	
	24 months				
*Suissa et al, 2006 ²³⁴	Retrospective cohort	RA pts from PharMetrics	Glucocortic oids	Glucocorticoid use associated with acute MI (RR,1.32; 95% CI, 1.02 to	Fair
	107,908	data (US)		1.72)	
	14 months				

^{*} New study added since last review.

AE = adverse event; BUD = budesonide; CI = confidence interval; CV = cardiovascular; DMARD = disease-modifying antirheumatic drugs; GI = gastrointestinal; mg = milligram; HR = hazard ratio; MI = myocardial infarction; MTX = methotrexate; NNH = number needed to harm; OR = odds ratio; PNL = prednisolone; PRED = prednisone; RA = rheumatoid arthritis; RCT = randomized controlled trial

Table 39. Infection in patients with rheumatoid arthritis treated with corticosteroids

Study	Study Design N Duration	Study Population	Drug	Results	Quality Rating
*Bernatsky et	Nested case-	RA pts	Glucocorticoids	The risk for all infections	Fair
al., 2007 ²¹⁸	control 23,733	registered in claims		requiring hospitalization was most elevated with	
		databases in		glucocorticoid agents (RR, 2.6;	
	Up to 23 years	Quebec		95% CI, 2.3 to 2.9); Similar effects were seen with pneumonia as the outcome	
*Brassard et	Retrospective	RA pts from	Several oral	(RR, 2.1; 95% CI, 2.4 to 3.1). Adjusted rate ratio of developing	Fair
al., 2006 ²¹⁹	cohort study	PharMetrics	DMARDs,	TB with corticosteroids: 1.7	
	112,300	data (U.S.)	biologic DMARDs,	(95% CI, 1.3 to 2.2).	
	Up to 5 years		corticosteroids		
Doran et al., 2002 ²²⁰	Retrospective cohort	RA patients	Several oral DMARDs,	In patients hospitalized for infection, corticosteroid use	Fair
2002	609		corticosteroids	increased risk (HR, 1.56; 95% CI, 1.20 to 2.04)	
	39 years				
*Lacaille et al., 2008 ²²¹	Retrospective cohort	Pts with RA from British	Oral DMARDs, corticosteroids	Adjusted Rate Ratio for serious infections:	Fair
	27,710	Columbia, Canada		DMARDs+corticosteroids:1.63 (95% CI, 1.5 to 1.77);	
	162,720 person years			corticosteroids alone: 1.9 (95% CI, 1.75 to 2.05)	
Greenberg et	Prospective	Pts with RA	MTX, oral	Adjusted incidence rate ratio of	Fair
al., 2010 ²²⁶	cohort	enrolled in the Consortium of	DMARDs, anti- TNF agents,	infection and opportunistic infection for PRED compared	
CORRONA	7,971	Rheumatology Researchers of North America	f	with oral DMARDs, respectively:	
	15,047 person- years			IRR 1.05 (0.97-1.15, <i>P</i> =0.251); IRR 1.63 (1.20-2.21, <i>P</i> =0.002)	
		(CORRONA) registry		PRED above 10 mg daily associated with risk of infection (IRR 1.30, 95% 1.11-1.53, <i>P</i> =0.001)	
*Schneeweiss et al., 2007 ²²²	Retrospective cohort	Medicare beneficiaries	Glucocorticoids	Compared with MTX use, glucocorticoid use associated	Fair
	15,597	ages 65 and older with RA		with serious bacterial infections (RR, 2.25; 95% CI, 1.57 to 3.22)	
	Up to 8 years				
*Smitten et al., 2008 ²²³	Retrospective cohort	RA pts from PharMetrics	Corticosteroids	Oral corticosteroid use increased risk of hospitalized	Good
	24,530	data (U.S.)		infection (RR, 1.92; 95% CI, 1.67 to 2.21). Risk increased	
*Smitten et al., 2007 ²²⁴	26.6 months Retrospective cohort	RA pts from PM database	Corticosteroids	with dose. Risk of herpes zoster infection with corticosteroids only:	Fair
	12,272 (PM) 38,621 (GPRD)	and UK GPRD		(PM: OR, 2.51; 95% CI, 2.05 to 3.06 GPRD: 1.46; 95% CI, 1.24 to 1.70)	
	12.3 to 38.8 months			-,	

Table 39. Infection in patients with rheumatoid arthritis treated with corticosteroids

	Study Design					
	N	Study	_		Quality	
Study	Duration	Population	Drug	Results	Rating	
*Strangfeld et	Prospective	RA pts	Glucocorticoids	Adjusted HR for herpes zoster.	Good	
al., 2009 ²²⁵	cohort	initiating		Glucocorticoids 1 mg to 9 mg		
	5.040	biologic		(HR, 1.86; 95% CI, 0.92 to		
	5,040	therapy or		3.78); Glucocorticoids 10+mg		
	up to 36	switching to		(HR, 2.52; 95% CI, 1.12 to 5.65)		
	months	another		,		
		DMARD				

^{*} New study added since last review.

AE = adverse event; BUD = budesonide; CI = confidence interval; DMARD = disease-modifying antirheumatic drugs; GI = gastrointestinal; GPRD = General Practice Research Database; mg = milligram; HR = hazard ratio; MTX = methotrexate; OR = odds ratio; PM = Pharmetrics; PNL = prednisolone; PRED = prednisone; RA = rheumatoid arthritis; RCT = randomized controlled trial; RR = relative risk; TB = tuberculosis

Other adverse events. Three additional observational studies assessed the risk of specific adverse events with corticosteroid treatment in patients with RA; one of septic (infectious) arthritis;²²⁷ one of sinus problems;²⁴⁴ and one of interstitial lung disease (Table 40).²²⁸ A large fair-rated retrospective cohort study found that prednisolone was associated with roughly a threefold increased risk of developing septic (infectious) arthritis compared with those not receiving any DMARD (IRR, 2.94; 95% CI, 1.93 to 4.46).²²⁷ A cross-sectional analysis of 6-month questionnaires from 7,243 patients enrolled in the NDB study found that prednisone use was not associated with an increased risk of sinus problems.²⁴⁴ Analysis of a larger group of patients from the NDB study (n=17,598) found that current and past prednisone use was associated with hospitalization for interstitial lung disease (respectively, HR, 2.5; 95% CI, 1.5 to 4.1, *P*<0.001, and HR, 3.0; 95% CI, 1.0 to 8.9, *P*=0.044).²²⁸

Oral DMARDs: overall tolerability. MTX, sulfasalazine, hydroxychloroquine and leflunomide all can produce several well-known, and similar, reactions. Frequently reported adverse reactions for these drugs found in package inserts include the following:

- MTX: ulcerative stomatitis, nausea and abdominal distress, fatigue, chills and fever, dizziness, leukopenia, and decreased resistance to infection;³¹⁴
- Sulfasalazine: stomatitis, nausea, dyspepsia, rash, headache, abdominal pain or vomiting, fever, dizziness, pruritus, and abnormal liver function tests;³¹⁵
- Hydroxychloroquine: dizziness, headache, abdominal pain/nausea/vomiting/diarrhea, pruritus, weight loss, hair bleaching, and alopecia;³¹⁶ and
- Leflunomide: diarrhea, rash, elevated liver enzymes, and alopecia. 317

Table 40. Other specific harms in patients with rheumatoid arthritis treated with corticosteroids

Study	Study Design N Duration	Study Population	Drug	Results	Quality Rating
*Edwards et al., 2007 ²²⁷	Retrospective cohort	RA pts (n=34,250)	Several oral DMARDs,	PNL (adjusted IRR, 2.94; 95% CI, 1.93 to 4.46, <i>P</i> <0.001) was associated	Fair
	136,997		PNL	with an increased incidence of septic arthritis when compared with those	
	15 years			not receiving any DMARD.	
*Michaud and Wolfe, 2006 ²⁴⁴	Cross-sectional analysis from prospective cohort	RA pts enrolled in the NDB study	PRED	Association of PRED treatment with visits to physician for sinus problems was OR,0.98; 95% CI, 0.86 to 1.11; <i>P</i> =0.776).	Fair
	7,243				
	Questionnaire in Dec 2003 related to previous 6 months				
*Wolfe et al., 2007 ²²⁸	Prospective cohort	RA pts in the NDB	PRED	Current treatment with PRED associated with hospitalization for	Fair
	17,598			interstitial lung disease (HR, 2.5; 95% CI, 1.5 to 4.1, <i>P</i> <0.001). Past	
	Up to 3.5 years			treatment with PRED was also associated with hospitalization for interstitial lung disease (HR, 3.0; 95% CI, 1.0 to 8.9, <i>P</i> =0.044)	

^{*} New study added since last review.

AE = adverse event; BUD = budesonide; CI = confidence interval; DMARD = disease-modifying antirheumatic drugs; GI = gastrointestinal; mg = milligram; HR = hazard ratio; NDB = National Data Bank for Rheumatic Diseases; OR = odds ratio; PNL = prednisolone; PRED = prednisone; RA = rheumatoid arthritis; RCT = randomized controlled trial

Tables 41 to 47 describe studies providing information on tolerability and various adverse events. Studies reporting overall tolerability of oral DMARDs and oral DMARD combinations are summarized in Table 41. For monotherapy with oral DMARDs, three trials^{56, 104, 105, 107, 108} and a meta-analysis with up to 2 years of data,⁵⁵ all described in more detail for KQ 1, indicated similar levels of general tolerability among leflunomide, MTX, and sulfasalazine, including similar discontinuation rates and frequency of serious adverse events. A retrospective cohort study found leflunomide given as monotherapy or in combination with MTX had fewer adverse event reports than MTX alone or other oral DMARDs.²²⁹ However, another meta-analysis of withdrawal rates from 71 RCTs and 88 observational studies, which included data up to 5 years, found that patients with RA stayed on MTX significantly longer than on either sulfasalazine or hydroxychloroquine.²³⁰ At 5 years, 36 percent of patients had remained on MTX to continue their treatment; 22 percent had remained on sulfasalazine. Patients on sulfasalazine were more likely to have withdrawn from medication because of toxicity than those on MTX (52 percent vs. 35 percent; RR, 1.68; *P*<0.0001). Withdrawal rates were not found to differ between samples reported in observational studies and RCTs.

Table 41. Overall tolerability in patients with rheumatoid arthritis treated with oral DMARDs

Study	Study Design N Duration	Study Population	Drug	Results	Quality Rating
Oral DMAR	Ds				
Cannon et al., 2004 ²²⁹	Retrospective cohort 40,594	RA pts	, ,	AE rates in LEF and LEF+MTX were lower than or similar to AE	Fair
	2 years (claims database)			rates for MTX and other DMARDs	
Emery et	RCT	RA 4 months to	LEF, MTX	Frequency of SAEs similar	Fair
al., 2000 ¹⁰⁵	999	10 years		between groups	
	1 year with optional 2nd year				
Maetzel et al., 2000 ²³⁰	Meta-analysis (RCT and observational)	RA pt studies including withdrawal	MTX, SSZ, HCQ (and gold)	Withdrawals due to toxicity for 5 years: MTX 35%, SSZ 52%	Fair
	159 studies MTX=2,875 SSZ=1,418	information		Pts treated with SSZ were 1.68 times more likely to fail therapy due to toxicity than MTX (RR, 1.68; <i>P</i> <0.0001)	
	5 years				
*Osiri et al., 2009 ⁵⁵	Systematic review and meta-analysis	Active RA		Withdrawals due to adverse events were 10% (95%CI: 6-15%) greater with leflunomide than placebo. NNH: 10 (7 to 17)	Good
	6 studies 1,220 patients				
	Mixed duration			Adverse events and withdrawal rates simiar for LEF, SSZ, and MTX	
Smolen et	RCT	Active RA	LEF, SSZ	Withdrawal due to AEs 14% vs.	Fair
al., 1999 ^{107,}	358			19%	
	24 weeks				
Strand, et	RCT	RA for at least 6	LEF, MTX	AEs constant over time for LEF	Fair
al., 1999 ^{56,}	482	months, MTX- naive		and MTX	
	12 months (1 year continuation)	naive		12 months: Higher discontinuation rate for LEF (22% vs. 10.4%, <i>P</i> =NR)	
Oral DMAR	D Combinations				
Boer et al.,	RCT	Early RA,	PNL	Lower withdrawal rate due to	Fair
1997 ⁹⁵ COBRA	155	DMARD naive	taper+MTX+SSZ vs. SSZ	AEs (2.6% vs. 7.6%, <i>P</i> =NR)	
study	56 weeks		332		
Capell et	RCT	Active RA	SSZ+MTX vs. SSZ	Similar withdrawal rate due to	Fair
al., 2006 ⁵⁹	165 (Phase 1 run-in: 687)		or MTX	AEs	
	6 months (18 months for those with DAS ≥2.4 at 6 months)				

Table 41. Overall tolerability in patients with rheumatoid arthritis treated with oral DMARDs (continued)

Study	Study Design N Duration	Study Population	Drug	Results	Quality Rating
Dougados et al.,	RCT	DMARD naive, early RA	SSZ +MTX vs. SSZ or MTX	Discontinuation rate due to AEs similar among groups	Fair
1999 ⁵⁷	209 (146) 52 weeks (5-year followup)	,		AEs higher in SSZ+MTX vs. SSZ vs. MTX (91% vs. 75% vs. 75%, <i>P</i> =0.025)	
*Goekoop- Ruiterman et al., 2005 ^{100-102,} 196 BeSt study	RCT 508 12 months	Early RA	Sequential monotherapy (starting with MTX) vs. step-up combination therapy (MTX, then SSZ, then HCQ, then PRED) vs. combination (MTX,	No significant differences in serious AEs in all groups	Good
			SSZ, tapered high- dose PRED) vs. combination with INF (3 mg/kg – could be titrated to 10 mg/kg based on DAS)		
Haagsma et al.,	RCT 105	DMARD naive, early RA	SSZ+MTX vs. SSZ or MTX	r No significant difference in number of withdrawals due to	Fair
1997 ⁵⁸	52 weeks			AEs	
Korpela et	RCT	Early RA	MTX+HCO+SS7+PN	Frequency of serious AEs similar	Fair
al., 1999 ⁹⁸	199	Lany . u .	L vs. DMARD ± PNL		
FIN-RACo study	24 months			Discontinuation due to AEs similar in both groups	
	Retrospective cohort	RA Pts	MTX vs. MTX	Use of GC significantly increased	Fair
et al., 2008 ²³³	154		+glucocorticoids vs. HCQ vs.	the time until withdrawal of DMARD therapy due to AE (18.6	
	2-62 months		HCQ+glucocorti- coids	\pm 2.3 months; P <0.05) compared with no use of GC (12.5 \pm 1.4 months)	
O'Dell et	Prospective cohort	Active RA,	ETA +SSZ vs.	Similar discontinuation rates due	Fair
al., 2006 ²³¹	119	previous use of DMARDs	ETA+HCQ	to AEs	
	48 weeks				
O'Dell et	RCT	RA pts not	MTX+SSZ+HCQ vs.	Similar withdrawal rate due to	Good
al., 2002 ⁶¹	171	previously treated with	MTX+HCQ vs. MTX+SSZ	AEs across groups	
	2 years	combination drugs			
O'Dell et	RCT	RA and poor		Similar withdrawal rate due to	Good
al., 1996 ⁶²	102	response to at least 1 DMARD	MTX vs. SSZ+HCQ	AEs across groups	

Table 41. Overall tolerability in patients with rheumatoid arthritis treated with oral DMARDs (continued)

Study	Study Design N Duration	Study Population	Drug	Results	Quality Rating
*Osiri et al., 2009 ⁵⁵	Systematic review and meta-analysis	Active RA	LEF+ MTX, MTX	Adverse events reported more frequently for LEF+ MTX than MTX. Withdrawal rates similar with	Good
	6 studies 1,220 patients			LEF+MTX vs. MTX	
	Mixed duration				
*Schipper et al., 2009 ²³²	Systematic review 515 24 to 52 weeks	- I	MTX+SSZ vs. MTX vs. SSZ	Pts naïve to MTZ or SSZ on combination therapy experienced significantly more nausea. Those on MTX+SSZ	Fair
				who previously failed SSZ had comparable tolerability	
*Schipper et al.,	Nonrandomized inception cohort	RA pts that had failed SSZ	SSZ+MTX vs. MTX switch	Rate of discontinuation significantly lower in MTX vs.	Fair
2009 110	230	treatment		SSZ+MTX group (<i>P</i> =0.01) Relative hazard to stop DMARD within 1 year in SSZ+MTX group vs. MTX group: 1.7 (95% CI, 1.11 to 2.46, <i>P</i> <0.01)	
	52 weeks				
	t Open-label RCT	Early RA	DMARD+PNL vs.	Similar number of	Fair
al., 2005 ⁶⁵	250		DMARD	discontinuations between groups	
	2 years				
Svensson e	t Open-label RCT	Early RA	MTX+PRED	Lower withdrawal rate due to	Fair
al., 2003 ³¹⁸	245		SSZ+PRED	AEs or inefficacy for PRED+MTX group vs. PRED+SSZ group (11.5% vs. 33.3%, <i>P</i> =0.0005)	
	2 years				

^{*} New study added since last review.

AEs = adverse events; CI = confidence interval; DMARD = disease-modifying antirheumatic drug; GC = glucocorticoids; hydroxychloroquine; HR = hazard ratio; LEF = leflunomide; MTX = methotrexate; OR = odds ratio; PNL = prednisolone; PRED = prednisone; Pts = patients; RA = rheumatoid arthritis; RCT = randomized controlled trial; RR = relative risk; SAEs = serious adverse events; SSZ = sulfasalazine

For combination therapies, eight studies of DMARD combinations (one up to 5 years⁵⁷) included MTX, sulfasalazine, hydroxychloroquine, and etanercept (described in detail under KQ 1). They generally had similar withdrawal rates attributed to adverse events.^{55, 57-59, 61, 62, 110, 231, 232} One nonrandomized inception cohort fournd higher disciontinuation rates for sulfasalazine plus MTX compared with MTX monotherapy (*P*=0.01).¹¹⁰ In two RCTs, discontinuation rates were similar, but rates of adverse events were higher for sulfasalazine plus MTX vs. MTX monotherapy (adverse events for combination therapy range from 53 percent to 91 percent; adverse events for monotherapy range from 50 percent to 75 percent).^{57, 58} Side effects included nausea, erythema, and elevated transaminases. One systematic review of leflunomide plus MTX vs. MTX monotherapy found increased frequency of adverse event reports with combination therapy.⁵⁵ Three RCTs of combination therapy including prednisone with one or more DMARDs (described in detail in KQ 1) showed similar discontinuation rates between groups.^{65, 98, 100} One open-label RCT of 155 patients comparing a prednisolone taper plus MTX plus sulfasalazine actually had a lower withdrawal rate because of adverse events than sulfasalazine only (2.6

percent vs. 7.6 percent, P=NR). Another open-label RCT of 245 patients found the withdrawal rate for adverse events to be lower in the prednisone plus MTX group than in the prednisone plus sulfasalazine group (11.5 percent vs. 33.3 percent, P=0.0005). A retrospective cohort study of 154 patients found that addition of a glucocorticoid to hydroxychloroquine or MTX increased the mean time until withdrawal of DMARD therapy due to adverse events by approximately 6 months (P<0.05). But the prednisone plus MTX patients found that addition of a glucocorticoid to hydroxychloroquine or MTX increased the mean time until withdrawal of DMARD therapy due to adverse events by approximately 6 months (P<0.05).

Oral DMARDs: specific adverse events. Oral DMARDs can produce several serious adverse events. The package inserts for MTX give several warnings.³¹⁴ It has been reported to cause congenital abnormalities. Severe and sometimes fatal bone marrow suppression and gastrointestinal toxicity have been reported with concomitant administration of MTX and nonsteroidal anti-inflammatory drugs (NSAIDs). MTX-induced lung disease can occur with doses as low as 7.5 mg per week. Malignant lymphoma may also occur in patients on low-dose MTX. Severe, occasionally fatal skin reactions have also been reported.

Less common but severe adverse and potentially fatal events for sulfasalazine include blood dyscrasias, hypersensitivity reactions including Stevens-Johnson syndrome, renal and liver damage, irreversible neuromuscular and central nervous system changes, and fibrosing alveolitis. The package insert for hydroxychloroquine describes irreversible retinal damage in some patients on long-term therapy or high dosage. Other serious reactions include blood dyscrasias, seizures, hypersensitivity reactions, and hepatotoxicity. Potentially severe adverse reactions for leflunomide include blood dyscrasias, hepatotoxicity, and hypersensitivity reactions including Stevens-Johnson syndrome. Studies of adverse events with oral DMARDs are summarized in Tables 42 to 47.

Cardiovascular and cerebrovascular events. Four observational studies assessed cardiovascular or cerebrovascular outcomes with oral DMARD treatment (Table 42). 214, 215, 234, 235 All found either a decrease or no difference in risk of these events for patients treated with oral DMARDs compared with no treatment or other comparator treatments.

Two studies found a decreased risk of broadly defined cardiovascular events with oral DMARDs. ^{215, 235} One study, the Quantitative Patient Questionnaires in Standard Monitoring of Patients with Rheumatoid Arthritis (QUEST-RA) project, was a cross-sectional review of 4,363 patient records from 15 countries. ²¹⁵ This fair-rated study reviewed clinical history and surveyed patients for information about cardiovascular events, including MI, angina, coronary disease, coronary bypass surgery, and stroke. Risk of all types of cardiovascular events was reduced among patients taking MTX, leflunomide, and sulfasalazine. The second study was a retrospective chart review of 613 patients from a single rheumatology clinic in the Netherlands. 235 Cardiovascular disease was defined as a verified medical history of coronary, cerebral, or peripheral arterial disease. Regression models considered patients treated with oral DMARD monotherapy, as well as combinations of MTX, hydroxychloroquine, and sulfasalazine. All oral DMARD monotherapy and combinations showed a decreased risk of cardiovascular disease (compared with no oral DMARD), although the risk reduction was only statistically significant for patients ever taking MTX and sulfasalazine (OR, 0.24; 95% CI, 0.07 to 0.85, P<0.05) and MTX, sulfasalazine, and hydroxychloroguine (OR, 0.27; 95% CI, 0.07 to 0.99, *P*<0.05).

Table 42. Cardiovascular and cerebrovascular events in patients with rheumatoid arthritis treated with oral DMARDs

Study	Study Design N Duration	Study Population	Drug	Results	Quality Rating	
*Naranjo et al., 2008 ²¹⁵	Cross-sectional	Sample of RA pts across 15	MTX, LEF, SSZ	MTX, LEF, and SSZ associated with reduced risk	Fair	
,	4,363 Clinician and patient recall	countries		for CV morbidity (HR, 0.85; 95% CI, 0.81 to 0.89; HR, 0.59; 95% CI, 0.43 to 0.79; HR, 0.92; 95% CI, 0.87 to 0.98; respectively).		
*Nadareishvili et al., 2008 ²¹⁴	Nested case- control	RA pts in National Data	MTX	Association of treatment with ischemic stroke:	Fair	
	269 cases among 7045 patients	Bank for Rheumatic Diseases		MTX: OR,0.63; 95% CI, 0.32 to 1.26; <i>P</i> =0.191)		
	8 years					
*Suissa et al, 2006 ²³⁴	Retrospective cohort	RA pts in PharMetrics U.S. data	PharMetrics [Traditional DMARDs	Traditional DMARD use associated with decreased	Fair
	107,908			acute MI: MTX: RR, 0.8; 95% CI, 0.60 to 1.08 LEF: RR, 0.28; 95% CI,0.12 to 0.64		
	14 months					
*van Halm et al., 2006 ²³⁵	Case-control 613	Pts with RA treated in a single clinic in	MTX, HCQ, SSZ, MTX+HCQ, MTX+SSZ,	Cardiovascular events compared with no DMARD treatment:	Fair	
	Eligible diagnosis from 1953-2004	Netherlands	SSZ+HCQ, MTX+HCQ+SSZ	MTX OR:0.47 (95% CI, 0.07 to 3.23), SSZ: 0.31 (95% CI, 0.07 to 1.33), HCQ: 0.45 (95% CI, 0.10 to 2.04), MTX+ SSZ: 0.24 (95% CI, 0.07 to 0.85, P<0.05), MTX+HCQ: 0.54 (95% CI, 0.08 to 3.66), SSZ+ HCQ: 0.34 (95% CI, 0.05 to 2.16), MTX+SSZ+HCQ: 0.27 (95% CI, 0.07 to 0.99, P<0.05)		

^{*} New study added since last review

CV = cardiovascular; CI = confidence interval; DMARD = disease-modifying antirheumatic drug; ETA = etanercept; GI = gastrointestinal; HCQ = hydroxychloroquine; HR = hazard ratio; INF = infliximab; LEF = leflunomide; MTX = methotrexate; OR = odds ratio; Pts = patients; RA = rheumatoid arthritis; RR = rate ratio; SSZ = sulfasalazine

One fair-rated retrospective cohort study of 107,908 commercially insured patients with RA found a decreased risk of acute MI among patients taking MTX (RR, 0.81; 95% CI, 0.60 to 1.08) or leflunomide (RR, 0.28; 95% CI, 0.12 to 0.65). A decreased risk also was observed among a heterogeneous group of "all other traditional DMARDs" (RR, 0.67; 95% CI, 0.46 to 0.97); this group included hydroxychloroquine and sulfasalazine among numerous other agents.

A fair-rated nested case-control study of 7,045 patients with RA from the NDB study found that while overall patients with RA have a significantly increased risk of stroke (OR, for all strokes 1.64; 95% CI, 1.16 to 2.30; OR, for ischemic strokes 2.66; 95% CI, 1.24 to 5.70),

treatment with MTX, hydroxychloroquine, leflunomide, and sulfasalazine does not increase this risk. 214

Hepatic events. Two retrospective cohorts examined hepatic events in patients with rheumatoid arthritis. ^{229, 236} Both studies found similar hepatic event rates for leflunomide and MTX (Table 43).

Table 43. Hepatic events in patients with rheumatoid arthritis treated with oral DMARDs

Study	Study Design N Duration	Study Population	Drug	Results	Quality Rating
Cannon et	Retrospective cohort	RA pts	LEF, MTX, other	Hepatic event:	Fair
al., 2004 ²²⁹	40,594		DMARD	LEF 4.1/1,000 PY, MTX 6.2/1,000 PY,	
	2 years (claims			Other 4.2/1,000 PY, LEF+MTX 4.6/1,000 PY	
	database)			LLI 1011X 4.0/1,0001 1	
Suissa et al., 2004 ²³⁶	2 retrospective cohorts (claims data)	RA diagnosis	LEF, biologics, traditional DMARDs, MTX	Serious hepatic events Fa compared with MTX: LEF rate ratio: 0.9 (95% CI, 0.2 to 4.9), traditional DMARD: 2.3 (95%	Fair
	41,885				
	3 years			CI, 0.8 to 6.5), biologic DMARD: 5.5 (95% CI, 1.2 to 24.6)	

^{*} New study added since last review.

CI = confidence interval; DMARD = disease-modifying antirheumatic drug; LEF = leflunomide; MTX = methotrexate; Pts = patients; PY = person years; RA = rheumatoid arthritis

A 2-year retrospective cohort from a U.S. insurance claims database (N=40,594) examined the incidence rates of serious hepatic events in patients treated with leflunomide, MTX, and other DMARDs (including gold, D-penicillamine, hydroxychloroquine, sulfasalazine, infliximab, and etanercept). The hepatic event rate for leflunomide was similar to that for other DMARDs (leflunomide, 4.1/1,000 person-years [95% CI, 2.4 to 7.0], MTX, 6.2/1,000 person-years [95% CI, 5.1 to 9.3]; other DMARDs, 4.2/1,000 person-years [95% CI, 3.3 to 5.3], *P*=NS, NR).

Another group examined data from claims databases for two retrospective cohorts of 41,885 patients over 3 years for serious hepatic events associated with treatment with leflunomide, MTX, traditional DMARDs (hydroxychloroquine, sulfasalazine, gold, minocycline, penicillamine, chlorambucil, cylcophosphamide and cyclosporine), or biologic DMARDs (infliximab, etanercept). Overall, the rate of serious hepatic events for all drugs was 4.9 per 10,000 patient years. Using MTX as the reference, they observed no higher rates in serious hepatic events for leflunomide (RR, 0.9; 95% CI, 0.2 to 4.9) or for traditional DMARDs (RR, 2.3; 95% CI, 0.8 to 6.5), but they did report higher rates for biologic DMARDs (RR, 5.5; 95% CI, 1.2 to 24.6).

Infection. Mixed evidence from 12 studies suggests that oral DMARDs do not significantly affect risk of infections (Table 44). ^{218, 220, 221, 223, 224, 226, 229, 237-240} A good-rated retrospective cohort study found that some oral DMARDs may decrease risk of infection. ²²³ In this study, 24,530 U.S. commercially insured patients with RA were evaluated for hospitalized infection. A nested case-control analysis was conducted on 1,993 cases of infection and 9,965 controls. The adjusted rate ratio showed a statistically significantly lower rate of infection for MTX- (RR, 0.81; 95% CI, 0.70 to 0.93) and hydroxychloroquine-treated patients (RR, 0.74; 95% CI, 0.62 to 0.89). Risk of infection was not increased with leflunomide (RR, 1.02; 95% CI, 0.79 to 1.32) or sulfasalazine (RR, 0.82; 95% CI, 0.58 to 1.16). In contrast, a fair-rated cohort study from the

Consortium of Rheumatology Research of North America (CORRONA) registry found MTX to be associated with an increased risk of infection (IRR, 1.30; 95% CI, 1.12 to 1.5; *P*<0.001). ²²⁶

Table 44. Infection in patients with rheumatoid arthritis treated with oral DMARDs

Study		Study Population	Drug	Results	Quality Rating
*Bernatsky	Nested case-control	RA pts	Oral DMARDs	Relative risk for infections	Fair
et al., 2007 ²¹⁸	23,733	registered in claims		requiring hospitalization: MTX 1.10 (95% CI, 0.98 to 1.23); all	
2001	Up to 23 years	databases in Quebec	EE1, 110Q, 002	other DMARDs (includes LEF, SSZ) 0.99 (95% CI, 0.84 to 1.16); Antimalarial (includes HCQ) 1.06 (95% CI, 0.92 to 1.22)	
*Brassard et al., 2009 ²³⁸	Retrospective cohort study	RA pts from Quebec	Traditional DMARDs including	Rate ratio of TB associated with any DMARD use: 3.0 (95% CI,	Fair
	24,282		MTX and LEF, corticosteroids	1.6 to 5.8).	
	1980-2003 for cohort and 1992-2003 for TB incidence rates				
*Brassard et al., 2006 ²¹⁹	Retrospective cohort study	the	Several oral DMARDs, biologic	Adjusted rate ratio of developing TB with use of traditional	Fair
	112,300	PharMetrics Patient-Centric	DMARDs, corticosteroids	DMARDs: 1.2 (95% CI, 1.0 to 1.5).	
	Up to 5 years	database		,	
Cannon et	Retrospective cohort	RA pts	LEF, MTX, other	Respiratory infection:	Fair
al., 2004 ²²⁹	40,594		DMARD	LEF 20/1,000 PY, MTX 38.9/1,000 PY, Other 36.9/1,000 PY	
	2 years (claims database)				
Doran et al.,	Retrospective cohort	RA pts	Several oral DMARDs, corticosteroids	Compared with oral DMARDs, corticosteroids increased risk of hospitalized infection (HR, 1.56; 95% CI, 1.20 to 2.04)	Fair
2002 ²²⁰	609				
	39 years				
	Prospective cohort	Pts with RA	MTX, oral	Adjusted incidence rate ratio (IRR) for infections: MTX (IRR, 1.30; 95% CI, 1.12 to 1.50, P<0.001)	Fair
et al., 2010 ²²⁶	7,971 15,047 patient years	enrolled in the Consortium of Rheumatology	DMARDs, anti-TNF agents, PRED		
CORRONA	10,071 panoin yeals	Researchers of North America (CORRONA) registry		Adjusted incidence rate ratio (IRR) for opportunistic infections: MTX (IRR, 0.93; 95% CI, 0.54 to 1.60, <i>P</i> =0.781)	
*Grijalva et	Prospective cohort	Tennesee	MTX, LEF, SSZ,	Compared with MTX; LEF, SSZ	Good
al., 2010 ²⁴⁰	28,906	Medicaid- enrolled RA pts	HCQ, biologic DMARDs,	or HCQ did not increase risks of hospitalizations due to	
	3 years	initiating DMARD use	glucocorticoids	pneumonia or serious infections	
*Lacaille et	Retrospective cohort		Oral DMARDs,	Adjusted rate ratio for serious	Fair
al., 2008 ²²¹	27,710	from British Columbia,	corticosteroids	infections: DMARDs+corticosteroids:1.63 (95% CI, 1.5 to 1.77); DMARDs alone: 0.92 (95% CI, 0.85 to 1.0)	
	162,720 person years	Canada			

Table 44. Infection in patients with rheumatoid arthritis treated with oral DMARDs (continued)

Study	Study Design N Duration	Study Population	Drug	Results	Quality Rating
*McDonald	Retrospective cohort		Traditional	No increased risk of infection with	Fair
et al., 2009 ²³⁹	20,357	the Veterans Affairs health	DMARDs	oral DMARDs; SSZ associated with a lower risk of herpes zoster	
	7 years	care system		infection (HR, 0.44; 95% CI, 0.21 to 0.91)	
*Smitten et	Retrospective cohort		MTX, LEF, HCQ,	MTX and HCQ decreased risk of hospitalized infection (RR, 0.81; 95% CI, 0.70 to 0.93; RR, 0.74;	Good
al., 2008 ²²³	24,530	from U.S. PharMetrics	SSZ		
	26.6 months	data		95% CI, 0.62 to 0.89; respectively).	
*Smitten et al., 2007 ²²⁴	Retrospective cohort	PM database	Corticosteroids, traditional	Risk of herpes zoster infection with traditional DMARDs alone	Fair
	12,272 (PM) 38,621 (GPRD)	and UK GPRD	RD DMARDs, biologic DMARDs	(PM: OR,1.37; 95% CI, 1.18 to 1.59; GPRD, 1.27; 95% CI, 1.10 to 1.48)	
	12.3 to 38.8 months			.,	
Wolfe et al.,	Prospective cohort	RA diagnosis	PRED, LEF, SSZ,	Risk for hospitalization for	Fair
2006 ²³⁷	16,788		MTX, ETA, INF, ADA	pneumonia: PRED HR, 1.7 (95% CI, 1.5 to 2.1), LEF HR, 1.3 (95%	
	3.5 years			CI, 1.0 to 1.5). No significant differences for SSZ, MTX	

^{*} New study added since last review.

ADA = adalimumab; AERS = adverse events reporting system; CI = confidence interval; DMARD = disease-modifying antirheumatic drug; ETA = etanercept; GI = gastrointestinal; GPRD = General Practict Research Database; HCQ = hydroxychloroquine; HR = hazard ratio; INF = infliximab; LEF = leflunomide; MTX = methotrexate; N/A = not applicable; NR = not reported; OR = odds ratio; PM = PharMetrics; PNL = prednisolone; PRED = prednisone; Pts = patients; PY = person years; RA = rheumatoid arthritis; RR = rate ratio; SSZ = sulfasalazine; TB = tuberculosis

Four other fair-rated studies showed no difference in infection rates with oral DMARDs. ^{218, 220, 221, 239} A 39-year population-based study of the Rochester, Minnesota, cohort examined potential risk factors for hospitalization for infection in RA patients (N=609). ²²⁰ The use of corticosteroids increased hospitalization for infection (HR, 1.56; 95% CI, 1.20 to 2.04), but oral DMARDs (including MTX, hydroxychloroquine, sulfasalazine, and leflunomide) had no increased risk of infection-related hospitalizations. This finding was similar in a retrospective cohort study of 27,710 patients with RA from British Columbia, ²²¹ where oral DMARDs given in combination with corticosteroids were associated with an increased risk of infection (RR, 1.63; 95% CI, 1.5 to 1.77), but oral DMARDs alone were not associated with an increased risk of infection (RR, 0.92; 95% CI, 0.85 to 1.0). A nested case-control study of 23,733 patients with RA from a Quebec database ²¹⁸ and a retrospective cohort study of 20,357 patients with RA treated at the U.S. Veterans Affairs health care system ²³⁹ also found no increased risk of infection with oral DMARDs.

Two fair-rated and one good-rated cohort studies examined the risk of hospitalization for pneumonia infection. ^{229, 237, 240} One study examined 16,788 patients from U.S. rheumatology practices and followed up semi-annually with questionnaires for 3.5 years. ²³⁷ Both prednisone and leflunomide use increased the risk of hospitalization for pneumonia compared with RA patients not on these drugs (HR, 1.7; 95% CI, 1.5 to 2.1; HR 1.3; 95% CI, 1.0 to 1.5); MTX, hydroxychloroquine, sulfasalazine, infliximab, etanercept, or adalimumab did not increase risks. A 2-year retrospective database study examined RA patients to determine the incidence rates of

adverse events during treatment with leflunomide, MTX, and other DMARDs (including gold, D-penicillamine, hydroxychloroquine, sulfasalazine, infliximab, and etanercept). Respiratory infection rates per person-year were highest in the MTX group (38.9/1,000 person-years), next highest in the other DMARD group (36.9/1,000 person-years), and lowest in the leflunomide group (20/1,000 person-years) (*P*<0.0001). The good-rated study found that, compared with MTX, hydroxychloroquine, leflunomide, and sulfasalazine do not increase risk of hospitalization due to pneumonia (adjuster HR, 1.61; 95% CI, 0.85 to 3.03). 240

Two retrospective cohort studies examined the risk of TB with oral DMARDs.^{219, 238} Both showed an increased risk of TB with oral DMARD treatment. One study examined 24,282 patients with RA from Quebec, Canada and found the risk of TB to be increased among oral DMARD users (RR, 3.0; 95% CI, 1.6 to 5.8).²³⁸ The risk was highest among leflunomide-treated patients (RR, 11.7; 95% CI, 2.1 to 65.1), although the sample size for this group was only 10 patients (3 cases, 7 controls). A similarly designed study using a U.S. claims database identified 112,300 patients with RA and found only a slight increase in risk of developing TB among oral DMARD users (RR, 1.2; 95% CI, 1.0 to 1.5).²¹⁹ Subgroup analyses from this study illustrate that the risk of developing TB is lower among patients concomitantly receiving corticosteroids (RR, 0.6; 95% CI, 0.4 to 1.0) compared with patients not receiving corticosteroids (RR, 1.4; 95% CI, 1.1 to 1.8).

One fair-rated retrospective cohort study examined the risk of herpes zoster infection with oral DMARDs.²²⁴ This study analyzed data from a U.S. commercial claims database as well as data from the UK General Practice Research Database. Analyses from both databases revealed an increased risk of herpes zoster infection with oral DMARDs (U.S. data: OR, 1.37; 95% CI, 1.18 to 1.59; UK data: OR, 1.27; 95% CI, 1.10 to 1.48).

Interstitial lung disease. Two fair-rated observational studies evaluated the risk of interstitial lung disease with oral DMARD treatment (Table 45). One 5-year retrospective cohort study examined claims data from 62,734 patients with RA given a DMARD 1 year prior to the date of diagnosis of interstitial lung disease. ²¹⁷ Patients were divided into four categories: leflunomide, MTX, biologic agents (infliximab, etanercept, adalimumab, anakinra), and traditional DMARDs (antimalarials, sulfasalazine, gold salts, minocycline, penicillamine, azathioprine, cyclosporine, other cytotoxic agents). In patients diagnosed with interstitial lung disease, those prescribed leflunomide were at increased risk compared with patients prescribed other DMARDs (RR, 1.9; 95% CI, 1.1 to 3.6) but not significantly higher with use of either MTX (RR, 1.4; 95% CI, 0.8 to 2.3) or biologic DMARDs (RR, 0.8; 95% CI, 0.4 to 1.5).²¹⁷ The second study analyzed data from 17,598 patients with RA followed prospectively in the NDB study. 228 Cases of interstitial lung disease were identified by searching patient descriptive reports, hospital records, physician records, and mortality records. The incidence of hospitalization for interstitial lung disease was 260 per 100,000 patient years. No significant association was observed between current or past treatment with MTX, hydroxychloroquine, leflunomide, or sulfasalazine. Current and past treatment with prednisone, as well as current treatment with infliximab, etanercept, and cyclophosphamide was associated with an increased risk of interstitial lung disease.

Table 45. Interstitial lung disease in patients with rheumatoid arthritis treated with oral DMARDs

Study	Study Design N Duration	Study Population	Drug	Results	Quality Rating
Suissa et al., 2006 ²¹⁷	Retrospective cohort (claims data)	RA diagnosis, on DMARD	MTX, LEF, biologics, traditional DMARDs	Risk of interstitial lung disease in LEF compared with other	Fair
	62,734			DMARDs: OR, 1.9 (95% CI, 1.1 to 3.6). No elevation noted in LEF pts with no history of MTX or no history of interstitial lung disease	
	5 years				
*Wolfe et al., 2007 ²²⁸	Prospective cohort	RA pts in the	MTX, LEF, HCQ, SSZ	No significant association	Fair
	17,598	National Databank for		between current and past MTX, LEF, HCQ, and SSZ use and	
	Up to 3.5 years	Rheumatic Diseases		hospitalization for interstitial lung disease.	

^{*} New study added since last review.

CI =confidence interval; DMARD = disease-modifying antirheumatic drug; HCQ = hydroxychloroquine; LEF = leflunomide; MTX = methotrexate; OR = odds ratio; Pts = patients; RA = rheumatoid arthritis; SSZ = sulfasalazine

Malignancies. Two observational studies assessed the risk of malignancy with oral DMARDs (Table 46). One retrospective study examined 756 patients with RA to determine the risk of lymphoma over a 30-year period.²⁴¹ This was a matched case-control of consecutive Swedish RA patients in whom lymphoma was diagnosed. Controls were RA patients matched for sex, year of birth, year of RA diagnosis, and county of residence. The investigators found no association between lymphoma and use of DMARDs, including MTX (OR, 0.7; 95% CI, 0.3 to 1.6) or sulfasalazine (OR, 0.6; 95% CI, 0.3 to 1.1).

Table 46. Malignancies in patients with rheumatoid arthritis treated with oral DMARDs

Study	Study Design N Duration	Study Population	Drug	Results	Quality Rating	
Baecklund	Retrospective cohort	•	MTX, SSZ	No significant risk for lymphoma	Good	
et al., 2006 ²⁴¹	756	diagnosis of lymphoma		for MTX or SSZ		
	30 years					
•	Retrospective cohort	RA pts	PRED, LEF, MTX	PRED was associated with increased risk for nonmelanoma skin cancer PRED: HR 1.28 (95% CI, 1.05 to 1.55, <i>P</i> =0.014)	Fair	
et al., 2005 ²⁴²	15,789 (RA)					
	4 years					

^{*} New study added since last review.

CI = confidence interval; HR = hazard ratio; LEF = leflunomide; MTX = methotrexate; OR = odds ratio; PRED = prednisone; Pts = patients; RA = rheumatoid arthritis; SSZ = sulfasalazine

Another retrospective cohort study examined the risk of nonmelanoma skin cancer in 15,789 U.S. patients with RA who were participating in a registry and returned semiannual questionnaires over a 4-year period in which they reported any current malignancies. Among RA patients, the development of nonmelanoma skin cancer was associated with use of prednisone (HR, 1.28; P=0.014). They found no association between this neoplasm and leflunomide plus MTX.

Other adverse events. Five studies provided additional data on oral DMARD-related adverse events (Table 47). One study evaluated the relationship of treatment with the incident rate of septic arthritis;²²⁷ one study examined whether MTX and leflunomide increased the risk of wound healing complications (both in combination with corticosteroids) in RA patients undergoing elective orthopedic surgery;²⁴³ one study examined evidence of kidney damage from combination therapy compared with monotherapy with suflasalazine or prednisone;²⁴⁵ one systematic review evaluated studies addressing fertility, pregnancy, and laction;²⁴⁶ and one study assessed whether oral DMARDs were related to sinus problems.²⁴⁴

Table 47. Other specific adverse events in patients with rheumatoid arthritis treated with oral DMARDs

Study	Study Design N Duration	Study Population	Drug	Results	Quality Rating
*Edwards et al., 2007 ²²⁷	Retrospective case- control	RA pts (n=34,250)	Several oral DMARDs, including MTX, LEF, HCQ, SSZ	Incident rate of septic arthritis in RA pts receiving DMARDs: 2.14 (95% CI, 1.64 to 2.78; <i>P</i> <.001) times greater than in patients	Fair
	136,997				
	15 years			with RA not receiving DMARDs.	
*Fuerst et al., 2006 ²⁴³	Prospective cohort 201	Pts with RA or PsA (n=8)	MTX, LEF, both in combination with	LEF+corticosteroids significantly increased the risk for wound	Fair
	6 weeks+	undergoing elective orthopedic surgery	corticosteroids	healing complications compared with MTX+corticosteroids (40.6% vs. 13.6%, <i>P</i> =0.01).	
*Karstila et al., 2010 ²⁴⁵	RCT 195 Up to 11 years	Pts with new onset RA naïve to DMARD treatment	Combination therapy with SSZ, MTX, HCQ, or PRED vs. monotherapy with SSZ with or without PRED	Culmulative incidence of abnormal renal findings in combination vs. monotherapy groups were comparable	Good
*Martinez Lopez et al., 2009 ²⁴⁶	Systematic review 6 studies 366 patients	Studies addressing pregnancy, fertility, and lactation	MTX	Evidence is insufficient for conclusions	Fair
*Michaud and Wolfe, 2006 ²⁴⁴	Cross-sectional analysis from prospective cohort 7,243 Questionnaire in Dec 2003 related to previous 6 months	RA pts enrolled in the NDB study	MTX, HCQ, LEF, SSZ	Association (OR) of treatment with visits to physician for sinus problems was • MTX: 1.06 (95% CI, 0.93 to 1.20; <i>P</i> =0.371); • HCQ: 1.08 (95% CI, 0.93 to 1.25; <i>P</i> =0.313) • LEF: 0.84 (95% CI, 0.70 to 0.99; <i>P</i> =0.041) • SSZ: 0.68 (95% CI, 0.51 to 0.90; <i>P</i> =0.007)	Fair

^{*} New study added since last review.

DMARD, = disease-modifying antirheumatic drug; HCQ = hydroxychloroquine; LEF = leflunomide; MTX = methotrexate; OR = odds ratio; Pts = patients; RA = rheumatoid arthritis; SSZ = sulfasalazine

In a retrospective cohort study of 136,977 patients with RA from the UK General Practice Research Database, the incidence rate of septic (infectious) arthritis was increased for patients receiving oral DMARDs compared with patients not receiving oral DMARDs (IR, 2.14; 95% CI,

1.64 to 2.78; P<0.001). ²²⁷ The increased incidence rate varied by drug, and was highest for penicillamine (IRR, 2.51; 95% CI, 1.29 to 4.89), sulfasalazine (IRR, 1.74; 95% CI, 1.04 to 2.91), and prednisolone (IRR, 2.51; 95% CI, 1.93 to 4.46).

A prospective cohort study of 201 patients with RA undergoing orthopedic surgery assessed whether leflunomide or MTX given in combination with corticosteroids increased the risk of wound healing complications. In comparison with patients who received MTX, the risk of postoperative wound healing complications was significantly higher than in patients who received leflunomide (MTX 13.6 percent vs. leflunomide 40.6 percent; P=0.01).

A good-rated RCT compared oral DMARD combination therapy with oral DMARD monotherapy in 195 DMARD-naïve patients with recent onset RA. Over an 11-year follow-up period, no statistically significant difference in renal complications was observed.²⁴⁵

A systematic review of studies addressing safety of MTX during pregnanancy, lactation, and related to fertility concluded that evidence is insufficient to adequately addresss the question. ²⁴⁶

A cross-sectional analysis of 7,243 patients followed in the NDB study assessed whether treatment with oral DMARDs was associated with physician visits for sinus problems.²⁴⁴ Treatment with MTX and hydroxychloroquine were not associated with an increased risk of sinus problems, and leflunomide and sulfasalazine had a slight protective effect (respectively, OR, 0.84; 95% CI, 0.70 to 0.99; P=0.041; and OR, 0.68; 95% CI, 0.51 to 0.90; P=0.007).

Biologic DMARDs. This section follows a similar format as the detailed analysis of corticosteroid and oral DMARD sections above, where results for overall tolerability are presented first, followed by general adverse events and then specific adverse events. This section follows a slightly different format to accommodate the presentation of quantitative analyses and detailed adverse event data. Data on tolerability and adverse events for biologic DMARDs are presented as follows: (1) results of quantitative analyses for withdrawal data; and (2) additional discontinuation data not captured by the quantitative analyses, (3) overall adverse event rates and reports of serious adverse events (not otherwise discussed in the specific adverse events section but that are reflective of tolerability profile), and (4) specific adverse events.

Overall tolerability quantitative analyses. RCTs identified by our systematic literature search were screened for inclusion in the meta-analysis of overall tolerability. This included mostly fairto-good quality efficacy trials, as well as some RCTs otherwise included in a good-quality metaanalysis covered in KQ 1 or KQ 2 of this report. Trials were excluded if they did not meet preestablished eligibility criteria for study design or duration, patient population, interventions, outcomes, and comparisons to medications outside our scope of interest. Eligible studies had to compare one more biologic DMARD with placebo. Concomitant use of MTX was allowed, as long as it was consistently used in the biologic DMARD and placebo groups. The outcome of interest was withdrawal (total, due to adverse events and due to lack of efficacy) of biologic DMARD treatment. These trials were not required to report adverse event data other than withdrawals, and thus not all of the studies are detailed further in other adverse event-related sections of this report. Trials had to be at least 12 weeks in duration. If multiple withdrawal rates were reported for more than one time point, we used the time point identified for the primary outcome measure. We limited included data to FDA-approved dosage ranges to achieve better equivalency across drugs. Note that sample sizes may not match sample sizes reported in individual trials since we excluded dosing arms outside of the FDA recommend range. We identified a total of 42 studies (43 comparisons) that were relevant for nine biologics. These included five studies for abatacept, eight for adalimumab, four for anakinra, three for certolizumab, six for etanercept, three for golimumab, six for infliximab, four for rituximab, and

four for tocilizumab. Table 48 lists trials included in the meta-analyses, along with the corresponding withdrawal rates overall and by reason.

Table 48. Overall tolerability: randomized controlled trials included in withdrawal quantitative analyses

	Duration			Number of Withdrawals by Reason		
Author, Year	(weeks)	Comparison	N	Overall	Tolerability	Efficacy
Kremer, 2005 ¹¹⁴	52	Abatacept	115	26 [‡]	6 [‡]	13 [‡]
		Placebo	119	48	11	30
Kremer, 2006 ¹¹⁶	52	Abatacept	433	48 [‡]	18 [‡]	13 [‡]
		Placebo	219	57	4	40
Schiff, 2008 ⁶⁶	26	Abatacept	156	9 [‡]	2 [‡]	2 [‡]
		Placebo	55	3	1	1
Weinblatt, 2006 ²⁵⁸	52	Abatacept	959	123 [‡]	52 [‡]	NR
		Placebo	482	87	20	NR
*Westhovens,	52	Abatacept	256	24	9	0
2009 ⁸⁹		Placebo	253	26	11	8
Breedveld, 2006 ⁷⁶	104	Adalimumab	268	65 [§]	32	13
		Placebo	257	112	19	46
Furst, 2003 ¹²¹	24	Adalimumab	318	28 [‡]	9 [‡]	5 [‡]
		Placebo	318	30	8	14
Kim, 2007 ¹²⁷	18	Adalimumab	65	6 [‡]	4 [‡]	NR
		Placebo	63	4	4	NR
Keystone, 2004 ¹²⁰	52	Adalimumab 20 mg	212	44 [‡]	16 [‡]	6 [‡]
•		Adalimumab 40 mg	207	48 [‡]	26 [‡]	6 [‡]
		Placebo	200	60	13	23
Miyasaka, 2008 ¹²⁵	24	Adalimumab	91	16 [‡]	12 [‡]	NR
•		Placebo	87	7	4	NR
Van de putte, 2003 ¹¹⁹	12	Adalimumab 20 mg	72	10 [‡]	0‡	2 [‡]
2003119		Adalimumab 40 mg	70	12 [‡]	3 [‡]	0 [‡]
		Placebo	70	24	1	1
Van de putte,	26	Adalimumab 20 mg	112	33 [‡]	3 [‡]	27 [‡]
2004 ¹²²		Adalimumab 40 mg biweekly	113	32 [‡]	6 [‡]	20 [‡]
		Adalimumab 40 mg weekly	103	15 [‡]	3 [‡]	10 [‡]
		Placebo	110	62	1	56
Weinblatt, 2003 ¹²³	16	Adalimumab	67	NR	0 [‡]	NR
		Placebo	62	NR	2 [‡]	NR
Breshnihan,	24	Anakinra 75 mg/day	116	22 [‡]	7 [‡]	14 [‡]
1998 ¹²⁸		Anakinra 150 mg/day	116	28 [‡]	11 [‡]	11 [‡]
		Placebo	121	32	5	24
Cohen, 2002 ¹³¹	24	Anakinra 1 mg/kg/day	59	13 [‡]	8 [‡]	4 [‡]
		Anakinra 2 mg/kg/day	72	19 [‡]	11 [‡]	4 [‡]
122		Placebo	74	14	3	5
Cohen, 2004 ¹³³	24	Anakinra	250	NR	14 [‡]	NR
		Placebo	251	NR	13 [‡]	NR
Fleishmann,	24	Anakinra	1116	241 [‡]	149 [‡]	NR
2003 ²⁵⁹		Placebo	283	53 [‡]	26 [‡]	NR
Fleishmann, 2009 ¹⁶⁵	24	Certolizumab	111	35 [‡]	5 [‡] 2	24 [†]
Keystone, 2008 ¹⁶⁸		Placebo	109	81 446 [‡]	<u>Z</u>	75
Neyslone, 2008	52	Certolizumab	390	116 [‡]		68 [‡]
Smolen, 2009 ¹⁶⁷	24	Placebo	199	156 65 [‡]	3 6 [‡]	125 53 [‡]
SHIUICH, ZUUS	24	Certolizumab Placebo	246 127	110	2	107
*Emery, 2008 ⁹⁰	52	Etanercept	274	53 [‡]	28 [‡]	9 [‡]
LITIET y, 2000	5 2					
		Placebo	268	79	34	24

Table 48. Overall tolerability: randomized controlled trials included in withdrawal quantitative analyses (continued)

	Duration			Number of Withdrawals by Reason		
Author, Year	(weeks)	Comparison	N	Overall	Tolerability	Efficacy
*Emery, 2010 ⁹¹	52 Etaner		90	16 [‡]	7 [‡]	1 [‡]
•		Placebo 99		23	9	7
Klareskog, 200486	52 Etaner	rce pt	231	38 [‡] 24	‡	6 [‡]
O.		Placebo 228		69	32	21
Moreland, 1997 ¹⁴⁴	12 Etaner	rce pt	44	3 [‡] NR		2 [‡]
		Placebo 44		21	NR	19
Moreland,1999 ¹⁴⁰	26 Etanerce pt		78	19 [§]	2 [†]	12 [§]
		Placebo 80		54	3	42
Weinblatt,1999 ¹⁴²	24 Etaner		59	2 [‡]	2 [‡]	0‡
Trombiatt, 1000	Z i Etanoi	Placebo 30		6	1	4
*Emery, 2009 ⁹²	24 Golimu		158	8 [‡]	5 [‡]	0‡
,,		Placebo 160		10	1	1
*Kay, 2008 ¹⁶⁶	16 Golimu		35	4 [‡]	2 [‡]	2 [‡]
,		Placebo 35		6	3	3
*Keystone,	16 Golimu		89	2 [‡]	2 [‡]	0 [‡]
2009 ¹⁶⁹		Placebo 133		6	4	0
Abe, 2006 ¹⁵³	14	Infliximab 3 mg/kg	49	NR	1 [‡] NR	
,		Infliximab 10 mg/kg	51	NR	4 [‡] NR	
		Placebo 47		NR	1	NR
Lipsky, 2000 ¹⁵¹	54	Infliximab 3 mg/kg every 8 wks	86	23 [‡]	5 [‡] 17	‡
_,, _,, _,,		Infliximab 3 mg/kg every 4 wks	86	20 [‡]	9 [‡] 19	‡
		Infliximab 10 mg/kg every 8 wks	87	12 [‡]	4 [‡]	6 [‡]
		Infliximab 10 mg/kg every 4 wks	81	16 [‡]	8 [‡]	7 [‡]
		Placebo 88		44	7	32
Schiff, 2008 ⁶⁶	26 Inflixim		165	13 [‡]	8 [‡]	2 [‡]
,		Placebo 55		2	1	1
St. Clair, 2004 ⁸²	54	Infliximab 3 mg/kg	373	66 [‡] 34	‡	7 [‡]
,		Infliximab 6 mg/kg	375	75 [‡] 35	[‡] 12	‡
		Placebo 298		60	9	27
Westhovens,	22	Infliximab 3 mg/kg	360	26 [‡] 18	[‡] NR	
2006 ¹⁵⁵		Infliximab 10 mg/kg	361	32 [‡] 20	[‡] NR	
		Placebo 363		23	8	NR
Zhang, 2006 ¹⁵⁶	18 Inflixim	na b	87	9 [‡]	6 [‡] NR	
		Placebo 86		15	4	NR
Cohen, 2006 ¹⁵⁸	24 Ritu	ximab	309	55 [‡]	2 [‡] NR	
		Placebo 208		96	8	NR
Edwards, 2004 ⁸⁴	24 Ritu	ximab	40	1 [‡]	1 [‡]	1 [‡]
		Placebo 40		3	0	2
Emery, 2006 ¹⁵⁷	24 Ritu	ximab	192	27 [‡]	6 [‡] 16	Ŧ
		Placebo 149		52	0	46
*Emery, 2010 ¹⁶²	24 Ritu	ximab	340	12 [‡]	5 [‡]	1 [‡]
		Placebo 172		13	2	7
*Emery, 2008 ¹⁷⁵	24 T	ocilizumab 4 mg/kg	163	24 [‡] 10	‡	6 [‡]
		Tocilizumab 8 mg/kg	175	23 [‡] 11	‡	4 [‡]
		Placebo 160		30	10	19
*Genovese,	16 T	ocilizumab	805	53 [‡] 32	[‡] NR	
2008 ¹⁷⁶		Placebo 415		43	88	NR
*Kremer, 2010 ¹⁷⁸	24 T	ocilizumab	797	NR	61 [‡]	3 [‡]
		Placebo 393		NR	11	12

Table 48. Overall tolerability: randomized controlled trials included in withdrawal quantitative analyses (continued)

	Duration			Number of Withdrawals by Reason		
Author, Year	(weeks)	Comparison	N	Overall	Tolerability	Efficacy
Smolen, 2008 ¹⁶⁴	24 T	ocilizumab 4 mg/kg	214	25 [‡] 14	‡	2 [‡]
		Tocilizumab 8 mg/kg	205	13 [‡] 12	‡	0‡
		Placebo 204		12	6	3

^{*} New studies since last review.

Kg = kilogram; mg = milligram; NR = not reported; NS = not significant

Overall tolerability: quantitative analysis of total withdrawals for biologic DMARD versus placebo. Using random effects models, we calculated the pooled odds ratios of total treatment withdrawal for each biologic relative to placebo (Figure 4). Overall, patients on biologics were approximately half as likely to withdraw from the treatment as compared with the patients on placebo. Among the individual biologics, the pooled estimates were statistically significant for abatacept (OR, 0.58; 95% CI, 0.39 to 0.86), certolizumab (OR, 0.10; 95% CI, 0.06 to 0.18), etanercept (OR, 0.32; 95% CI, 0.18 to 0.57) and rituximab (OR, 0.29; 95% CI, 0.22 to 0.39). Patients taking these drugs were less likely to withdraw from a trial than patients taking placebo. The likelihood of withdrawal of adalimumab, anakinra, golimumab, infliximab, and tocilizumab was not statistically significantly different than placebo. We estimated heterogeneity using I2 statistic. I2 was found to be 86.5 percent overall, which suggested a high amount of heterogeneity among the studies. This heterogeneity may be attributed to several reasons. First, real heterogeneity may exist across study designs and patient populations. Second, the withdrawal outcome—which measures a combination of withdrawals due to adverse events and withdrawals due to lack of efficacy—can be a potential source of heterogeneity. These reasons for withdrawal may not be in agreement with each other, and introduce measurement concerns when combining studies. For example, total withdrawal for one drug can be higher because it is less efficacious while for another drug, it might just be because of high adverse events. This can lead to potential heterogeneity concerns when looking across all studies. We assessed publication bias using funnel plots. Visual examination of funnel plots illustrated potential for some publication bias. However, given the small number of component studies, results of these tests must be viewed cautiously.

Overall tolerability: quantitative analysis of withdrawals due to lack of efficacy for biologic DMARD versus placebo. We also calculated the pooled odds ratios of treatment withdrawal because of lack of efficacy for each biologic relative to placebo (Figure 5). Patients randomized to biologic DMARDs were nearly 5 times less likely to withdraw from the treatment due to lack of efficacy as compared with the patients on placebo (OR, 0.21; 95% CI, 0.17 to 0.27). All individual biologics, except golimumab, were less likely to be withdrawn compared with placebo for lack of efficacy. I2 was found to be 52.8 percent, which suggested slightly lower heterogeneity when just looking at lack of efficacy compared with overall withdrawals. This result suggests that some of the heterogeneity with the total withdrawals analysis was probably

 $^{^{\}dagger}$ P=NS

 $^{^{\}ddagger}$ P=NR

[§] P<0.01

Figure 4. Meta-analysis of overall withdrawals from randomized controlled trials of biologic DMARDs

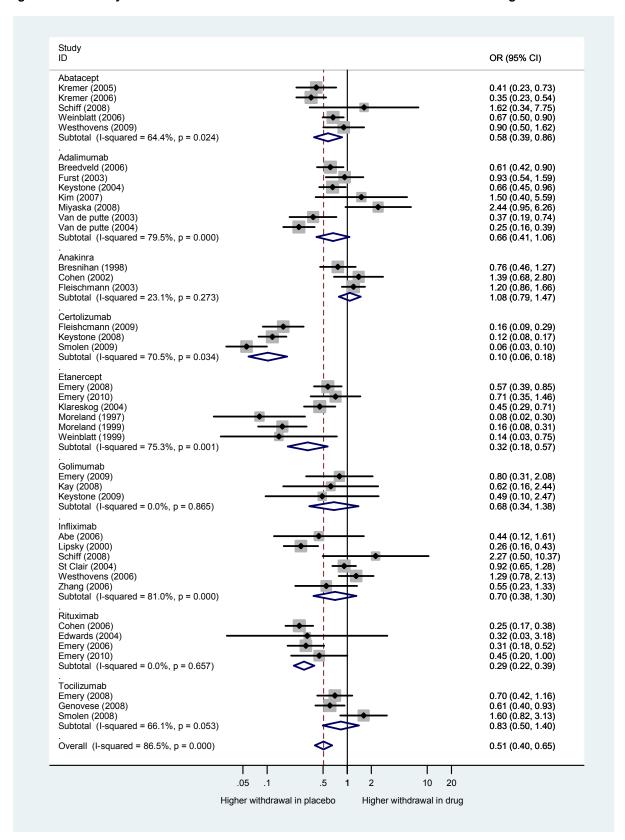
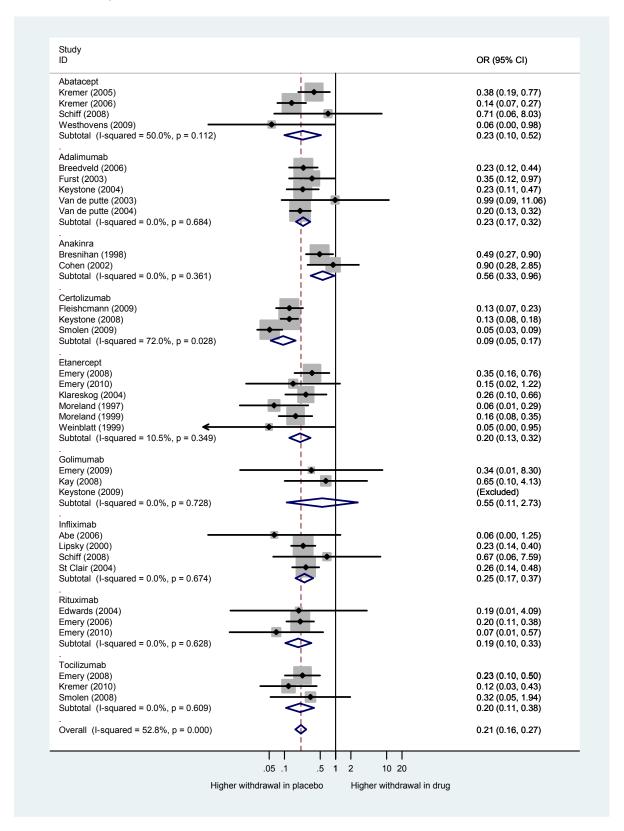


Figure 5. Meta-analysis of withdrawals due to lack of efficacy in randomized controlled trials of biologic DMARDs



due to combining withdrawals for all the reasons together. Visual examination of funnel plots did not show evidence of publication bias.

Overall tolerability: quantitative analysis of withdrawals due to adverse events for biologic DMARD versus placebo. We also calculated the pooled odds ratios of treatment withdrawal because of adverse events for each biologic relative to placebo. Patients on biologics were 44 percent more likely to withdraw from the treatment due to adverse events compared with the patients on placebo (OR, 1.43; 95% CI, 1.18 to 1.74). Among individual biologics, the pooled estimates for adalimumab (OR, 1.60; 95% CI, 1.13 to 2.28), anakinra (OR, 1.59; 95% CI, 1.10 to 2.31), certolizumab (OR, 2.73; 95% CI, 1.18 to 6.31), infliximab (OR, 2.09; 95% CI, 1.38 to 3.18), and tocilizumab (OR, 1.94; 95% CI, 1.22 to 3.09) were statistically significant, suggesting that patients on these drugs were more likely to withdraw from the trial due to adverse events than patients on placebo. Heterogeneity I² was found to be 31.3 percent, which suggests relatively low heterogeneity among this outcome in these studies. Visual examination of funnel plots did not show evidence of publication bias.

Overall tolerability: mixed treatment comparisons for overall withdrawals. Indirect comparisons were made using the studies described in Table 49 and shown in meta-analyses (Figures 4 to 6). Thirty-eight studies contributed data to the analysis of overall withdrawals. Results are presented for each possible drug-drug comparison (Figure 7). Odds ratios less than 1 favor the first drug listed in the comparison (Drug A), indicating that there were fewer total withdrawals for this drug in comparison with the second drug listed (Drug B). Odds ratios greater than 1 favor drug B in terms of a more favorable withdrawal rate. Most comparisons suggest no difference in overall withdrawals. A few exceptions were found: certolizumab pegol had a more favorable overall withdrawal profiles than all other biologic DMARDs. Etanercept and rituximab also had fewer overall withdrawals in some comparisons. For etanercept, results were statistically significant for the comparison with adalimumab (OR, 0.51; 95% CI, 0.22 to 0.97), anakinra (OR, 0.32; 95% CI, 0.12 to 0.70), infliximab (OR, 0.38; 95% CI, 0.18 to 0.89), and tocilizumab (OR, 0.33; 95% CI, 0.14 to 0.89). For rituximab, results were statistically significant for only the comparisons with anakinra (OR, 0.33; 95% CI, 0.11 to 0.78), infliximab (OR, 0.45; 95% CI, 0.17 to 1.00), and tocilizumab (OR, 0.32; 95% CI, 0.13 to 0.99). These results should be interpreted cautiously because of the relatively small number of contributing studies and the corresponding wide confidence intervals. Plus, evaluating overall withdrawals provides only a rough proxy for tolerability.

Overall tolerability: mixed treatment comparisons for withdrawals due to lack of efficacy. Thirty-one studies contributed data to the analysis of withdrawals due to lack of efficacy. Results are presented for each possible drug-drug comparison (Figure 8). Odds ratios less than 1 favor the first drug listed in the comparison (Drug A), indicating that there were fewer withdrawals due to lack of efficacy for this drug in comparison with the second drug listed (Drug B). Odds ratios greater than 1 favor drug B in terms of a more favorable efficacy-related withdrawal rate. Most comparisons suggest no difference in withdrawals due to lack of efficacy. Similar to the analysis of overall withdrawals, certolizumab pegol had lower rates of withdrawals due to lack of efficacy than adalimumab (OR, 0.41; 95% CI, 0.18 to 0.76), anakinra (OR, 0.18; 95% CI, 0.06 to 0.39), and infliximab (OR, 0.33; 95% CI, 0.16 to 0.77). Withdrawals due to lack of efficacy were lower for abatacept (OR, 0.31; 95% CI, 0.13 to 0.93), etanercept (OR, 0.33; 95% CI, 0.11 to 0.74), rituximab (OR, 0.31; 95% CI, 0.08to 0.78), and tocilizumab (OR, 0.37; 95% CI, 0.11 to 0.93) than for anakinra. These results should be interpreted cautiously because of the relatively small

Figure 6. Meta-analysis of withdrawals due to adverse events in randomized controlled trials of biologic DMARDs

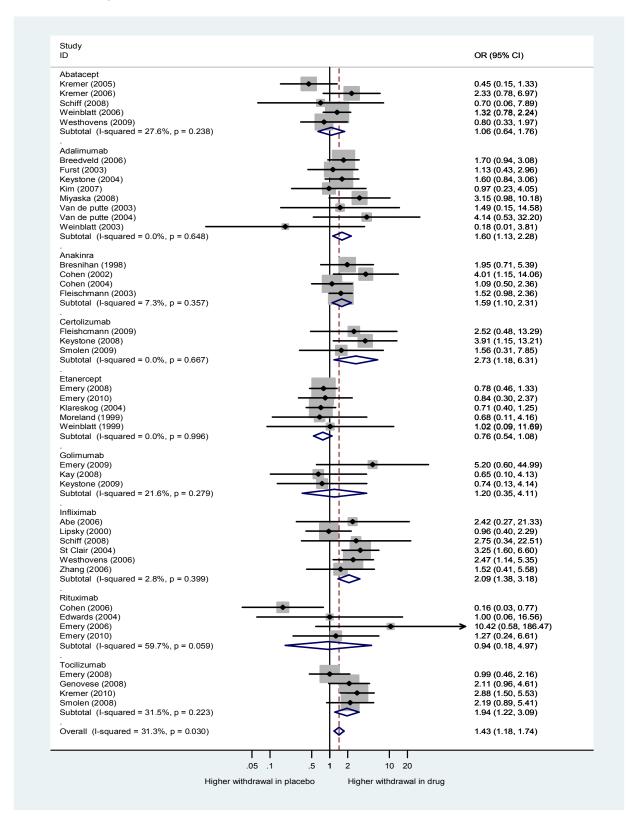


Figure 7. Mixed treatment comparisons for overall withdrawals in randomized controlled trials of biologic DMARDs

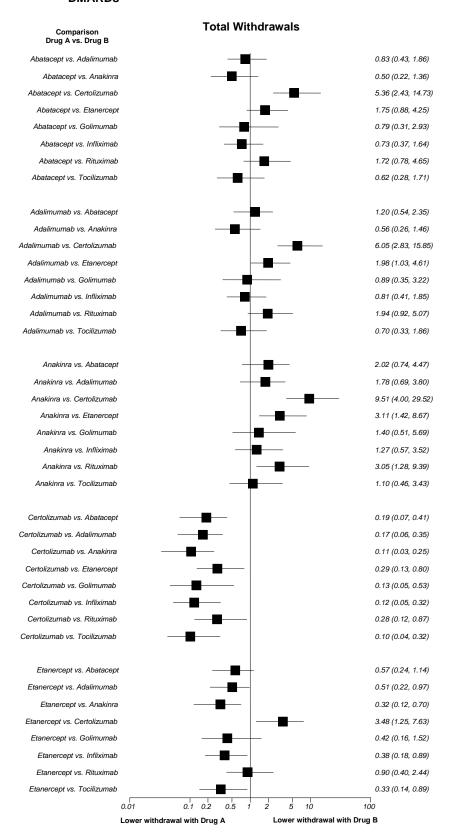


Figure 7. Mixed treatment comparisons for overall withdrawals in randomized controlled trials of biologic DMARDs (continued)

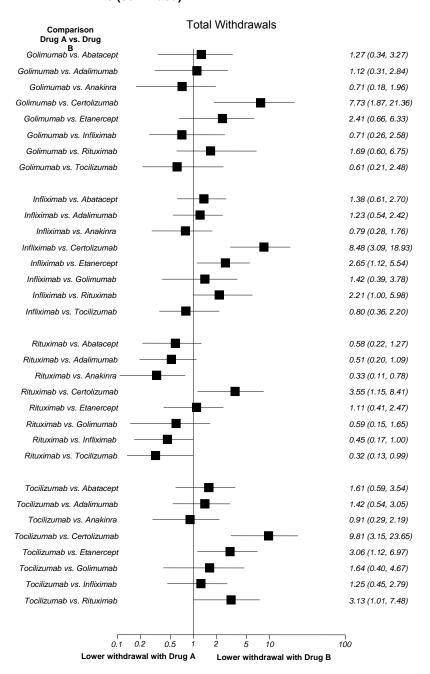


Figure 8. Mixed treatment comparisons for withdrawals due to lack of efficacy in randomized controlled trials of biologic DMARDs

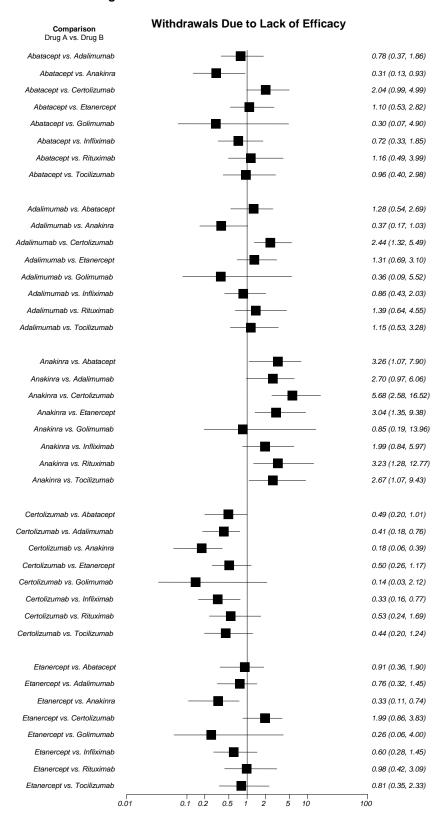
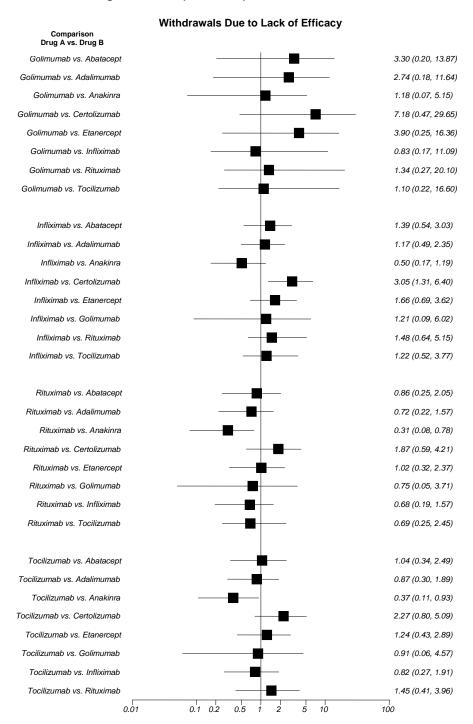


Figure 8. Mixed treatment comparisons for withdrawals due to lack of efficacy in randomized controlled trials of biologic DMARDs (continued)



number of contributing studies and the corresponding wide confidence intervals. Plus, evaluation of withdrawals due to lack of efficacy is only a rough proxy for tolerability.

Overall tolerability: mixed treatment comparisons for withdrawals due to adverse events. Indirect comparisons were made using the studies described in Table 48 and shown in meta-analyses (Figure). Forty-one studies contributed data to the analysis of withdrawals due to adverse events. Results are presented for each possible drug-drug comparison (Figure 9). Odds ratios less than 1 favor the first drug listed in the comparison (Drug A), indicating that there were fewer withdrawals due to adverse events for this drug in comparison with the second drug listed (Drug B). Odds ratios greater than 1 favor drug B in terms of a more favorable adverse-event-related withdrawal rate. Most comparisons suggest no difference in withdrawals due to adverse events, with a few exceptions. Both certolizumab pegol and infliximab had more withdrawals due to adverse events than some other drugs. For certolizumab, the likelihood of withdrawal because of an adverse event was greater than for abatacept (OR, 3.28; 95% CI, 1.05 to 8.53), etanercept (OR, 3.48; 95% CI, 1.44 to 11.65) and rituximab (OR, 2.82; 95% CI, 1.01 to 13.26).

For infliximab, the likelihood of withdrawal because of an adverse event was greater than for abatacept (OR, 2.35; 95% CI, 1.20 to 4.22), etanercept (OR, 3.31; 95% CI, 1.62 to 6.07), and rituximab (OR, 2.40; 95% CI, 1.00 to 7.43). Withdrawals because of adverse events tended to be lower with abatacept and etanercept when comparing them with some other drugs. For abatacept, statistically significantly fewer withdrawals occurred due to adverse events when compared with certolizumab (OR, 0.30; 95% CI, 0.12 to 0.96), infliximab (OR, 0.43; 95% CI, 0.24 to 0.83), and tocilizumab (OR, 0.50; 95% CI, 0.27 to 1.00), and for etanercept, differences were statistically significant for comparisons with adalimumab (OR, 0.50; 95% CI, 0.25 to 0.91), anakinra (OR, 0.48; 95% CI, 0.23 to 0.85), certolizumab (OR, 0.29; 95% CI, 0.09 to 0.69), infliximab (OR, 0.30; 95% CI, 0.16 to 0.62), and tocilizumab (OR, 0.35; 95% CI, 0.20 to 0.73). All of these results should be interpreted cautiously because of the relatively small number of contributing studies and the very wide confidence intervals.

Biologic DMARDs—overall tolerability: studies on discontinuation rates not otherwise covered in quantitative analyses. Table 49 presents studies providing discontinuation data not otherwise covered by quantitative analyses. One good-quality RCT compared etanercept with the combination of etanercept and abatacapt. This RCT was not included in our meta-analysis of withdrawal rates because it compared two biologic DMARDs with a single biologic DMARD. Withdrawals due to adverse events occurred more in the combination group (11.8 percent) than in the monotherapy etanercept group (2.8 percent).

Figure 9. Mixed treatment comparisons for withdrawals due to adverse events in randomized controlled trials of biologic DMARDs

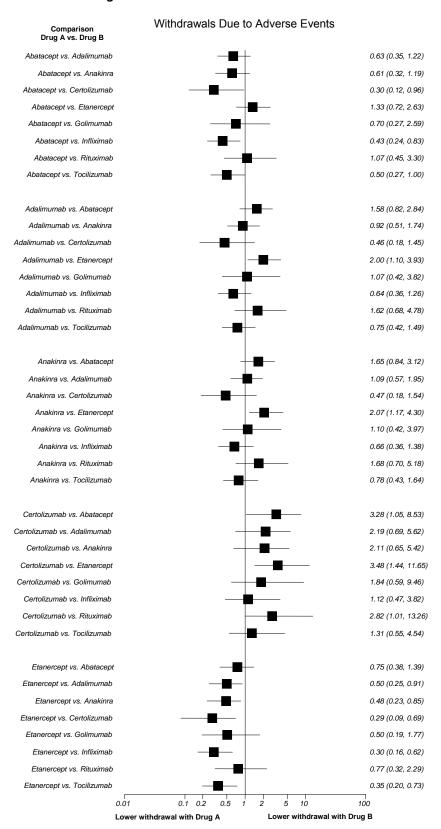


Figure 9. Mixed treatment comparisons for withdrawals due to adverse events in randomized controlled trials of biologic DMARDs (continued)

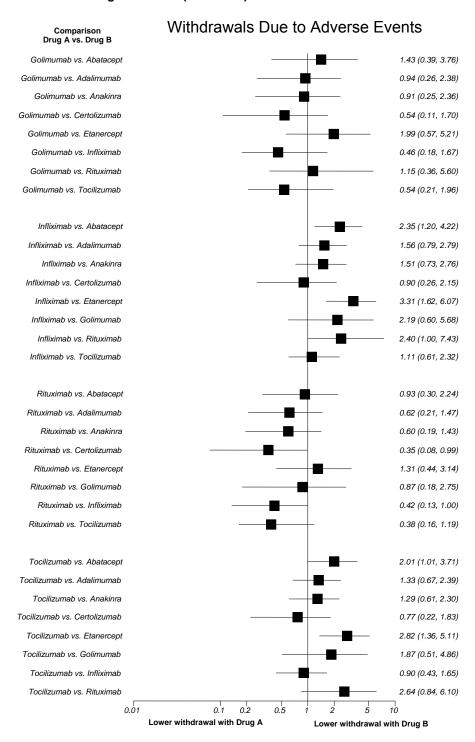


Table 49. Overall tolerability: discontinuation data not otherwise covered by quantitative analyses

	Study Design N				
Study	Duration	Study Population	Drug	Results	Rating
*Alonoso-Ruiz et al. 2008 ¹²⁶	Systematic review and meta-analysis 13 trials	Pts with RA	ADA ETA, INF	Relative risk of withdrawal due to adverse event compared with control group: ADA (RR, 1.4;	Good
	7,087 patients At least 6 months			95% CI, 1.0 to 2.0); ETA (RR, 0.7; 95% CI, 0.5 to 0.9); INF (RR, 2.0; 95% CI, 1.3 to 3.1)	
*Duclos et al.,		Dto with inflammatory	ADA ETA	· · · · · · · · · · · · · · · · · · ·	Coir
2006 ²⁴⁸	Retrospective cohort	Pts with inflammatory rheumatism (mostly RA) that received an anti-TNF	ADA, ETA, INF	Trend towards better tolerability with ETA and ADA compared with INF	ган
	770	agent		(P=0.06)	
	7 years			,	
Flendrie et al., 2003 ²⁴⁷	Retrospective cohort study	Pts with RA initiating therapy with biologic	ADA, ETA, INF	No significant differences in discontinuation rates among	Fair
	230 NB	DMARDs		anti-TNF drugs	
ki lada a alada l	NR	Diaitle DA initiation	ADA ETA	Hannad askin for days	- -:-
'Hetiand et al., 2010 ⁷³	•	Pts with RA initiating therapy with biologic	ADA, ETA, INF	Hazard ratio for drug withdrawal: INF vs. ETA HR	Fair
DANBIO	2,326	DMARDs		1.98 (95% CI, 1.63 to 2.40); INF	
DANBIO	48 months			vs. ADA 1.35 (95% CI, 1.15 to 1.58); ADA vs. ETA 1.47 (95% CI, 1.20 to 1.80)	
'Hjardem et al., 2007 ²⁴⁹	Retrospective cohort	RA pts who had received 2+ biologics (INF, ETA, or ADA only)	ADA,ETA, INF	Similar reasons for switching treatments: Lack of efficacy;	Fair
	235			ADA 54%; ETA 44%; INF 45%. Adverse events: ADA 21%;	
	Varied			ETA 22%; INF 34%	
*Hyrich et al.,	Prospective cohort	Pts with RA in the British	ADA, ETA,	Differences in reason for	Fair
2007 ²⁵⁰	6,739	Society for Rheumatology Biologics Register	INF	discontinuation (P=NR): Lack of efficacy; ADA 6.7%; ETA	
	Minimum 6 months	Diologico i togiciei		4.8%; INF 10%. Adverse	
				events: ADA 2.9%; ETA 2.6%; INF 8.4%	
*Karanikolas et al., 2008 ⁹³	Prospective cohort	Pts with RA with inadequate response to	MTX+ ANK LEF+ANK	No statistically significant differences in number of	Fair
ot al., 2000	128 48 weeks	traditional DMARD	LEFTAINN	withdrawals due to adverse events	
Kristensen et	Prospective cohort	Pts with RA in southern	ETA,	Early discontinuation threefold	Fair
al., 2006 ²⁵¹	1,161 Up to 6 years	Sweden	ETA+MTX, INF, INF+MTX, other DMARDs	higher for INF than for ETA (P <.001). Addition of MTX improved treatment continuation rates (P <0.01).	
Marchesoni et al., 2009 ²⁵²	-	Pts with RA treated with at least one dose of an anti-	ADA, ETA, INF	Risk of discontinuation due to adverse events higher for ADA	Fair
_OHREN	1,064	TNF agent		than ETA	
	23.32 months				

Table 49. Overall tolerability: discontinuation data not otherwise covered by quantitative analyses (continued)

Study	Study Design N Duration	Study Population	Drug	Results	Quality Rating
*Mertens and Singh, 2009 ¹³⁴	Meta-analysis 2,876 5 trials	Pts with RA included in placebo-controlled RCTs	ANK	No difference in total number of withdrawals, adverse events, or serious adverse events for ANK vs. placebo	Fair
*Singh et al., 2009 ^{27, 180}	Review of Cochrane reviews and network meta- analysis	Pts with RA	ABA, ADA, ANK, ETA, INF, RTX	ADA, ANK, and INF more likely to have withdrawals due to adverse events vs. ETA: (OR, 1.89; 95% CI, 1.18 to 3.04; OR, 2.05; 95% CI, 1.27 to 3.29; OR, 2.70; 95% CI, 1.43 to 5.26, respectively)	Good
*Singh et al., 2010 ¹⁷⁷	Systematic review and meta-analysis	Pts with RA	TCZ	Fewer overall trial withdrawals with TCZ than	Fair
	8 studies 3,334 patients			placebo; no statistically significant diffence in withdrawals due to adverse	
	8 to 52 weeks			events	
*Singh et al., 2010 ²¹⁰	Systematic review and meta-analysis	Pts with RA	GOL+MTX, MTX	Fewer overall withdrawals for GOL+MTX than MTX alone	Good
	4 studies 1,231 patients				
	20 to 52 weeks				
*Weinblatt	RCT	Pts with active RA	ETA,	Discontinuation due to	Good
et al., 2007 ⁸⁰	121		ABA+ETA	adverse events occurred more in ABA+ETA group	
	1 year (LTE: 2 years)			(11.8%) vs. ETA group (2.8%).	
Zink et al., 2005 ⁸⁸	Retrospective cohort study	Pts with RA who had a change in treatment	ANK, ETA, INF, LEF	Significantly higher overall discontinuation rates for	Good
	1,523	regimen		ANK than ETA and INF after 12 months; no	
	1 year			differences in discontinuation rates due to adverse events	

^{*} New study added since last review.

ABA = abatacept; ADA = adalimumab; AE = adverse event; ANK = anakinra; DMARD = disease-modifying antirheumatic drug; ETA = etanercept; GOL = golimumab; INF = infliximab; LEF = leflunomide; LOHREN = Italian Lombardi Rheumatology Network; MTX = methotrexate; NR = not reported; Pts = patients; RA = rheumatoid arthritis; RCT = randomized controlled trial; RTX = rituximab; TCZ = tocilizumab; TNF = tumor necrosis factor

Additional evidence on comparative discontinuation rates is provided by systematic reviews ^{27, 126, 134, 177, 180, 210} and observational studies. ^{73, 88, 93, 247-252} While some studies did not find clinically or statistically significant differences in drug discontinuation rates, 247, 249 others did. Consistent with our mixed treatment comparisons analysis, a good-rated meta-analysis found etanercept to have fewer withdrawals due to adverse events than adalimumab, anakinra, and infliximab. A second good-rated meta-analysis found the highest rate of withdrawals due to adverse events for infliximab and the lowest rate for adalimumab. ¹²⁶
Observational evidence generally supports these findings. ^{73, 88, 248, 250-252} A Swedish

population-based, prospective cohort study reported statistically significantly higher rates of

overall discontinuation (HR, 2.92; 95% CI, 2.32 to 3.69; P<0.001) for patients on infliximab than for those on etanercept.²⁵¹ These differences were not statistically significant for discontinuations due to adverse events or due to lack of efficacy. A German retrospective, population-based cohort study, based on the RABBIT database, reported that overall discontinuation rates among biologics were significantly higher for anakinra-treated patients (41 percent) than for patients on etanercept (31 percent; P=0.004 for anakinra vs. etanercept) or those on infliximab (35 percent; P=0.03 for anakinra vs. infliximab). 88 Treatment discontinuations because of adverse events, after 12 months of treatment, were lowest for etanercept (13 percent for etanercept, 16 percent for anakinra, and 19 percent for infliximab; P=NR). This finding is also consistent with a retrospective cohort study of patients treated with adalimumab, etanercept, and infliximab, where there was a trend towards better tolerability with adalimumab and etanercept compared with infliximab (P=0.06). Another prospective cohort study reported higher rates of switching treatments with infliximab compared with adalimumab and etanercept (P=NR). 250 In the Danish DANBIO registry, the hazard ratios for drug withdrawal were 1.98 for infliximab versus etanercept (95% CI, 1.63 to 2.40), 1.35 for infliximab versus adalimumab (95% CI, 1.15 to 1.58), and 1.47 for adalimumab versus etanercept (95% CI, 1.20 to 1.80).⁷³ In the Italian Lombardi Rheumatology Network (LOHREN) registry, the risk of discontinuation due to adverse events was higher for adalimumab than for etanercept (AHR 2.09; 95% CI, 1.29 to 3.38).²⁵²

Biologic DMARDs—overall tolerability: adverse event rates and serious adverse events. Table 50 presents the comparative harms for biologic DMARDs. Only two studies compared adverse event rates and serious adverse events with biologic DMARDs; one RCT⁶⁶ and one retrospective cohort study. 253 Both studies found more serious adverse events among patients treated with infliximab. The RCT included 431 patients with RA who were receiving MTX and were naïve to biologic DMARDs. Patients were randomized to abatacept plus MTX, infliximab plus MTX, or placebo plus MTX. At 6 months, 5.1 percent of the abatacept group reported serious adverse events, but 11.8 percent and 11.5 percent of the placebo and infliximab groups, respectively, reported serious adverse events (P=NR). After 1 year, 18.2 percent of infliximabtreated and 9.6 percent of abatacept-treated reported a serious adverse event (P=NR; placebo arm stopped at 6 months). Acute infusional events were lower with abatacept (7.1 percent) than with infliximab (24.8 percent). The retrospective cohort study followed 2.364 patients with RA newly treated with an anti-TNF agent in the Swiss Clinical Quality Management for Rheumatoid Arthritis (SCOM-RA) registry. There was an increased risk of adverse events in the infliximab compared with adalimumab and etanercept groups (HR, 1.4; 99% CI, 1.0-1.96). More specifically, there was an increased risk of infusion or systemic allergic reactions with infliximab compared with adalimumab and etanercept (*P*=0.018).

Table 50. Comparative harms in patients with rheumatoid arthritis and treated with biologic DMARDs

	Study Design N				Quality
Study	Duration	Study Population	Drug	Results	Rating
		Biologic DMARDs Overa	II Tolerabili	ty	
*Alonoso-Ruiz et al., 2008 ¹²⁶	Systematic review and meta- analysis		ADA ETA, INF	Relative risk of serious adverse events compared with control group: ADA (RR,	Good
	13 trials			1.0; 95% CI, 0.7 to .4); ETA (RR, 1.0; 95% CI, 0.5 to 1.6),	
	7,087 patients			INF (RR, 1.4; 95% CI, 1.0 to	
	at least 6 months			2.0)	
Bathon et al.,	RCT		ETA, MTX	Significantly more patients on	Fair
2000 ^{77, 188, 189} ERA study	632 (512)	naive		MTX than on ETA had nausea (29% vs. 15%; <i>P</i> <0.05) or	
,	12 months (1 year open-label extension)			mouth ulcers (14% vs. 5%; <i>P</i> <0.05)	
Breedveld et al.,	RCT	Early, aggressive RA; MTX-	ADA,	No statistically significant	Fair
2006 ⁷⁶ PREMIER study	799		MTX, ADA+MT	differences in adverse events	
	2 years		X		
*Burmester et al., 2007 ²⁵⁷	Prospective cohort		ADA, ADA+DM	Serious adverse events occurred in 7.3% of pts treated with ADA vs. 5.3% treated with ADA+DMARDs	Fair
ReACT trial	6,610	traditional DMARD	ARDs		
	12 weeks				
Combe et al.,	RCT	Pts with active RA despite treatment with sulfasalazine	ETA,	Noninfectious serious adverse events were significantly greater in patients receiving ETA (20.8% for the combination and 20.4% for ETA alone) compared with 4% for patients receiving SSZ (<i>P</i> <0.01)	Fair
2009 ¹⁴⁵	260		SSZ, ETA+SSZ		
	2 years				
Edwards et al.,	RCT	Active RA despite MTX	RTX,	No significant differences in	Fair
2004 ⁸⁴	161	treatment	MTX, RTX+MT	adverse events	
	24 weeks		X, RTX+CYP		
*Emery et al., 2008 ¹⁷⁵ RADIATE study	RCT	Pts with active RA resistant		The overall occurrence of	Fair
	499	to 1 or more TNF-alpha antagonist agents	+MTX	adverse events was similar among groups.	
	24 weeks				
Emery et al.,	RCT	Early, moderate to severe	MTX,	Serious adverse events were	Fair
2008 ⁹⁰ COMET trial	542	RA; MTX-naive	ETA+MTX similar among groups	similar among groups	
	52 weeks				

	Study Design N				Quality
Study	Duration	Study Population	Drug	Results	Rating
*Emery et al.,	RCT	Pts with RA; MTX-naive	MTX,	More adverse events occurred	Fair
200992	637		GOL, GOL+	in the GOL+MTX and MTX monotherapy group compared	
	24 weeks		MTX	with GOL monotherapy (P=NR)	
Feltelius et al.,	Case series	Pts with RA initiating ETA	ETA		Fair
2005 ²⁶⁰	1,073	therapy		events remained constant over time	
	2 years				
*Fernandez- Nebro et al.,	Prospective cohort	RA pts with no response to DMARDs, including MTX	ADA, ETA, INF	No difference in adverse events among groups	Fair
2007 ⁷⁰	161				
	6 years				
*Fleischmann et	RCT	Pts with RA treatment	CTZ	Overall, adverse events	Fair
al., 2009 ¹⁶⁵ FAST4WARD	220	resistant to at least one DMARD		occurred in 75.4% of pts treated with CTZ and 57.8% of placebo pts	
.,	24 weeks				
Fleischmann et	RCT	Pts with active RA despite AMTX treatment	ANK No	, , , , , , , , , , , , , , , , , , , ,	Fair
al., 2003 ²⁵⁹	1,414			differences in adverse events (except infusion reactions)	
	6 months			(choopt illiadion roadione)	
Fleischmann et al., 2006 ³¹⁹	Open-label extension of RCT	Pts with active RA despite MTX treatment	ANK	Incidence of serious adverse events remained constant over time	Fair
	1,346				
	Up to 3 years				
Furst et al.,	RCT	Pts with active RA despite	ADA No	statistically significant differences in adverse events	Fair
2003 ¹²¹ STAR study	636	MTX treatment			
,	6 months				
Geborek et al., 2002 ⁶⁷	Nonrandomized, open-label trial	Population-based; active RA; had failed at least 2		No statistically significant differences in adverse events	Fair
	369	DMARDs			
	12 months				
Genovese et al., 2002 ¹⁸⁸	Open-label extension of RCT	Pts with early, aggressive RA; MTX-naive	ETA	Incidence of serious adverse events remained constant over time	Fair
	632				
	2 years				
Genovese et al.,	RCT	Inadequate control of	ETA,	Significantly higher rates of	Fair
2004 ⁷⁹	242	disease with MTX	ETA+AK A	serious adverse events in combination group	
	24 weeks			STSindhon Group	

Study	Study Design N Duration	Study Population	Drug	Results	Quality Rating
Genovese et al., 2005 ¹⁸⁹	Uncontrolled extension of RCT	Pts with early, aggressive RA; MTX-naive	ETA	Rates of serious adverse events did not increase with long-term exposure	Fair
	369				
	5 years				
*Karanikolas et al., 2008 ⁹³	Prospective cohort	Pts with RA with inadequate response to	MTX+ANK, LEF+ANK	No statistically significant differences in adverse events	Fair
	128	traditional DMARD			
	48 weeks				
*Kay et al., 2008 ¹⁶⁶	RCT 172	Pts with active RA despite treatment with MTX	MTX, GOL+MTX,	Serious adverse events occurred in 9% of pts treated	Fair
	52 weeks			with GOL vs. 6% in pts treated with MTX alone	
*Keystone et al.,	RCT	Pts with active RA on	MTX,	Serious adverse events	Fair
2004 ¹²⁰	619	MTX therapy	ADA+MTX	occurred more frequently in ADA pts (3.8%) vs. MTX pts	
	52 weeks			(0.5%; <i>P</i> ≤0.02)	
*Kim et al.,	RCT	•	ADA+MTX,	No statistically significant	Fair
2007 ¹²⁷	128		MTX	differences in adverse events	
	24 weeks				
Klareskog et al., 2004 ^{86, 136, 138}	RCT		ETA, MTX, ETA+MTX	No statistically significant differences in adverse events	Good
TEMPO study	686 (503 for 2 year results)				
	52 weeks (2 years, 100 weeks)				
*Kremer et al.,	RCT	Pts with RA with	TCZ+MTX,	Rate of serious adverse	Fair
2011 ¹⁷⁸	1,196	inadequate response to MTX	MTX	events were not statistically significantly different between	
	12 months			groups	
Langer et al., 2003 ³²⁰	Postmarketing surveillance	Pts with RA, initiating AKA treatment	AKA	Rate of adverse events was generally similar to those	Fair
	454			reported in efficacy trials	
	6 months				
*Leombruno et al., 2009 ²⁵⁵	Meta-analysis	RA pts on anti-TNF	ADA, ETA,	Anti-TNF treatment did not	Fair
ai., 2009	18 trials 8,808 patients	therapy	INF	F increase death (OR, 1.39; 95% CI, 0.74 to 2.62) or serious adverse events (OR, 1.11; 95% CI, 0.94 to 1.32)	
	Average 0.8 years				

Study	Study Design N Duration	Study Population	Drug	Results	Quality Rating
Maini et al., 2004 ¹⁴⁹	Open-label extension of RCT	Pts with active RA despite MTX treatment	INF	Incidence of serious adverse events remained constant over time	Fair
	259				
	2 years				
*Martin Du Pan et al., 2009 ²⁵³	Retrospective cohort	Pts with RA in the Swiss Clinical Quality	ADA, ETA, INF	Increased overall risk for adverse events in INF vs. ETA	Fair
	2,364	Management for Rheumatoid Arthritis		and ADA (HR, 1.4; 99% CI,1.00-1.96)	
	9 years	(SCQM-RA) registry treated with an anti-TNF agent		3,1.50 1.50)	
Moreland et al., 2006 ²⁶¹	Open-label extension of clinical trials	Pts treated with ETA	ETA	Incidence of serious adverse events remained constant over time	Fair
	714				
Nishimoto et al.,	RCT	Pts w ith ac tive RA despite MTX treatment	TCZ, MTX	Adverse events occurred in 91.8% of pts treated with TCZ vs. 71.9% of those treated	Fair
2009 ¹⁷³ SATORI	127				
5 , 1, 5 , 1,	24 weeks			with MTX	
Nuki et al., 2002 ¹²⁹	Uncontrolled extension of RCT	Pts with active RA despite MTX treatment	AKA	Incidence of serious adverse events remained constant	Fair
	309			over time	
	19 months				
O'Dell et al., 2006 ²³¹	Nonrandomized, open-label trial	Pts with active RA despite treatment with	ETA+SSZ ETA+HCQ	No differences in adverse event rates among 3	Fair
	119	SSZ, HCQ, or gold	ETA+gold	treatment groups	
Russell et al., 2007 ^{116, 254}	RCT	Pts with RA despite	ABA,	Incidence of serious	Good
AIM	652	treatment with MTX	ABA+MTX	adverse events similar between groups	
	12 months				
Schiff et al.,	RCT	Pts with RA despite treatment with MTX,	ABA +MTX, INF +MTX,	The occurrence of serious adverse events was lower	Fair
2008 ⁶⁶	431	anti-TNF therapy naive	MTX	in those treated with ABA	
Cobiff of al	1 year	Dto trooted with ADA	ADA	(9.6%) vs. INF (18.2%).	Foi-
Schiff et al., 2006 ²⁹⁸	Retrospective data analysis of clinical trials; postmarketing surveillance	Pts treated with ADA	ADA	Incidence of serious adverse events remained constant over time	Fair
	10,050 12,506 pt years				

Study	Study Design N Duration	Study Population	Drug	Results	Quality Rating
*Singh et al., 2010 ¹⁷⁷	Systematic review and meta-analysis	Pts with RA	Drug TCZ	Occurrence of adverse event in TCZ group compared with placebo (74% vs. 65%); RR, 1.17;	Fair
	8 studies 3,334 patients			95% CI, 0.83 to 1.64	
	8 to 52 weeks				
*Singh et al., 2010 ²¹⁰	Systematic review and meta-analysis	Pts with RA	GOL+MTX , MTX	No difference in occurrence of adverse events in GOL+MTX vs. MTX (RR,	Good
	4 studies 1,231			1.1; 95% CI, 0.9 to 1.2; P=0.44). No differences in GOL vs.	
	patients 20 to 52 weeks			placebo for serious adverse events	
*Smolen et al.,	RCT	Pts with RA that failed	MTX,	Adverse events occurred	Fair
2008 ¹⁶⁴ OPTION study	623	treatment with MTX	TCZ+MTX	more frequently in pts treated with TCZ (71%) vs.	
Smolen et al.,	32 weeks RCT	Pts with RA with prior	MTX,	MTX monotherapy (63%) Serious adverse events	Fair
2009 ¹⁶⁷ RAPID 2 study	619	MTX use for ≥6 months	CTZ+MTX	occurred more frequently in CTZ pts vs. pts treated with	raii
·O	24 weeks	Dt. with DA to the divide	001	MTX monotherapy	
*Smolen et al., 2009 ¹⁷⁰	RCT 461	Pts with RA treated with at least one dose of an TNF inhibitor	GOL	No statistically significant differences in adverse events	Fair
	24 weeks				
Van Riel et al., 2006 ⁸⁷	Open-label RCT	Inadequate control of disease with MTX	ETA, ETA+MTX	No statistically significant differences in adverse events	Fair
	315			events	
	16 weeks				
Weinblatt et	RCT	Pts with active RA	ABA	Higher incidence of serious	Fair
al., 2006 ²⁵⁸ ASSURE study	1,456 1 year	despite background biologic or synthetic DMARD treatment		adverse events in pts on ABA and a biologic background DMARD	
Weinblatt et al., 2006 ¹²⁴	Uncontrolled extension of RCT	Pts with active RA despite MTX treatment	ADA	Incidence of serious adverse events remained constant over time	Fair
	162				
	3.4 years				
Westhovens	RCT	Pts with active RA	INF+MTX,	No statistically significant	Good
et al., 2006 ¹⁵⁵ START study	1,084 22 weeks	despite MTX treatment	MTX	differences in adverse events, except infection (higher in 10 mg/kg)	
Westhovens	RCT	RA pts naïve to MTX	ABA+	No statistically significant	Fair
et al., 2009 ⁸⁹	509		MTX, MTX	differences in adverse events	

Table 50. Comparative harms in patients with rheumatoid arthritis and treated with biologic DMARDs (continued)

Study	Study Design N Duration	Study Population	Drug	Results	Quality Rating
*Wiens et al., 2009 ²⁵⁶	Meta-analysis 2,385 8 weeks to 3 years	Pts with RA with or without concomitant MTX	ETA, MTX	No statistically significant differences in withdrawals due to adverse events, serious adverse events, serious infections, malignancies, or deaths.	Fair
*Wiens et al.,	Meta-analysis	Pts with RA with or without concomitant MTX	ADA, ETA, INF	Similar incidence of serious adverse events for ADA, ETA, and INF compared with placebo	Fair
2010 ¹⁸³	21 studies 6,503 patients				
	8 weeks to 3 years			•	
*Zhang et al., 2006 ¹⁵⁶	RCT	Pts with active RA despite	MTX,	Rate of adverse events similar between groups	Fair
	173	treatment with MTX	INF+MTX		
	18 weeks				

^{*} New study added since last review.

ABA = abatacept; ADA = adalimumab; AE = adverse event; AERS = adverse event reporting system; ANK = anakinra; CTZ = certolizumab; CYP = cyclophosphamide; DMARD = disease-modifying antirheumatic drug; ETA = etanercept; GOL = golimumab; HCQ = hydroxychloroquine; INF = infliximab; IR = incidence rate; IRR = incidence rate ratio; LEF = leflunomide; MTX = methotrexate; NA = not applicable; NR = not reported; OR = odds ratio; Pts = patients; RA = rheumatoid arthritis; RCT = randomized controlled trial; RR = rate ratio; RTX = rituximab; SSZ = sulfasalazine; TCZ = tocilizumab; TNF = tumor necrosis factor

One good-rated 126 and one fair-rated 183 systematic review and meta-analysis provided indirect evidence regarding comparative differences in adverse events with adalimumab, etanercept, and infliximab. In the good-rated meta-analysis, the relative risk of serious adverse events for biologic DMARDs compared with control was statistically significant only for infliximab (RR, 1.4; 95% CI, 1.0 to 2.0; P=0.048). 126 The infliximab-treated patients in this analysis were more likely than control group patients to withdraw from studies because of adverse events, had more severe adverse events, infection, and infusion reactions. In the fair-rated meta-analysis of adalimumab, etanercept, and infliximab compared with placebo, no statistically significant differences were noted in serious adverse events, serious infections, malignancy, or death (P>0.05 for all comparisons). 183 Based on unadjusted comparison of risk ratios from meta-analyses, infliximab had the highest rate of withdrawal due to adverse events (RR, 2.05; 95% CI, 1.33 to 3.16).

Indirect evidence from additional efficacy trials, cohort studies, and meta-analyses suggests that the overall tolerability profiles are similar among biologic and oral DMARDs, or combinations of biologic and oral DMARDs. ^{67, 70, 76, 84, 86, 87, 89, 90, 116, 121, 127, 136, 138, 156, 170, 175, 177, 178, 210, 254-256} However, several studies suggested that adverse events were more common with biologic DMARDs, given alone or in combination with an oral DMARD. ^{120, 145, 164-167, 173} One prospective cohort study found a slightly lower rate of serious adverse events among patients who had an oral DMARD added to adalimumab, compared with patients who only received adalimumab (5.3 percent vs. 7.3 percent, respectively; *P*=NR). ²⁵⁷ In one RCT of MTX-naïve patients that compared golimumab monotherapy, MTX monotherapy, and golimumab plus MTX, serious adverse events were least common among the golimumab monotherapy group (3.2 percent vs. 6.9 percent vs. 6.3 percent, respectively; *P*=NR). ⁹²

Four RCTs were designed to assess adverse events as primary outcomes. 121, 155, 258, 259 Overall, adverse event rates were similar for abatacept, 258 adalimumab, 121 anakinra, 259 or infliximab 155 and placebo. Other efficacy trials suggested that overall adverse events are higher with biologic DMARDs than with placebo.

In placebo-controlled efficacy trials of biologic DMARDs, injection site reactions, abdominal pain, nausea, headache, diarrhea, upper respiratory tract infections, and urinary tract infections were commonly reported adverse events. The combination of two biologic DMARDs consistently had more adverse events than monotherapy. A 24-week RCT, described in more detail for KQ 1, assessed a combination treatment of etanercept (25 mg or 50 mg/week) and anakinra (100 mg/day) compared with etanercept monotherapy. The frequency of serious adverse events was substantially higher in the combination groups than the etanercept-only group (14.8 percent for 50 mg etanercept plus anakinra; 4.9 percent for 25 mg etanercept plus anakinra; 2.5 percent for etanercept only; *P*=NR). Furthermore, a study determining the efficacy of abatacept combined with different background treatments found substantially higher rates of serious adverse events in patients on abatacept combined with a biologic background treatment (22.3 percent) than in those not on a combination of two biologic DMARDs (12.5 percent).

One nonrandomized open-label trial determined the comparative harms among combinations of biologic DMARDs and oral DMARDs other than MTX. No differences in adverse events could be detected between a combination of etanercept and either sulfasalazine or hydroxychloroquine. Similar evidence of similarities in adverse events among background oral DMARDs comes from an RCT comparing rituximab, MTX, rituximab plus MTX, and rituximab plus cyclophosphamide, and a prospective cohort study comparing anakinra plus MTX with anakinra plus leflunomide. Both studies reported no significant differences in adverse events among these combinations of biologic and oral DMARDs.

The ERA study,⁷⁷ described in more detail in KQ 1, had an open-label extension of up to 2 years,¹⁸⁸ and an uncontrolled extension with etanercept (25 mg twice weekly) of up to 5 years.¹⁸⁹ The rates of adverse events for etanercept did not rise during long-term treatment compared with rates reported from the short-term RCT. These results are consistent with findings from long-term extension studies of efficacy RCTs on adalimumab,¹²⁴ anakinra,^{129, 319} and infliximab.^{149, 261} Likewise, safety analyses of postmarketing surveillance data showed that the incidence of adverse events did not rise over time in patients treated with adalimumab²⁹⁸ and etanercept.²⁶⁰

Biologic DMARDs—specific adverse events. Biologic DMARDs can produce several serious adverse events (Table 51). Studies of adverse events with biologic DMARDs are summarized in Tables 51 to 56.

Cardiovascular and cerebrovascular events. No direct evidence compared the risk of cardiovascular or cerebrovascular events for one biologic DMARD with another. Eleven observational studies provide evidence for the risk of cardiovascular and cerebrovascular events (Table 51). ^{214, 216, 234, 262-267, 321} These studies use a variety of comparator groups, including oral DMARDs, "conventional" DMARDs, and placebo. In some cases, the comparison group is unclear. Whenever possible, we specify the comparator in the tables and summary text.

One additional RCT conducted in a population with CHF³²² is discussed because it provides general evidence for risk of using infliximab in patients with existing heart failure (even though these patients did not have RA).

Table 51. Cardiovascular and cerebrovascular events in patients with rheumatoid arthritis and treated with biologic DMARDs

	Study Design				Ouglits
Study	N Duration	Study Population	Drug	Results	Quality Rating
*Curtis et al., 2007 ²⁶³	Retrospective cohort study	(Also Crohn's disease but	ETA, INF	Cumulative incidence of heart failure among pts treated with	Fair
	2,121	excluded here)		ETA or INF vs. those not: 4.4 cases per 1,000 persons and	
	5 years			1.0 case per 1,000 persons in the unexposed group (RR, 4.3; <i>P</i> =NS).	
*Dixon et al., 2007 ²⁶⁷	Prospective cohort	Pts with RA in the British Society for Rheumatology		IRR, of MI among anti-TNF users compared with oral	Good
BSRBR	10,755	Biologics Register (BSRBR)	DMARDs	DMARDs:1.44 (95% CI, 0.56 to 3.67)	
	1.66 years median followup	,		,	
Jacobsson et al., 2005 ²⁶⁶	Retrospective cohort study	Pts with RA in daily clinical care in Sweden	ETA, INF	Pts on anti-TNF treatment had a lower rate of cardiovascular	Fair
	983			events than pts on traditional RA therapy	
	NR				
*Listing et al., 2008 ²⁶⁴	Prospective cohort	the RABBIT German	ADA, ETA, INF, oral DMARDs	HR for incident HF among those using anti-TNFs vs. conventional DMARDs: 1.66, (95% CI, 0.67 to 4.10; <i>P</i> =0.28); HR for worsening HF among prevalent cases: 1.18, (95% CI, 0.30 to 4.73; <i>P</i> =0.81)	Good
	4,248				
	5 years				
*Nadareishvili et al., 2008 ²¹⁴	Nested case- control	RA pts in National Data Bank for Rheumatic Diseases	ADA, ETA, INF	Association of treatment with ischemic stroke: Anti-TNF: OR,0.79; 95% CI, 0.34 to 1.82; <i>P</i> =0.584)	Fair
	269 cases among 7045 patients				
	8 years				
*Naranjo et al., 2008 ²¹⁵	Cross-sectional	Sample of RA pts across	TNF-alpha	Anti-TNF agents associated	Fair
2000	4,363	15 countries	antagonists (not	with reduced risk for CV morbidity (HR, 0.64; 95% CI,	
	Clinician and patient recall		specified)	0.49 to 0.83).	
Kwon et al., 2003 ³²¹	Database analysis AERS	Pts on ETA or INF therapy	ETA, INF	Most pts with CHF did not have preexisting conditions	Fair
	47 cases of CHF				
	NA, AERS data				
*Setoguchi et al., 2008 ²⁶⁵	Retrospective cohort	Medicare pts with RA from 2 states	ADA, ETA, INF, MTX	Effect of anti-TNFs compared with MTX on heart failure and/or death; HR,1.70; 95% CI, 1.07 to 2.69	Good
	5,593				
	10 years				

Table 51. Cardiovascular and cerebrovascular events in patients with rheumatoid arthritis and treated with biologic DMARDs (continued)

Study	Study Design N Duration	Study Population	Drug	Results	Quality Rating
*Solomon et al., 2006 ²¹⁶	Case-control study 3,501	Pennsylvania Medicare enrollees with RA	Biologic DMARDs	No statistically significant association between use of biologic DMARDs and cardiovascular events	Fair
	24 months			cardiovascular events	
*Suissa et al, 2006 ²³⁴	Prospective cohort	RA pts in U.S. PharMetrics Adata	ADA,ETA, INF	Biologic DMARD use slightly associated with acute MI (RR,1.30; 95% CI, 0.92 to 1.83)	Fair
	107,908				
	14 months			,	
Wolfe et al., 2004 ²⁶²	Retrospective cohort study	•	ADA, ETA, INF	Pts on anti-TNF treatment had a lower rate of CHF than pts on traditional RA therapy	Fair
	13,171				
	2 years				

^{*} New study added since last review.

ABA = abatacept; ADA = adalimumab; AE = adverse event; AERS = adverse event reporting system; ANK = anakinra; CHF = congestive heart failure; CV = cardiovascular; DMARD = disease-modifying antirheumatic drug; ETA = etanercept; HF = heart failure; HR = hazard ratio; INF = infliximab; IR = incidence rate; IRR = incidence rate ratio; LEF = leflunomide; MI = myocardial infarction; MTX = methotrexate; NA = not applicable; OR = odds ratio; Pts = patients; RA = rheumatoid arthritis; RCT = randomized controlled trial; RR = rate ratio; TCZ = tocilizumab; TNF = tumor necrosis factor; vs. = versus

The evidence on the risk of congestive heart failure (CHF) with anti-TNF therapy is mixed. One observational study reported lower rates of CHF²⁶² for RA patients on anti-TNF therapy than for those on conventional RA therapies. This large retrospective cohort study (N=13,171) reported an absolute risk reduction for CHF of 1.2 percent (95% CI, -1.9 to -0.5; *P*=NR) for patients treated with anti-TNF therapy compared with those not treated with anti-TNF medications over a 2-year period. This study contrasts with three other cohort studies that found an increased risk of heart failure with adalimumab, etanercept, and infliximab compared with no treatment or oral DMARD. While the increased risk was not statistically significant in two of these studies, one good-rated retrospective cohort study of 5,593 Medicare patients with RA from two U.S. states reported statistically significant increases in the risk of heart failure and death (HR, 1.70; 95% CI, 1.07 to 2.69).

An analysis of the FDA AERS data reported that half of the patients who developed new onset CHF under etanercept or infliximab treatment did not have any identifiable risk factors. ³²¹ Indirect evidence comes from three trials, two on etanercept ³²³ and one on infliximab, ³²² that evaluated the efficacy of these drugs for the treatment of CHF. Study populations did not have any rheumatoid illnesses. One of the two etanercept trials was terminated early because interim analyses indicated higher mortality rates in patients treated with etanercept. Similarly, the infliximab study presented higher mortality rates in the 10 mg/kg arm than in the placebo and 5 mg/kg arm. ³²² The package insert of infliximab issues a contraindication regarding use in patients with CHF; the package inserts of etanercept and adalimumab emphasize precaution.

Three observational studies assessed the risk of cardiovascular events (broadly defined). 215, 216, 266 One case-control study of Medicare patients with RA found no statistically significant association between use of biologic DMARDs and cardiovascular events, 216 while two studies

reported a decreased risk of cardiovascular events with biologic DMARDs. ^{215, 266} A good-quality Swedish retrospective cohort study (N=983), using data from population-based databases, reported a statistically significantly lower risk of cardiovascular events in patients treated with anti-TNF medications than in those on conventional therapy (age-sex adjusted rate ratio: 0.46/1,000 person-years; 95% CI, 0.25 to 0.85; P=0.013). ²⁶⁶ A cross-sectional analysis of patients from 15 countries participating in the QUEST-RA study reported that patients exposed to biologic DMARDs had a reduced risk of cardiovascular morbidity (HR, 0.42; 95% CI, 0.21 to 0.81; P<0.05). ²¹⁵

One nested case-control study assessed the risk of stroke with adalimumab, etanercept, and infliximab, ²¹⁴ and two cohort studies assessed the risk of MI with these same biologic DMARDs. ^{234, 267} The study assessing stroke was conducted in the National Data Bank for Rheumatic Diseases, finding a slight decrease in the risk of stroke with adalimumab, etanercept, and infliximab (OR, 0.79; 95% CI, 0.34 to 1.82; *P*=NS). ²¹⁴ The two studies assessing risk of MI also found no statistically significant differences in the risk of MI, although results trended towards an increased risk of MI for these biologic DMARDs. In a good-rated analysis of 10,755 patients from the British Society for Rheumatology Biologics Register, the incidence rate ratio was 1.44 (95% CI, 0.56 to 3.67) for biologic DMARDs compared with oral DMARDs. In a larger fair-rated analysis of 107,908 patients from a U.S. claims database, biologic DMARDs were associated with a similar nonstatistically significant increase in the risk of MI (RR, 1.30; 95% CI, 0.92 to 1.83). ²³⁴

Infections. Because of the immunosuppressive nature of biologic DMARDs, serious infections including TB, pneumonia, osteomyelitis, progressive multifocal leucoencephalopathy (PML), and sepsis are of special concern. The FDA has issued black box warnings about an increased risk of infections for adalimumab and infliximab. The package inserts of anakinra and etanercept also contain bold letter warnings. Recently, the FDA issued an alert for health care professionals highlighting the death of two patients from PML who had been treated with rituximab for systemic lupus erythematosus. ³²⁴ The available head-to-head evidence is insufficient to draw firm conclusions about the comparative risk of biologic DMARDs.

The best comparative evidence stems from an RCT⁶⁶ and two prospective cohort studies. ²⁶⁸, ²⁶⁹ The trial randomized 431 patients with RA to MTX, abatacept plus MTX, or infliximab plus MTX. Serious infections were reported more often in the infliximab group than the abatacept group (*P*=NR). ⁶⁶ One cohort study enrolled 8,973 patients with severe RA from the British Society for Rheumatology Biologics Register (BSRBR). Patients were treated with adalimumab (n=1,190), etanercept (n=3,596), infliximab (n=2,878), or oral DMARDs (n=1,354). The overall followup included 11,220 person-years. Results indicated no differences in risks among anti-TNF drugs. Compared with oral DMARDs, anti-TNF drugs did not lead to a higher overall risk for serious infections (IRR, 1.03; 95% CI, 0.68 to 1.57). The frequency of serious skin infections, however, was fourfold higher in patients treated with anti-TNF drugs than with oral DMARDs (IRR, 4.28; 95% CI, 1.06 to 17.17). A second cohort study conducted in BSRBR followed 15,396 patients with RA who were taking adalimumab, etanercept, or infliximab. ²⁶⁹ As a class, these anti-TNF drugs increased risk of serious infections (HR, 1.2; 95% CI, 1.1 to 1.5). No statistically significant difference in the incidence rate was observed comparing across the individual drugs.

Although the statistical analysis for the prospective cohort studies controlled for multiple confounding factors, residual confounding in such a study design is likely. Results, therefore,

must be interpreted cautiously. Event rates of serious infections in efficacy trials comparing anti-TNF drugs with oral DMARDs were generally too low to draw meaningful conclusions.

The following paragraphs summarize the evidence on the general risk of biologic DMARDs for serious infections (i.e., the risk of biologic DMARDs compared with that of placebo treatment). Table 52 presents studies reporting on infections in those patients treated with biologic DMARDs.

Charder	Study Design N	Chudu Damidatian	Davis	Passide	Quality
*Alonoso-Ruiz	Duration Mota analysis	Study Population Pts with RA	Drug ADA ETA, INF	Results Relative risk of infections	Rating Good
et al. 2008 ¹²⁶	Meta-analysis 13 trials 7,087 patients	T IS WILLTON	ADA ETA, INF	compared with control group: ADA (RR, 1.1; 95% CI, 0.9 to 1,2); ETA (RR, 1.0; 95% CI,	Good
	St least 6 months			0.9 to 1.0); INF (RR, 1.2; 95% CI, 1.1 to 1.3)	
Askling et al., 2005 ²⁸¹	Retrospective cohort study	Pts with RA in daily clinical care in	ETA, INF	Fourfold increase of risk for TB for ETA and INF compared	Good
	62,321	Sweden		with conventional DMARDs	
	467,770 person- years				
Bergstrom et al., 2004 ³²⁵	Retrospective cohort study	Pts with inflammatory arthritis in daily clinical	ETA, INF	Pts treated with INF or ETA are more likely to develop	Fair
	985	care, U.S.		symptomatic coccidiomycosis than pts on synthetic	
	3 years			DMARDs	
*Bernatsky et al., 2007 ²¹⁸	Nested case- control	RA pts registered in claims databases in Quebec	Anti-TNFs (not specified), oral DMARDs, corticosteroids	No statistical association between anti-TNF use and risk for all infections requiring hospitalization (RR, 1.9; 95%	Fair
	23,733				
	Up to 23 years			CI, 0.7 to 5.3)	
*Bernatsky et al., 2010 ²⁷⁰	Meta-analysis	Studies estimating	Biologic DMARD use vs. no use	Biologic DMARD use increased risk of serious infection (pooled adjusted RR, 1.37, 95% CI, 1.18 to 1.60)	Fair
al., 2010	7 studies of administrative claims or electronic health records				
Bongartz et al.,	Meta-analysis	Pts with active RA	ADA, INF	Statistically significantly higher	Fair
2006 ²⁷¹	5,014	despite MTX treatment		risk of serious infections for ADA and INF compared with	
	3 to 12 months			placebo (3.6% vs. 1.7%; OR, 2.0; 95% CI, 1.3 to 3.1)	
*Brassard et al., 2006 ²¹⁹	Retrospective cohort	RA pts with ≥1 claim for anti-RA drugs in	Several oral DMARDs,	Adjusted rate ratio of developing TB:	Fair
	112,300	U.S. database	ANK, ETA, INF,	Biologic DMARDs:1.5 (95% CI, 1.1 to 1.9); INF:1.6 (95% CI, 1.0 to 2.6) ETA:1.2 (95% CI, 0.9 to 1.8) ANK:1.3 (95% CI, 0.8 to 2.1)	
	Up to 5 years		corticosteroids		

	Study Design				0!!
Study	N Duration	Study Population	Drug	Results	Quality Rating
*Cohen et al.,	RCT	Pts with RA with	RTX+MTX,	The rate of serious infection	Fair
2006 ¹⁵⁸	520	inadequate response to previous or current	MTX	was 5.2 and 3.7 per 100 pt-yrs in the RTX+MTX and MTX	
REFLEX Trial	24 weeks	treatment with anti- TNF agents		groups, respectively	
Combe et al.,	RCT	Active RA despite	ETA, SSZ,	Significantly more infections in	Fair
2006 ¹⁴⁵	260	SSZ treatment	ETA+SSZ	ETA and ETA+SSZ than in SSZ group (47% vs. 31% vs.	
	Up to 2 years			13%; <i>P</i> <0.05) at 6 months; similar pattern at 2 years (<i>P</i> <0.001)	
*Curtis et al., 2007 ^{277, 278}	Retrospective cohort study	Pts with RA enrolled in a large U.S. health	alpha	Risk of hospitalization with a bacterial infection for those	Good
	5,326	care organization	antagonists	receiving TNF-alpha antagonists was 1.94 (95% CI,	
	Up to 67 months			1.32 to 2.83) compared with pts that received MTX only; risk highest in first 6 months – ETA: 1.61, 95% CI, (0.75 to 3.47) INF 2.40, 95% CI, (1.23 to 4.68)	
*den Broeder et al., 2007 ³²⁶	Retrospective cohort	RA pts that were TNF-	TNF-alpha antagonists	Perioperative continuation of anti-TNFs not associated with	Fair
et al., 2007	1,219	alpha antagonist naïve	anagonists	increased risk of surgical site infection. Wound dehiscence in patients that continued anti-TNFs compared with patients that temporarily discontinued anti-TNF treatment (OR, 11.2; 95% CI, 1.4 to 90).	
	1 year followup				
Dixon et al., 2006 ²⁶⁸	Prospective cohort study	Pts with active RA despite MTX treatment	ADA, ETA, INF	No differences among anti-TNF drugs for risk of serious infections. Similar risk for serious infections between anti-	Fair
	8,973				
	11,220 pt-years			TNF drugs and oral DMARDs	
*Dixon et al., 2010 ²⁷⁹	Prospective cohort study	Pts with RA from the British Society for	ADA, ETA, INF vs. oral	Adjusted incidence rate ratio of TB cases compared with ETA:	Fair
BSRBR	13,739 7,345 person- years (DMARD cohort) 34,025 person- years (anti-TNF cohort)	Rheumatology Biologics Register (BSRBR)	S UMARDS	INF 3.1 (95% CI, 1.0 to 9.5) and ADA 4.2 (1.4-12.4)	
*Galloway et al., 2011 ²⁶⁹	Prospective cohort study	Pts with RA from the British Society for	ADA, ETA, INF vs. oral	Adjusted hazard ratio for serious infection in anti-TNF	Fair
BSRBR	15,396	Rheumatology Biologic Register (BSRBR)	s DMARDs	cohort: 1.2 (95% CI, 1.1 to 1.5). No significant difference in	
BONDIN	3.9 years (anti- TNF cohort) 2.6 years (DMARD cohort)	. regional (BONDIN)		serious infection incidence between ADA, ETA, and INF	

Study Design N				Quality
Duration	Study Population		Results	Rating
Retrospective cohort study	Pts with RA in daily clinical care in Spain	ETA, INF	Higher risk of TB for ETA and INF than oral DMARDs	Fair
1,540				
1.1 years				
Prospective cohort	Pts with RA enrolled in the Consortium of	MTX, oral DMARDs,	Adjusted incidence rate ratio (IRR) for infections withanti-TNF	Fair
7,971	Researchers of North			
15,047 person- years	America (CORRONA) registry	PRED	1.30 to 1.78, <i>P</i> <0.001); opportunistic infections (IRR, 1.67; 95% CI, 0.95 to 2.94 <i>P</i> =0.077)	
Retrospective cohort	Tennesee Medicaid- enrolled RA pts	MTX, LEF, SSZ, HCQ,	Compared with MTX biologic DMARDs increased risk of	Good
28,906	<u>Г</u> (л	DMARDs (ADA, ETA,	•	
Up to 180 days			0.78 to 2.19) or serious infections (HR, 1.65; 95% CI, 0.85 to 3.03)	
Case-control 128	Pts with RA that underwent joint surgery	ETN, INF, DMARDs	Higher risk of surgical site infections in anti-TNF group vs. oral DMARD group (OR, 21.80; 95% CI,1.231 to 386.1, <i>P</i> =0.036)	Fair
Database analysis	Pts treated with INF	INF	TB may develop soon after initiation of INF treatment	Fair
70 cases of TB				
NA, AERS data				
RCT	Pts with RA that	MTX,	Occurrence of serious	Fair
982		CIZ+MIX	• •	
52 weeks			MTX alone	
Database analysis	Pts treated with ETA and INF	ETA, INF	Histoplasmosis infections may be a serious complication of	Fair
10 cases of histo- plasmosis			pts on INF had a higher rate of infections than pts on ETA	
NA, AERS data			· 	
Meta-analysis	RA pts on anti-TNF	ADA, ETA,	Anti-TNF treatment did not	Fair
18 trials 8,808 patients	tnerapy	INF	increase seirious infection (OR, 1.21; 95% CI, 0.89 to 1.63)	
	N Duration Retrospective cohort study 1,540 1.1 years Prospective cohort 7,971 15,047 personyears Retrospective cohort 28,906 Up to 180 days Case-control 128 Database analysis 70 cases of TB NA, AERS data RCT 982 52 weeks Database analysis 10 cases of histoplasmosis NA, AERS data Meta-analysis 18 trials	N DurationStudy PopulationRetrospective cohort studyPts with RA in daily clinical care in Spain1,540 1.1 yearsPts with RA enrolled in the Consortium of Rheumatology Researchers of North America (CORRONA) registryRetrospective cohort 28,906 Up to 180 daysTennesee Medicaid- enrolled RA pts initiating DMARD useCase-control 128Pts with RA that underwent joint surgeryDatabase analysis 70 cases of TB NA, AERS dataPts treated with INFRCT 982 Database analysisPts with RA that received MTX for ≥6 months prior to baseline52 weeksPts treated with ETA and INF10 cases of histo- plasmosis NA, AERS dataPts treated with ETA and INF10 cases of histo- plasmosis NA, AERS dataRA pts on anti-TNF therapy	N DurationStudy PopulationDrugRetrospective cohort studyPts with RA in daily clinical care in SpainETA, INF1,540 1.1 yearsPts with RA enrolled in the Consortium of Rheumatology Researchers of North America (CORRONA) registryMTX, oral DMARDs, anti-TNF agents, PREDRetrospective cohort 28,906 Up to 180 daysTennesee Medicaid- enrolled RA pts initiating DMARD useMTX, LEF, SSZ, HCQ, biologic DMARDs (ADA, ETA, INF), steroidsCase-control 128Pts with RA that underwent joint surgeryETN, INF, DMARDsDatabase analysis 70 cases of TB NA, AERS dataPts with RA that received MTX for ≥6 months prior to baselineINF52 weeksPts treated with ETA and INFETA, INFDatabase analysisPts treated with ETA and INFETA, INF10 cases of histo- plasmosis NA, AERS dataRA pts on anti-TNF therapyADA, ETA, INF	Nometion Study Population Drug Results Retrospective cohort study Pts with RA in daily clinical care in Spain ETA, INF Higher risk of TB for ETA and INF than oral DMARDs 1,540 1.1 years Prospective cohort With RA enrolled in the Consortium of Rheumatology and The Consortium of Rheumatology assers compared with anti-TNF agents, anti-TNF agents, and the CORRONA) registry Adjusted incidence rate ratio (IRR) for infections withanti-TNF agents compared with oral DMARDs agents compared with oral DMARDs (IRR, 1.52; 95% CI, 1.30 to 1.78, P<0.001) (IRR, 1.50; 95% CI, 0.95 to 2.94 P=0.077)

(continued)					
Study	Study Design N Duration	Study Population	Drug	Results	Quality Rating
Listing et al., 2005 ²⁷⁴	Prospective cohort study	clinical care in	AKA, ETA, INF	Higher risk of infections for AKA, ETA, INF compared with	Fair
	1,529	Germany		DMARDs	
	Up to 12 months				
*Migliore et al., 2009 ³²⁸	Retrospective cohort	Pts 65 years old or more with RA, PsA, or	ETA, ADA, INF	Infection rate: ETN 18.51%, ADA 20.51%, INF 15.55%	Fair
	138 with RA	Ankylosing Spondylitis			
	Followup not specified				
Mohan et al., 2004 ²⁸⁴	Database analysis	Pts treated with ETA	ETA	Median interval between first dose and diagnosis of TB was	Fair
	25 cases of TB			11.5 months	
	NA, AERS data				
*Salliot et al., 2009 ²⁷²	Meta-analysis	RA patients receiving ABA, ANK, or RTX	ABA, ANK,	No increase in risk of serious	Fair
2009	12 RCTs		RTX	infection for ABA or RTX; high doses of ANK increased risk of serious infection	
Salliot et al.,	Case series	Pts with different rheumatic diseases; primary care-based cohort	ADA, ETA,	Rates of serious infections in daily practice were higher than ones reported in efficacy trials	Fair
2006 ²⁷⁵	709		INF		
	NR				
*Schiff et al.,	RCT	Pts with RA despite	ABA +MTX, INF +MTX, MTX	Serious infections were reported more with INF (8.5%) than ABA (1.9%)	Fair
2008 ⁶⁶	431	treatment with MTX, anti-TNF therapy naive			
	1 year	, , , , , , , , , , , , , , , , , , , ,		(2.13)	
*Schneeweiss et al., 2007 ²²²	Retrospective cohort	Medicare beneficiaries ages 65 and older with	TNF-alpha antagonists	Compared with MTX use, TNF-alpha did not increase risk of	
	15,597	RA	(ADA, ETA, INF)	serious bacterial infections (RR, 1.04; 95% CI, 0.63 to 1.72)	
	Up to 8 years		,	,	
Slifman et al., 2003 ²⁸⁷	Database analysis	Pts treated with ETA and INF	ETA, INF	Pts on INF had a higher rate of infections than pts on ETA	Fair
	15 cases of listeria infection				
	NA, AERS data				
*Smitten et al., 2008 ²²³	Retrospective cohort	Pts with RA from U.S. PharMetrics data	ADA, ANK, ETA, INF	Biologic DMARDs slightly increased risk of hospitalized	Good
	24,530			infection (RR, 1.21; 95% CI, 1.02 to 1.43).	
	26.6 months			•	

Ctd	Study Design N	Ctualis Daniel etter	D	Daguita	Quality
Study	Duration	Study Population	Drug	Results	Rating
*Smitten et al., 2007 ²²⁴	Retrospective cohort		ANK, ETA, INF	Risk of herpes zoster infection with biologic DMARD: (PM: OR,1.54; 95% CI, 1.04 to	Fair
	12,272 (PM) 38,621 (GPRD)	General Practice Research database		2.29)	
	12.3 to 38.8 months	(GPRD)			
*Smolen et al.,	RCT	Pts with RA with prior	MTX,	Serious infection occurred more	Fair
2009 ¹⁶⁷ RAPID 2 study	619	MTX use for ≥6 months	CIZ+MIX	frequently in CTZ pts vs. pts treated with MTX monotherapy	
	24 weeks			, , , , , , , , , , , , , , , , , , , ,	
St. Clair et al.,	RCT	Early, aggressive RA;	MTX, INF+	Significantly more patients in	Fair
2004 ⁸² ASPIRE study	1,049	MTX-naive N	MTX	the INF+MTX than in the MTX group had more than one	
iter in a diday	54 weeks		serious infection (5.3 vs. 2.1%; <i>P</i> <0.05)		
*Strangfeld et al., 2009 ²²⁵	Prospective cohort		ADA, ETA, INF	Adjusted HR for Herpes Zoster. All anti-TNFs: (HR, 1.63; 95% CI, 0.97 to 2.74)	Good
	5,040				
	up to 36 months	ADA or INF (HR, 1.82; 95% CI, 1.05 to 3.15) ETA (HR, 1.36; 95% CI, 0.73 to 2.55)			
Wallis et al., 2004 ²⁸⁰	Database analysis	Pts treated with ETA and INF	ETA, INF	Pts on INF had a higher rate of granulomatous infections than	Fair
	649 cases of granulomatous infections			pts on ETA	
	NA, AERS data				
'Wiens et al., 2010 ¹⁸³	Meta-analysis	Pts with RA with or	ADA, ETA,	Effect estimate of serious	Fair
2U IU	21 studies 6,503 patients	without concomitant MTX	INF	infections compared with placebo: ADA (2.22, 95% CI, 0.83 to 5.99, <i>P</i> =0.11), ETA	
	8 weeks to 3 years			(0.89, 95%Cl, 0.54 to 1.48, <i>P</i> =0.66), INF (0.96, 95%Cl, 0.39 to 2.38, <i>P</i> =0.93)	
Nesthovens et	RCT	Pts with active RA	INF+MTX,	Risk of serious infections was	Good
al., 2006 ¹⁵⁵ START study	1,084	despite MTX treatment	MTX	similar between placebo and 3 mg/kg infliximab. 10 mg/kg	
Ciriti olddy	22 weeks			infliximab led to increased risk of serious infections	
Wolfe et al., 2004 ²⁸⁵	Prospective cohort study with historic control	Pts with RA in daily clinical care in U.S.	INF, oral DMARDs	TB was more common in pts treated with INF than with oral DMARDs	Fair
	17,242				
	3 years				

Table 52. Infections in patients with rheumatoid arthritis and treated with biologic DMARDs (continued)

Study	Study Design N Duration	Study Population	Drug	Results	Quality Rating
Wolfe et al., 2006 ²³⁷	Prospective cohort study	Pts with RA	ADA, ETA, INF	No increased risk for hospitalization for pneumonia	Fair
	16,788			for ADA, ETA, and INF compared with a historic	
3	3.5 years			control	

^{*} New study added since last review.

ABA = abatacept; ADA = adalimumab; AE = adverse event; AERS = adverse event reporting system; ANK = anakinra; CI = confidence interval; CTZ = certolizumab; DMARD = disease-modifying antirheumatic drug; ETA = etanercept; HR = hazard ratio; INF = infliximab; kg = kilogram; LEF = leflunomide; mg = milligram; MTX = methotrexate; NA = not applicable; OR = odds ratio; RA = rheumatoid arthritis; RCT = randomized controlled trial; RR = rate ratio; RTX = rituximab; SSZ = sulfasalazine; TB = tuberculosis; TCZ = tocilizumab; TNF = tumor necrosis factor

Most studies defined serious infections as those that required antibiotic treatment or led to hospitalization or death. In placebo-controlled safety RCTs, the incidence of serious infections was consistently higher in biologic-treated than in placebo-treated patients. 82, 85, 155, 158, 167, 168 Although clinically significant, these differences rarely reached statistical significance because of low power. For example, in one large safety RCT (N=1,414), a trend towards an increased risk of serious infections in anakinra-treated patients was apparent during the 6 months of treatment (2.1 percent vs. 0.4 percent; P=0.068). The START (Trial for Rheumatoid Arthritis with Remicade) study, another safety RCT (N=1,084) conducted to assess the risk of serious infections during infliximab treatment for RA, indicated a dose-dependent risk for patients on infliximab. 155 After 22 weeks of treatment, patients on 3 mg/kg infliximab had similar rates of serious infections as patients on placebo (1.7 percent vs. 1.7 percent; RR, 1.0; 95% CI, 0.3 to 3.1). Patients treated with 10 mg/kg infliximab had a significantly higher rate of serious infections than patients on placebo (5.0 percent vs. 1.7 percent; RR, 3.1; 95 percent CI, 1.2 to 7.9). The REFLEX (Randomized Evaluation of Long-Term Efficacy of Rituximab) trial randomized 520 patients to 24 weeks of treatment with MTX or rituximab plus MTX. 158 The rate of serious infections was slightly higher among rituximab-treated patients (5.2 vs. 3.7 per 100 person-years). In both the RAPID1 and RAPID2 (RA Prevention of Structural Damage) trials, 167, 168 two trials assessing the efficacy of certolizumab in RA patients previously treated with MTX, serious infections occurred more frequently among the certolizumab-treated patients.

Six systematic reviews and meta-analyses have assessed serious infections with biologic DMARDs. ^{126, 183, 255, 270-272} Some of these analyses provide drug-specific effect size estimates, although none provide adjusted indirect comparisons or mixed treatment comparisons to adequately compare risk of infection among biologic DMARDs. Effect size estimates generally suggest that infection rates are increased with biologic DMARDs; several analyses found this increase to be statistically nonsignficant. ^{183, 255} In a fair-rate meta-analysis of efficacy studies of adalimumab- and infliximab-treated patients, the pooled odds ratio for serious infections was 2.0 (95% CI, 1.3 to 3.1) relative to placebo. ²⁷¹ A fair-rated meta-analysis of large cohort studies (excluding trials) of anti-TNF drugs also found an increased risk of serious infections (RR, 1.37; 95% CI, 1.18 to 1.60). ²⁷⁰ In a good-rated meta-analysis of 13 trials (7,087 patients) of adalimumab, etanercept, and infliximab, a statistically significant increase in risk of infection was observed only among the infliximab group (RR, 1.2; 95% CI, 1.1 to 1.3). ¹²⁶ Another fair

meta-analysis of 12 RCTs did not find an increased risk of serious infections with abatacept or rituximab, but found that high doses of anakinra did increase risk.²⁷²

Long-term observational studies generally support an increased risk of infection with biologic DMARDs, although not in across all studies. 158, 218, 222, 223, 226, 240, 273-279, 328 A large, French case series of 709 patients with various rheumatic diseases treated with adalimumab, etanercept, or infliximab in daily clinical practice reported a substantially higher rate of serious infections (10.5 per 100 person-years) than rates reported in phase 3 efficacy trials (3 to 4 per 100 person-years).²⁷⁵ A prospective cohort study of 7,971 patients (15,047 patient years) with RA in the Consortium of Rheumatology Researchers of North America (CORRONA) registry reported an increased rate of infection for anti-TNF drugs compared with oral DMARDs (IRR, 1.52; 95% CI, 1.30 to 1.78). 226 A large good-rated U.S. cohort study (N=5,326) of patients with RA enrolled in a U.S. health care organization found an increased risk of hospitalization with bacterial infection for those treated with adalimumab, etanercept, or infliximab (HR, 1.94; 95% CI, 1.32 to 2.83) compared with patients that only received MTX. ^{277, 278} This finding contrasts with a large retrospective cohort study of 15,597 U.S. Medicare patients receiving adalimumab, etanercept, or infliximab;²²² compared with MTX use there was no increased risk of serious infection with these biologic DMARDs. Two additional good-rated cohort studies showed an increased risk of infection hospitalization. ^{223, 240} One retrospective cohort study using U.S. administrative claims data showed a slightly increased risk of hospitalized infection with adalimumab, anakinra, etanercept, and infliximab (RR, 1.21; 95% CI, 1.02 to 1.43).²²³ Another retrospective cohort study of Tennessee Medicaid patients did not find a statistically significant increase in risk of hospitalization due to pneumonia (HR, 1.31; 95% CI, 0.78 to 2.19) or serious infection (HR, 1.65; 95% CI, 0.85 to 3.03) for patients treated with adalimumab, etanercept, or infliximab compared with MTX. 240

In addition to bacterial pathogens, serious infections included cases of TB, ²⁸³ coccidiomycosis, ³²⁵ histoplasmosis, ²⁸⁶ listeriosis, ²⁸⁷ candida, ²⁸³ and herpes. ^{224, 225}

In a fair-rated cohort study of 13,739 patients with RA in the BSRBR the incidence of TB with oral DMARDs was compared with adalimumab, etanercept, and infliximab.²⁷⁹ No cases of TB were observed among oral DMARD users and only 40 cases of TB were observed among the biologic DMARD users, so statistical analyses only compared biologic DMARDs. Compared with etanercept, the incidence rate ratio of TB was higher for infliximab (IRR, 3.1; 95% CI, 1.0 to 9.5) and adalimumab (IRR, 4.2; 95% CI, 1.4- to 12.4).

Six additional cohort studies determined the risk of TB or granulomatous infections during treatment with infliximab or etanercept. All studies reported a significant increase in risk attributable to biologic DMARDs relative to placebo. For example, in a fair-rated retrospective cohort study of 112,300 U.S. patients with RA, the rate ratio for developing TB was 1.5 with biologic DMARDs (95% CI, 1.1 to 1.9). For the individual agents, the rate ratio was highest with infliximab (RR, 1.6; 95% CI, 1.0 to 2.6) compared with etanercept and anakinra (respectively, RR, 1.2; 95% CI, 0.9 to 1.8; and RR, 1.3; 95% CI, 0.8 to 2.1).

Other evidence regarding the risk of TB comes from Spanish, Swedish, and U.S. databases that collected data on patients treated with biologic DMARDs. ^{281, 282, 285} The U.S. study, using data from the National Data Bank of Rheumatic Diseases (NBI), reported an eightfold higher rate of TB in patients treated with infliximab than in patients in a historic control group who had been treated with synthetic DMARDs. ²⁸⁵ The analysis yielded rates of 6.2 cases per 100,000 person-years in the control group and 52.5 cases per 100,000 person-years in patients on infliximab. The other two studies were based on the Spanish BIOBADASER (Base de Datos de

Productos Biologicos de la Sociedad Espanola de Reumatologia)²⁸² and several Swedish databases.²⁸¹ Both studies analyzed data on infliximab and etanercept and indicated a substantially higher risk for TB in patients treated with etanercept or infliximab than in those on synthetic RA therapy. The Swedish study reported a fourfold increased risk of TB (RR, 4.0; 95% CI, 1.3 to 12) for patients on anti-TNF treatment compared with the risk for RA patients not exposed to etanercept or infliximab.²⁸¹ The incidence of TB in patients treated with infliximab was 145 per 100,000 (95% CI, 58 to 299) person years; in patients treated with etanercept, the incidence was 80 (95% CI, 16 to 232) per 100,000 person years.

Three studies based on spontaneously reported adverse events from the FDA AERS database provided similar results. ^{280, 283, 284} These studies reflecte reports of adverse events, but are subject to reporting and other biases. One analysis of AERS data focused on granulomatous infections in general. It indicated a higher rate among patients treated with infliximab (239 cases per 100,000 patients) than with etanercept (74 cases per 100,000 patients). ²⁸⁰ The rate of TB in this study was 144 cases per 100,000 patients for infliximab and 35 cases per 100,000 patients for etanercept. However, incidence rates must be compared cautiously because this study reported cases per treated patients and not per patient years. ²⁸⁰ Another AERS analysis reported histoplasmosis to be related to treatment with etanercept and infliximab. ²⁸⁶

Two observational studies assessed the risk of herpes zoster infection with biologic DMARDs. ^{224, 225} A good-rated prospective cohort study of 5,040 patients with RA initiating treatment with adalimumab, etanercept, or infliximab reported a statistically nonsignificant but potentially clinically significant increase in the risk of herpes zoster infection (HR, 1.63; 95% CI, 0.97 to 2.74). ²²⁵ This risk was greatest among patients treated with adalimumab or infliximab (HR, 1.82; 95% CI, 1.03 to 3.15) in comparison with those treated with etanercept (HR, 1.36; 95% CI, 0.73 to 2.55). A fair-rated retrospective cohort study of patient in a U.S. claims database and patients from the UK General Practice Research Database found a risk of herpes zoster infection of similar magnitude (OR, 1.54; 95% CI, 1.04 to 2.29). ²²⁴

One case-control study compared the risk of surgical site infections in patients taking anti-TNF drugs and patients taking oral DMARDs among patients with RA undergoing joint surgery.³²⁷ In this relatively small study (N=128) the risk of infection was significantly greater among patients in the anti-TNF drug group (OR, 21.8; 95% CI, 1.2 to 386.1; *P*=0.036).

Infusion and injections site reactions. Infusion reactions (abatacept, infliximab, rituximab, tocilizumab) and injection site reactions (adalimumab, anakinra, certolizumab, etanercept, golimumab) were the more commonly and consistently reported adverse events. Most infusion reactions were nonspecific symptoms such as headache, dizziness, nausea, pruritus, chills, or fever. Studies reporting infusion or injection site reactions in patients treated with biologic DMARDs are presented in Table 53.

In clinical trials of infliximab for the treatment of RA or Crohn's disease, 17 percent of patients experienced infusion reactions; 0.5 percent were severe and resembled acute anaphylactic conditions or led to convulsions.²⁷³ In these trials, however, less than 2 percent of patients discontinued because of infusion reactions.²⁷³ A prospective cohort study of infliximab in a Canadian clinical care setting reported substantially higher rates of reactions than did the clinical trials.³²⁹ Specifically, in the community study (113 patients with 1,183 infusions), 53 percent of patients experienced at least one infusion reaction during the course of the therapy (mean 15 months). Reactions with infliximab were reported more commonly than with other biologic DMARDs in an RCT comparing abatacept and infliximab,⁶⁶ and in a retrospective cohort study comparing adalimumab (injection site reaction), etanercept, and infliximab.²⁵³ In the

Table 53. Infusion or injection site reactions in patients with rheumatoid arthritis and treated with biologic DMARDs

	Study Design				Ouglit
Study	N Duration	Study Population	Drug	Results	Quality Rating
*Cohen et al.,	RCT	Pts with RA with inadequate		Infusion reactions occurred	Fair
2006 ¹⁵⁸ REFLEX Trial	520	response to previous or current treatment with anti-	MTX	in 23% of RTX+MTX pts vs. 18% in MTX alone	
INCI LEX IIIai	24 weeks	TNF agents		1070 III WITX dione	
Emery et al.,	RCT		RTX+MTX,	Acute infusion reaction	Fair
2006 ¹⁶¹ DANCER trial	465	treatment with at least 1 but not more than 5 DMARDs	MTX	occurred more frequently in pts treated with RTX (23%	
	24 weeks	(other than MTX) and/or biologic response modifiers		and 32% in the 500-mg and 1,000-mg groups, respectively) vs. MTX alone (17%)	
leischmann et	RCT	Pts with active RA despite	ANK	Higher rates of injection site	Fair
al., 2003 ²⁵⁹	1,414	MTX treatment		reactions with ANK than placebo	
	6 months				
Gartlehner et al., 2006 ⁷⁴	Meta-analysis	Patients who have failed MTX treatment; mean	ADA, ANK, ETA,INF	Higher rates of injection site/infusion reactions for	Good
ai., 2000	5,248	disease duration: varied	□ 17 t, 11 ti	ANK than ADA and ETA	
Langer et al	NA Postmarketing	Pts with RA, initiating ANK	ANK	(56% vs. 19% vs. 25%)	Fair
Langer et al., 2003 ³²⁰	Postmarketing surveillance	treatment	AINK	Lower rates of injection site reactions than in clinical trials	raii
	454			uiais	
*N.4 - 1' - D	6 months	Die W. DAirelle O. ive	4D4 ET4	The second of the first of the first	-
*Martin Du Pan et al., 2009 ²⁵³	Retrospective cohort	Pts with RA in the Swiss Clinical Quality Management for	ADA, ETA, INF	Increased risk for injection site/infusion or systemic allergic reaction in INF vs.	Fair
2009	2,364	Rheumatoid Arthritis		ETA and ADA (HR,	
	9 years	(SCQM-RA) registry treated with an anti-TNF agent		2.11;99%CI,1.23-3.62; <i>P</i> =0.018)	
*Miyasaka et	RCT	Pts with RA that failed 1	ADA	Injection site reactions	Fair
al., 2008 ¹²⁵ CHANGE	352	DMARD, including MTX		occurred more frequently in ADA pts vs. placebo	
study	24 weeks			(<i>P</i> <0.05); Placebo 2.3%; ADA 20 mg 31%; ADA 40 mg 30.8%; ADA 80 mg 33.3%	
Schaible et al., 2000 ²⁷³	Retrospec-tive data analysis of clinical trials	Pts with RA or Crohn's disease	INF	17% of pts on INF in clinical trials had acute infusion reactions	Fair
	913				
	12 weeks to 3 years				
*Schiff et al.,	RCT	Pts with RA despite	ABA+MTX,	Acute infusional events	Fair
2008 ⁶⁶	431	treatment with MTX, anti- TNF therapy naive	INF+MTX, MTX	occurred in 7.1% of those treated with ABA vs. 24.8%	
	1 year			treated with INF.	

Table 53. Infusion or injection site reactions in patients with rheumatoid arthritis and treated with biologic DMARDs (continued)

	Study Design N				Quality
Study	Duration	Study Population	Drug	Results	Rating
Wasserman et al., 2004 ³²⁹	Prospective cohort study 113	Pts with RA starting INF treatment in a clinical care setting	INF	53% of pts on INF experienced at least one infusion reaction	Fair
	15 months				

^{*} New study added since last review.

ABA = abatacept; ADA = adalimumab; ANK = anakinra; DMARD = disease-modifying antirheumatic drug; ETA = etanercept; INF = infliximab; MTX = methotrexate; NA = not applicable; OR = odds ratio; RA = rheumatoid arthritis; RCT = randomized controlled trial; RTX = rituximab; TNF = tumor necrosis factor

randomized trial, 7.1 percent of those treated with abatacept and 24.8 percent of those treated with infliximab had an infusion reaction. In the retrospective cohort study, the risk of infusion reaction (or systemic allergic reaction with adalimumab) was more than twofold greater with infliximab compared with injection site reactions with adalimumab and etanercept (HR, 2.11; 95% CI, 1.23 to 3.62; P=0.018). While comparative data on infusion reactions were not available for rituximab and tocilizumab, two RCTs reported similar rates of infusion reactions; 23 percent and 28 percent.

Injection site reactions were mainly erythema, pruritus, rash, and pain of mild to moderate severity, and they were the most common reason for discontinuation blamed on adverse events. A systematic review reported that the mean, crude incidence rates of injection site reactions in RCTs and observational studies were 17.5 percent (95% CI, 7.1 to 27.9) for adalimumab, 22.4 percent (95% CI, 8.5 to 36.3) for etanercept, and 67.2 percent (95% CI, 38.7 to 95.7) for anakinra. Injection site reactions for adalimumab were slightly higher than this estimate (31.7 percent) in an RCT of 352 patients with RA. The substantially higher incidence of injection site reactions for anakinra than for adalimumab and etanercept is consistent with rates reported in the respective package inserts. A German retrospective study based on postmarketing surveillance data, however, reported a lower incidence of injection site reaction for anakinra than was reported in clinical trials (20 percent).

Interstitial lung disease. The risk of interstitial lung disease with biologic DMARDs was assessed by one fair-quality prospective cohort study conducted in 17,598 patients with RA in the NDB study (Table 54). This study found that current treatment with etanercept and infliximab was not associated with hospitalization for interstitial lung disease. However, past treatment with etanercept (HR, 1.7; 95% CI, 1.0 to 3.0; P=0.056) and infliximab (HR, 2.1; 95% CI, 1.1 to 3.8; P=0.019) was associated with hospitalization for interstitial lung disease.

Table 54. Interstitial lung disease in patients with rheumatoid arthritis and treated with biologic DMARDs

Study	Study Design N Duration	Study Population	Drug	Results	Quality Rating
*Wolfe et al., 2007 ²²⁸	Prospective cohort	Pts with RA in U.S.	ETA, INF	Current treatment with ETA	Fair
	17,598	National Databank for Rheumatic Diseases		and INF not associated with hospitalization for interstitial	
	Up to 3.5 years			lung disease. Past treatment with ETA and INF was associated with hospitalization for interstitial lung disease (HR, 1.7; 95% CI, 1.0 to 3.0; <i>P</i> =0.056; HR, 2.1; 95% CI, 1.1 to 3.8; <i>P</i> =0.019	

^{*} New study added since last review.

ETA = etanercept; HR = hazard ratio; INF = infliximab

Malignancies. The risk of lymphoma, both Hodgkin and non-Hodgkin lymphoma, is generally increased in patients with RA compared with the general population.³³² Data from controlled trials do not provide sufficient evidence concerning a further increase in their risk of cancer attributable to the use of either biologic DMARDs or a combination of biologic and synthetic DMARDs. Findings from retrospective observational studies are mixed (Table 55).

Table 55. Malignancies in patients with rheumatoid arthritis and treated with biologic DMARDs

Study	Study Design N Duration	Study Population	Drug	Results	Quality Rating
Askling et al., 2005 ²⁷⁶	Prospective cohort study	clinical care in Sweden IN	ADA, ETA, INF, oral DMARDs	No increase in solid cancers for pts treated with anti-TNF	Fair
	60,930		DIVIARDS	drugs	
	NR				
Askling et al., 2005 ²⁹²	Prospective cohort study	Pts with RA in daily clinical care in Sweden	ADA, ETA, INF, oral DMARDs	No increase in lymphoma for pts treated with anti-TNF drugs	Fair
	53,067				
	NR				
*Askling et	Prospective cohort	Pts with RA in Sweden	ADA, ETA,	Relative risk of first primary	Fair
al., 2009 ²⁹⁵	6,366		INF	cancer in comparison to biologic-naïve patients: ADA	
	25,693 person-years	3		(RR 1.32, 95% CI, 0.87 to 1.98); ETA (RR 0.78, 95% CI, 0.61 to 1.00); INF (RR 1.09, 95% CI, 0.91 to 1.30); <i>P</i> =0.034	

Study	Study Design N Duration	Study Population	Drug	Results	Quality Rating
	Meta-analysis	Pts with active RA	ADA, INF	Statistically significantly	Fair
al., 2006 ²⁷¹	5,014	despite MTX treatment	ADA, IINI	higher risk of malignancies for	ı alı
	3 to 12 months			ADA and INF compared with placebo (0.8% vs. 0.2%; OR, 3.3; 95% CI, 1.2 to 9.1)	
*Bongartz	Meta-analysis	Pts with RA	ETA	Risk of maliginancy in ETA	Good
et al., 2009 ²⁹⁴	9 studies 3,316 patients			not statistically significantly higher than placebo: HR 1.84 (95% CI, 0.79 to 4.28)	
	At least 12 weeks				
Brown et al., 2002 ³³³	Database analysis AERS	RA or CD pts treated with ETA and INF	INF, ETA	Median interval between initiation of therapy and	Fair
	26 cases of lymphoma			lymphoma 8 weeks; some spontaneous remissions after discontinuation of therapy	
NA, AERS	NA, AERS data			reported	
Chakravarty et al.,	Retrospective cohort study	RA or osteoarthritis pts treated with ETA or INF	ETA, INF	Statistically significant association between anti-TNF (HR, 1.97; 95% CI, NR; <i>P</i> =0.001) and corticosteroid	Fair
2005 ²⁴²	15,789				
	NR			(HR, 1.28; 95% CI, NR; P=0.014) use and nonmelanoma skin cancer	
Geborek et al., 2005 ²⁹¹	Retrospective cohort study	Pts with RA in daily clinical care in Sweden	ETA, INF	Higher risk of lymphoma for anti-TNF drugs than oral	Fair
	1,557			DMARDs	
	5,551 pt-years				
Lebwohl et al., 2005 ³³⁴	Postmarketing database review	Pts with RA treated with ETA	ETA	No increase in the incidence of cutaneous squamous cell	Fair
	1,442			carcinoma for ETA-treated pts	
	3.7 years				
*Leombruno	Meta-analysis	RA pts on anti-TNF	ADA, ETA,	Anti-TNF treatment did not	Fair
et al., 2009 ²⁵⁵	18 trials 8,808 patients	therapy	INF	increase lymphoma (OR 1.26 95% CI, 0.52 to 3.06), nonmelanoma skin cancers	
	Average 0.8 years			(OR 1.27, 95% CI, 0.67 to 2.42), or noncutaneuous cancers plus melanomas (OR 1.31, 95% CI, 0.69 to 2.48)	
*Pallavicini et al.,	Prospective cohort 1,114	RA pts that failed to respond to traditional	ADA, ETA, INF	Similar cancer incidence rate as general population	Fair
2010 ²⁹⁶ LORHEN	Mean 23.32 months	DMARDs		Hazard ratio of cancer risk compared with ETN: ADA (HR 1.66, 95% CI, 0.50 to 5.52, <i>P</i> =0.407); INF (HR 0.59, 95% CI, 0.17 to 2.09, <i>P</i> =0.412)	

	Study Design N				Quality
Study	Duration	Study Population	Drug	Results	Rating
Setoguchi et al., 2006 ²⁹³	Retrospective cohort study	clinical care in U.S. and	ADA, ETA, INF	No increased risk of hematologic and overall	Good
	8,458	Canada		malignancies for pts treated with anti-TNF drugs	
	2,940 person- years (Biologic DMARD) to 30,300 person-years (MTX)			compared with those on oral DMARDs	
*Strangfeld	Prospective cohort	Pts with RA in Germany	ADA, ANK,	No statistically significant	Fair
et al., 2010 ²⁹⁷	5,120	that failed at least one other DMARD therapy	ETA, INF, oral	difference in the overall incidence of new or recurrent	
RABBIT	60 months		DMARDs	malignancies	
*Wiens et	Meta-analysis	Pts with RA with or	ADA, ETA, INF	Effect estimate of malignancies compared with placebo: ADA (0.55, 95% CI, 0.14 to 2.11, <i>P</i> =0.38), ETA (0.98, 95% CI, 0.32 to 3.02, <i>P</i> =0.97), INF (1.64, 95% CI, 0.30 to 8.89, <i>P</i> =0.57)	Fair
al., 2010 ¹⁸³	21 studies 6,503 patients	without concomitant MTX			
	8 weeks to 3 years				
*Wolfe et al.,	Prospective cohort	Pts with RA in U.S. NDB study	ADA, ANK, ETA, INF	Biologics were associated with an increased risk of nonmelanotic skin cancer	Fair
2007 ³³⁵	13,869				
	4. years (mean)			(OR, 1.5; 95% CI, 1.2 to 1.8) and melanoma (OR, 2.3; 95% CI, 0.9 to 5.4). No other malignancy was associated with biologic use. The overall risk of any cancer was 1.0 (95% CI, 0.8 to 1.2).	
Wolfe et al., 2004 ²⁸⁹		Pts with RA in daily clinical care in U.S.	INF, ETA	Pts with RA treated with INF or ETA are more likely to develop lymphoma than the	Fair
	18,572			general population	
	Up to 3 years				
*Wolfe and	Prospective cohort	Pts with RA in U.S. NDB	MTX, ADA,	Pts treated with any anti-	Fair
Michaud, 2007 ²⁹⁰	19,591	study	ETA, INF	TNFs did not have an increases risk for lymphoma compared with RA pts who had not received anti-TNFs.	
*Updates Wolfe 2004 ²⁸⁹	89,710 person- years				

^{*} New study added since last review.

ABA = abatacept; ADA = adalimumab; AE = adverse event; AERS = adverse event reporting system; ANK = anakinra; CD = Crohns disease; CI = confidence interval; DMARD = disease-modifying antirheumatic drug; ETA = etanercept; HR = hazard ratio; INF = infliximab; MTX = methotrexate; NA = not applicable; OR = odds ratio; RA = rheumatoid arthritis; TNF = tumor necrosis factor

Several cohort studies have assessed risk of lymphoma with anti-TNF drugs. An analysis of spontaneously reported cases of lymphoma associated with etanercept or infliximab suggested a

median time of 8 weeks from start of therapy to lymphoma diagnosis, and some cases spontaneously remitted after biologic DMARD discontinuation. ³³³ A large prospective cohort study followed 18,572 RA patients in a registry for up to 3 years. ²⁸⁹ The risk of lymphoma was higher for patients on anti-TNF therapies than for those on oral DMARDs, although not statistically significantly so. Confidence intervals for treatment groups overlapped and the results were insufficient to establish a causal relationship between RA treatments and lymphoma or to delineate differences in risks among treatments. The standardized incidence rate (SIR) in the overall cohort was 1.9 cases per 100,000. The SIR for patients not receiving MTX or any biologic agents was 1.0. The SIRs for patients on specific drugs were as follows: MTX, 1.7 (95% CI, 0.9 to 3.2); infliximab, 2.6 (95% CI, 1.4 to 4.5); and etanercept, 3.8 (95% CI, 1.9 to 7.5). An update of this analysis with additional patients and follow-up time confirmed that the risk of lymphoma was not increased among patients taking adalimumab, etanercept, and infliximab.

Three community-based, retrospective cohort studies from Sweden, Canada, and the United States, however, did not detect any differences in the risks of lymphoma between patients on anti-TNF treatment and those on oral DMARDs. ²⁹¹⁻²⁹³ The largest study included 4,160 patients treated with anti-TNF drugs. ²⁹² Results yielded an adjusted relative risk of 1.1 (95% CI, 0.6 to 2.1) for anti-TNF patients relative to patients on oral DMARDs.

Data from observartional studies and meta-analyses are also mixed regarding an increased risk for overall malignancies in patients treated with biologic DMARDs. Four meta-analyses have evaluated risk of malignancy with anti-TNF drugs. ^{183, 255, 271, 294} Effect size estimates were not statistically significant in three of these analyses, but one fair-rated meta-analysis of more than 5,000 RA patients from adalimumab and infliximab efficacy trials reported a pooled odds ratio for malignancies of 3.3 (95% CI, 1.2 to 9.1). The number needed to harm (NNH) was 154 (95% CI, 91 to 500) within a treatment period of 3 months to 12 months.

Five large cohort studies do not suggest a statistically significant increase in risk of malignancy. 276, 293, 295-297 For example, the largest of these two studies, based on data on more than 60,000 Swedish patients, found SIRs for solid cancers to be similar for RA patients treated with anti-TNF medications and those on conventional therapy using both a contemporary and a historic control group. In another Swedish analysis of 6,366 patients with RA during 25,693 person years of followup, the risk of first cancer did not differ for patients starting anti-TNF drug therapy and patients starting MTX (RR, 1.00; 95% CI, 0.86 to 1.15).²⁹⁵ In a cohort of 8,458 patients with RA from the U.S. and Canada, no increase in risk of overall malignancies was observed for patients taking anti-TNF drugs relative to patients taking oral DMARDs.²⁹³ In a German cohort of 5,120 patients with RA who had failed at least one other DMARD therapy (RABBIT), no statistically significant increase in the adjusted risk of developing malignancy was observed for anti-TNF drugs (HR, 0.7; 95% CI, 0.44 to 1.12; *P*=0.133) and anakinra (HR, 1.39; 95% CI, 0.56 to 3.48; P=0.48). ²⁹⁷ An Italian cohort from the Lombardi Rheumatology Network (LOHREN) registry reported an overall cancer risk for 1,114 RA patients treated with anti-TNF drugs to be similar to the general population, with no statistically significant differences observed among anti-TNF drugs.²⁹⁶

A clinical trial database review did not detect a higher incidence of squamous cell carcinoma in 1,442 RA patients (4,257 person-years) treated with etanercept (crude rate: 2.8 cases/1,000 patients) than for those on placebo; ³³⁴ the median follow-up time was only 3.7 years. A larger retrospective cohort study (N=15,789), however, reported a statistically significant association of a combination of anti-TNF and MTX treatment and nonmelanoma skin cancer (hazard ratio [HR]: 1.28; 95% CI, NR; P=0.014). ²⁴² This finding also was observed in a large prospective

cohort study of 13,869 patients in the U.S. NDB study taking adalimumab, anakinra, etanercept, and infliximab. ³³⁵ These biologic DMARDs were associated with an increased risk of nonmelanotic skin cancer (OR, 1.5; 95% CI, 1.2 to 1.8) and melanoma (OR, 2.3; 95% CI, 0.9 to 5.4).

Other adverse events. Evidence from randomized trials and observational studies is insufficient to draw conclusions regarding the comparative risk of rare but serious adverse events such as demyelination, autoimmunity, pancytopenia, and hepatotoxicity (Table 56). Reports based on data from the FDA's AERS indicated that adalimumab, etanercept, and infliximab might be associated with demyelination. Service Similar cases have been seen in regulatory trials of adalimumab. All neurologic events partially or completely resolved after discontinuation of treatment.

Table 56. Other specific adverse events in patients with rheumatoid arthritis and treated with biologic DMARDs

Study	Study Design N Duration	Study Population	Drug	Results	Quality Rating
De Bandt et al.,		Pts with RA in daily	ETA, INF	Similar incidence of lupus	Fair
2005 ³⁰²	22 cases with lupus syndrome	clinical care in France	,	syndrome between ETA and INF	
Flendrie et al., 2005 ³⁰⁴	Prospective cohort study with historic control	Pts with RA starting anti-TNF therapy	ADA, ETA, INF	Higher rates of dermatological conditions in pts on anti-TNF drugs compared with DMARDs	Fair
	578				
	911 person-years				
*Harrison et al., 2009 ³⁰⁵	Retrospective cohort study	Pts with severe RA from The British	ADA, ETA, INF, oral DMARDs	Anti-TNF vs. oral DMARDs: IR 1.04 (95% CI, 0.67 to 1.54);	Fair
BSRBR	12,706	Society for Rheumatology Biologics Register (BSRBR)		Among anti-TNF: ADA had a significantly increased risk of psoriasis compared with those treated with ETA (IRR, 4.6; 95% CI, 1.7 to 12.1) and INF (IRR, 3.5; 95% CI, 1.3 to 9.3)	
	1 to 2 years				
*Harrison et al., 2009 ³⁰⁵	Retrospective cohort study	Pts with severe RA from The British Society for Rheumatology Biologics Register (BSRBR)	ADA, ETA, INF, oral DMARDs	Anti-TNF vs. oral DMARDs: IR 1.04 (95% CI, 0.67 to 1.54); Among anti-TNF: ADA had a significantly increased risk of psoriasis compared with those treated with ETA (IRR, 4.6; 95% CI, 1.7 to 12.1) and INF (IRR, 3.5; 95% CI, 1.3 to 9.3)	Fair
BSRBR	12,706				
	1 to 2 years				
*Kawakami et	Case-control	Pts with RA that	ETN, INF,	Increased risk of surgical site	Fair
al., 2010 ³²⁷	128	underwent joint surgery	DMARDs	infection and deep vein thrombosis in anti-TNF group vs.	
	Post-surgery			oral DMARD group	
*Maini et al., 2006 ¹⁷⁴	RCT	Pts with RA despite	MTX,	Liver enzymes (AST) increased	Fair
CHARISMA	359	MTX treatment	TCZ+MTX, TCZ	 TX, with TOC use but was highest in TOC+MTX. No change in liver enzymes occurred with MTX alone 	
OFFACTORIA	20 weeks		. 3 <u>-</u>		

Table 56. Other specific adverse events in patients with rheumatoid arthritis and treated with

biologic DMARDs (continued)

	Study Design N				Quality
Study	Duration	Study Population	Drug	Results	Rating
*Michaud and Wolfe, 2006 ²⁴⁴	Cross-sectional analysis from prospective cohort	RA pts enrolled in the NDB study	ADA, ETA, INF	Association (OR) of treatment with visits to physician for sinus problems:	Fair
	7,243			• ADA: 1.09 (95% CI, 0.79 to 1.51; <i>P</i> =0.600)	
	Questionnaire in Dec 2003 related to previous 6 months			 ETA: 1.21 (95% CI, 1.02 to 1.42; P=0.025) INF: 1.00 (95% CI, 0.88 to 1.15; P=0.973) 	
Mohan et al., 2001 ²⁹⁹	Database analysis AERS	Pts on anti-TNF therapy	ETA, INF	Discontinuation of therapy led to partial or complete resolution of	Fair
	19 cases of demyelination			all cases	
	NA, AERS data				
Shin et al., 2006 ³³⁶	Database analysis AERS	Pts on anti-TNF therapy	ADA, ETA, INF	Demyelination is a potential adverse event of anti-TNF	Fair
	15 cases of Guillain- Barre and Miller Fisher syndromes			therapy	
	NA, AERS data				
*Sokolove et	Prospective cohort	Pts with RA enrolled	ADA, ETA,	Adjusted odds ratio of elevated	Fair
al., 2010 ³³⁷	6861	in the Consortium of Rheumatology	INF, DMARDs	liver enzymes (ALT and/or AST>2xULN) compared with	
CORRONA	Mean 17 months	Researchers of North America (CORRONA) registry	2	non-biologic DMARD users: ADA (OR, 1.72; 95% CI, 0.99 to 3.01); ETN (OR, 1.10; 95% CI, 0.64 to 1.88); INF (OR, 2.40; 95% CI, 1.53 to 3.76)	

^{*} New study added since last review.

ABA = abatacept; ADA = adalimumab; AE = adverse event; AERS = adverse event reporting system; ANK = anakinra; DMARD = disease-modifying antirheumatic drug; ETA = etanercept; INF = infliximab; IR = incidence rate; IRR = incidence rate ratio; LEF = leflunomide; MTX = methotrexate; NA = not applicable; OR = odds ratio; RA = rheumatoid arthritis; RCT = randomized controlled trial; TCZ = tocilizumab; TNF = tumor necrosis factor

Similarly, reports of autoimmunity have not been confirmed in controlled trials and observational studies. However, case reports suggest an association between infliximab and drug-induced lupus and other autoimmune diseases. ^{273, 301-303} Lupus-like syndromes have also been reported for adalimumab.²⁹⁸ Development of antinuclear, antidouble-stranded DNA, or antihistone antibodies have also been reported in regulatory trials of other anti-TNF- α drugs. 300,

The infliximab package insert reports that 34 percent of patients treated with infliximab and MTX experienced transient elevations of liver function parameters. 301 Severe liver injury, including acute liver failure, has been reported. One study, the Chugai Humanized Anti-Human Recombinant Interleukin-6 Monoclonal Antibody (CHARISMA) trial, ¹⁷⁴ reported data on liver function tests. This trial compared MTX, tocilizumab plus MTX, and tocilizumab monotherapy over 20 weeks in 359 patients with RA. Both tocilizumab groups had elevated liver enzymes compared with MTX monotherapy. Liver enzymes were most elevated in the tocilizumab plus

MTX group. In a prospective cohort of 6,861 patients from the Consortium of Rheumatology Researchers of North America (CORRONA) registry, compared with patients receiving other nonbiologic DMARD treatments, liver enzymes were elevated for adalimumab- (OR, 1.72; 95% CI, 0.99 to 3.01) and infliximab-treated (OR, 2.40; 95% CI, 1.53 to 3.76) patients but not for etanercept-treated patients (OR, 1.10; 95% CI, 0.64 to 1.88). 337

A prospective cohort study (N=578) indicated that patients on anti-TNF treatments developed dermatological conditions (skin infections, eczema, drug-related eruptions) statistically significantly more often than anti-TNF-naive patients over a median treatment time of 2.3 years (25 percent vs. 13 percent; P<0.0005). Another retrospective cohort study of 12,076 patients with severe RA from the BSRBR failed to find an overall association of anti-TNF drugs with risk of psoriasis. Among the three biologic DMARDs included, adalimumab had a significantly increased risk of psoriasis compared with those treated with etanercept (IRR, 4.6; 95% CI, 1.7 to 12.1) and infliximab (IRR, 3.5; 95% CI, 1.3 to 9.3).

One cross-sectional analysis of data from 7,243 patients in the prospective cohort of the NDB study assessed the relationship of treatment with adalimumab, etanercept, and infliximab with physician visits for sinus problems.²⁴⁴ A small elevated risk was observed among patients treated with etanercept (OR, 1.21; 95% CI, 1.02 to 1.42). No statistically significant increased risk of sinus problems was observed with adalimumab (OR, 1.09; 95% CI, 0.79 to 1.51) or infliximab (OR, 1.00; 95% CI, 0.88 to 1.15).

Adherence. The published literature in this area frequently uses the terms *compliance* and *adherence* interchangeably. *Compliance* has traditionally been used to describe a patient's ability to take medications as prescribed. Some authors argue, however, that *adherence* better represents the more complex relationship among patients, providers, and medications; it is meant to reflect the fact that following a medication regimen is not necessarily a simple choice. ³³⁸ Given the lack of a clear definition, we use the term *adherence*. Table 57 summarizes studies for adherence.

Table 57. Studies assessing adherence in patients with rheumatoid arthritis

Author, Year	Study Type and Interventions	N	Results	
Boers et al., 1997 ⁹⁵	RCT MTX+SSZ+prednisolone vs. SSZ	155 Co	mpliance	satisfactory in 85%
Emery et al., 2000 ¹⁰⁵	RCT LEF vs. MTX	999 Re	noncomplia LEF 11 (29 noncomplia	r withdrawal: ance in the 1st year: %) vs. MTX 14 (3%) ance in the 2nd year: o) vs. MTX 6 (2%)
Fleischmann et al., 2003 ²⁵⁹	RCT AKA vs. placebo	1,414	43.8% vs. <70% adh 0.8% vs. 1 >40% miss	erent with use of study drug: 47.8% erent with use of study drug:
Goekoop- Ruiterman et al., 2005 ¹⁰⁰	RCT Four treatment strategies	508	24 (5%) we	ere nonadherent

Table 57. Studies assessing adherence in patients with rheumatoid arthritis (continued)

Author, Year	Study Type and Interventions	N	Results
*Grijalva et al., 2007 ³³⁹	Retrospective cohort study Oral and Biologic DMARDs	6,018	SSZ, MTX+HCQ, MTX+INF, MTX+ETN, MTX+ADA, and ANK or ANK+MTX less adherent than MTX (<i>P</i> =0.014; <i>P</i> <0.001; <i>P</i> <0.001; <i>P</i> <0.001; <i>P</i> =0.008; respectively)
			LEF, INF, ETN, ADA more adherent than MTX (<i>P</i> <0.001; <i>P</i> <0.001; <i>P</i> <0.001; <i>P</i> =0.005; respectively)
Haagsma et al., 1997 ⁵⁸	RCT SSZ+MTX vs. SSZ or MTX	105	Percentage of tablets taken>90% (pill count)
Harley et al., 2003 ³⁰⁶	Retrospective database analysis INF vs. ETN vs. MTX	2,662	INF more adherent than ETA or MTX (<i>P</i> <0.05)
*Hetland et al., 2010 ⁷³	Prospective cohort ADA vs. ETA vs. INF	2,326	Drug adherence rates at 48 months: ADA, 52% (95% CI, 46 to 57); ETN, 56% (95% CI, 51 to 62); INF, 41% (95% CI, 37 to 44); <i>P</i> <0.0001
Hyrich et al., 2006 ⁸¹	Prospective observational study	2,711	Remained on treatment at 6 months: ETN 80% vs. INF 79% ETN subgroups (22% monotherapy, 16% MTX co- therapy, 19% DMARD co-therapy) INF subgroups (30% vs. 21% MTX co-therapy, vs. 22% DMARD co-therapy)
*Li et al., 2010 ³⁰⁷	Retrospective cohort ANK vs. ETA vs. INF	5,390	Adherence rates measured by PDC ≥0.8): ANK: 10.5% (<i>P</i> <0.05) ETA:32% INF:43%
*Kristensen et al., 2006 ⁶⁹	Prospective cohort study ETN vs. INF	949	Withdrawals due to adverse events (<i>P</i> <0.001) and withdrawals due to lack of efficacy (<i>P</i> =0.018) more common for INF than for ETN
*Kristensen et al., 2006 ²⁵¹	Prospective cohort study ETN vs. INF	1,161	INF less adherent than ETN for all subgroups (<i>P</i> <0.001). Adherence at 5 years 69% for INF+MTX vs. 89% for ETN+MTX (<i>P</i> <0.001).
Kremer et al., 2002 ³⁴⁰	RCT LEF+MTX vs. placebo+MTX	263	Overall, 98% adherent Adherence rates 80%-120% LEF, 87.7% placebo 90.2%
*Russell et al.,2007 ^{116,254}	RCT ABA+MTX vs. placebo+MTX	652	ABA+MTX adherence 89% MTX placebo adherence 74%
Strand et al., 1999 ¹⁰⁴	RCT LEF vs. MTX vs. placebo	402	Nonadherence as the reason for withdrawal: LEF (1) MTX (1)

^{*} New study added since last review.

ABA = abatacept; ADA = adalimumab; AKA = anakinra; DMARD = disease-modifying antirheumatic drug; ETA = etanercept; HCQ = hydroxychloroquine; INF = infliximab; LEF = leflunomide; MTX = methotrexate; RCT = randomized controlled trial; SSZ = sulfasalazine

The majority of RCTs that reported adherence stated a rate between 85 percent and 100 percent. Seven published studies reported levels of adherence in RCTs. 58, 95, 100, 105, 116, 254, 259, 340 Most, however, contained only minimal information, and many did not stratify by treatment. Furthermore, they provided little or no information on the methods of assessment. For example, one study reported that adherence was satisfactory in 85 percent of patients, but the investigators did not describe their method of determining adherence. 95 Only four of the seven RCTs reported adherence rates for different treatment arms. 105, 116, 254, 259, 340 None of these studies noted a

significant difference in adherence (although differences in discontinuation rates were noted in many trials). To what extent results from these highly controlled efficacy trials can be extrapolated to effectiveness settings remains unclear.

A retrospective database analysis used a large U.S. health plan, which included commercial and Medicare insurance, to examine adherence levels in 2,662 patients being treated with infliximab, etanercept, or MTX from November 1999 to December 31, 2001. 306 The primary outcome measured was the number of drug administrations or prescriptions filled, divided by the expected number during a 365-day period. Their primary finding was that patients on infliximab were significantly more adherent than patients on etanercept or MTX. After controlling for baseline covariates (age, sex, baseline cost, insurance type, health plan region, history of therapy of RA, comorbidities, type of physician), 81 percent of the patients receiving infliximab were adherent compared with 68 percent of the etanercept and 64 percent of the MTX patients (P<0.05 for infliximab vs. both other drugs) over 1 year. This finding was supported by a retrospective cohort study of 5,390 patients taking anakinra, etanercept, or infliximab. In this study, adherence measured by the proportion of days covered was 43 percent for infliximab, but only 32 percent for etanercept and 10.5 percent for anakinra (P<0.05). Another observational study reported similar adherence for etanercept and infliximab. 81 However, this is contradicted by three additional cohort studies. ^{69, 73, 251} A prospective cohort study of 1,161 patients taking etanercept or infliximab, where infliximab-treated patients were less adherent than etanercepttreated patients (P<0.001). Adherence at 5 years was 69 percent for the infliximab group and 89 percent for the etanercept group. In an analysis of 949 patients derived from the same Swedish registry, withdrawals due to adverse events (P<0.001) and withdrawals due to lack of efficacy (P=0.018) were more common for infliximab than for etanercept. ⁶⁹ In a prospective cohort study of 2,326 patients taking adalimumab, etanercept, or infliximab, drug adherenc rates at 48 months were 52 percent for adalimumab, 56 percent for etanercept, and 41 percent for infliximab (*P*<0.0001).⁷³

A retrospective cohort study of 6,018 patients measured adherence with multiple oral DMARDs, biologic DMARDs, and combinations of DMARDs. Compared with patients on MTX monotherapy, patients taking monotherapy sulfasalazine or anakinra, and patients taking MTX plus hydroxychloroquine, adalimumab, anakinra, etanercept, and infliximab had lower adherence. Patients on monotherapy leflunomide, adalimumab, etanercept, or infliximab had better adherence than patients on monotherapy MTX. However, these differences might also be capturing decrements in adherence related to measurement or to behavior with taking more than one treatment at the same time (since combination treatments had lower adherence).

Key Question 4: Benefits and Harms for Selected Populations

This key question (KQ) addressed the comparative benefits and harms of drug therapies for rheumatoid arthritis (RA) in subgroups of patients based on stage of disease, history of prior therapy, demographics, concomitant therapies, or comorbidities. Early RA as a stage of disease and history of prior therapy were addressed under KQ 1; however, we present one study here that grouped subjects by early RA versus more advanced RA. We did not find studies that exclusively compared MTX-naive RA groups with those with RA who were MTX-experienced.

Overview

We focused on groups defined by stage of disease, demographics (age, sex, race, or ethnicity), concomitant therapies, and comorbidities (any comorbidity, cardiovascular disease,

osteoporosis, and renal disease). We included five good or fair quality studies: two RCTs, one subgroup analysis of multiple RCTs, one database analysis, and one systematic review met the inclusion criteria for this key question.

Stage of disease. One fair quality post-hoc analysis of two RCTs³⁴¹ compared those treated with MTX or etanercept or a combination of both in patients with moderate RA with those in a severe disease activity state. Generally, patients with moderate RA achieved significantly better DAS28 and HAQ results than those with severe RA; however, those with severe disease activity on etanercept or MTX monotherapies had greater change scores from baseline in DAS28.

Demographics. We found no studies that conducted comparisons by sex, race, or ethnicity, but we did include one fair systematic review that addressed age, ³⁴² one pooled analysis of RCTs, ²⁹⁸ and a secondary database analysis of Medicare patients. ²¹⁶

One systematic review by the Rheumatoid Arthritis Clinical Trial Archive Group found an inverse relationship between age and major clinical improvement.³⁴² Of the three trials reviewed, the differences between the odds ratios was small.³⁴² One study directly compared the efficacy of etanercept in elderly RA patients (65 years of age or older) with younger RA patients (under 64 years of age and older than 18) and found no significant difference in functional status between age groups.²⁹⁸ The secondary database analysis reported that in the elderly, the risk of cardiovascular events was higher in those who were treated with oral glucocorticoids or cyctotoxic immunosuppressant agents such as leflunomide, whereas biologic agents (abatacept, intanercept, infliximab, anakina) were found to have no beneficial or harmful effect.²¹⁶

Concomitant therapies. We found no evidence from head-to-head comparisons, placebo-controlled trials, or observational studies on other treatment therapies. Differences based on comparisons of various combinations of RA medications are addressed in KQs 1 through 3. An analysis of data from one placebo-controlled trial involving RA patients receiving anakinra determined that the safety profiles did not differ in subjects receiving antihypertensive, antidiabetic, or statin medication treatments. 343

Comorbidities. We identified two studies that addressed outcomes of RA patients with comorbidities. For RA patients with various high-risk conditions, one large placebo-controlled RCT of anakinra reported that there was no difference in serious adverse events or infections between the treated and placebo groups. A systematic review of 11 MTX trials of RA patients determined that those with renal impairment were directly at greater risk for experiencing MTX toxicity, and the greater the renal impairment the greater the toxicity effects. At 2

We present detailed analyses below for the population groups noted above. Details about included studies are presented by subgroup analysis in Tables 64 to 68 (listed alphabetically within outcome sections).

Detailed Analysis

Stage of disease. A fair quality post-hoc analysis of TEMPO and ERA study data (Table 58)³⁴¹ looked at response to etanercept or MTX, or a combination of both, in regard to the patient's stage of RA—moderate (DAS20>3.2 and ≤5.1) or severe (DAS28>5.1). Although there were similarities between the two trial populations, the TEMPO subjects in this analysis had RA longer (6.6 vs. 1 mean years) and greater prior MTX use (43 percent vs. 0 percent) than the ERA group. Both analysis groups were primarily patients with severe RA (94 percent vs. 84.3 percent); however, the percentage of ERA patients with moderate RA was more than twice that in the TEMPO group (15.7 percent vs. 6 percent), making the TEMPO analysis group a more

severe population than the ERA group overall. The authors did not report any *P* values for differences between groups on baseline characteristics.

Table 58. Study characteristics, outcomes, and quality ratings of adult subpopulations with rheumatoid arthritis: By stage of disease

Study	Study Design N Duration	Study Population	Interventions	Outcomes	Quality Rating
Keystone et al., 2009 ³⁴¹	Post-hoc analysis of two RCTs 1,091 12 months	Adults with moderate vs. severe RA treated with MTX, etanercept monotherapies or combinations	MTX (dose NR), ETN (25 mg twice weekly), MTX+ETN	Significant differences favored those with moderate RA in DAS28 and HAQ scores vs. those with severe stage, but greater gains from baseline scores for DAS28 were seen in the those with severe RA	Fair

ETN = etanercept; MTX = methotrexate; NR = not reported; RA = rheumatoid arthritis; RCT = randomized controlled trial

Investigators reported significant differences in DAS28 remission at 6 months in TEMPO patients with moderate RA treated with MTX or etanercept monotherapies or combination compared with those with severe RA. This significant trend continued for the MTX-only or MTX-etanercept combination groups at 12 months, but not for those treated with etanercept alone (MTX: P=0.0035; MTX plus etanercept: P=0.0006). In the ERA analysis, both those treated with MTX or etanercept monotherapies for moderate RA,achieved significant DAS28 improvements at both 6 months (MTX: P=0.0058; etanercept: P=0.0003) and 12 months (MTX: P=0.0094; etanercept: P<0.0001).

A significant difference in low disease activity level was achieved by those with moderate RA in both trial groups at both 6 and 12 months in all treatment groups except those treated with etanercept monotherapy in the TEMPO study. Mean DAS28 scores were consistently lower in moderate RA groups in comparison with those with severe RA; however, mean changes in DAS28 scores at 12 months were significantly greater in those with severe RA (ERA trial: MTX only: 1.2 vs. 2.4, P<0.0001; etanercept only: 1.7 vs. 2.4 P<0.0110; TEMPO trial: MTX only: 1.6 vs. 2.6, P<0.0076; etanercept only: 1.5 vs. 2.7, P<0.0268; MTX plus etanercept 2.5 vs. 3.5, P<0.0069).

Twelve-month changes in HAQ scores from baseline showed significant differences between moderate and severe disease activity in the MTX-only group from the TEMPO trial and the two monotherapies in the ERA trial (TEMPO trial: MTX only 0.29 vs. 0.68, P=0.0138; etanercept only 0.42 vs. 0.74, P=0.1329; MTX plus etanercept 0.74 vs. 1.00, P=0.0895; ERA trial: MTX only 0.44 vs. 0.77, P=0.0107; etanercept only 0.45 vs. 0.75, P=0.0070). 341

In regard to radiographic changes, only the MTX monotherapy group in the TEMPO trial showed significant differences in median change of total sharp scores between moderate and severe RA patients (1.00 vs. 2.57, P=0.014).

Demographics. We identified one study analyzing MTX use in the elderly and one database analysis of various agents of a Medicare population. ^{216, 342} Table 59 presents the studies of adults with RA that conducted comparisons by age groups.

Table 59. Study characteristics, outcomes, and quality ratings of adult subpopulations with rheumatoid arthritis: By age

Study	Study Design N Duration	Study Population	Interventions	Outcomes	Quality Rating
Rheumatoid Arthritis Clinical Trial Archive Group 1995 ³⁴²	Systematic review 496 ≥12 weeks	Adults with RA by age subgroups: under 60 years of age; 60 to 64 years; 65 to 69 years; and 70 years or above	MTX	Adjusted analysis demonstrated that as age increases, the odds ratio for major clinical improvement decreases; no effect found on toxicity	Fair
Solomon et al., 2006 ²¹⁶	Nested case control database analysis (Medicare and PACE) 946 ≤24 months	Elderly adults with RA	MTX, ADA, ETN, INF, AKA, AZA, CSA, LEF, HCQ, SSZ, gold, and all oral glucocorticoid agents	Oral glucocorticoids and cytotoxic immunosuppressive agents increased risks for cardiovascular events, biologics neither increased risk or decreased risk	Fair

ADA = adalimumab; AERS = adverse events reporting system; AKA = anakinra; AZA = azathioprine; CHF = congestive heart failure; CSA = cyclosporine A; ETN = etanercept; HCQ = hydroxychloroquine; INF = infliximab; LEF = leflunomide; MTX = methotrexate; NA = not applicable; PACE = pharmaceutical assistance contract for the elderly; RA = rheumatoid arthritis; RCT = randomized controlled trial; SSZ = sulfasalazine; TNF = tumor necrosis factor

The Rheumatoid Arthritis Clinical Trial Archive Group 1995 review of 11 MTX trials for adults with RA evaluated the effects of age or renal impairment on adverse events or treatment efficacy. Although the authors reported that the odds for major clinical improvement dropped slightly as age increases, among all clinical trial patients, age did not affect MTX efficacy or the rate of side effects. Using the group under age 60 as the referent, the odds of major clinical improvement for those 60 to 64 years of age was 1.4 (95% CI, 0.7 to 2.6), 1.0 (95% CI, 0.5 to 2.2) for those 65 to 69 years of age, and 0.7 (95% CI, 0.3 to 1.7) for those 70 years of age or older (*P*=NR).

A fair quality nested case control study investigating cardiovascular events in 946 RA patients was conducted using data from Medicare enrollees also receiving benefits from the state of Pennsylvania Pharmaceutical Assistance Contract for the Elderly Program. Index dates were established as the first cardiovascular event within patients who had a diagnosis of RA on at least two visits and a prescription of an immunosuppressant agent (MTX, adalimumab, etanercept, infliximab, anakinra, azathioprine, cyclosporine, leflunomide, gold, hydroxychloroquine, sulfasalazine, and all oral glucocorticoid agents) within 90 days of the index event. Using MTX as the reference group, oral glucocorticoids (monotherapy: OR, 1.5; 95% CI, 1.1 to 2.1; combinations: OR, 1.3; 95% CI, 0.8 to 2.0) and cytotoxic immunosuppressive agents: azathioprine, cyclosporine, and leflunomide (OR, 1.8; 95% CI, 1.1 to 3.0) were associated with an increased risk for cardiovascular events. Biologics (adalimumab, etanercept, infliximab), on the other hand, had no effect on risk for developing or preventing a cardiovascular event (monotherapy: OR, 1.0; 95% CI, 0.5 to 1.9; combination with MTX: OR 0.8; 95% CI, 0.3 to 2.0; combination with other immunosuppressive agents OR, 1.2; 95% CI, 0.7 to 2.2).

Concomitant therapies. One placebo-controlled trial of 1,399 adults with active RA disease examined safety profiles of those treated with 100mg/day anakinra (Table 60). Investigators failed to find any differences in the adverse event profiles of the subjects taking or not taking

concomitant antihypertensive, antidiabetic, or statin pharmacotherapies. Even when the analysis compared those treated with anakinra with those on placebo, no differences emerged (P=NR).

Table 60. Study characteristics, outcomes, and quality ratings of adult subpopulations with rheumatoid arthritis: By concomitant therapies

Study	Study Design N Duration	Study Population	Intervention	Outcomes	Quality Rating
Tesser et al., 2004 ³⁴³	RCT	Adults with RA	ANK, 100mg/day	No significant difference	Fair
	1,399	taking or not taking		found in safety profiles	
	6 months	antihypertensive, antidiabetic, or statin pharma- cotherapies			

ANK = anakinra; RA = rheumatoid arthritis; RCT = randomized controlled trial

Comorbidities. Table 61 presents three studies identified as addressing comorbidities.

Table 61. Study characteristics, outcomes, and quality ratings of adult subpopulations with rheumatoid arthritis by comorbidities

Study	Study Design N Duration	Study Population	Interventions	Outcomes	Quality Rating
Rheumatoid Arthritis Clinical Trial Archive Group, 1995 ³⁴²	Systematic review of 11 RCTs 454 NA	RA patients with impaired renal function treated with MTX	MTX	Severe toxicity (severe upper abdominal pain, renal failure, proteinurea, cytopenias and liver toxicity) and respiratory toxicity (cough, pneumonitis, dyspnea, wheezing) worse with greater renal impairment	Fair
Schiff et al., 2004 ³⁴⁴	RCT 951 6 months	RA patients with high- risk comorbid conditions	ANK, 100 mg/day	In patients with comorbid conditions, no differences were found between treatment groups in regard to incidence of serious adverse events or overall infectious events	Fair

ANK = anakinra; MTX = methotrexate; NA = not applicable; RA = rheumatoid arthritis; RCT = randomized controlled trial

Any comorbidity. We did not identify any study specifically designed to assess the comparative efficacy and risk of biologic DMARDs (abatacept, adalimumab, anakinra, certolizumab, etanercept, golimumab, infliximab, rituximab, or tocilizumab) in RA patients with common comorbidities. A post-hoc subgroup analysis of a large safety trial determined the safety profile of anakinra in patients with various comorbidities (cardiovascular events, pulmonary events, diabetes, infections, malignancies, renal impairment, and central nervous system-related events). Overall, the incidence rates of adverse events were similar regardless of comorbidity status.

Cardiovascular morbidity. No direct evidence exists on the comparative risk of biologic DMARDs in patients with both RA and cardiovascular disease.

Renal function. A systematic review of 11 RCTs of MTX use in 496 adults with RA concluded that toxicity worsened with greater renal impairment. Patients with high renal impairment had a fourfold risk (OR, 4.5; 95% CI, 0.9 to 22.6) for severe toxicity (severe upper

abdominal pain, renal failure, proteinurea, cytopenias, and liver toxicity) than those with no renal impairment. Slightly more (4 percent vs. 1 percent) had respiratory toxicity (cough, pneumonitis, dyspnea, wheezing). No effect was found between renal impairment and increased liver toxicity. Baseline renal function was found to be a significant predictor of toxicity, with the lower creatinine clearances ending up with greater toxicity (P=0.027). 342

Discussion

This report provides a comprehensive review of the comparative efficacy, effectiveness, and harms of members of the main classes of drugs used to treat adult patients with rheumatoid arthritis (RA). These include oral disease-modifying antirheumatic drugs (DMARDs), and biologic DMARDs. The objective of our report was to evaluate the comparative efficacy, effectiveness, and harms of monotherapies, combination therapies, and different treatment strategies.

Table 62 summarizes our findings and the strength of evidence for three Key Questions (KQs) addressed by this report.

Table 62. Summary of findings with strength of evidence

Key Comparisons	Efficacy Strength of Evidence	Harms Strength of Evidence		
Oral DMARD vs. Oral	DMARD			
Leflunomide vs. MTX	No differences in ACR 20 or radiographic responses Low	No consistent differences in tolerability and discontinuation rates Low		
	No clinically significant difference for functional capacity Low	Mixed results for specific adverse events Insufficient		
	Greater improvement in health-related quality of life (SF-36 physical component) for leflunomide Low			
Leflunomide vs. sulfasalazine	Mixed ACR response rates Insufficient	No differences in tolerability and discontinuation rates Low		
	No differences in radiographic changes Low	Mixed results for specific adverse events Insufficient		
	Greater improvement in functional capacity for leflunomide Low			
Sulfasalazine vs. MTX	No differences in ACR 20 response, disease activity scores and radiographic changes* Moderate	No differences in tolerability; more patients stayed on MTX long-term Low		
	No differences for functional capacity* Moderate	Mixed results for specific adverse events Insufficient		
Oral DMARD Combinations vs. Oral DMARD				
Sulfasalazine plus MTX vs. sulfasalazine or MTX monotherapy	In patients with early RA, no differences in ACR 20 response rates or radiographic changes Moderate	Withdrawal rates attributable to adverse events higher with combination Low		
	No differences in functional capacity Moderate	Insufficient evidence for specific adverse events Insufficient		

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Table 62. Summary	/ OI IIIIAIIIAS WILII	Suenam or	evidence	Continuear

Key Comparisons	Efficacy Strength of Evidence	Harms Strength of Evidence	
Oral DMARD plus prednisone vs. oral DMARD	Mixed results for disease activity Insufficient	No differences in discontinuation rates; addition of corticosteroid may increase time to discontinuation of treatment	
	Less radiographic progression In patients on DMARD plus prednisone Low	Moderate	
	In patients with early RA, significantly lower radiographic progression and fewer eroded joints Low	No differences in specific adverse events, except addition of corticosteroid may increase wound-healing complications Low	
	Greater improvement in functional capacity for one oral DMARD plus prednisolone than for oral DMARD monotherapy Moderate		
	No difference in quality of life Low		
Biologic DMARD vs.	Biologic DMARD		
Abatacept vs. Infliximab	Greater improvement in disease activity for abatacept, but no difference in remission or functional capacity. Statistically significant difference between groups for quality of life (SF-36 PCS) that did not reach the minimal clinically important difference. Low	Discontinuation rates and severe adverse events higher with infliximab Low	
Biologic vs. biologic (Mixed treatment comparisons)	No significant differences in disease activity (ACR 50) in MTC analyses between abatacept, adalimumab, golimumab, infliximab, rituximab, and tocilizumab in patients resistant to MTX Low Less improvement in disease activity (ACR 50) for anakinra compared to etanercept and compared to adalimumab in MTC analyses in patients resistant to MTX. Comparisons with abatacept, golimumab, infliximab, rituximab and tocilizumab did not reach statistical significance. Low Greater improvement in disease activity (ACR 50) for etanercept compared to abatacept, adalimumab, anakinra, infliximab, rituximab, and tocilizumab in MTC analyses. No significant differences when compared with golimumab Low	DMARDs. Also, etanercept and rituximab had a more favorable overall withdrawal profile than some other biologic DMARDs. Certolizumab pegol had fewer	
		Low Mixed results for specific adverse events Insufficient	

Key Comparisons	Efficacy Strength of Evidence	Harms Strength of Evidence
Biologic DMARD vs. (Oral DMARD	
Anti-tumor necrosis factor drugs vs. MTX	In patients with early RA, no clinically significant differences in clinical response between adalimumab or etanercept and MTX; in patients on biologic DMARDs, better radiographic outcomes than in patients on oral DMARDs Moderate No difference in functional capacity between adalimumab and MTX for MTX-naïve subjects with early RA; mixed results for etanercept vs. MTX Low ; Insufficient	No differences in adverse events in efficacy studies Low Insufficient evidence on differences in the risk for rare but severe adverse events Insufficient
	Faster improvement in quality of life with etanercept than MTX Low	
Biologic DMARD Con	nbinations	
Biologic DMARD plus biologic DMARD vs. biologic DMARD	No additional benefit in disease activity or functional capacity from combination of etanercept plus anakinra compared with etanercept monotherapy or combination of etanercept plus abatacept compared with abatacept monotherapy, but greater improvement in quality of life with etanercept plus abatacept vs. etanercept Low	Substantially higher rates of serious adverse events from combination of two biologic DMARDs than from monotherapy Moderate
Biologic DMARDs plus MTX vs. biologic DMARDs	Better improvements in disease activity from combination therapy of biologic DMARDs (adalimumab, etanercept, infliximab, rituximab) plus MTX than from monotherapy with biologics Moderate In MTX-naive patients with early aggressive RA, better ACR 50 response, significantly greater clinical remission, and less radiographic progression in the combination therapy group Low In MTX-naïve subjects or those not recently on MTX, greater improvement in functional capacity (Moderate) and quality of life (Low) with combination therapy In subjects with active RA despite treatment with MTX, no difference in functional capacity or quality of life Low	No differences in adverse events in efficacy studies Low Insufficient evidence on differences in the risk for rare but severe adverse events Insufficient

Table 62. Summary of findings with strength of evidence (continued	Table 62. Summar	y of findings with	strength of evider	ce (continued)
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-	Efficacy	Harms	
Key Comparisons	Strength of Evidence	Strength of Evidence	
Biologic DMARDs plus oral DMARD other than MTX vs. biologic DMARDs	No difference in clinical response rates, functional capacity, and quality of life between etanercept plus sulfasalazine and etanercept monotherapy Low	No differences in adverse events in efficacy studies Low	
		Insufficient evidence on differences in the risk for rare but severe adverse events Insufficient	
Biologic DMARD plus MTX vs. MTX	Better clinical response rates, functional capacity, and quality of life from combination therapy of biologic DMARDs and MTX than from MTX monotherapy	Better tolerability profile for MTX plus abatacept, adalimumab, certolizumab, etanercept, and rituximab than for MTX monotherapy from meta-analysis Low	
	High for clinical response and functional capacity,		
	Moderate for quality of life	Mixed evidence on differences in the risk for rare but severe adverse events Insufficient	
Strategies in Early RA	1		
Two oral DMARDs plus prednisone vs. oral DMARD	In patients on two oral DMARDs, improved ACR 50 response rates, disease activity scores, but no difference at 56 weeks Low	No differences in discontinuation rates Moderate	
	In patients with early RA, significantly lower radiographic progression and fewer eroded joints at 56 weeks Low		
	More rapid improvement in functional capacity by 28 weeks but no differences by 56 weeks. Low		
Three oral DMARDs plus prednisone vs. 1 oral DMARD	In patients on three oral DMARDs, improved ACR 50 response rates, disease activity scores, and less, less work disability Low	No differences in discontinuation rates Moderate	
	In patients with early RA, significantly lower radiographic progression and fewer eroded joints Low		
Sequential monotherapy starting with MTX vs. step-up combination therapy vs. combination with tapered high-dose prednisone vs. combination with infliximab	Less radiographic progression, lower disease activity scores, and better functional ability and health-related quality of life from initial combination therapy of MTX, sulfasalazine, and tapered high-dose prednisone or initial combination therapy with infliximab plus MTX than from sequential DMARD monotherapy or step-up combination therapy. However no differences between groups for functional ability and quality of life by 2 years and no difference in remission at 4 years Low		

† at MTX doses ranging from 7.5-25 mg per week ACR = American College of Rheumatology; DMARD = disease modifying antirheumatic drug; MTC = mixed treatment comparisons; MTX = methotrexate; RA = rheumatoid arthritis; vs. = versus

Key Findings

Existing comparative evidence permits us to draw some conclusions for monotherapies of oral and biologic DMARDs. Overall, the evidence supports similar efficacy and effectiveness for methotrexate (MTX) and sulfasalazine. ⁵⁷⁻⁵⁹ However, it is important to note that MTX dosing for two of these studies ranged in the lower part of the dosing range. The evidence is insufficient to draw conclusions about disease activity for sulfasalazine and leflunomide, but improvement in functional capacity was greater for patients on leflunomide in one study (low strength of evidence). ^{107, 200} All three drugs have similar discontinuation rates attributed to adverse events in short-term efficacy trials up to 2 years. ^{104, 105, 107, 345}

Although several biologic DMARDs are available, the head-to-head evidence remains very limited. Current evidence comparing biologic DMARDs is limited to one head-to-head randomized controlled trial (RCT), several observational studies, indirect analyses, and our mixed treatment comparisons (MTC) meta-analyses. Based on one RCT, abatacept lessens disease activity more than infliximab, but remission rates are not significantly different at 1 year (low strength of evidence). Discontinuation rates and severe adverse events appear higher with infliximab; these results are also supported by observational studies. 158, 248, 250, 251

Our MTC of RCTs of subjects with active RA despite MTX treatment suggest a higher odds of reaching the ACR 50 for etanercept compared to most other biologic DMARDs (low strength of evidence). Similarly, our indirect analyses from randomized trials indicate that patients taking certolizumab or etanercept are less likely to withdraw treatment than patients taking other biologic DMARDs. In contrast prior analyses found no differences among the set of anti-tumor necrosis factor (anti-TNF) drugs (namely, etanercept, infliximab, and adalimumab). ^{28, 74, 75, 179} The differences between our results and those of previous indirect analyses may be attributed to newer studies and drugs (certolizumab, golimumab, and tocilizumab) added to the analyses, which provide additional data. Further, unlike previous indirect analyses, our MTC meta-analysis uses methods that do not rely solely on placebo-controlled trials; it also allows the inclusion of data from head-to-head studies or those with active comparators, thus increasing statistical power. In addition, for efficacy, we limited our MTC inclusion criteria to studies enrolling patient populations who had an inadequate response to MTX and excluded studies with MTX-naïve populations, those with early RA, or those who had failed anti-TNF therapy.

Our MTC meta-analysis indicates that anakinra trended toward lower efficacy. Prior indirect comparisons consistently indicated that anakinra is less efficacious than biologics for patients with RA. Adjusted indirect comparisons, in general, have to be interpreted cautiously because the validity of results is based on assumptions that cannot be verified, particularly the similarity of study populations.

The evidence comparing monotherapy using a biologic DMARD with monotherapy using an oral DMARD is mixed. Monotherapies of adalimumab in early RA⁷⁶ and etanercept in longstanding RA^{77, 86} generally did not reveal a benefit relative to MTX monotherapy for response rates and had mixed results for functional capacity. There was faster improvement in quality of life for etanercept. Radiographic outcomes were also significantly better in patients on biologic DMARDs than on MTX. Whether such differences are clinically relevant and can alter the long-term progression of the disease remains unclear.

Although a substantial percentage of patients respond well to DMARD monotherapy, ^{76, 77, 86, 136, 138, 345} some patients do not achieve an acceptable treatment response. As the BeSt study (Dutch acronym for Behandel Strategieen, "treatment strategies"), a Dutch effectiveness trial assessing different treatment strategies for RA, has indicated, tight disease control and an

individualized treatment approach are paramount in achieving a satisfactory treatment response or remission. Therefore, if dose escalation of a monotherapy does not achieve low levels of disease activity, combination therapies have to be taken into consideration. This is supported by multiple efficacy studies that indicate that combinations of biologic and oral DMARDs appear to be more efficacious than monotherapy of either drug in populations failing DMARD therapy.

The existing evidence supports combination strategies of up to three oral DMARDs, including corticosteroids, compared with strategies using one or two drugs. The data are limited, however, by the number of supporting studies for each drug combination. Moderate strength evidence from two efficacy trials reported higher proportions of patients meeting American College of Rheumatology (ACR) 20 criteria at 2 years for the combination of MTX plus sulfasalazine and hydroxychloroquine than for one or two drugs. 61, 62

Combination therapy of biologic DMARDs with MTX achieved better results in clinical outcomes, functional capacity, and quality of life than monotherapy with biologic DMARDs in MTX-naïve subjects or those not recently on MTX. ^{76, 86, 87, 136, 138} Whether these results can be extrapolated to combinations of biologic DMARDs with other oral DMARDs is uncertain. In clinical practice, patients often receive biologic DMARDs as an add-on therapy to an existing regimen of various oral DMARDs.

Combinations of two biologic DMARDs did not yield an additional treatment benefit but rather led to substantially higher rates of serious adverse events than with biologic DMARD monotherapies (14.8 percent vs. 2.5 percent; *P*=NR [not reported]). ^{79, 80, 258}

The evidence is limited to draw firm conclusions about whether one combination strategy is better than another in early RA. Current evidence also suggests improved functional capacity^{65, 95, 97, 202} and less radiographic progression^{65, 95, 98} for combination strategies with corticosteroids and one or more oral DMARDs compared with oral DMARD monotherapy. For most of these comparisons, the evidence is limited to a single study. One effectiveness trial for patients with early RA reported less radiographic progression over 12 months with either (1) combination therapy of MTX, sulfasalazine, and high-dose tapered prednisone or (2) MTX and infliximab versus (3) sequential DMARD therapy or (4) step-up combination therapy.¹⁰⁰ At 2 years,¹⁰² results of this study reinforced the conclusion that patients on initial combination therapy of MTX, sulfasalazine, and tapered high-dose prednisone or initial combination therapy with MTX and infliximab had less radiographic progression. They also had more rapid improvement in disease activity functional capacity and quality of life, although the differences between groups were no longer present by 2 years. By 4 years, there was no difference in remission among the groups.¹⁹⁶

Evidence of moderate strength suggests that studies of combinations of two or three DMARDs, including MTX, sulfasalazine, hydroxychloroquine, and etanercept versus one or two DMARDs had similar withdrawal rates attributable to adverse events. Studies of combinations including prednisone with one or more DMARDs had similar discontinuation rates between groups.

Similarly, patients on combinations of biologic and oral DMARDs were less likely than patients on oral DMARD monotherapy to withdraw from trials because of lack of efficacy. Combinations of biologic and oral DMARDs had similar rates of adverse events than monotherapies of either drugs However, because biologic DMARDs are relatively new medications, long-term data on safety are generally still missing. Especially rare but severe adverse events such as serious infections, lymphoma, autoimmunity, or congestive heart failure are of concern. One obvious difference among biologic DMARDs that might be clinically useful

for choosing a particular drug involves dosing and administration. Abatacept, infliximab, and rituximab require intravenous administration at different intervals and present the danger of rare but severe infusion reactions. Adalimumab, anakinra, and etanercept can be administered subcutaneously by the patient. Administration intervals differ substantially: adalimumab requires an injection once a week or once every other week, anakinra has to be administered daily, and etanercept once or twice per week. The route of administration is also the cause of the main differences in short-term tolerability. Anakinra appears to have a substantially higher rate of injection site reactions than anti-TNF drugs. Abatacept, infliximab, and rituximab carry the risk of severe infusion reactions that cannot occur in drugs administered subcutaneously. Fatal infusion reactions have been reported for infliximab and rituximab.

The existing evidence remains insufficient to draw firm conclusions on the best treatment regimen for patients with early RA. Studies conducted in patients with early aggressive RA suggested that an early start of a biologic DMARD can improve disease activity, radiographic findings, functional capacity, and quality of life compared to an oral DMARD. Because the studies were of limited duration, however, they do not allow conclusions on whether early initiation of a biologic regimen can improve the long-term prognosis of RA. Currently, clinical practice guidelines recommend that clinicians start biologic DMARDs if patients have suboptimal response to oral DMARDs or only if there is high disease activity. For those patients with longer disease duration, biologics are recommended. ^{23, 346}

Furthermore, we did not find any studies directly comparing efficacy, effectiveness, and harms of drug therapies between subgroups.

Applicability

A considerable limitation of our conclusions is that we have had to derive them primarily from efficacy trials that typically enroll a narrow spectrum of patients and are conducted in ideal settings. However, the direction and effect sizes of findings from effectiveness trials and observational studies were generally consistent with those from efficacy trials. Nonetheless, differences in the incidence of reported adverse events and discontinuation rates were obvious between clinical trials and population-based observational studies.

For example, clinical efficacy trials of infliximab reported infusion reactions, on average, in 17 percent of patients.²⁷³ A prospective cohort study in a Canadian clinical care setting, however, reported substantially higher percentages.³²⁹ Patients who were enrolled in efficacy trials usually suffered from more severe disease than the average patient in clinical practice.³⁴⁷ For example, only a small proportion of consecutive patients with RA who were under the care of a private practice rheumatologist in Nashville, Tennessee, would have met eligibility criteria of the ERA (Early Rheumatoid Arthritis) trial;⁷⁷ only 31 percent of patients with early RA who had not taken MTX would have met the ERA criteria. The same pattern was true for the ATTRACT (anti-TNF trial in RA with concomitant therapy) study trials;^{148, 347} only 5 percent of patients in a long-term RA database would have been eligible for this trial. Therefore, the applicability of results from efficacy trials to the average patient in community practice appears to be limited.

Additionally, some trials comparing MTX started with a lower dosing range than what is commonly given in practice. ^{57, 58, 110} This hinders evaluating some of the comparisons of MTX with other oral DMARDs. Otherwise, the dosing and frequencies of the included studies are directly applicable to community-based populations.

Conclusions

Despite the limitations of the available literature, this comprehensive review describes similar efficacy, functional capacity, and tolerability among oral DMARDs. Biologic DMARD comparisons are limited to mostly observational studies and findings from MTC meta-analyses. Our MTC meta-analysis, suggest some differences, such as etanercept having a higher probability of improvement in disease activity than most other biologic DMARDs, but are limited primarily to indirect evidence (Low SOE) and, therefore, should be interpreted with caution. The limited evidence precludes drawing firm conclusions about whether one combination strategy is better than another in early RA. Overall tolerability is similar among biologic and among oral DMARDs; however, several studies suggest that adverse events are more common with biologic DMARDs compared with oral DMARDs. Limited evidence does not suggest an increased risk of severe adverse events, including cardiovascular or cancer, with oral DMARDs. Most studies found no risk of cardiovascular events and malignancy with biologic DMARDs, except for cohort studies, which describe an increased risk of heart failure with adalimumab, etanercept, and infliximab compared with oral DMARDs.

Clinical Relevance

Although the studies comparing oral DMARDs show therapeutic equivalence, the data are sparse and of lower strength, given the range of MTX dosing used in available trials. Vast clinical experience supports the use of MTX as the oral DMARD of choice unless there are contraindications. In addition, MTX is almost universally used as the anchor drug in studies of multidrug regimens. Data on the use of other oral DMARDs in combination with biologic therapy are sparse.

Data suggest that early institution of biologic therapy improves radiographic outcomes and should be considered in patients with poor prognostic features. Clearly, however, many patients can be effectively managed with oral DMARDs alone. There are few direct comparisons that can guide the selection of a specific biologic agent. Most agents have roughly equivalent efficacy using validated RA outcome measures (except anakinra, which is less effective). The apparent superiority of etanercept in MTCs is an unexpected finding and warrants further study.

Future Research

We have identified several areas that need further research to help clinicians and researchers arrive at stronger conclusions on the comparative efficacy, effectiveness, quality of life, and harms of medications for RA. Important areas that will influence clinical decisionmaking include three critical topics: (1) specific head-to-head comparisons focusing on different combination strategies and different biologic DMARDs, (2) timing of initiation of therapies, and (3) applicability of combination strategies and biologic DMARD therapy in community practice.

Currently, evidence from systematic reviews, placebo-controlled trials, and observational studies does not allow us to draw any firm conclusions for the head-to-head comparisons between biologic DMARDs (i.e., those with greater than low strength of evidence). Although results of the MTC found some differences among biologics, the strength of evidence remains low, and head-to-head studies are needed to confirm or refute these results. Head-to-head RCTs are ideal to establish the comparative effectiveness and safety of biologic DMARDs. However, these types of trials would be costly and may be unrealistic. Although less rigorous, one initial approach could be to collect real data generated in clinical practice; for example, large databases

created from electronic medical records. This type of data would be more likely to reflect real practice.

Furthermore, we did not find any studies directly comparing efficacy, effectiveness, and harms of drug therapies between subgroups. Analyses involving subpopulations, specifically those defined by age and coexisting conditions, will be beneficial, given that RA disease onset generally occurs in middle age, when the risk of comorbidities increases.

Timing of initiation of therapies needs to be addressed, including whether aggressive early treatment in RA influences the course and prognosis beneficially. Adequately powered, long-term RCTs must examine different treatment strategies with and without corticosteroids, oral DMARDs, and biologic DMARDs to determine the best therapy to prevent or minimize debilitating joint damage in this population. These trials should be conducted over multiple years to guarantee that results provide a relevant assessment of the long-term prognosis of RA under different treatment strategies. Such trials would also provide insight about whether the long-term benefits of any combination of drugs outweigh the adverse effects.

Given that available long-term data indicate high discontinuation rates for drugs used to treat RA, having backup regimens is crucial. Additional well-conducted research is needed to assess the comparative efficacy and safety of oral DMARDs in patients who currently do not qualify for a treatment with a biologic DMARD. Also still unclear is whether newer oral DMARDs such as leflunomide have a better, long-term adverse events profile than older oral DMARDs such as MTX. Additionally, although combination strategies with oral DMARDs with or without corticosteroids appear more effective, further research examining *which* combination strategy is more effective would be beneficial for medical treatment decisionmaking.

Further studies need to be designed to mimic clinical decisionmaking. If patients are not doing well after 3 months of a therapy that takes less than 3 months to work, then the protocol needs to give them something different. Additionally, long-term outcomes are potentially more meaningful when protocols attempt to follow what would happen in real life. For example, radiographic progression becomes less meaningful if a clinician would have switched to a different drug due to lack of clinical effect earlier. Biologic DMARDs differ substantially in the route and frequency of administration, which can influence the choice of a biologic agent by patients and physicians. Establishing the comparative effectiveness and safety of biologic DMARDs, therefore, is helpful for balanced, informed decisionmaking.

The risk of rare but serious adverse events such as malignancies, serious infections, demyelinations, severe infusion reactions, or congestive heart failure must be established in well-conducted observational studies, such as large cohort or case-control studies. The balance of risks and benefits of biologic DMARDs can be determined reliably only if good long-term data on such harms are available.

In general, all future studies have to ensure applicability to patients seen in community practices. Future research has to establish the comparative effectiveness, health-related quality of life, and safety of all therapies, but especially biologic DMARDs, in settings that reflect daily clinical care and take into account factors such as varying adherence due to administration schedules, costs, and adverse events. The current evidence indicates that severity of disease and population characteristics may differ substantially between the highly selected populations enrolled in efficacy trials and those treated in daily clinical practice. Future trials must plan subgroup analyses in older patients or patients with comorbidities a priori.

References

- 1. Bolen J, Helmick CG, Sacks JJ, et al. Prevalence of self-reported arthritis or chronic joint symptoms among adults--United States, 2001. MMWR Morb Mortal Wkly Rep. 2002 Oct 25;51(42):948-50. PMID: 12437034.
- 2. Helmick CG, Felson DT, Lawrence RC, et al. Estimates of the prevalence of arthritis and other rheumatic conditions in the United States. Part I. Arthritis Rheum. 2008
 Jan;58(1):15-25. PMID: 18163481.
- 3. Bruce TO. Comorbid depression in rheumatoid arthritis: pathophysiology and clinical implications. Curr Psychiatry Rep. 2008 Jun;10(3):258-64. PMID: 18652795.
- 4. Husted JA, Gladman DD, Farewell VT, et al. Health-related quality of life of patients with psoriatic arthritis: a comparison with patients with rheumatoid arthritis. Arthritis Rheum. 2001 Apr;45(2):151-8. PMID: 11324779.
- Sokoll KB, Helliwell PS. Comparison of disability and quality of life in rheumatoid and psoriatic arthritis. J Rheumatol. 2001 Aug;28(8):1842-6. PMID: 11508587.
- 6. Borman P, Toy GG, Babaoglu S, et al. A comparative evaluation of quality of life and life satisfaction in patients with psoriatic and rheumatoid arthritis. Clin Rheumatol. 2006 Apr 19PMID: 16622591.
- 7. Li X, Gignac MA, Anis AH. The indirect costs of arthritis resulting from unemployment, reduced performance, and occupational changes while at work. Med Care. 2006 Apr;44(4):304-10. PMID: 16565630.
- 8. Mau W, Listing J, Huscher D, et al. Employment across chronic inflammatory rheumatic diseases and comparison with the general population. J Rheumatol. 2005 Apr;32(4):721-8. PMID: 15801031.

- 9. Michaud K, Messer J, Choi HK, et al. Direct medical costs and their predictors in patients with rheumatoid arthritis: a three-year study of 7,527 patients. Arthritis Rheum. 2003 Oct;48(10):2750-62. PMID: 14558079.
- 10. Hallert E, Husberg M, Skogh T. Costs and course of disease and function in early rheumatoid arthritis: a 3-year follow-up (the Swedish TIRA project). Rheumatology (Oxford). 2006 Mar;45(3):325-31. PMID: 16287927.
- 11. Huscher D, Merkesdal S, Thiele K, et al. Cost of illness in rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis and systemic lupus erythematosus in Germany. Ann Rheum Dis. 2006 Sep;65(9):1175-83. PMID: 16540552.
- 12. Ozminkowski RJ, Burton WN, Goetzel RZ, et al. The impact of rheumatoid arthritis on medical expenditures, absenteeism, and short-term disability benefits. J Occup Environ Med. 2006 Feb;48(2):135-48. PMID: 16474262.
- 13. National and state medical expenditures and lost earnings attributable to arthritis and other rheumatic conditions--United States, 2003. MMWR Morb Mortal Wkly Rep. 2007 Jan 12;56(1):4-7. PMID: 17218935.
- 14. Pugner KM, Scott DI, Holmes JW, et al. The costs of rheumatoid arthritis: an international long-term view. Semin Arthritis Rheum. 2000 Apr;29(5):305-20. PMID: 10805355.
- 15. Orozco G, Rueda B, Martin J. Genetic basis of rheumatoid arthritis. Biomed Pharmacother. 2006 Dec;60(10):656-62. PMID: 17055211.
- 16. Turesson C, Schaid DJ, Weyand CM, et al. The impact of HLA-DRB1 genes on extraarticular disease manifestations in rheumatoid arthritis. Arthritis Res Ther. 2005;7(6):R1386-93. PMID: 16277691.

- 17. Muller-Ladner U, Pap T, Gay RE, et al. Mechanisms of disease: the molecular and cellular basis of joint destruction in rheumatoid arthritis. Nat Clin Pract Rheumatol. 2005 Dec;1(2):102-10. PMID: 16932639.
- 18. Choy EH, Panayi GS. Cytokine pathways and joint inflammation in rheumatoid arthritis. N Engl J Med. 2001 Mar 22;344(12):907-16. PMID: 11259725.
- 19. Greiner A, Plischke H, Kellner H, et al. Association of anti-cyclic citrullinated peptide antibodies, anti-citrullin antibodies, and IgM and IgA rheumatoid factors with serological parameters of disease activity in rheumatoid arthritis. Ann N Y Acad Sci. 2005 Jun;1050:295-303. PMID: 16014545.
- Liao KP, Batra KL, Chibnik L, et al. Anticyclic citrullinated peptide revised criteria for the classification of rheumatoid arthritis.
 Ann Rheum Dis. 2008 Nov;67(11):1557-61.

 PMID: 18234714.
- 21. Arnett FC, Edworthy SM, Bloch DA, et al. The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. Arthritis Rheum. 1988 Mar;31(3):315-24. PMID: 3358796.
- 22. Aletaha D, Neogi T, Silman AJ, et al. 2010 Rheumatoid arthritis classification criteria: an American College of Rheumatology/European League Against Rheumatism collaborative initiative. Ann Rheum Dis. 2010 Sep;69(9):1580-8. PMID: 20699241.
- 23. Saag KG, Gim GT, Patkar NM, et al.
 American College of Rheumatology 2008
 recommendations for the use of nonbiologic
 and biologic disease-modifying
 antirheumatic drugs in rheumatoid arthritis.
 Arthritis Care Res. 2008;59(6):762-84.
- 24. Donahue KE, Gartlehner G, Jonas DE, et al. Systematic review: comparative effectiveness and harms of disease-modifying medications for rheumatoid arthritis. Ann Intern Med. 2008 Jan 15;148(2):124-34. PMID: 18025440.

- 25. Chen YF, Jobanputra P, Barton P, et al. A systematic review of the effectiveness of adalimumab, etanercept and infliximab for the treatment of rheumatoid arthritis in adults and an economic evaluation of their cost-effectiveness. Health Technol Assess. 2006;10(42).
- 26. Donahue KE, Gartlehner G, Jonas DE, et al. Comparative effectiveness of drug therapy for rheumatoid arthritis and psoriatic arthritis in adults. Comparative Effectiveness Review No. 11.(Prepared by RTI-University of North Carolina Evidence-based Practice Center under Contract No. 290-02-0016.) Rockville, MD: Agency for Healthcare Research and Quality; 2007. www.effectivehealthcare.ahrq.gov/reports/final.cfm.
- Singh JA, Christensen R, Wells GA, et al. A network meta-analysis of randomized controlled trials of biologics for rheumatoid arthritis: a Cochrane overview. Can Med Assoc J. 2009;181:787.
- 28. Wailoo A, Brennan A, Bansback N, et al. Modeling the cost effectiveness of etanercept, adalimumab and anakinra compared to infliximab in the treatment of patients with rheumatoid arthritis in the Medicare program (prepared by University of Sheffeld under contract no: RFQ 01R000206). Agency for Healthcare Research and Quality. Technology Assessment. Rockville, MD: 2006.
- 29. National Institute for Health, Clinical Excellence. Adalimumab, etanercept and infliximab for the treatment of rheumatoid arthritis. London: National Institute for Health and Clinical Excellence; 2007.
- 30. Harris RP, Helfand M, Woolf SH, et al. Current methods of the US Preventive Services Task Force: a review of the process. Am J Prev Med. 2001 Apr;20(3 Suppl):21-35. PMID: 11306229.
- 31. Anonymous. Undertaking systematic reviews of research on effectiveness: CRD's guidance for those carrying out or commissioning reviews. CRD Report Number 4 (2nd edition). 2001.

- 32. Deeks JJ, Dinnes J, D'Amico R, et al. Evaluating non-randomised intervention studies. Health Technol Assess. 2003;7(27):iii-x, 1-173. PMID: 14499048.
- 33. Agency for Healthcare Research and Quality. Methods reference guide for effectiveness and comparative effectiveness reviews, version 1.0. Rockville, MD: Agency for Healthcare Research and Quality; October 2007 (draft). http://effectivehealthcare.ahrq.gov/repFiles/2007_10DraftMethodsGuide.pdf.
- 34. Owens DK, Lohr KN, Atkins D, et al. AHRQ series paper 5: grading the strength of a body of evidence when comparing medical interventions--agency for healthcare research and quality and the effective healthcare program. J Clin Epidemiol. 2010 May;63(5):513-23. PMID: 19595577.
- 35. Lu G, Ades AE. Combination of direct and indirect evidence in mixed treatment comparisons. Stat Med. 2004 Oct 30;23(20):3105-24. PMID: 15449338.
- 36. Higgins JP, Whitehead A. Borrowing strength from external trials in a meta-analysis. Stat Med. 1996 Dec 30;15(24):2733-49. PMID: 8981683.
- 37. Goodman SN. Toward evidence-based medical statistics. 2: The Bayes factor. Ann Intern Med. 1999 Jun 15;130(12):1005-13. PMID: 10383350.
- 38. Whitehead A. Meta-analysis of controlled clinical trials. Chichester, UK: John Wiley & Sons, Ltd.; 2002.
- Stevens A. The BUGS Project. Cambridge, UK: Hosted by the MRC Biostatistics Unit. www.mrcbsu.cam.ac.uk/bugs/welcome.shtml Accessed on May 2, 2011.
- Multi-Parameter Evidence Synthesis
 (MPES) Research Group. Mixed Treatment Comparisons. University of Bristol,
 Community-Based Medicine.
 www.bris.ac.uk/cobm/research/mpes/mtc.ht
 ml. Accessed May 3, 2011.

- 41. Bucher HC, Guyatt GH, Griffith LE, et al. The results of direct and indirect treatment comparisons in meta-analysis of randomized controlled trials. J Clin Epidemiol. 1997 Jun;50(6):683-91. PMID: 9250266.
- 42. Song F, Altman DG, Glenny AM, et al. Validity of indirect comparison for estimating efficacy of competing interventions: empirical evidence from published meta-analyses. BMJ. 2003 Mar 1;326(7387):472. PMID: 12609941.
- 43. Sauriol L, Laporta M, Edwardes MD, et al. Meta-analysis comparing newer antipsychotic drugs for the treatment of schizophrenia: evaluating the indirect approach. Clin Ther. 2001 Jun;23(6):942-56. PMID: 11440294.
- 44. Felson DT, Anderson JJ, Boers M, et al. ACR preliminary definition of improvement in rheumatoid arthritis. Arthritis Rheum. 1995;38(6):727-35.
- 45. van Tuyl LH, Vlad SC, Felson DT, et al. Defining remission in rheumatoid arthritis: results of an initial American College of Rheumatology/European League Against Rheumatism consensus conference. Arthritis Rheum. 2009 May 15;61(5):704-10. PMID: 19405006.
- 46. Prevoo ML, van Gestel AM, van T. Hof MA, et al. Remission in a prospective study of patients with rheumatoid arthritis. American Rheumatism Association preliminary remission criteria in relation to the disease activity score. Br J Rheumatol. 1996 Nov;35(11):1101-5. PMID: 8948296.
- 47. Landewe R, van der Heijde D, van der Linden S, et al. Twenty-eight-joint counts invalidate the DAS28 remission definition owing to the omission of the lower extremity joints: a comparison with the original DAS remission. Ann Rheum Dis. 2006 May;65(5):637-41. PMID: 16219709.
- 48. Wells GA, Tugwell P, Kraag GR, et al. Minimum important difference between patients with rheumatoid arthritis: the patient's perspective. J Rheumatol. 1993 Mar;20(3):557-60. PMID: 8478873.

- 49. Kosinski M, Zhao SZ, Dedhiya S, et al.
 Determining minimally important changes
 in generic and disease-specific health-related
 quality of life questionnaires in clinical trials
 of rheumatoid arthritis. Arthritis Rheum.
 2000 Jul;43(7):1478-87. PMID: 10902749.
- 50. Walters SJ, Brazier JE. What is the relationship between the minimally important difference and health state utility values? The case of the SF-6D. Health Qual Life Outcomes. 2003;1:4. PMID: 12737635.
- 51. Ware JE, Snow KK, Kosinski M, et al. SF-36® Health Survey Manual and Interpretation Guide. Boston, MA: New England Medical Center, The Health Institute; 1993.
- 52. Angst F, Aeschlimann A, Stucki G. Smallest detectable and minimal clinically important differences of rehabilitation intervention with their implications for required sample sizes using WOMAC and SF-36 quality of life measurement instruments in patients with osteoarthritis of the lower extremities. Arthritis Rheum. 2001 Aug;45(4):384-91. PMID: 11501727.
- 53. Bruynesteyn K, van der Heijde D, Boers M, et al. Determination of the minimal clinically important difference in rheumatoid arthritis joint damage of the Sharp/van der Heijde and Larsen/Scott scoring methods by clinical experts and comparison with the smallest detectable difference. Arthritis Rheum. 2002 Apr;46(4):913-20. PMID: 11953967.
- 54. Kirwan JR, Hallgren R, Mielants H, et al. A randomised placebo controlled 12 week trial of budesonide and prednisolone in rheumatoid arthritis. Ann Rheum Dis. 2004;63(6):688-95. PMID: 15140776.
- Osiri M, Shea B, Robinson V, et al.
 Leflunomide for the treatment of rheumatoid arthritis. Cochrane Database Syst Rev.
 2003(1):CD002047. PMID: 12535423.

- 56. Cohen S, Cannon G, Schiff M, et al. Twoyear, blinded, randomized, controlled trial of treatment of active rheumatoid arthritis with leflunomide compared with methotrexate. Utilization of leflunomide in the treatment of rheumatoid arthritis. Arthritis Rheum. 2001;44(9):1984-92. PMID: 11592358.
- 57. Dougados M, Combe B, Cantagrel A, et al. Combination therapy in early rheumatoid arthritis: a randomised, controlled, double blind 52 week clinical trial of sulphasalazine and methotrexate compared with the single components. Ann Rheum Dis. 1999;58(4):220-5.
- 58. Haagsma CJ, van Riel PL, de Jong AJ, et al. Combination of sulphasalazine and methotrexate versus the single components in early rheumatoid arthritis: a randomized, controlled, double-blind, 52 week clinical trial. Br J Rheumatol. 1997;36(10):1082-8.
- 59. Capell H, Madhok R, Porter D, et al.
 Combination therapy with sulphasalazine
 and methotrexate is more effective than
 either drug alone in rheumatoid arthritis (ra)
 patients with a suboptimal response to
 sulphasalazine: Results from the double
 blind placebo controlled mascot study. Ann
 Rheum Dis. 2007 Feb;66(2):235-41.
- 60. Larsen A, Kvien TK, Schattenkirchner M, et al. Slowing of disease progression in rheumatoid arthritis patients during long-term treatment with leflunomide or sulfasalazine. Scand J Rheumatol. 2001;30(3):135-42.
- 61. O'Dell JR, Leff R, Paulsen G, et al.
 Treatment of rheumatoid arthritis with
 methotrexate and hydroxychloroquine,
 methotrexate and sulfasalazine, or a
 combination of the three medications:
 results of a two-year, randomized, doubleblind, placebo-controlled trial. Arthritis
 Rheum. 2002;46(5):1164-70.
- 62. O'Dell JR, Haire CE, Erikson N, et al. Treatment of rheumatoid arthritis with methotrexate alone, sulfasalazine and hydroxychloroquine, or a combination of all three medications. N Engl J Med. 1996 May 16;334(20):1287-91. PMID: 8609945.

- 63. Kirwan JR, Bijlsma JW, Boers M, et al. Effects of glucocorticoids on radiological progression in rheumatoid arthritis. Cochrane Database Syst Rev. 2007(1):CD006356. PMID: 17253590.
- 64. Choy EH, Smith CM, Farewell V, et al. Factorial randomised controlled trial of glucocorticoids and combination disease modifying drugs in early rheumatoid arthritis. Ann Rheum Dis. 2008
 May;67(5):656-63. PMID: 17768173.
- 65. Svensson B, Boonen A, Albertsson K, et al. Low-dose prednisolone in addition to the initial disease-modifying antirheumatic drug in patients with early active rheumatoid arthritis reduces joint destruction and increases the remission rate: a two-year randomized trial. Arthritis Rheum. 2005;52(11):3360-70.
- 66. Schiff M, Keiserman M, Codding C, et al. Efficacy and safety of abatacept or infliximab vs placebo in ATTEST: a phase III, multi-centre, randomised, double-blind, placebo-controlled study in patients with rheumatoid arthritis and an inadequate response to methotrexate. Ann Rheum Dis. 2008 Aug;67(8):1096-103. PMID: 18055472.
- 67. Geborek P, Crnkic M, Petersson IF, et al. Etanercept, infliximab, and leflunomide in established rheumatoid arthritis: clinical experience using a structured follow up programme in southern Sweden. Ann Rheum Dis. 2002 Sep;61(9):793-8. PMID: 12176803.
- 68. Weaver AL, Lautzenheiser RL, Schiff MH, et al. Real-world effectiveness of select biologic and DMARD monotherapy and combination therapy in the treatment of rheumatoid arthritis: results from the RADIUS observational registry. Curr Med Res Opin. 2006 Jan;22(1):185-98. PMID: 16393444.

- 69. Kristensen LE, Saxne T, Geborek P. The LUNDEX, a new index of drug efficacy in clinical practice: results of a five-year observational study of treatment with infliximab and etanercept among rheumatoid arthritis patients in southern Sweden.

 Arthritis Rheum. 2006 Feb;54(2):600-6.
 PMID: 16447237.
- 70. Fernandez-Nebro A, Irigoyen MV, Urena I, et al. Effectiveness, predictive response factors, and safety of anti-tumor necrosis factor (TNF) therapies in anti-TNF-naive rheumatoid arthritis. J Rheumatol. 2007 Dec;34(12):2334-42. PMID: 17985409.
- 71. Kievit W, Adang EM, Fransen J, et al. The effectiveness and medication costs of three anti-tumour necrosis factor alpha agents in the treatment of rheumatoid arthritis from prospective clinical practice data. Ann Rheum Dis. 2008 Sep;67(9):1229-34. PMID: 18174220.
- 72. Finckh A, Ciurea A, Brulhart L, et al. B cell depletion may be more effective than switching to an alternative anti-tumor necrosis factor agent in rheumatoid arthritis patients with inadequate response to anti-tumor necrosis factor agents. Arthritis Rheum. 2007 May;56(5):1417-23. PMID: 17469098.
- 73. Hetland ML, Christensen IJ, Tarp U, et al. Direct comparison of treatment responses, remission rates, and drug adherence in patients with rheumatoid arthritis treated with adalimumab, etanercept, or infliximab results from eight years of surveillance of clinical practice in the Nationwide Danish DANBIO Registry. Arthritis Rheum. 2010;62(1):22-32.
- 74. Gartlehner G, Hansen RA, Jonas BL, et al. The comparative efficacy and safety of biologics for the treatment of rheumatoid arthritis: a systematic review and metaanalysis. J Rheumatol. 2006 Dec;33(12):2398-408.

- 75. Clark W, Jobanputra P, Barton P, et al. The clinical and cost-effectiveness of anakinra for the treatment of rheumatoid arthritis in adults: a systematic review and economic analysis. Health Technol Assess. 2004 May;8(18):iii-iv, ix-x, 1-105. PMID: 15130461.
- 76. Breedveld FC, Weisman MH, Kavanaugh AF, et al. The PREMIER study: A multicenter, randomized, double-blind clinical trial of combination therapy with adalimumab plus methotrexate versus methotrexate alone or adalimumab alone in patients with early, aggressive rheumatoid arthritis who had not had previous methotrexate treatment. Arthritis Rheum. 2006 Jan;54(1):26-37. PMID: 16385520.
- 77. Bathon JM, Martin RW, Fleischmann RM, et al. A comparison of etanercept and methotrexate in patients with early rheumatoid arthritis. N Engl J Med. 2000 Nov 30;343(22):1586-93. PMID: 11096165.
- 78. Listing J, Strangfeld A, Rau R, et al. Clinical and functional remission: even though biologics are superior to conventional DMARDs overall success rates remain low-results from RABBIT, the German biologics register. Arthritis Res Ther. 2006;8(3):R66. PMID: 16600016.
- 79. Genovese MC, Cohen S, Moreland L, et al. Combination therapy with etanercept and anakinra in the treatment of patients with rheumatoid arthritis who have been treated unsuccessfully with methotrexate. Arthritis Rheum. 2004 May;50(5):1412-9. PMID: 15146410.
- 80. Weinblatt M, Schiff M, Goldman A, et al. Selective costimulation modulation using abatacept in patients with active rheumatoid arthritis while receiving etanercept: a randomised clinical trial. Ann Rheum Dis. 2007 Feb;66(2):228-34. PMID: 16935912.

- 81. Hyrich KL, Symmons DP, Watson KD, et al. Comparison of the response to infliximab or etanercept monotherapy with the response to cotherapy with methotrexate or another disease-modifying antirheumatic drug in patients with rheumatoid arthritis: Results from the British Society for Rheumatology Biologics Register. Arthritis Rheum. 2006 May 30;54(6):1786-94. PMID: 16736520.
- 82. St Clair EW, van der Heijde DM, Smolen JS, et al. Combination of infliximab and methotrexate therapy for early rheumatoid arthritis: a randomized, controlled trial. Arthritis Rheum. 2004 Nov;50(11):3432-43. PMID: 15529377.
- 83. Smolen JS, Han C, van der Heijde D, et al. Infliximab treatment maintains employability in patients with early rheumatoid arthritis. Arthritis Rheum. 2006 Mar;54(3):716-22. PMID: 16508932.
- 84. Edwards JC, Szczepanski L, Szechinski J, et al. Efficacy of B-cell-targeted therapy with rituximab in patients with rheumatoid arthritis. N Engl J Med. 2004 Jun 17;350(25):2572-81. PMID: 15201414.
- 85. Combe B, Codreanu C, Fiocco U, et al. Etanercept and sulfasalazine, alone and combined, in patients with active rheumatoid arthritis despite receiving sulfasalazine: a double-blind comparison. Ann Rheum Dis. 2006;65(10):1357-62.
- 86. Klareskog L, van der Heijde D, de Jager JP, et al. Therapeutic effect of the combination of etanercept and methotrexate compared with each treatment alone in patients with rheumatoid arthritis: double-blind randomised controlled trial. Lancet. 2004 Feb 28;363(9410):675-81. PMID: 15001324.
- 87. van Riel PL, Taggart AJ, Sany J, et al. Efficacy and safety of combination etanercept and methotrexate versus etanercept alone in patients with rheumatoid arthritis with an inadequate response to methotrexate: The ADORE study. Ann Rheum Dis. 2006 Feb 7;65(11):1478-83. PMID: 16464988.

- 88. Zink A, Listing J, Kary S, et al. Treatment continuation in patients receiving biological agents or conventional DMARD therapy. Ann Rheum Dis. 2005 Sep;64(9):1274-9. PMID: 15708884.
- 89. Westhovens R, Robles M, Ximenes AC, et al. Clinical efficacy and safety of abatacept in methotrexate-naive patients with early rheumatoid arthritis and poor prognostic factors. Ann Rheum Dis. 2009

 Dec;68(12):1870-7. PMID: 16935912.
- 90. Emery P, Breedveld FC, Hall S, et al.
 Comparison of methotrexate monotherapy
 with a combination of methotrexate and
 etanercept in active, early, moderate to
 severe rheumatoid arthritis (COMET): a
 randomised, double-blind, parallel treatment
 trial. Lancet. 2008 Aug 2;372(9636):375-82.
 PMID: 18635256.
- 91. Emery P, Breedveld F, van der Heijde D, et al. Two-year clinical and radiographic results with combination etanerceptmethotrexate therapy versus monotherapy in early rheumatoid arthritis: a two-year, double-blind, randomized study. Arthritis Rheum. 2010 Mar;62(3):674-82. PMID: 20187135.
- 92. Emery P, Fleischmann RM, Moreland LW, et al. Golimumab, a human anti-tumor necrosis factor alpha monoclonal antibody, injected subcutaneously every four weeks in methotrexate-naive patients with active rheumatoid arthritis: twenty-four-week results of a phase III, multicenter, randomized, double-blind, placebocontrolled study of golimumab before methotrexate as first-line therapy for early-onset rheumatoid arthritis. Arthritis Rheum. 2009 Aug;60(8):2272-83. PMID: 19644849.
- 93. Karanikolas G, Charalambopoulos D, Vaiopoulos G, et al. Adjunctive anakinra in patients with active rheumatoid arthritis despite methotrexate, or leflunomide, or cyclosporin-A monotherapy: a 48-week, comparative, prospective study. Rheumatology (Oxford). 2008
 Sep;47(9):1384-8. PMID: 18603660.

- 94. Finckh A, Dehler S, Gabay C. The effectiveness of leflunomide as a co-therapy of tumour necrosis factor inhibitors in rheumatoid arthritis: a population-based study. Ann Rheum Dis. 2009 Jan;68(1):33-9. PMID: 18230627.
- 95. Boers M, Verhoeven AC, Markusse HM, et al. Randomised comparison of combined step-down prednisolone, methotrexate and sulphasalazine with sulphasalazine alone in early rheumatoid arthritis. Lancet. 1997 Aug 2;350(9074):309-18. PMID: 9251634.
- 96. Landewe RB, Boers M, Verhoeven AC, et al. COBRA combination therapy in patients with early rheumatoid arthritis: long-term structural benefits of a brief intervention. Arthritis Rheum. 2002 Feb;46(2):347-56. PMID: 11840436.
- 97. Mottonen T, Hannonen P, Leirisalo-Repo M, et al. Comparison of Combination Therapy With Single-Drug Therapy in Early Rheumatoid Arthritis: a Randomised Trial. Lancet. 1999;353(9164):1568-73.
- 98. Korpela M, Laasonen L, Hannonen P, et al. Retardation of joint damage in patients with early rheumatoid arthritis by initial aggressive treatment with disease-modifying antirheumatic drugs: five-year experience from the Fin-Raco Study. Arthritis Rheum. 2004;50(7):2072-81.
- 99. van Vollenhoven RF, Ernestam S, Geborek P, et al. Addition of infliximab compared with addition of sulfasalazine and hydroxychloroquine to methotrexate in patients with early rheumatoid arthritis (Swefot trial): 1-year results of a randomised trial. Lancet. 2009 Aug 8;374(9688):459-66. PMID: 19665644.
- 100. Goekoop-Ruiterman YP, de Vries-Bouwstra JK, Allaart CF, et al. Clinical and radiographic outcomes of four different treatment strategies in patients with early rheumatoid arthritis (the BeSt study): a randomized, controlled trial. Arthritis Rheum. 2005 Nov;52(11):3381-90. PMID: 16258899.

- 101. Allaart CF, Goekoop-Ruiterman YP, de Vries-Bouwstra JK, et al. Aiming at low disease activity in rheumatoid arthritis with initial combination therapy or initial monotherapy strategies: the BeSt study. Clin Exp Rheumatol. 2006 Nov-Dec;24(6 Suppl 43):S-77-82. PMID: 17083767.
- 102. Goekoop-Ruiterman YPM, De Vries-Bouwstra JK, Allaart CF, et al. Comparison of treatment strategies in early rheumatoid arthritis: a randomized trial. Ann Intern Med. 2007;146(6):406-15. PMID: 2008225574.
- van der Kooij SM, de Vries-Bouwstra JK, Goekoop-Ruiterman YP, et al. Patientreported outcomes in a randomized trial comparing four different treatment strategies in recent-onset rheumatoid arthritis. Arthritis Rheum. 2009 Jan 15;61(1):4-12. PMID: 19116965.
- 104. Strand V, Cohen S, Schiff M, et al.
 Treatment of active rheumatoid arthritis
 with leflunomide compared with placebo
 and methotrexate. Arch Intern Med.
 1999;159(21):2542-50.
- 105. Emery P, Breedveld FC, Lemmel EM, et al. A comparison of the efficacy and safety of leflunomide and methotrexate for the treatment of rheumatoid arthritis. Rheumatology (Oxford). 2000;39(6):655-65.
- 106. Gaujoux-Viala C, Smolen JS, Landewe R, et al. Current evidence for the management of rheumatoid arthritis with synthetic disease-modifying antirheumatic drugs: a systematic literature review informing the EULAR recommendations for the management of rheumatoid arthritis. Ann Rheum Dis. 2010 Jun;69(6):1004-9. PMID: 20447954.
- 107. Smolen JS, Kalden JR, Scott DL, et al. Efficacy and safety of leflunomide compared with placebo and sulphasalazine in active rheumatoid arthritis: a doubleblind, randomised, multicentre trial. Lancet. 1999;353(9149):259-66.
- 108. Smolen JS. Efficacy and safety of the new DMARD leflunomide: comparison to placebo and sulfasalazine in active rheumatoid arthritis. Scand J Rheumatol. 1999;112(Supplement):15-21.

- 109. Sharp JT, Strand V, Leung H, et al.
 Treatment with leflunomide slows
 radiographic progression of rheumatoid
 arthritis: results from three randomized
 controlled trials of leflunomide in patients
 with active rheumatoid arthritis. Arthritis
 Rheum. 2000;43(3):495-505.
- 110. Schipper LG, Fransen J, Barrera P, et al. Methotrexate therapy in rheumatoid arthritis after failure to sulphasalazine: to switch or to add? Rheumatology (Oxford). 2009 Oct;48(10):1247-53. PMID: 19638454.
- 111. Maillefert JF, Combe B, Goupille P, et al. Long term structural effects of combination therapy in patients with early rheumatoid arthritis: five year follow up of a prospective double blind controlled study. Ann Rheum Dis. 2003;62(8):764-6.
- 112. BlueCross BlueShield Technology Evaluation Center (TEC). Special report: evidence on sequencing of conventional and biological disease-modifying anti-rheumatic drugs. 2003 2003;18(11).
- 113. Kremer JM, Westhovens R, Leon M, et al. Treatment of rheumatoid arthritis by selective inhibition of T-cell activation with fusion protein CTLA4Ig. N Engl J Med. 2003 Nov 13;349(20):1907-15. PMID: 14614165.
- 114. Kremer JM, Dougados M, Emery P, et al. Treatment of rheumatoid arthritis with the selective costimulation modulator abatacept: twelve-month results of a phase iib, double-blind, randomized, placebo-controlled trial. Arthritis Rheum. 2005 Aug;52(8):2263-71. PMID: 16052582.
- 115. Emery P, Kosinski M, Li T, et al. Treatment of rheumatoid arthritis patients with abatacept and methotrexate significantly improved health-related quality of life. J Rheumatol. 2006 Apr;33(4):681-9. PMID: 16568505.
- 116. Kremer JM, Genant HK, Moreland LW, et al. Effects of abatacept in patients with methotrexate-resistant active rheumatoid arthritis a randomized trial. Ann Intern Med. 2006 Dec;144:865-76.

- 117. Genovese MC, Becker JC, Schiff M, et al. Abatacept for rheumatoid arthritis refractory to tumor necrosis factor alpha inhibition. N Engl J Med. 2005 Sep 15;353(11):1114-23. PMID: 16162882.
- 118. Navarro-Sarabia F, Ariza-Ariza R, Hernandez-Cruz B, et al. Adalimumab for treating rheumatoid arthritis. Cochrane Database Syst Rev. 2005(3):CD005113
- 119. van de Putte LB, Rau R, Breedveld FC, et al. Efficacy and safety of the fully human anti-tumour necrosis factor alpha monoclonal antibody adalimumab (D2E7) in DMARD refractory patients with rheumatoid arthritis: a 12 week, phase II study. Ann Rheum Dis. 2003

 Dec;62(12):1168-77. PMID: 14644854.
- 120. Keystone EC, Kavanaugh AF, Sharp JT, et al. Radiographic, clinical, and functional outcomes of treatment with adalimumab (a human anti-tumor necrosis factor monoclonal antibody) in patients with active rheumatoid arthritis receiving concomitant methotrexate therapy: a randomized, placebo-controlled, 52-week trial. Arthritis Rheum. 2004 May;50(5):1400-11. PMID: 15146409.
- 121. Furst DE, Schiff MH, Fleischmann RM, et al. Adalimumab, a fully human anti tumor necrosis factor-alpha monoclonal antibody, and concomitant standard antirheumatic therapy for the treatment of rheumatoid arthritis: results of STAR (Safety Trial of Adalimumab in Rheumatoid Arthritis). J Rheumatol. 2003 Dec;30(12):2563-71. PMID: 14719195.
- 122. van de Putte LB, Atkins C, Malaise M, et al. Efficacy and safety of adalimumab as monotherapy in patients with rheumatoid arthritis for whom previous disease modifying antirheumatic drug treatment has failed. Ann Rheum Dis. 2004

 May;63(5):508-16. PMID: 15082480.
- 123. Weinblatt ME, Keystone EC, Furst DE, et al. Adalimumab, a fully human anti-tumor necrosis factor alpha monoclonal antibody, for the treatment of rheumatoid arthritis in patients taking concomitant methotrexate: the ARMADA trial. Arthritis Rheum. 2003 Jan;48(1):35-45. PMID: 12528101.

- 124. Weinblatt ME, Keystone EC, Furst DE, et al. Long term efficacy and safety of adalimumab plus methotrexate in patients with rheumatoid arthritis: ARMADA 4 year extended study. Ann Rheum Dis. 2006 Jun;65(6):753-9. PMID: 16308341.
- 125. Miyasaka N. Clinical investigation in highly disease-affected rheumatoid arthritis patients in Japan with adalimumab applying standard and general evaluation: the CHANGE study. Mod Rheumatol. 2008;18(3):252-62. PMID: 18330677.
- 126. Alonso-Ruiz A, Pijoan JI, Ansuategui E, et al. Tumor necrosis factor alpha drugs in rheumatoid arthritis: Systematic review and metaanalysis of efficacy and safety. BMC Musculoskeletal Disorders. 2008 April 17;9:52. PMID: 18419803.
- 127. Kim HY, Lee SK, Song YW, et al. A randomized, double-blind, placebo-controlled, phase III study of the human anti-tumor necrosis factor antibody adalimumab administered as subcutaneous injections in Korean rheumatoid arthritis patients treated with methotrexate. APLAR J Rheumatol. 2007;10(1):9-16.
- 128. Bresnihan B, Alvaro-Gracia JM, Cobby M, et al. Treatment of rheumatoid arthritis with recombinant human interleukin-1 receptor antagonist. Arthritis Rheum. 1998
 Dec;41(12):2196-204. PMID: 9870876.
- 129. Nuki G, Bresnihan B, Bear MB, et al. Long-term safety and maintenance of clinical improvement following treatment with anakinra (recombinant human interleukin-1 receptor antagonist) in patients with rheumatoid arthritis: extension phase of a randomized, double-blind, placebo-controlled trial. Arthritis Rheum. 2002 Nov;46(11):2838-46. PMID: 12428223.
- 130. Jiang Y, Genant HK, Watt I, et al. A multicenter, double-blind, dose-ranging, randomized, placebo-controlled study of recombinant human interleukin-1 receptor antagonist in patients with rheumatoid arthritis: radiologic progression and correlation of Genant and Larsen scores. Arthritis Rheum. 2000 May;43(5):1001-9. PMID: 10817552.

- 131. Cohen S, Hurd E, Cush J, et al. Treatment of rheumatoid arthritis with anakinra, a recombinant human interleukin-1 receptor antagonist, in combination with methotrexate: results of a twenty-four-week, multicenter, randomized, double-blind, placebo-controlled trial. Arthritis Rheum. 2002 Mar;46(3):614-24. PMID: 11920396.
- 132. Cohen SB, Woolley JM, Chan W. Interleukin 1 receptor antagonist anakinra improves functional status in patients with rheumatoid arthritis. J Rheumatol. 2003 Feb;30(2):225-31. PMID: 12563672.
- 133. Cohen SB, Moreland LW, Cush JJ, et al. A multicentre, double blind, randomised, placebo controlled trial of anakinra (Kineret), a recombinant interleukin 1 receptor antagonist, in patients with rheumatoid arthritis treated with background methotrexate. Ann Rheum Dis. 2004 Sep;63(9):1062-8. PMID: 15082469.
- 134. Mertens M, Singh JA. Anakinra for rheumatoid arthritis. Cochrane Database Syst Rev. 2009(1):CD005121. PMID: 19160248.
- 135. Jobanputra P, Barton P, Bryan S, et al. The effectiveness of infliximab and etanercept for the treatment of rheumatoid arthritis: a systematic review and economic evaluation. Health Technol Assess. 2002;6(21):1-110. PMID: 12387732.
- 136. van der Heijde D, Klareskog L, Singh A, et al. Patient reported outcomes in a trial of combination therapy with etanercept and methotrexate for rheumatoid arthritis: the TEMPO trial. Ann Rheum Dis. 2006 Mar;65(3):328-34. PMID: 16079172.
- 137. van der Heijde D, Klareskog L, Boers M, et al. Comparison of different definitions to classify remission and sustained remission: 1 year TEMPO results. Ann Rheum Dis. 2005 Nov;64(11):1582-7. PMID: 15860509.

- Van der Heijde D, Klareskog L, Rodriguez-Valverde V, et al. Comparison of etanercept and methotrexate, alone and combined, in the treatment of rheumatoid arthritis: two-year clinical and radiographic results from the TEMPO study, a double-blind, randomized trial. Arthritis Rheum. 2006 Apr;54(4):1063-74. PMID: 16572441.
- 139. Blumenauer B, Judd M, Cranney A, et al. Etanercept for the treatment of rheumatoid arthritis. Cochrane Database of Systematic Review. 2003(3):CD004525.
- 140. Moreland LW, Schiff MH, Baumgartner SW, et al. Etanercept therapy in rheumatoid arthritis. A randomized, controlled trial. Ann Intern Med. 1999 Mar 16;130(6):478-86. PMID: 10075615.
- 141. Mathias SD, Colwell HH, Miller DP, et al. Health-related quality of life and functional status of patients with rheumatoid arthritis randomly assigned to receive etanercept or placebo. Clin Ther. 2000 Jan;22(1):128-39. PMID: 10688396.
- 142. Weinblatt ME, Kremer JM, Bankhurst AD, et al. A trial of etanercept, a recombinant tumor necrosis factor receptor:Fc fusion protein, in patients with rheumatoid arthritis receiving methotrexate. N Engl J Med. 1999 Jan 28;340(4):253-9. PMID: 9920948.
- 143. Lan JL, Chou SJ, Chen DY, et al. A comparative study of etanercept plus methotrexate and methotrexate alone in Taiwanese patients with active rheumatoid arthritis: a 12-week, double-blind, randomized, placebo-controlled study. J Formos Med Assoc. 2004 Aug;103(8):618-23. PMID: 15340661.
- 144. Moreland LW, Baumgartner SW, Schiff MH, et al. Treatment of rheumatoid arthritis with a recombinant human tumor necrosis factor receptor (p75)-Fc fusion protein. N Engl J Med. 1997 Jul 17;337(3):141-7. PMID: 9219699.

- 145. Combe B, Codreanu C, Fiocco U, et al. Efficacy, safety and patient-reported outcomes of combination etanercept and sulfasalazine versus etanercept alone in patients with rheumatoid arthritis: a double-blind randomised 2-year study. Ann Rheum Dis. 2009 Jul;68(7):1146-52. PMID: 18794178.
- 146. Blumenauer B, Judd M, Wells G, et al. Infliximab for the treatment of rheumatoid arthritis. Cochrane Database Syst Rev. 2002(3):CD003785.
- 147. Taylor P, Steuer A, Gruber J, et al.

 Ultrasonographic and radiographic results
 from a two-year controlled trial of
 immediate or one-year-delayed addition of
 infliximab to ongoing methotrexate therapy
 in patients with erosive early rheumatoid
 arthritis. Arthritis Rheum. 2006;54(1):47-53.
- 148. Maini R, St Clair EW, Breedveld F, et al. Infliximab (chimeric anti-tumour necrosis factor alpha monoclonal antibody) versus placebo in rheumatoid arthritis patients receiving concomitant methotrexate: a randomised phase III trial. ATTRACT Study Group. Lancet. 1999 Dec 4;354(9194):1932-9. PMID: 10622295.
- 149. Maini RN, Breedveld FC, Kalden JR, et al. Sustained improvement over two years in physical function, structural damage, and signs and symptoms among patients with rheumatoid arthritis treated with infliximab and methotrexate. Arthritis Rheum. 2004 Apr;50(4):1051-65. PMID: 15077287.
- 150. Smolen JS, Han C, Bala M, et al. Evidence of radiographic benefit of treatment with infliximab plus methotrexate in rheumatoid arthritis patients who had no clinical improvement: a detailed subanalysis of data from the anti-tumor necrosis factor trial in rheumatoid arthritis with concomitant therapy study. Arthritis Rheum. 2005
 Apr;52(4):1020-30. PMID: 15818697.
- 151. Lipsky PE, van der Heijde DM, St Clair EW, et al. Infliximab and methotrexate in the treatment of rheumatoid arthritis. Anti-Tumor Necrosis Factor Trial in Rheumatoid Arthritis with Concomitant Therapy Study Group. N Engl J Med. 2000 Nov 30;343(22):1594-602. PMID: 11096166.

- 152. Breedveld FC, Emery P, Keystone E, et al. Infliximab in active early rheumatoid arthritis. Ann Rheum Dis. 2004 Feb;63(2):149-55. PMID: 14722203.
- 153. Abe T, Takeuchi T, Miyasaka N, et al. A multicenter, double-blind, randomized, placebo controlled trial of infliximab combined with low dose methotrexate in Japanese patients with rheumatoid arthritis. J Rheumatol. 2006 Jan;33(1):37-44. PMID: 16395748.
- 154. Kavanaugh A, St Clair EW, McCune WJ, et al. Chimeric anti-tumor necrosis factor-alpha monoclonal antibody treatment of patients with rheumatoid arthritis receiving methotrexate therapy. J Rheumatol. 2000 Apr;27(4):841-50. PMID: 10782805.
- 155. Westhovens R, Yocum D, Han J, et al. The safety of infliximab, combined with background treatments, among patients with rheumatoid arthritis and various comorbidities: a large, randomized, placebo-controlled trial. Arthritis Rheum. 2006 Apr;54(4):1075-86. PMID: 16572442.
- 156. Zhang FC, Hou Y, Huang F, et al. Infliximab versus placebo in rheumatoid arthritis patients receiving concomitant methotrexate: a preliminary study from China. APLAR J Rheumatol. 2006;9(2):127-30. PMID: 2006338105.
- 157. Emery P, Fleischmann R, Filipowicz-Sosnowska A, et al. The efficacy and safety of rituximab in patients with active rheumatoid arthritis despite methotrexate treatment: results of a phase IIB randomized, double-blind, placebocontrolled, dose-ranging trial. Arthritis Rheum. 2006 May;54(5):1390-400. PMID: 16649186.
- 158. Cohen SB, Emery P, Greenwald MW, et al. Rituximab for rheumatoid arthritis refractory to anti-tumor necrosis factor therapy: results of a multicenter, randomized, double-blind, placebo-controlled, phase III trial evaluating primary efficacy and safety at twenty-four weeks. Arthritis Rheum. 2006;54(9):2793-806. PMID: 2006485778.

- 159. Keystone E, Emery P, Peterfy CG, et al. Rituximab inhibits structural joint damage in patients with rheumatoid arthritis with an inadequate response to tumour necrosis factor inhibitor therapies. Ann Rheum Dis. 2009 Feb;68(2):216-21. PMID: 18388156.
- 160. Keystone E, Burmester GR, Furie R, et al. Improvement in patient-reported outcomes in a rituximab trial in patients with severe rheumatoid arthritis refractory to anti-tumor necrosis factor therapy. Arthritis Rheum. 2008 Jun 15;59(6):785-93. PMID: 18512710.
- 161. Emery P, Fleischmann R, Filipowicz-Sosnowska A, et al. The efficacy and safety of rituximab in patients with active rheumatoid arthritis despite methotrexate treatment results of a phase IIb randomized, double-blind, placebocontrolled, dose-ranging trial. Arthritis Rheum. 2006 May 1;54(May):1390-400.
- 162. Emery P, Deodhar A, Rigby WF, et al.
 Efficacy and safety of different doses and retreatment of rituximab: a randomised, placebo-controlled trial in patients who are biological naive with active rheumatoid arthritis and an inadequate response to methotrexate (Study Evaluating Rituximab's Efficacy in MTX iNadequate rEsponders (SERENE)). Ann Rheum Dis. 2010 Sep;69(9):1629-35. PMID: 20488885.
- 163. Finckh A, Ciurea A, Brulhart L, et al. Which subgroup of patients with rheumatoid arthritis benefits from switching to rituximab versus alternative anti-tumour necrosis factor (TNF) agents after previous failure of an anti-TNF agent? Ann Rheum Dis. 2010 Feb;69(2):387-93. PMID: 19416802.
- 164. Smolen JS, Beaulieu A, Rubbert-Roth A, et al. Effect of interleukin-6 receptor inhibition with tocilizumab in patients with rheumatoid arthritis (OPTION study): a double-blind, placebo-controlled, randomised trial. Lancet. 2008 Mar 22;371(9617):987-97. PMID: 18358926.

- 165. Fleischmann R, Vencovsky J, van Vollenhoven RF, et al. Efficacy and safety of certolizumab pegol monotherapy every 4 weeks in patients with rheumatoid arthritis failing previous disease-modifying antirheumatic therapy: the FAST4WARD study. Ann Rheum Dis. 2009 Jun;68(6):805-11. PMID: 19015206.
- 166. Kay J, Matteson EL, Dasgupta B, et al. Golimumab in patients with active rheumatoid arthritis despite treatment with methotrexate: a randomized, double-blind, placebo-controlled, dose-ranging study. Arthritis Rheum. 2008 Apr;58(4):964-75. PMID: 18383539.
- 167. Smolen J, Landewe RB, Mease P, et al. Efficacy and safety of certolizumab pegol plus methotrexate in active rheumatoid arthritis: the RAPID 2 study. A randomised controlled trial. Ann Rheum Dis. 2009 Jun;68(6):797-804. PMID: 19015207.
- 168. Keystone E, Heijde D, Mason D, Jr., et al.
 Certolizumab pegol plus methotrexate is significantly more effective than placebo plus methotrexate in active rheumatoid arthritis: findings of a fifty-two-week, phase III, multicenter, randomized, double-blind, placebo-controlled, parallel-group study.
 Arthritis Rheum. 2008 Nov;58(11):3319-29.
 PMID: 18975346.
- 169. Keystone EC, Genovese MC, Klareskog L, et al. Golimumab, a human antibody to tumour necrosis factor {alpha} given by monthly subcutaneous injections, in active rheumatoid arthritis despite methotrexate therapy: the GO-FORWARD Study. Ann Rheum Dis. 2009 Jun;68(6):789-96. PMID: 19066176.
- 170. Smolen JS, Kay J, Doyle MK, et al.
 Golimumab in patients with active
 rheumatoid arthritis after treatment with
 tumour necrosis factor alpha inhibitors (GOAFTER study): a multicentre, randomised,
 double-blind, placebo-controlled, phase III
 trial. Lancet. 2009 Jul 18;374(9685):210-21.
 PMID: 19560810.

- 171. Keystone E, Genovese MC, Klareskog L, et al. Golimumab in patients with active rheumatoid arthritis despite methotrexate therapy: 52-week results of the GO-FORWARD study. Ann Rheum Dis. 2010(6):1129-35. PMID: CN-00748612.
- 172. Nishimoto N, Hashimoto J, Miyasaka N, et al. Study of active controlled monotherapy used for rheumatoid arthritis, an IL-6 inhibitor (SAMURAI): evidence of clinical and radiographic benefit from an x ray reader-blinded randomised controlled trial of tocilizumab. Ann Rheum Dis. 2007 Sep;66(9):1162-7. PMID: 17485422.
- 173. Nishimoto N, Miyasaka N, Yamamoto K, et al. Study of active controlled tocilizumab monotherapy for rheumatoid arthritis patients with an inadequate response to methotrexate (SATORI): significant reduction in disease activity and serum vascular endothelial growth factor by IL-6 receptor inhibition therapy. Mod Rheumatol. 2009;19(1):12-9. PMID: 18979150.
- 174. Maini RN, Taylor PC, Szechinski J, et al. Double-blind randomized controlled clinical trial of the interleukin-6 receptor antagonist, tocilizumab, in European patients with rheumatoid arthritis who had an incomplete response to methotrexate. Arthritis Rheum. 2006 Sep;54(9):2817-29. PMID: 16947782.
- 175. Emery P, Keystone E, Tony HP, et al. IL-6 receptor inhibition with tocilizumab improves treatment outcomes in patients with rheumatoid arthritis refractory to antitumour necrosis factor biologicals: results from a 24-week multicentre randomised placebo-controlled trial. Ann Rheum Dis. 2008 Nov;67(11):1516-23. PMID: 18625622.
- 176. Genovese MC, McKay JD, Nasonov EL, et al. Interleukin-6 receptor inhibition with tocilizumab reduces disease activity in rheumatoid arthritis with inadequate response to disease-modifying antirheumatic drugs: the tocilizumab in combination with traditional disease-modifying antirheumatic drug therapy study. Arthritis Rheum. 2008;58(10):2968-80. PMID: 2008506176.

- 177. Singh JA, Beg S, Lopez-Olivo MA.
 Tocilizumab for rheumatoid arthritis.
 Cochrane Database Syst Rev. 2010 Jul
 7(7)PMID: CD008331.
- 178. Kremer JL, Blanco R, Brzosko M, et al.
 Tocilizumab inhibits structural joint damage in rheumatoid arthritis patients with inadequate responses to methotrexate: results from the double-blind treatment phase of a randomized placebo-controlled trial of tocilizumab safety and prevention of structural joint damage at one year. Arthritis Rheum. 2010 Mar;63(3):609-21. PMID: 21360490.
- 179. Hochberg MC, Tracy JK, Hawkins-Holt M, et al. Comparison of the efficacy of the tumour necrosis factor alpha blocking agents adalimumab, etanercept, and infliximab when added to methotrexate in patients with active rheumatoid arthritis. Ann Rheum Dis. 2003 2003;62 Suppl 2:ii13-6.
- 180. Singh Jasvinder A, Christensen R, Wells George A, et al. Biologics for rheumatoid arthritis: an overview of Cochrane reviews. Cochrane Database Syst Rev. 2009(4)PMID: CD007848.
- 181. Glenny AM, Altman DG, Song F, et al. Indirect comparisons of competing interventions. Health Technol Assess. 2005 Jul;9(26):1-134, iii-iv. PMID: 16014203.
- 182. Chen DY, Chou SJ, Hsieh TY, et al.
 Randomized, double-blind, placebocontrolled, comparative study of human
 anti-TNF antibody adalimumab in
 combination with methotrexate and
 methotrexate alone in Taiwanese patients
 with active rheumatoid arthritis. J Formos
 Med Assoc. 2009 Apr;108(4):310-9. PMID:
 19369178.
- 183. Wiens A, Venson R, Correr CJ, et al. Metaanalysis of the efficacy and safety of adalimumab, etanercept, and infliximab for the treatment of rheumatoid arthritis. Pharmacotherapy. 2010 Apr;30(4):339-53. PMID: 20334454.

- 184. Nixon RM, Bansback N, Brennan A. Using mixed treatment comparisons and metaregression to perform indirect comparisons to estimate the efficacy of biologic treatments in rheumatoid arthritis. Stat Med. 2007;26(6):1237-54.
- 185. Devine EB, Alfonso-Cristancho R, Sullivan SD. Effectiveness of biologic therapies for rheumatoid arthritis: an indirect comparisons approach. Pharmacotherapy. 2011 Jan;31(1):39-51. PMID: 21182357.
- 186. Bergman GJ, Hochberg MC, Boers M, et al. Indirect comparison of tocilizumab and other biologic agents in patients with rheumatoid arthritis and inadequate response to disease-modifying antirheumatic drugs. Semin Arthritis Rheum. 2010 Jun;39(6):425-41. PMID: 20223500.
- 187. Canadian Agency for Drugs and Technologies in Health (CADTH). CADTH Therapeutic Review: Clinical and Economic Overview: Biological Response Modifier Agents for Adults with Rheumatoid Arthritis. Ottawa, ON: CADTH; 2010. www.cadth.ca/media/pdf/TR_RA_Clinical_and_Economic_Overview_e.pdf. Accessed December 1, 2010.
- 188. Genovese MC, Bathon JM, Martin RW, et al. Etanercept versus methotrexate in patients with early rheumatoid arthritis: two-year radiographic and clinical outcomes.

 Arthritis Rheum. 2002 Jun;46(6):1443-50.
 PMID: 12115173.
- 189. Genovese MC, Bathon JM, Fleischmann RM, et al. Longterm safety, efficacy, and radiographic outcome with etanercept treatment in patients with early rheumatoid arthritis. J Rheumatol. 2005 Jul;32(7):1232-42. PMID: 15996057.
- 190. Hoff M, Kvien TK, Kalvesten J, et al. Adalimumab therapy reduces hand bone loss in early rheumatoid arthritis: explorative analyses from the PREMIER study. Ann Rheum Dis. 2009 Jul;68(7):1171-6. PMID: 18801760.

- 191. Visser K, Katchamart W, Loza E, et al. Multinational evidence-based recommendations for the use of methotrexate in rheumatic disorders with a focus on rheumatoid arthritis: integrating systematic literature research and expert opinion of a broad international panel of rheumatologists in the 3E Initiative. Ann Rheum Dis. 2009;68(7):1086-93.
- 192. Kavanaugh A, Klareskog L, van der Heijde D, et al. Improvements in clinical response between 12 and 24 weeks in patients with rheumatoid arthritis on etanercept therapy with or without methotrexate. Ann Rheum Dis. 2008 Oct;67(10):1444-7. PMID: 18535115.
- 193. Kuriya B, Arkema EV, Bykerk VP, et al. Efficacy of initial methotrexate monotherapy versus combination therapy with a biological agent in early rheumatoid arthritis: a meta-analysis of clinical and radiographic remission. Ann Rheum Dis. 2010 Jul;69(7):1298-304. PMID: 20421343.
- 194. Smolen JS, Han C, van der Heijde DM, et al. Radiographic changes in rheumatoid arthritis patients attaining different disease activity states with methotrexate monotherapy and infliximab plus methotrexate: the impacts of remission and tumour necrosis factor blockade. Ann Rheum Dis. 2009 Jun;68(6):823-7. PMID: 18593759.
- 195. Hyrich KL, Watson KD, Silman AJ, et al. Predictors of response to anti-TNF-alpha therapy among patients with rheumatoid arthritis: results from the British Society for Rheumatology Biologics Register. Rheumatology (Oxford). 2006;45(Dec):1558-65.
- 196. van der Kooij SM, Goekoop-Ruiterman YP, de Vries-Bouwstra JK, et al. Drug-free remission, functioning and radiographic damage after 4 years of response-driven treatment in patients with recent-onset rheumatoid arthritis. Ann Rheum Dis. 2009 Jun;68(6):914-21. PMID: 18662933.

- 197. Van Der Kooij SM, Goekoop-Ruiterman YPM, De Vries-Bouwstra JK, et al. Probability of continued low disease activity in patients with recent onset rheumatoid arthritis treated according to the disease activity score. Ann Rheum Dis. 2008;67(2):266-9. PMID: 2008057728.
- 198. Samsa G, Edelman D, Rothman ML, et al.
 Determining clinically important differences in health status measures: a general approach with illustration to the Health Utilities Index Mark II.
 Pharmacoeconomics. 1999 Feb;15(2):141-55. PMID: 10351188.
- 199. Strand V, Tugwell P, Bombardier C, et al. Function and health-related quality of life: results from a randomized controlled trial of leflunomide versus methotrexate or placebo in patients with active rheumatoid arthritis. Leflunomide Rheumatoid Arthritis Investigators Group. Arthritis Rheum. 1999 Sep;42(9):1870-8. PMID: 10513801.
- 200. Scott DL, Smolen JS, Kalden JR, et al.
 Treatment of active rheumatoid arthritis
 with leflunomide: two year follow up of a
 double blind, placebo controlled trial versus
 sulfasalazine. Ann Rheum Dis.
 2001;60(10):913-23.
- 201. Van Riel PLCM, Freundlich B, MacPeek D, et al. Patient-reported health outcomes in a trial of etanercept monotherapy versus combination therapy with etanercept and methotrexate for rheumatoid arthritis: The ADORE trial. Ann Rheum Dis. 2008;67(8):1104-10. PMID: 2008355994.
- 202. Puolakka K, Kautiainen H, Mottonen T, et al. Impact of initial aggressive drug treatment with a combination of disease-modifying antirheumatic drugs on the development of work disability in early rheumatoid arthritis: a five-year randomized followup trial. Arthritis Rheum. 2004;50(1):55-62.
- 203. Emery P, Kosinski M, Li T, et al. Treatment of rheumatoid arthritis patients with abatacept and methotrexate significantly improved health-related quality of life. J Rheumatol. 2006 04/01/;33(Apr):681-9.

- 204. Wells G, Li T, Maxwell L, et al.
 Responsiveness of patient reported outcomes including fatigue, sleep quality, activity limitation, and quality of life following treatment with abatacept for rheumatoid arthritis. Ann Rheum Dis. 2008 Feb;67(2):260-5. PMID: 17846044.
- 205. Hassett AL, Li T, Buyske S, et al. The multi-faceted assessment of independence in patients with rheumatoid arthritis: preliminary validation from the ATTAIN study. Curr Med Res Opin. 2008 May;24(5):1443-53. PMID: 18402714.
- 206. Westhovens R, Cole JC, Li T, et al. Improved health-related quality of life for rheumatoid arthritis patients treated with abatacept who have inadequate response to anti-TNF therapy in a double-blind, placebo-controlled, multicentre randomized clinical trial. Rheumatology (Oxford). 2006 10/01/;45(Oct):1238-46.
- 207. Li T, Gignac M, Wells G, et al. Decreased external home help use with improved clinical status in rheumatoid arthritis: an exploratory analysis of the Abatacept in Inadequate responders to Methotrexate (AIM) trial. Clin Ther. 2008 Apr;30(4):734-48. PMID: 18498922.
- 208. Mease PJ, Revicki DA, Szechinski J, et al. Improved health-related quality of life for patients with active rheumatoid arthritis receiving rituximab: results of the Dose-Ranging Assessment: International Clinical Evaluation of Rituximab in Rheumatoid Arthritis (DANCER) Trial. J Rheumatol. 2008 Jan;35(1):20-30. PMID: 18050385.
- 209. Kavanaugh A, Smolen JS, Emery P, et al. Effect of certolizumab pegol with methotrexate on home and work place productivity and social activities in patients with active rheumatoid arthritis. Arthritis Rheum. 2009 Nov 15;61(11):1592-600. PMID: 19877104.
- Singh JA, Noorbaloochi S, Singh G.
 Golimumab for rheumatoid arthritis.
 Cochrane Database Syst Rev.
 2010(1):CD008341. PMID: 20091667.

- 211. Kosinski M, Kujawski SC, Martin R, et al. Health-related quality of life in early rheumatoid arthritis: impact of disease and treatment response. Am J Manag Care. 2002 Mar;8(3):231-40. PMID: 11915973.
- 212. Kekow J, Moots RJ, Emery P, et al. Patient-reported outcomes improve with etanercept plus methotrexate in active early rheumatoid arthritis and the improvement is strongly associated with remission: The COMET trial. Ann Rheum Dis. 2010 Jan;69(1):222-5. PMID: 2010021141.
- 213. ICH. International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use ICH Harmonised Tripartite Guideline Clinical Safety Data Management: Definitions and Standards for Expedited Reporting E2A. 1994. www.ich.org/LOB/media/MEDIA436.pdf.
- 214. Nadareishvili Z, Michaud K, Hallenbeck JM, et al. Cardiovascular, rheumatologic, and pharmacologic predictors of stroke in patients with rheumatoid arthritis: a nested, case-control study. Arthritis Rheum. 2008 Aug 15;59(8):1090-6. PMID: 18668583.
- 215. Naranjo A, Sokka T, Descalzo MA, et al. Cardiovascular disease in patients with rheumatoid arthritis: results from the QUEST-RA study. Arthritis Res Ther. 2008;10(2):R30. PMID: 18325087.
- 216. Solomon DH, Avorn J, Katz JN, et al. Immunosuppressive medications and hospitalization for cardiovascular events in patients with rheumatoid arthritis. Arthritis Rheum. 2006 12/01/;54(Dec):3790-8.
- 217. Suissa S, Hudson M, Ernst P. Leflunomide use and the risk of interstitial lung disease in rheumatoid arthritis. Arthritis Rheum. 2006 May;54(5):1435-9. PMID: 16645972.
- 218. Bernatsky S, Hudson M, Suissa S. Antirheumatic drug use and risk of serious infections in rheumatoid arthritis. Rheumatology (Oxford). 2007
 Jul;46(7):1157-60. PMID: 17478469.

- 219. Brassard P, Kezouh A, Suissa S. Antirheumatic drugs and the risk of tuberculosis. Clin Infect Dis. 2006 Sep 15;43(6):717-22. PMID: 16912945.
- 220. Doran MF, Crowson CS, Pond GR, et al. Predictors of infection in rheumatoid arthritis. Arthritis Rheum. 2002 Sep;46(9):2294-300. PMID: 12355476.
- 221. Lacaille D, Guh DP, Abrahamowicz M, et al. Use of nonbiologic disease-modifying antirheumatic drugs and risk of infection in patients with rheumatoid arthritis. Arthritis Rheum. 2008 Aug 15;59(8):1074-81. PMID: 18668604.
- 222. Schneeweiss S, Setoguchi S, Weinblatt ME, et al. Anti-tumor necrosis factor alpha therapy and the risk of serious bacterial infections in elderly patients with rheumatoid arthritis. Arthritis Rheum. 2007 Jun;56(6):1754-64. PMID: 17530704.
- 223. Smitten AL, Choi HK, Hochberg MC, et al. The risk of hospitalized infection in patients with rheumatoid arthritis. J Rheumatol. 2008 Mar;35(3):387-93. PMID: 18260176.
- 224. Smitten AL, Choi HK, Hochberg MC, et al. The risk of herpes zoster in patients with rheumatoid arthritis in the United States and the United Kingdom. Arthritis Rheum. 2007 Dec 15:57(8):1431-8. PMID: 18050184.
- 225. Strangfeld A, Listing J, Herzer P, et al. Risk of herpes zoster in patients with rheumatoid arthritis treated with anti-TNF-alpha agents. JAMA. 2009 Feb 18;301(7):737-44. PMID: 19224750.
- 226. Greenberg JD, Reed G, Kremer JM, et al. Association of methotrexate and tumour necrosis factor antagonists with risk of infectious outcomes including opportunistic infections in the CORRONA registry. Ann Rheum Dis. 2010 Feb;69(2):380-6. PMID: 19359261.
- 227. Edwards CJ, Cooper C, Fisher D, et al. The importance of the disease process and disease-modifying antirheumatic drug treatment in the development of septic arthritis in patients with rheumatoid arthritis. Arthritis Rheum. 2007 Oct 15;57(7):1151-7. PMID: 17907232.

- 228. Wolfe F, Caplan L, Michaud K. Rheumatoid arthritis treatment and the risk of severe interstitial lung disease. Scand J Rheumatol. 2007 May-Jun;36(3):172-8. PMID: 17657669.
- 229. Cannon GW, Holden WL, Juhaeri J, et al. Adverse events with disease modifying antirheumatic drugs (DMARD): a cohort study of leflunomide compared with other DMARD. J Rheumatol. 2004 Oct;31(10):1906-11. PMID: 15468352.
- 230. Maetzel A, Wong A, Strand V, et al. Metaanalysis of treatment termination rates among rheumatoid arthritis patients receiving disease-modifying anti-rheumatic drugs. Rheumatology (Oxford). 2000 Sep;39(9):975-81. PMID: 10986302.
- 231. O'Dell JR, Petersen K, Leff R, et al. Etanercept in combination with sulfasalazine, hydroxychloroquine, or gold in the treatment of rheumatoid arthritis. J Rheumatol. 2006 Feb;33(2):213-8. PMID: 16358366.
- 232. Schipper LG, Fransen J, Barrera P, et al. Methotrexate in combination with sulfasalazine is more effective in rheumatoid arthritis patients who failed sulfasalazine than in patients naive to both drugs. Rheumatology (Oxford). 2009

 Jul;48(7):828-33. PMID: 19458163.
- 233. Malysheva OA, Wahle M, Wagner U, et al. Low-dose prednisolone in rheumatoid arthritis: adverse effects of various disease modifying antirheumatic drugs. J Rheumatol. 2008 Jun;35(6):979-85. PMID: 18412314.
- Suissa S, Bernatsky S, Hudson M.
 Antirheumatic drug use and the risk of acute myocardial infarction. Arthritis Rheum.
 2006 Aug 15;55(4):531-6. PMID: 16874796.
- 235. van Halm VP, Nurmohamed MT, Twisk JW, et al. Disease-modifying antirheumatic drugs are associated with a reduced risk for cardiovascular disease in patients with rheumatoid arthritis: a case control study. Arthritis Res Ther. 2006;8(5):R151. PMID: 16984661.

- 236. Suissa S, Ernst P, Hudson M, et al. Newer disease-modifying antirheumatic drugs and the risk of serious hepatic adverse events in patients with rheumatoid arthritis. Am J Med. 2004 Jul 15;117(2):87-92. PMID: 15234643.
- 237. Wolfe F, Caplan L, Michaud K. Treatment for rheumatoid arthritis and the risk of hospitalization for pneumonia: associations with prednisone, disease-modifying antirheumatic drugs, and anti-tumor necrosis factor therapy. Arthritis Rheum. 2006 Feb;54(2):628-34. PMID: 16447241.
- 238. Brassard P, Lowe AM, Bernatsky S, et al. Rheumatoid arthritis, its treatments, and the risk of tuberculosis in Quebec, Canada. Arthritis Rheum. 2009 Mar 15;61(3):300-4. PMID: 19248128.
- 239. McDonald JR, Zeringue AL, Caplan L, et al. Herpes zoster risk factors in a national cohort of veterans with rheumatoid arthritis. Clin Infect Dis. 2009 May 15;48(10):1364-71. PMID: 19368499.
- 240. Grijalva CG, Kaltenbach L, Arbogast PG, et al. Initiation of rheumatoid arthritis treatments and the risk of serious infections. Rheumatology (Oxford). 2010;49:82-90.
- 241. Baecklund E, Iliadou A, Askling J, et al. Association of chronic inflammation, not its treatment, with increased lymphoma risk in rheumatoid arthritis. Arthritis Rheum. 2006 Mar;54(3):692-701. PMID: 16508929.
- 242. Chakravarty EF, Michaud K, Wolfe F. Skin cancer, rheumatoid arthritis, and tumor necrosis factor inhibitors. J Rheumatol. 2005 Nov;32(11):2130-5. PMID: 16265690.
- 243. Fuerst M, Mohl H, Baumgartel K, et al. Leflunomide increases the risk of early healing complications in patients with rheumatoid arthritis undergoing elective orthopedic surgery. Rheumatol Int. 2006 Oct;26(12):1138-42. PMID: 16736164.
- 244. Michaud K, Wolfe F. The association of rheumatoid arthritis and its treatment with sinus disease. J Rheumatol. 2006
 Dec;33(12):2412-5. PMID: 17143978.

- 245. Karstila KL, Rantalaiho VM, Mustonen JT, et al. Renal safety of initial combination versus single DMARD therapy in patients with early rheumatoid arthritis: an 11-year experience from the FIN-RACo Trial. Clin Exp Rheumatol. 2010 Jan-Feb;28(1):73-8. PMID: 20346242.
- 246. Martinez Lopez JA, Loza E, Carmona L. Systematic review on the safety of methotrexate in rheumatoid arthritis regarding the reproductive system (fertility, pregnancy, and breastfeeding). Clin Exp Rheumatol. 2009 Jul-Aug;27(4):678-84. PMID: 19772806.
- 247. Flendrie M, Creemers MC, Welsing PM, et al. Survival during treatment with tumour necrosis factor blocking agents in rheumatoid arthritis. Ann Rheum Dis. 2003 Nov;62 Suppl 2:ii30-3. PMID: 14532145.
- 248. Duclos M, Gossec L, Ruyssen-Witrand A, et al. Retention rates of tumor necrosis factor blockers in daily practice in 770 rheumatic patients. J Rheumatol. 2006
 Dec;33(12):2433-8. PMID: 17014004.
- 249. Hjardem E, Ostergaard M, Podenphant J, et al. Do rheumatoid arthritis patients in clinical practice benefit from switching from infliximab to a second tumor necrosis factor alpha inhibitor? Ann Rheum Dis. 2007 Sep;66(9):1184-9. PMID: 17389656.
- 250. Hyrich KL, Lunt M, Watson KD, et al.
 Outcomes after switching from one antitumor necrosis factor alpha agent to a
 second anti-tumor necrosis factor alpha
 agent in patients with rheumatoid arthritis:
 results from a large UK national cohort
 study. Arthritis Rheum. 2007 Jan;56(1):1320. PMID: 17195186.
- 251. Kristensen LE, Saxne T, Nilsson JA, et al. Impact of concomitant DMARD therapy on adherence to treatment with etanercept and infliximab in rheumatoid arthritis. Results from a six-year observational study in southern Sweden. Arthritis Res Ther. 2006;8(6):R174. PMID: 17121678.

- 252. Marchesoni A, Zaccara E, Gorla R, et al. TNF-alpha antagonist survival rate in a cohort of rheumatoid arthritis patients observed under conditions of standard clinical practice. Ann N Y Acad Sci. 2009 Sep;1173:837-46. PMID: 19758236.
- 253. Pan SM, Dehler S, Ciurea A, et al.
 Comparison of drug retention rates and
 causes of drug discontinuation between antitumor necrosis factor agents in rheumatoid
 arthritis. Arthritis Rheum. 2009 May
 15;61(5):560-8. PMID: 19405000.
- 254. Russell AS, Wallenstein GV, Li T, et al. Abatacept improves both the physical and mental health of patients with rheumatoid arthritis who have inadequate response to methotrexate treatment. Ann Rheum Dis. 2007 Feb;66(2):189-94. PMID: 16984942.
- 255. Leombruno JP, Einarson TR, Keystone EC. The safety of anti-tumour necrosis factor treatments in rheumatoid arthritis: meta and exposure-adjusted pooled analyses of serious adverse events. Ann Rheum Dis. 2009 Jul;68(7):1136-45. PMID: 18753157.
- 256. Wiens A, Correr CJ, Pontarolo R, et al. A systematic review and meta-analysis of the efficacy and safety of etanercept for treating rheumatoid arthritis. Scand J Immunol. 2009 Oct;70(4):337-44. PMID: 19751268.
- 257. Burmester GR, Mariette X, Montecucco C, et al. Adalimumab alone and in combination with disease-modifying antirheumatic drugs for the treatment of rheumatoid arthritis in clinical practice: the Research in Active Rheumatoid Arthritis (ReAct) trial. Ann Rheum Dis. 2007 Jun;66(6):732-9. PMID: 17329305.
- 258. Weinblatt M, Combe B, Covucci A, et al. Safety of the selective costimulation modulator abatacept in rheumatoid arthritis patients receiving background biologic and nonbiologic disease-modifying antirheumatic drugs: A one-year randomized, placebo-controlled study. Arthritis Rheum. 2006 Aug 31;54(9):2807-16. PMID: 16947384.

- 259. Fleischmann RM, Schechtman J, Bennett R, et al. Anakinra, a recombinant human interleukin-1 receptor antagonist (r-metHuIL-1ra), in patients with rheumatoid arthritis: A large, international, multicenter, placebo-controlled trial. Arthritis Rheum. 2003 Apr;48(4):927-34. PMID: 12687534.
- 260. Feltelius N, Fored CM, Blomqvist P, et al. Results from a nationwide postmarketing cohort study of patients in Sweden treated with etanercept. Ann Rheum Dis. 2005 Feb;64(2):246-52. PMID: 15208177.
- 261. Moreland LW, Weinblatt ME, Keystone EC, et al. Etanercept treatment in adults with established rheumatoid arthritis: 7 years of clinical experience. J Rheumatol. 2006 May;33(5):854-61. PMID: 16541481.
- 262. Wolfe F, Michaud K. Heart failure in rheumatoid arthritis: rates, predictors, and the effect of anti-tumor necrosis factor therapy. Am J Med. 2004 Mar 1;116(5):305-11. PMID: 14984815.
- 263. Curtis JR, Kramer JM, Martin C, et al. Heart failure among younger rheumatoid arthritis and Crohn's patients exposed to TNF-alpha antagonists. Rheumatology (Oxford). 2007 Nov;46(11):1688-93. PMID: 17938138.
- 264. Listing J, Strangfeld A, Kekow J, et al. Does tumor necrosis factor alpha inhibition promote or prevent heart failure in patients with rheumatoid arthritis? Arthritis Rheum. 2008 Mar;58(3):667-77. PMID: 18311816.
- 265. Setoguchi S, Schneeweiss S, Avorn J, et al. Tumor necrosis factor-alpha antagonist use and heart failure in elderly patients with rheumatoid arthritis. Am Heart J. 2008 Aug;156(2):336-41. PMID: 18657665.
- 266. Jacobsson LT, Turesson C, Gulfe A, et al. Treatment with tumor necrosis factor blockers is associated with a lower incidence of first cardiovascular events in patients with rheumatoid arthritis. J Rheumatol. 2005 Jul;32(7):1213-8. PMID: 15996054.

- 267. Dixon WG, Watson KD, Lunt M, et al. Reduction in the incidence of myocardial infarction in patients with rheumatoid arthritis who respond to anti-tumor necrosis factor alpha therapy: Results from the British Society for Rheumatology Biologics Register. Arthritis Rheum. 2007;56(9):2905-12. PMID: 2007480319.
- 268. Dixon WG, Watson K, Lunt M, et al. Rates of serious infection, including site-specific and bacterial intracellular infection, in rheumatoid arthritis patients receiving antitumor necrosis factor therapy: Results from the British Society for Rheumatology Biologics Register. Arthritis Rheum. 2006 Jul 25;54(8):2368-76. PMID: 16868999.
- 269. Galloway JB, Hyrich KL, Mercer LK, et al. Anti-TNF therapy is associated with an increased risk of serious infections in patients with rheumatoid arthritis especially in the first 6 months of treatment: updated results from the British Society for Rheumatology Biologics Register with special emphasis on risks in the elderly. Rheumatology (Oxford, England). 2011 Jan;50(1):124-31. PMID: 20675706.
- 270. Bernatsky S, Habel Y, Rahme E.
 Observational studies of infections in rheumatoid arthritis: a metaanalysis of tumor necrosis factor antagonists. J
 Rheumatol. 2010;37:928-31.
- 271. Bongartz T, Sutton AJ, Sweeting MJ, et al. Anti-TNF antibody therapy in rheumatoid arthritis and the risk of serious infections and malignancies: systematic review and meta-analysis of rare harmful effects in randomized controlled trials. JAMA. 2006 May 17;295(19):2275-85. PMID: 16705109.
- 272. Salliot C, Dougados M, Gossec L. Risk of serious infections during rituximab, abatacept and anakinra treatments for rheumatoid arthritis: meta-analyses of randomised placebo-controlled trials. Ann Rheum Dis. 2009 Jan;68(1):25-32. PMID: 18203761.

- 273. Schaible TF. Long term safety of infliximab. Can J Gastroenterol. 2000 Sep;14(Suppl C):29C-32C. PMID: 11023558.
- 274. Listing J, Strangfeld A, Kary S, et al. Infections in patients with rheumatoid arthritis treated with biologic agents.

 Arthritis Rheum. 2005 Nov;52(11):3403-12. PMID: 16255017.
- 275. Salliot C, Gossec L, Ruyssen-Witrand A, et al. Infections during tumour necrosis factor-{alpha} blocker therapy for rheumatic diseases in daily practice: a systematic retrospective study of 709 patients. Rheumatology (Oxford). 2007 July 31, 2006;46(2):327-34.
- 276. Askling J, Fored CM, Brandt L, et al. Risks of solid cancers in patients with rheumatoid arthritis and after treatment with tumour necrosis factor antagonists. Ann Rheum Dis. 2005 Oct;64(10):1421-6. PMID: 15829572.
- 277. Curtis JR, Patkar N, Xie A, et al. Risk of serious bacterial infections among rheumatoid arthritis patients exposed to tumor necrosis factor alpha antagonists. Arthritis Rheum. 2007 Apr;56(4):1125-33. PMID: 17393394.
- 278. Curtis JR, Xi J, Patkar N, et al. Drugspecific and time-dependent risks of bacterial infection among patients with rheumatoid arthritis who were exposed to tumor necrosis factor alpha antagonists. Arthritis Rheum. 2007 Dec;56(12):4226-7. PMID: 18050253.
- 279. Dixon WG, Hyrich KL, Watson KD, et al. Drug-specific risk of tuberculosis in patients with rheumatoid arthritis treated with anti-TNF therapy: results from the British Society for Rheumatology Biologics Register (BSRBR). Ann Rheum Dis. 2010 Mar;69(3):522-8. PMID: 19854715.
- 280. Wallis RS, Broder MS, Wong JY, et al. Granulomatous infectious diseases associated with tumor necrosis factor antagonists. Clin Infect Dis. 2004 May 1;38(9):1261-5. PMID: 15127338.

- 281. Askling J, Fored CM, Brandt L, et al. Risk and case characteristics of tuberculosis in rheumatoid arthritis associated with tumor necrosis factor antagonists in Sweden.

 Arthritis Rheum. 2005 Jul;52(7):1986-92.
 PMID: 15986370.
- 282. Gomez-Reino JJ, Carmona L, Valverde VR, et al. Treatment of rheumatoid arthritis with tumor necrosis factor inhibitors may predispose to significant increase in tuberculosis risk: a multicenter active-surveillance report. Arthritis Rheum. 2003 Aug;48(8):2122-7. PMID: 12905464.
- 283. Keane J, Gershon S, Wise RP, et al. Tuberculosis associated with infliximab, a tumor necrosis factor alpha-neutralizing agent. N Engl J Med. 2001 Oct 11;345(15):1098-104. PMID: 11596589.
- 284. Mohan AK, Cote TR, Block JA, et al. Tuberculosis following the use of etanercept, a tumor necrosis factor inhibitor. Clin Infect Dis. 2004 Aug 1;39(3):295-9. PMID: 15306993.
- 285. Wolfe F, Michaud K, Anderson J, et al. Tuberculosis infection in patients with rheumatoid arthritis and the effect of infliximab therapy. Arthritis Rheum. 2004 Feb;50(2):372-9. PMID: 14872478.
- 286. Lee JH, Slifman NR, Gershon SK, et al. Life-threatening histoplasmosis complicating immunotherapy with tumor necrosis factor alpha antagonists infliximab and etanercept. Arthritis Rheum. 2002 Oct;46(10):2565-70. PMID: 12384912.
- 287. Slifman NR, Gershon SK, Lee JH, et al. Listeria monocytogenes infection as a complication of treatment with tumor necrosis factor alpha-neutralizing agents. Arthritis Rheum. 2003 Feb;48(2):319-24. PMID: 12571839.
- 288. Anonymous. Rituxan (rituximab) package insert. Genentech, Inc. South San Francisco, CA. 2007.
- 289. Wolfe F, Michaud K. Lymphoma in rheumatoid arthritis: the effect of methotrexate and anti-tumor necrosis factor therapy in 18,572 patients. Arthritis Rheum. 2004 Jun;50(6):1740-51. PMID: 15188349.

- 290. Wolfe F, Michaud K. The effect of methotrexate and anti-tumor necrosis factor therapy on the risk of lymphoma in rheumatoid arthritis in 19,562 patients during 89,710 person-years of observation. Arthritis Rheum. 2007 May;56(5):1433-9. PMID: 17469100.
- 291. Geborek P, Bladstrom A, Turesson C, et al. Tumour necrosis factor blockers do not increase overall tumour risk in patients with rheumatoid arthritis, but may be associated with an increased risk of lymphomas. Ann Rheum Dis. 2005 May;64(5):699-703. PMID: 15695534.
- 292. Askling J, Fored CM, Baecklund E, et al. Haematopoietic malignancies in rheumatoid arthritis: lymphoma risk and characteristics after exposure to tumour necrosis factor antagonists. Ann Rheum Dis. 2005
 Oct;64(10):1414-20. PMID: 15843454.
- 293. Setoguchi S, Solomon DH, Weinblatt ME, et al. Tumor necrosis factor alpha antagonist use and cancer in patients with rheumatoid arthritis. Arthritis Rheum. 2006 Sep;54(9):2757-64. PMID: 16947774.
- 294. Bongartz T, Warren FC, Mines D, et al. Etanercept therapy in rheumatoid arthritis and the risk of malignancies: a systematic review and individual patient data meta-analysis of randomised controlled trials. Ann Rheum Dis. 2009 Jul;68(7):1177-83. PMID: 19019889.
- 295. Askling J, van Vollenhoven RF, Granath F, et al. Cancer risk in patients with rheumatoid arthritis treated with anti-tumor necrosis factor alpha therapies: does the risk change with the time since start of treatment?

 Arthritis Rheum. 2009 Nov;60(11):3180-9. PMID: 19877027.
- 296. Pallavicini FB, Caporali R, Sarzi-Puttini P, et al. Tumour necrosis factor antagonist therapy and cancer development: analysis of the LORHEN registry. Autoimmun Rev. 2010 Jan;9(3):175-80. PMID: 19647103.

- 297. Strangfeld A, Hierse F, Rau R, et al. Risk of incident or recurrent malignancies among patients with rheumatoid arthritis exposed to biologic therapy in the German biologics register RABBIT. Arthritis Res Ther. 2010;12(1):R5. PMID: 20064207.
- 298. Schiff MH, Burmester GR, Kent JD, et al. Safety analyses of adalimumab (HUMIRA) in global clinical trials and US postmarketing surveillance of patients with rheumatoid arthritis. Ann Rheum Dis. 2006 Jul;65(7):889-94. PMID: 16439435.
- 299. Mohan N, Edwards ET, Cupps TR, et al. Demyelination occurring during anti-tumor necrosis factor alpha therapy for inflammatory arthritides. Arthritis Rheum. 2001 Dec;44(12):2862-9. PMID: 11762947.
- Anonymous. Humira (adalimumab) package insert. Abbott Labs. North Chicago, IL.
 2006.
- 301. Anonymous. Remicade (infliximab) package insert. Centocor, Inc. Malvern, PA. 2006.
- 302. De Bandt M, Sibilia J, Le Loet X, et al. Systemic lupus erythematosus induced by anti-tumour necrosis factor alpha therapy: a French national survey. Arthritis Res Ther. 2005;7(3):R545-51. PMID: 15899041.
- 303. Shakoor N, Michalska M, Harris CA, et al. Drug-induced systemic lupus erythematosus associated with etanercept therapy. Lancet. 2002 Feb 16;359(9306):579-80. PMID: 11867114.
- 304. Flendrie M, Vissers WH, Creemers MC, et al. Dermatological conditions during TNF-alpha-blocking therapy in patients with rheumatoid arthritis: a prospective study. Arthritis Res Ther. 2005;7(3):R666-76. PMID: 15899052.
- 305. Harrison MJ, Dixon WG, Watson KD, et al. Rates of new-onset psoriasis in patients with rheumatoid arthritis receiving anti-tumour necrosis factor alpha therapy: results from the British Society for Rheumatology Biologics Register. Ann Rheum Dis. 2009 Feb;68(2):209-15. PMID: 18385277.

- 306. Harley CR, Frytak JR, Tandon N. Treatment compliance and dosage administration among rheumatoid arthritis patients receiving infliximab, etanercept, or methotrexate. Am J Manag Care. 2003 Oct;9(6 Suppl):S136-43. PMID: 14577718.
- 307. Li P, Blum MA, Von Feldt J, et al. Adherence, discontinuation, and switching of biologic therapies in medicaid enrollees with rheumatoid arthritis. Value Health. 2010 Sep-Oct;13(6):805-12. PMID: 21054657.
- Anonymous. Dexamethasone package insert. Roxane Laboratories, Inc. Columbus, OH. 2003.
- 309. Anonymous. PredniSONE package insert. Roxane Laboratories, Inc. Columbus, OH. 2003.
- 310. Anonymous. MethylPREDNIsolone package insert. Sandoz, Inc. Princeton, NJ. 2006.
- 311. Anonymous. Cortisone Acetate package insert. Pharmacia & Upjohn Co. Kalamazoo, MI. 2002.
- 312. Anonymous. Cortef (hydrocortisone) package insert. Pharmacia & Upjohn Co. Kalamazoo, MI. 2002.
- 313. Saag KG, Koehnke R, Caldwell JR, et al. Low dose long-term corticosteroid therapy in rheumatoid arthritis: an analysis of serious adverse events. Am J Med. 1994 Feb:96(2):115-23. PMID: 8109596.
- 314. Anonymous. Methotrexate package insert. Mayne Pharma (USA) Inc. Paramus, NJ. 2005.
- 315. Anonymous. Azulfidine (sulfasalazine) package insert. Pharmacia & Upjohn Co. NY, NY. 2006.
- 316. Anonymous. Hydroxychloroquine package insert. Sandoz, Inc. Broomfield, CO. 2004.
- Anonymous. Arava (leflunomide) package insert. Aventis Pharmaceuticals Inc. Kansas City, MO. 2005.

- 318. Svensson B, Ahlmen M, Forslind K.
 Treatment of early RA in clinical practice: a comparative study of two different
 DMARD/corticosteroid options. Clin Exp
 Rheumatol. 2003 May-Jun;21(3):327-32.
 PMID: 12846051.
- 319. Fleischmann RM, Tesser J, Schiff MH, et al. Safety of extended treatment with anakinra in patients with rheumatoid arthritis. Ann Rheum Dis. 2006 Aug;65(8):1006-12. PMID: 16396977.
- 320. Langer HE, Missler-Karger B. Kineret: efficacy and safety in daily clinical practice: an interim analysis of the Kineret response assessment initiative (kreative) protocol. Int J Clin Pharmacol Res. 2003;23(4):119-28. PMID: 15224501.
- 321. Kwon HJ, Cote TR, Cuffe MS, et al. Case reports of heart failure after therapy with a tumor necrosis factor antagonist. Ann Intern Med. 2003 May 20;138(10):807-11. PMID: 12755552.
- 322. Chung ES, Packer M, Lo KH, et al. Randomized, double-blind, placebocontrolled, pilot trial of infliximab, a chimeric monoclonal antibody to tumor necrosis factor-alpha, in patients with moderate-to-severe heart failure: results of the anti-TNF Therapy Against Congestive Heart Failure (ATTACH) trial. Circulation. 2003 Jul 1;107(25):3133-40. PMID: 12796126.
- 323. Coletta AP, Clark AL, Banarjee P, et al. Clinical trials update: RENEWAL (RENAISSANCE and RECOVER) and ATTACH. Eur J Heart Fail. 2002 Aug;4(4):559-61. PMID: 12167397.
- 324. Food and Drug Administration. FDA alert on rituximab. 2006. www.fda.gov/cder/drug/infopage/rituximab/default.htm. Accessed March 25, 2007.
- 325. Bergstrom L, Yocum DE, Ampel NM, et al. Increased risk of coccidioidomycosis in patients treated with tumor necrosis factor alpha antagonists. Arthritis Rheum. 2004 Jun;50(6):1959-66. PMID: 15188373.

- den Broeder AA, Creemers MC, Fransen J, et al. Risk factors for surgical site infections and other complications in elective surgery in patients with rheumatoid arthritis with special attention for anti-tumor necrosis factor: a large retrospective study. J Rheumatol. 2007 Apr;34(4):689-95. PMID: 17117492.
- 327. Kawakami K, Ikari K, Kawamura K, et al. Complications and features after joint surgery in rheumatoid arthritis patients treated with tumour necrosis factor-alpha blockers: perioperative interruption of tumour necrosis factor-alpha blockers decreases complications? Rheumatology (Oxford). 2010;49:341-7.
- 328. Migliore A, Bizzi E, Lagana B, et al. The safety of anti-TNF agents in the elderly. Int J Immunopathol Pharmacol. 2009 Apr-Jun;22(2):415-26. PMID: 19505394.
- 329. Wasserman MJ, Weber DA, Guthrie JA, et al. Infusion-related reactions to infliximab in patients with rheumatoid arthritis in a clinical practice setting: relationship to dose, antihistamine pretreatment, and infusion number. J Rheumatol. 2004
 Oct;31(10):1912-7. PMID: 15468353.
- 330. Anonymous. Kineret (anakinra) package insert. Amgen, Inc. Thousand Oaks, CA. 2004.
- 331. Anonymous. Enbrel (etanercept) package insert. Immunex Corporation. Thousand Oaks, CA. 2006.
- 332. Baecklund E, Ekbom A, Sparen P, et al. Disease activity and risk of lymphoma in patients with rheumatoid arthritis: nested case-control study. BMJ. 1998 Jul 18;317(7152):180-1. PMID: 9665898.
- 333. Brown SL, Greene MH, Gershon SK, et al. Tumor necrosis factor antagonist therapy and lymphoma development: twenty-six cases reported to the Food and Drug Administration. Arthritis Rheum. 2002 Dec;46(12):3151-8. PMID: 12483718.

- 334. Lebwohl M, Blum R, Berkowitz E, et al. No evidence for increased risk of cutaneous squamous cell carcinoma in patients with rheumatoid arthritis receiving etanercept for up to 5 years. Arch Dermatol. 2005
 Jul;141(7):861-4. PMID: 16027301.
- 335. Wolfe F, Michaud K. Biologic treatment of rheumatoid arthritis and the risk of malignancy: Analyses from a large US observational study. Arthritis Rheum. 2007;56(9):2886-95. PMID: 2007480317.
- 336. Shin IS, Baer AN, Kwon HJ, et al. Guillain-Barre and Miller Fisher syndromes occurring with tumor necrosis factor alpha antagonist therapy. Arthritis Rheum. 2006 May;54(5):1429-34. PMID: 16645971.
- 337. Sokolove J, Strand V, Greenberg JD, et al. Risk of elevated liver enzymes associated with TNF inhibitor utilisation in patients with rheumatoid arthritis. Ann Rheum Dis. 2010 Sep;69(9):1612-7. PMID: 20448284.
- 338. Miller LG, Hays RD. Adherence to combination antiretroviral therapy: synthesis of the literature and clinical implications. AIDS Read. 2000 Mar;10(3):177-85. PMID: 10758022.
- 339. Grijalva CG, Chung CP, Arbogast PG, et al. Assessment of adherence to and persistence on disease-modifying antirheumatic drugs (DMARDs) in patients with rheumatoid arthritis. Med Care. 2007 Oct;45(10 Supl 2):S66-76. PMID: 17909386.
- 340. Kremer JM, Genovese MC, Cannon GW, et al. Concomitant leflunomide therapy in patients with active rheumatoid arthritis despite stable doses of methotrexate. A randomized, double-blind, placebocontrolled trial. Ann Intern Med. 2002;137(9):726-33.
- 341. Keystone E, Freundlich B, Schiff M, et al. Patients with moderate rheumatoid arthritis (RA) achieve better disease activity states with etanercept treatment than patients with severe RA. J Rheumatol. 2009

 Mar;36(3):522-31. PMID: 19228659.

- 342. Rheumatoid Arthritis Clinical Trial Archive Group. The effect of age and renal function on the efficacy and toxicity of methotrexate in rheumatoid arthritis. J Rheumatol. 1995;22(2):218-23.
- 343. Tesser J, Fleischmann R, Dore R, et al. Concomitant medication use in a large, international, multicenter, placebo controlled trial of anakinra, a recombinant interleukin 1 receptor antagonist, in patients with rheumatoid arthritis. J Rheumatol. 2004;31(4):649-54.
- 344. Schiff MH, DiVittorio G, Tesser J, et al. The safety of anakinra in high-risk patients with active rheumatoid arthritis: six-month observations of patients with comorbid conditions. Arthritis Rheum. 2004
 Jun;50(6):1752-60. PMID: 15188350.

- 345. Osiri M, Shea B, Robinson V, et al.
 Leflunomide for the treatment of rheumatoid arthritis: a systematic review and metaanalysis. J Rheumatol. 2002
 Jun;30(6):1182-90. PMID: 12784387.
- 346. Ledingham J, Deighton C. Update on the British Society for Rheumatology guidelines for prescribing TNFalpha blockers in adults with rheumatoid arthritis (update of previous guidelines of April 2001). Rheumatology (Oxford). 2005 Feb;44(2):157-63. PMID: 15637039.
- 347. Sokka T, Pincus T. Eligibility of patients in routine care for major clinical trials of antitumor necrosis factor alpha agents in rheumatoid arthritis. Arthritis Rheum. 2003 Feb;48(2):313-8. PMID: 12571838.

Appendix A. Search Strings

2007 Search

Search	Most Recent Queries	Result
	Search ("Arthritis, Psoriatic"[MeSH] OR "Arthritis, Rheumatoid"[MeSH])	82356
	Search ("Arthritis, Psoriatic" [MeSH] OR "Arthritis, Rheumatoid" [MeSH]) Limits: All Adult: 19+ years, English, Publication Date from 1990, Humans	16462
#5	Search "Adrenal Cortex Hormones" [MeSH] OR corticosteroid*	190820
#6	Search #3 AND #5	686
#7	Search #3 AND #5 Limits: Editorial, Letter, Practice Guideline	18
#8	Search #6 NOT #7	668
#18	Search "Methotrexate" [MeSH] OR "leflunomide" [Substance Name] OR "Sulfasalazine" [MeSH] OR "Hydroxychloroquine" [MeSH]	28712
	Search "TNFR-Fc fusion protein" [Substance Name] OR etanercept OR "infliximab" [Substance Name] OR "adalimumab" [Substance Name] OR "cytotoxic T lymphocyte-associated antigen 4-immunoglobulin" [Substance Name] OR abatacept OR remicade OR enbrel OR humira OR "rituximab" [Substance Name] OR "interleukin 1 receptor antagonist protein" [Substance Name] OR anakinra	8701
#29	Search #3 AND #18	1365
#30	Search #3 AND #28	777
#31	Search #3 AND #18 Limits: Editorial, Letter, Practice Guideline	237
#32	Search #29 NOT #31	1128
#33	Search #3 AND #28 Limits: Editorial, Letter, Practice Guideline	178
#34	Search #30 NOT #33	599
#35	Search #8 OR #30 OR #34	1405

July 2009 Search

Search	Most Recent Queries	Result
<u>#1</u>	Search "Arthritis, Psoriatic" [MeSH] OR "Arthritis, Rheumatoid" [MeSH]	<u>85528</u>
<u>#2</u>	Search "Adrenal Cortex Hormones" [MeSH] OR corticosteroid*	<u>239378</u>
<u>#3</u>	Search "Methotrexate" [MeSH] OR "leflunomide" [Substance Name] OR "Sulfasalazine" [MeSH] OR "Hydroxychloroquine" [MeSH]	31900
<u>#4</u>	Search "TNFR-Fc fusion protein" [Substance Name] OR etanercept OR "infliximab" [Substance Name] OR "adalimumab" [Substance Name] OR "cytotoxic T lymphocyte-associated antigen 4-immunoglobulin" [Substance Name] OR abatacept OR remicade OR enbrel OR humira OR "rituximab" [Substance Name] OR "interleukin 1 receptor antagonist protein" [Substance Name] OR anakinra	15567
<u>#5</u>	Search ((("CDP870 "[Substance Name] OR certolizumab OR cimzia) OR "efalizumab "[Substance Name] OR raptiva) OR "alefacept "[Substance Name] OR amevive) OR "natalizumab "[Substance Name] OR tysabri	<u>1127</u>
<u>#6</u>	Search "golimumab "[Substance Name]	<u>12</u>
<u>#7</u>	Search #2 OR #3 OR #4 OR #5 OR #6	<u>283303</u>
<u>#8</u>	Search #7 AND #1	<u>11283</u>
<u>#9</u>	Search #7 AND #1 Limits: Editorial, Letter, Practice Guideline	<u>1368</u>
<u>#10</u>	Search #8 NOT #9	<u>9915</u>
<u>#11</u>	Search #8 NOT #9 Limits: Humans, English, All Adult: 19+ years	<u>4079</u>
<u>#12</u>	Search Limits: Entrez Date from 2006/06/01, Humans, English, All Adult: 19+ years	498212
<u>#</u> 13	Search #11 AND #12	<u>1027</u>

August 2009 Search (for Tocilizumab)

Search	Most Recent Queries	Result
<u>#1</u>	Search "Arthritis, Psoriatic" [MeSH] OR "Arthritis, Rheumatoid" [MeSH]	<u>85692</u>
<u>#2</u>	Search actemra	<u>4</u>
<u>#4</u>	Search "tocilizumab "[Substance Name]	<u>103</u>
<u>#5</u>	Search #2 OR #4	<u>104</u>
<u>#6</u>	Search #5 AND #1	<u>75</u>
<u>#7</u>	Search #5 AND #1 Limits: Editorial, Letter, Practice Guideline	<u>8</u>
<u>#8</u>	Search #6 NOT #7	<u>67</u>
<u>#9</u>	Search #6 NOT #7 Limits: Humans, English, All Adult: 19+ years	<u>14</u>
<u>#10</u>	Search #9 Limits: Entrez Date from 2006/06/01	<u>14</u>

March 2010 Search

Search	Most Recent Queries	Result
#1	Search "Arthritis, Psoriatic" [MeSH] OR "Arthritis, Rheumatoid" [MeSH]	87507
#2	Search "Adrenal Cortex Hormones" [MeSH] OR corticosteroid*	244454
#3	Search "Methotrexate"[MeSH] OR "leflunomide"[Substance Name] OR "Sulfasalazine"[MeSH] OR "Hydroxychloroquine"[MeSH]	32512
#12	Search "TNFR-Fc fusion protein" [Substance Name] OR etanercept OR "infliximab" [Substance Name] OR "adalimumab" [Substance Name] OR "cytotoxic T lymphocyte-associated antigen 4-immunoglobulin" OR abatacept OR remicade OR enbrel OR humira OR "rituximab" [Substance Name] OR "interleukin 1 receptor antagonist protein" [Substance Name] OR anakinra	16979
#13	Search ((("CDP870 "[Substance Name] OR certolizumab OR cimzia) OR "efalizumab "[Substance Name] OR raptiva) OR "alefacept "[Substance Name] OR amevive) OR "natalizumab "[Substance Name] OR tysabri	1309
#14	Search actemra OR "tocilizumab" [Substance Name]	134
#15	Search "golimumab "[Substance Name]	32
#16	Search #2 OR #3 OR #12 OR #13 OR #14 OR #15	290354
#17	Search #16 AND #1	11855
#18	Search #17 Limits: Editorial, Letter, Practice Guideline	1450
#19	Search #17 NOT #18	10405
#20	Search #19 Limits: Humans, English, All Adult: 19+ years	4358
#21	Search "2009/05/01"[Entrez Date] : "3000"[Entrez Date] Limits: Humans, English, All Adult: 19+ years	89610
#22	Search #20 AND #21 Limits: Humans, English, All Adult: 19+ years Sort by: PublicationDate	176

August 2010 Search

Search	Most Recent Queries	Result
#1	Search "Arthritis, Psoriatic" [MeSH] OR "Arthritis, Rheumatoid" [MeSH]	89162
#2	Search "Adrenal Cortex Hormones" [MeSH] OR corticosteroid*	248455
#3	Search "Methotrexate" [MeSH] OR "leflunomide" [Substance Name] OR "Sulfasalazine" [MeSH] OR "Hydroxychloroquine" [MeSH]	33034
#4	Search "TNFR-Fc fusion protein" [Substance Name] OR etanercept OR "infliximab" [Substance Name] OR "adalimumab" [Substance Name] OR "cytotoxic T lymphocyte-associated antigen 4-immunoglobulin" OR abatacept OR remicade OR enbrel OR humira OR "rituximab" [Substance Name] OR "interleukin 1 receptor antagonist protein" [Substance Name] OR anakinra	18212
#5	Search ((("CDP870 "[Substance Name] OR certolizumab OR cimzia) OR "efalizumab "[Substance Name] OR raptiva) OR "alefacept "[Substance Name] OR amevive) OR "natalizumab "[Substance Name] OR tysabri	1468
#6	Search actemra OR "tocilizumab" [Substance Name]	250
#7	Search "golimumab "[Substance Name]	47
#8	Search #2 OR #3 OR #4 OR #5 OR #6 OR #7	296041
#9	Search #1 AND #8	12290
#10	Search #9 Limits: Editorial, Letter, Practice Guideline	1498
#11	Search #9 NOT #10	10792
#12	Search #11 Limits: Humans, English, All Adult: 19+ years	4578
#13	Search ((#12) AND "2010/01/01"[Entrez Date] : "3000"[Entrez Date]) AND "0"[Entrez Date] : "3000"[Entrez Date] Sort by: Author	125

January 2011 Search

Search	Most Recent Queries	Result
#1	Search "Arthritis, Psoriatic" [MeSH] OR "Arthritis, Rheumatoid" [MeSH]	90392
#2	2 Search "Adrenal Cortex Hormones" [MeSH] OR corticosteroid*	251312
#3	3 Search "Methotrexate" [MeSH] OR "leflunomide" [Substance Name] OR "Sulfasalazine" [MeSH] OR "Hydroxychloroquine" [MeSH]	33430
#4	4 Search "TNFR-Fc fusion protein" [Substance Name] OR etanercept OR "infliximab" [Substance Name] OR "adalimumab" [Substance Name] OR "cytotoxic T lymphocyte-associated antigen 4-immunoglobulin" OR abatacept OR remicade OR enbrel OR humira OR "rituximab" [Substance Name] OR "interleukin 1 receptor antagonist protein" [Substance Name] OR anakinra	19150
#5	5 Search ((("CDP870 "[Substance Name] OR certolizumab OR cimzia) OR "efalizumab "[Substance Name] OR raptiva) OR "alefacept "[Substance Name] OR amevive) OR "natalizumab "[Substance Name] OR tysabri	1583
#6	Search actemra OR "tocilizumab"[Substance Name]	305
#7	7 Search "golimumab "[Substance Name]	56
#8	8 Search #2 OR #3 OR #4 OR #5 OR #6 OR #7	300191
#9	9 Search #1 AND #8	12597
#10	Search #9 Limits: Editorial, Letter, Practice Guideline	1540
#11	1 Search #9 NOT #10	11057
#12	2 Search #11 Limits: Humans, English, All Adult: 19+ years	4714
#13	3 Search ((#12) AND "2010/05/01"[Entrez Date]: "3000"[Entrez Date]) AND "0"[Entrez Date]: "3000"[Entrez Date] Sort by: Author	116

Appendix B. Review and Abstraction Forms

Abstract Review Questions:		
Original research (no review articles,	Yes	
editorials, letters to the editor) published	No	
in English after 1990 in adult patients with	Cannot determine	
rheumatoid or psoriatic arthritis AND is	No, but article will be used for background	
not a case report or case series?	No, but afficie will be used for background	
Otrodo in alcoda a sua su mana at the	Continue to units	
Study includes one or more of the following pharmaceutical interventions	Corticosteroids Oral DMADDs including methotroyets defunced to	
(check all that apply):	Oral DMARDs including methotrexate, leflunomide,	
(check all that apply).	sulfasalazine, cyclosporine, hydroxychloroquine Biologic DMARDs including anakinra, etanercept,	
	infliximab, adalimumab, abatacept, certolizumab,	
	golimumab, tocilizumab, rituximab	
	Cannot determine	
	Comparison is not of interest	
Study compares:	Two of the included drugs	
	Biological DMARD (TIM) versus placebo	
	One of the included drugs versus placebo but is of	
	interest because of specific outcomes such as	
	adverse events	
	Nothing of interest and article should not be included Cannot determine	
	Cannot determine	
Addresses one or more of the following	KQ1 For patients with rheumatoid arthritis or	
key questions (check all that apply):	psoriatic arthritis, do drug therapies differ in their	
noy quoenone (encon un mar apply).	ability to reduce patient-reported symptoms, to slow	
	or limit progression of radiographic joint damage, or	
	to maintain remission (reduce the incidence flare-	
	ups?	
	KQ2- For patients with rheumatoid arthritis or	
	psoriatic arthritis, do drug therapies differ in their	
	ability to improve functional capacity or quality of life? KQ3 For patients with rheumatoid arthritis or	
	psoriatic arthritis, do drug therapies differ in harms,	
	tolerability, adherence, or adverse effects?	
	KQ4 What are the comparative benefits and harms	
	of drug therapies for rheumatoid arthritis and	
	psoriatic arthritis in subgroups of patients based on	
	stage of disease, history of prior therapy,	
	demographics, concomitant therapies, or	
	comorbidities?	
	Cannot determine by the title or abstract	
	None of the above	
Study design is one of the following:	RCT 3 months or longer	
ctualy accign to one of the following.	Meta-analysis or systematic review	
	Observational Study (N is greater or equal to 100) 3	
	months or longer	
	Case series	
	Case report	
	None of the above- so exclude	
	None of the above- but include	
	Cannot determine	



Previewing at Level 2

Reviewer Comments (Add a Comment)	
Refid: 2161, P. Efthimiou, A. Kontzias, C. M. Ward and N. S. Ogden, Adult-onset Still's disease: can recent advances i understanding of its pathogenesis lead to targeted therapy?, <i>Nat Clin Pract Rheumatol</i> , 3(6), 2007, p. 328-35 State: Excluded, Level: 1	in our
Save to finish later Submit Data	
1. Should the article be excluded for any of the following reasons?	
Study reported only in abstract	
Wrong outcome (i.e. pharmakinetic or intermediate outcomes)	
Wrong drug (not one of the following: corticosteroids, methotrexate, leflunomide, sulfasalazine, cyclosporine, hydroxychloroquine, anakinra, etanercept, infliximab, adalimumab, abatacept, certolizumab, golimumab, tocilizumab, rituximab)	
Wrong population (For example pediatric studies)	
Wrong publication type (e.g. letter or editorial)	
Wrong design (i.e. nonsystematic meta-analysis or no comparision arm)	
☐ RCT (n<100)	
Other? (Please explain!)	₽
☐ Background article	
■ None of the above- should be included!	
If the article has been excluded in the above question, the next two questions do not need to be answered.	
2. Which of the following key questions are addressed by the article	
☐ KQ1- For patients with rheumatoid arthritis or psoriatic arthritis, do drug therapies differ in their ability to reduce patereported symptoms, to slow or limit progression of radiographic joint damage, or to maintain remission (reduce the incidence-ups)?	
☐ KQ2- For patients with rheumatoid arthritis or psoriatic arthritis, do drug therapies differ in their ability to improve furch capacity or quality of life?	nctional
KQ3- For patients with rheumatoid arthritis or psoriatic arthritis, do drug therapies differ in harms, tolerability, adheradverse effects?	rence, or
☐ KQ4- What are the comparative benefits and harms of drug therapies for rheumatoid arthritis and psoriatic arthritis subgroups of patients based on stage of disease, history of prior therapy, demographics, concomitant therapies, or comorbidities?	in
None of the above	
3. What is the study design?	
RCT > or equal to 100	
Observational > or equal to 100	
Meta-analysis or systematic review (i.e. Cochrane Review)	

O None of the above, but it should be abstracted- please note why in the box!	B
None of the above, so exclude.	
Clear Selection	
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Previewing at Level 1

Reviewer Comments (Add a Comment)			

Refid: 2161, P. Efthimiou, A. Kontzias, C. M. Ward and N. S. Ogden, Adult-onset Still's disease: can recent advances in our understanding of its pathogenesis lead to targeted therapy?, *Nat Clin Pract Rheumatol*, 3(6), 2007, p. 328-35 State: Excluded, Level: 1

Keywords: Save to finish later Submit Data Adrenal Cortex Hormones/therapeutic use 1. Original research (no review articles, editorials, letters to the Increase Font Size Decrease Font Size editor) published in English after 1990 in adult patients with rheumatoid or psoriatic arthritis AND is not a case report or case series? Yes O No Abstract: Adult-onset Still's disease is a rare systemic inflammatory O Cannot determine disease of unknown etiology, characterized by daily high, No, but article will be used for background spiking fevers, evanescent rash, and arthritis. There is no Clear Selection single diagnostic test for adult-onset Still's disease; rather, the 2. Study includes one or more of the following pharmaceutical diagnosis is based on clinical criteria and necessitates the interventions (check all that apply): exclusion of infectious, neoplastic, and other 'autoimmune' diseases. Proinflammatory cytokines such as interleukin (IL)-1, Corticosteroids IL-6, and IL-18, interferon-gamma, tumor necrosis factor, and macrophage colony-stimulating factor are elevated in patients Oral DMARDs including methotrexate, leflunomide, with adult-onset Still's disease and are thought to have a sulfasalazine, cyclosporine, hydroxychloroquine major role in the pathogenesis of the disease. Treatment Biologic DMARDs including anakinra, etanercept, consists of nonsteroidal anti-inflammatory drugs. infliximab, adalimumab, abatacept, certolizumab, golimumab, corticosteroids, immunosuppressants (methotrexate, gold, tocilizumab, rituximab azathioprine, leflunomide, cyclosporin, and cyclophosphamide), intravenous immunoglobulin, and Cannot determine cytokine (tumor necrosis factor, IL-1 and IL-6) inhibitors. Recent advances in basic immunology have enhanced our Comparison is not of interest ability to hinder the pathogenic mechanisms associated with 3. Study comparesadult-onset Still's disease and have led to a paradigm shift where targeted treatments have an increasingly important Two of the included drugs role. Biological DMARD (TIM) versus placebo Increase Font Size Decrease Font Size One of the included drugs versus placebo but is of interest because of specific outcome such as adverse events Nothing of interest and article should not be included Cannot determine Clear Selection 4. Addresses one or more of the following key questions (check all that apply): KQ1 For patients with rheumatoid arthritis or psoriatic arthritis, do drug therapies differ in their ability to reduce patient-reported symptoms, to slow or limit progression of radiographic joint damage, or to maintain remission (reduce the incidence flare-ups)? KQ2- For patients with rheumatoid arthritis or psoriatic arthritis, do drug therapies differ in their ability to improve functional capacity or quality of life? KQ3 For patients with rheumatoid arthritis or psoriatic arthritis, do drug therapies differ in harms, tolerability, adherence, or adverse effects? KQ4 What are the comparative benefits and harms of drug therapies for rheumatoid arthritis and psoriatic arthritis in subgroups of patients based on stage of disease, history of prior therapy, demographics, concomitant therapies, or comorbidities? Cannot determine by the title or abstract None of the above 5. Study design is one of the following:

RCT 3 months or longer

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1 Oral DMARD vs 1 BIOLOGIC
1 Oral DMARD vs 1 Corticosteroid
1 BIOLOGIC vs 1 BIOLOGIC
1 BIOLOGIC vs 1 Corticosteroid

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Previewing at Level 3	
Reviewer Comments (Add a Comment)	
Refid: 2161, P. Efthimiou, A. Kontzias, C. M. Ward and N. S. Ogden, Adult-onset State: Excluded, Level: 1	ill's disease: can recent advances in our understa
Save to finish later Submit Data	
1. Author, Year, Study name if applicable (i.e. BeST):	
Enlarge Shrink	
2. Country and setting:	
If more than a couple of countries are included just call it multinational. S	ettings include primary care, hospitals, uni
3. Source of funding	
Pharmaceutical company or other commercial source- please list name.	₽
Government or non-profit organization- please list name.	₽
■ Not reported	
4. Condition being treated:	
Rheumatoid arthritis	
Psoriatic arthritis	
Other? Please explain	
5. STUDY DESIGN	
O Controlled Trials	
Observational	
Clear Selection	
6. What is being compared?	
☐ 1 Oral DMARD vs 1 Oral DMARD	

1 BIOLOGIC vs Placebo					
Combination therapy vs Combination therapy					
SINGLE DRUG vs Combination therapy					
Strategy (Describe the strategy in detail for each arm in	Strategy (Describe the strategy in detail for each arm in the 'Other' text box for numbers 8-12)				
7. How many comparison arms does this study hav	e?				
O 2 ARMS					
O 3 ARMS					
O 4 ARMS					
© 5 ARMS Clear Selection					
8. Check off the drug(s) studied for ARM 1 and put	dosage and frequency in the adjacent box				
	₽				
Prednisone	₽				
☐ Prednisolone	₽				
Methotrexate	₽				
☐ Leflunomide	₽				
Sulfasalazine	₽				
Hydroxychlorquine	₽				
☐ Etanercept	₽				
☐ Infliximab	₽				
Adalimumab	₽				
☐ Anakinra	₽				
Abatacept	₽				
Rituximab	₽				
Certolizumab	₽				
Golimumab	₽				
☐ Tocilizumab	₽				
□ Placebo					
Other (describe)					
9. Check off the drug(s) studied for ARM 2 and put dosage and frequency in the adjacent box					
☐ Methylprednisolone					
☐ Prednisone					
Prednisolone	B				

Methotrexate	₩
Leflunomide	₽
Sulfasalazine	₽
Hydroxychlorquine	₽
Etanercept	₽
☐ Infliximab	₽
Adalimumab	₽
Anakinra	₽
Abatacept	₽
Rituximab	₽
Certolizumab	₽
Golimumab	₽
Tocilizumab	₽
Placebo	₽
Other (describe)	₽
Check off the drug(s) studied for ARM 3 and put	dosage and frequency in the adjacent box
Methylprednisolone	₽
Prednisone	₽
Prednisolone	₽
☐ Methotrexate	₿
Leflunomide	₽
Sulfasalazine	₽
Hydroxychlorquine	₽
☐ Etanercept	₽
☐ Infliximab	₽
Adalimumab	₿
Anakinra	₽
■ Abatacept	₿
Rituximab	₿
Certolizumab	₽

Golimumab	₩		
Tocilizumab	B		
Placebo	B		
Other (describe)	B		
11. Check off the drug(s) studied for ARM 4 and put	dosage and frequency in the adjacent box		
☐ Methylprednisolone	₽		
Prednisone	₽		
☐ Prednisolone	₽		
Methotrexate	₽		
Leflunomide	B		
Sulfasalazine	₽		
Hydroxychlorquine	B		
☐ Etanercept	₽		
☐ Infliximab	₽		
Adalimumab	3		
□ Anakinra	₽		
Abatacept	₽		
Rituximab	B		
Certolizumab	₽		
Golimumab	₽		
Tocilizumab	₽		
Placebo	₽		
Other (describe)	B		
12. Check off the drug(s) studied for ARM 5 and put dosage and frequency in the adjacent box			
Methylprednisolone	₽		
Prednisone	₽		
Prednisolone	₽		
☐ Methotrexate	₽		
Leflunomide	B		
Sulfasalazine	3		

Hydroxychlorquine	<u>-</u>
Etanercept	B
☐ Infliximab	B
Adalimumab	<u>B</u>
Anakinra	<u>B</u>
Abatacept	B
Rituximab	B
Certolizumab	<u>B</u>
Golimumab	B
Tocilizumab	<u></u>
Placebo	₽
Other (describe)	B
13. Research objective (<i>Please be brief and con</i>	cise):
Enlarge Shrink 14. Overall study n = Enlarge Shrink 15. Duration of study:	
Enlarge Shrink	
16. Inclusion criteria (check all that apply and list	
Early RA	<u> </u>
☐ Treatment resistant	<u> </u>
Additional inclusion criteria 17.	B
Exclusion criteria	
Enlarge Shrink	
POPULATION CHARACTERISTICS	

B-12

_	ARM 1		ARM 2	_
18. Intervention/Treatment		₽		₽
19. # in group (n):		₽		3
20. Age (mean):		₽		3 -
21. Sex, female (%):		₽		3 -
22. Race, white (%):		B		3
23. Race, black (%):		B		3
24. Ethnicity, Latino (%):		₽		3
25. Disease duration (mean & SD):		<u>B</u>		3
26. DMARD use (%):		₽		3
27. Corticosteroid use (%):		₽		3
28. MTX naive (%):		₽		3
29. Treatment resistant (%):		₽		3
30. Patients with early RA, three years or less, (%):		₽		3
31. Baseline DAS score:		₽		3
32. Tender joint count:		₽		3 -
33. Swollen joint count:		₽		3 -
34. Required treatment for latent TB:		<u>B</u>		3
35. Other population characteristics?		<u> </u>		3

RESULTS: Outcome Measures and Health Outcomes (Enter results for all time points and please specify units for all results)

	ARM 1	ARM 2	
36. ACR 20, %, (CI/SD/P value):	B	₽	
37. ACR 50, %, (CI/SD/P value):	B	₽	
38. ACR 70, %, (CI/SD/P value):	B	₽	
39. PASI 20, %, (CI/SD/P value):	B	B	

40. PASI 50, %, (CI/SD/P value):	6	·	B
41. PASI 70, %, (CI/SD/P value):	<u> </u>	}	B
42. HAQ, mean difference/absolute difference (CI/SD/P Value):	<u>•</u>	>	B
43. DAS, mean difference/absolute difference (CI/SD/P Value):	<u>-</u>	>	B
44. SF-36, mean difference/absolute difference (CI/SD/P Value):	3	>	B
45. PsARC, mean difference/absolute difference (CI/SD/P Value):	3	>	B
46. Radiographic measures, mean difference/absolute difference (CI/SD/P Value):	<u> </u>	>	B
47. Quality of life scales (please name), mean difference/absolute difference (CI/SD/P Value):	<u> </u>	>	₽
48. Others, (please name); mean difference/absolute difference (CI/SD/P Value):	•	·	
ATTRITION AND ADHERENCE			
49. Overall attrition/withdrawal	ARM 1	ARM 2	
(n):	B	ł	₽
50. Withdrawals due to adverse events (n):	•	}	B
51. Withdrawals due to lack of efficacy (n):	<u> </u>	·	B
52.			
Adherent/compliant (n):	B	?	₽
53. Other attrition related comments	?		
Enlarge Shrink			

54. Overall adverse events 4 4. reported (n): J. J. 55. Death (n): y. 56. Lymphoma or leukemia (n): 57. Skin cancer (basal cell or 4 J. squamous cell) (n): 58. Other cancer (specify) (n): J. 59. Cardiovascular events (specify) (n): 60. Hepatotoxicity/elevated liver 4 enzymes (n): J. 61. Tuberculosis (n): 4. 62. Pneumonia (n): 63. Upper respiratory infection (n): 4 √. √. 64. Urinary tract infection (n): 65. Other infections (specify) 4 ¥. (n): 4 66. Fractures (n): 67. Infusion/injection site 4 reactions (n): ¥, 68. Skin rash (n): y. 69. Demyelenation or multiple sclerosis (n): 70. Progressive multifocal ₹. leukoencephalopathy (n): 4 P 71. Headache (n): ¥. P 72. Dizziness (n): 4 P 73. Nausea or vomiting (n): ¥. P 74. Abdominal pain (n): 4 75. GI bleed or ulcer (n): J. 4 76. Bowel obstruction (n): 77. Other GI symptoms (specify) ¥. 4 (n): 4 ¥. 78. Other AEs 1 (n): 79. Other AEs 2 (n): 4 y. 80. Other AEs 3 (n): J.

ARM 1

ARM 2

81. Other AEs 4 (n):		3	B
82. Any other AEs:			
Enlarge Shrink	es this study address (che	ck all that apply)?	
• • • • • • • • • • • • • • • • • • • •	· ·		neir ability to reduce disease activity, to
KQ2- For patients with rheuma	toid arthritis or psoriatic arthri	tis, do drug therapies differ in th	neir ability to improve functional capac
			arms, tolerability, adherence, or adver
	•		is and psoriatic arthritis in subgroups (
<u></u>			
Quality Review for C	ontrolled Trials		
84. Randomization adequate?			
O Yes			
○ No			
Not randomized			
Method not reported			
Clear Selection			
85. Allocation concealment ade	equate?		
O Yes			
No Not randomized			
Method not reported			
Clear Selection			
86. Groups similar at baseline?	ı		
O Yes			
No (what are the differences)		₽	
Not reported			
Not applicable		B	
Clear Selection	10		
87. Outcome assessors blinded	1?		
O Yes O No			
Yes, but method not described			
Not reported			
Clear Selection			
88. Care provider blinded?			
O Yes			
O No			
Yes, but method not described			
Not reported			

Clear Selection 89. Patient blinded?	
O Yes	
O No	
Yes, but method not described	
O Not reported	
Clear Selection	
90. Overall attrition high (≥ 20%)?	
◯ Yes (please state how high)	
O No	
Clear Selection	
91. Differential attrition high (≥ 15%)?	
◯ Yes (please state difference)	
○ No	
Clear Selection 92. Were the outcome measures valid and reliable?	
O Yes	
○ No	
O Not reported	
Clear Selection	
93. Were the outcome measures equally applied?	
O Yes	
○ No ○ Not reported	
Clear Selection	
94. Was the statistical analysis based on intention-to-treat (ITT)?	
O Yes	
○ No	
O Cannot tell	
O Not applicable	
Clear Selection 95. Were there any post-randomization exclusions?	
O Yes (how many?)	
○ No	
O Cannot tell	
Clear Selection 96. Quality rating for efficacy/effectiveness	
Good	
Fair	
Poor	
If poor, why?	

Quality Review for Observational Studies

97. Were both groups selected from the same source population?
O Yes
○ No
Yes, but method not described
O Not reported
Clear Selection 98. Did both groups have the same risk of having the outcome of interest at baseline?
O Yes
○ No
O Not reported
Clear Selection
99. Were subjects in both groups recruited over the same time period?
O Yes
○ No
Yes, but method not described
O Not reported
Clear Selection 100. Were measurement methods adequate and equally applied to both groups?
○ Yes
○ No
O Not reported
Clear Selection 101. Was an attempt made to blind the outcome assessors?
O Yes
○ No
Yes, but method not described
O Not reported
Clear Selection 102. Was the time of follow-up equal in both groups?
○ Yes
○ No
O Not reported
Clear Selection 103. Overall attrition high (≥ 20%)?
O Yes (please state how high)
○ No
Clear Selection
104. Differential attrition high (≥ 15%)?
O Yes (please state difference)
O No.

Clear Selection 105. Was confounding accounted for either through study design or statistical analysis?
O Yes
O No
Yes, but method not described
O Not reported
Clear Selection
106. Did the statistical analysis adjust for different lengths of follow-up?
O Yes
○ No
Yes, but method not described
O Not reported
Clear Selection
107. Was the length of follow-up adequate to assess the outcome of interest?
O Yes
O No
O Not reported
Clear Selection
108. Quality <u>rating</u> for observational studies
Good
Fair
☐ Poor
Why?
109. Any other quality related comments?
Enlarge Shrink
Quality Review for Adverse Events
110. Methods of adverse effects assessment
Patient reported
Physical exam at study visits
Lab evaluations
Standardized scale (e.g. WHO, UKU-SES)
other (please specify)
111. Adverse events pre-specified and defined?
O Yes
O No
Clear Selection
112.
Measurement techniques non-biased and adequately described?
O Yes
○ No
Clear Selection

113. Quality rating adverse events assessment:		
O Good		
O Fair		
O Poor		
Clear Selection		
114. First abstraction done by:		
Karen Crotty		
Katrina Donahue		
Rick Hansen		
O Dan Jonas		
O Linda Lux		
Robert Roubey		
Rachael Scheinman		
Other (please write your name in the adjacent box):		B
Clear Selection		
115. Second abstraction done by:		
Karen Crotty		
Katrina Donahue		
Rick Hansen		
O Dan Jonas		
C Linda Lux		
Robert Roubey		
Rachael Scheinman		
Other (please write your name in the adjacent box):		B
Clear Selection		
116. Study is already included in systematic review	w/meta-analysis and does not	need to be put in an evidence table
O Yes		
○ No		
Clear Selection		
Save to finish later Submit Data		
Form took 1.550781 seconds to render Form Creation Date: Not available		
Form Last Modified: Nov 6 2009 2:28PM		

B-20

Appendix C. Articles by Database Searched

Reference Source: PubMed

- 1. Juvenile and adult systemic-onset Still's disease. Lancet. 1990 Jul 14;336(8707):92.
- 2. Double blind controlled phase III multicenter clinical trial with interferon gamma in rheumatoid arthritis. German Lymphokine Study Group. Rheumatol Int. 1992;12(5):175-85.
- 3. A randomized trial of hydroxychloroquine in early rheumatoid arthritis: the HERA Study. Am J Med. 1995 Feb;98(2):156-68.
- 4. Treatment methods. Nonsurgical treatment methods for diseases in multiple joints (polyarthritis). Scand J Rheumatol Suppl. 1999;110:7-14.
- 5. Etanercept and infliximab for rheumatoid arthritis. Drug Ther Bull. 2001 Jul;39(7):49-52.
- 6. One million U.S. adults may suffer from psoriatic arthritis. Dermatol Nurs. 2002 Jun;14(3):207-8.
- 7. Anakinra (Kineret) for rheumatoid arthritis. Med Lett Drugs Ther. 2002 Feb 18;44(1124):18-9.
- 8. Summaries for patients. Tumor necrosis factor antagonists and heart failure. Ann Intern Med. 2003 May 20;138(10):I48.
- 9. Is it true that vaccines may not be safe for people with rheumatoid arthritis (which I have)? Does that mean I shouldn't get a flu shot? Johns Hopkins Med Lett Health After 50. 2004 Oct;17(8):8.
- 10. Summaries for patients. Abatacept for people with active rheumatoid arthritis. Ann Intern Med. 2006 Jun 20;144(12):I18.
- 11. Rituximab and abatacept for rheumatoid arthritis. Drug Ther Bull. 2008 Aug;46(8):57-61.

- 12. The Chinese herbal remedy Tripterygium wilfordii Hook F in the treatment of rheumatoid arthritis. Ann Intern Med. 2009 Aug 18;151(4):I-36.
- 13. New drug information: Simponi. Jaapa. 2009 Aug;22(8):13.
- 14. Abarca J, Malone DC, Armstrong EP, et al. Longitudinal analysis of the use of etanercept versus infliximab determined from medical chart audit. J Manag Care Pharm. 2004 Nov-Dec;10(6):538-42.
- 15. Abe K, Mitsuka T, Kanamori S, et al. Gynecomastia associated with low-dose methotrexate therapy for rheumatoid arthritis. Mod Rheumatol. 2007;17(6):511-3.
- 16. Abe T, Takeuchi T, Miyasaka N, et al. A multicenter, double-blind, randomized, placebo controlled trial of infliximab combined with low dose methotrexate in Japanese patients with rheumatoid arthritis. J Rheumatol. 2006 Jan;33(1):37-44.
- 17. Abedin M, Scheurich D, Reimold SC, et al. Acute coronary syndrome after infliximab infusion. Cardiol Rev. 2006 Jan-Feb;14(1):50-2.
- 18. Ablin JN, Boguslavski V, Aloush V, et al. Effect of anti-TNFalpha treatment on circulating endothelial progenitor cells (EPCs) in rheumatoid arthritis. Life Sci. 2006 Nov 17;79(25):2364-9.
- 19. Aboulafia DM, Bundow D, Wilske K, et al. Etanercept for the treatment of human immunodeficiency virus-associated psoriatic arthritis. Mayo Clin Proc. 2000 Oct;75(10):1093-8.
- 20. Abramovits W, Arrazola P, Gupta AK. Enbrel (etanercept). Skinmed. 2004 Nov-Dec;3(6):333-5.
- 21. Acero J, Navarro-Cuellar C, Menarguez J, et al. Naso-maxillary non-Hodgkin lymphoma

- associated with methotrexate treatment in a patient with rheumatoid arthritis. J Oral Maxillofac Surg. 2006 Apr;64(4):708-11.
- 22. Adachi J, Cranney A, Goldsmith CH, et al. Intermittent cyclic therapy with etidronate in the prevention of corticosteroid induced bone loss. J Rheumatol. 1994
 Oct;21(10):1922-6.
- 23. Adam DJ, Nawroz I, Petrie PW. Pyoderma gangrenosum severely affecting both hands. J Hand Surg [Br]. 1996 Dec;21(6):792-4.
- 24. Adebayo D, Popat R, Thjodleifsson B, et al. Granulomatous ileitis in a patient with ankylosing spondylitis. Nat Clin Pract Gastroenterol Hepatol. 2007 Jun;4(6):347-51.
- 25. Adhikesavan LG, Newman ED, Diehl MP, et al. American College of Rheumatology quality indicators for rheumatoid arthritis: benchmarking, variability, and opportunities to improve quality of care using the electronic health record. Arthritis Rheum. 2008 Dec 15;59(12):1705-12.
- 26. Adisen E, Karaca F, Gurer MA. When there is no single best biological agent: psoriasis and psoriatic arthritis in the same patient responding to two different biological agents. Clin Exp Dermatol. 2008

 Mar;33(2):164-6.
- 27. Adzic TN, Stojsic JM, Radosavljevic-Asic GD, et al. Multinodular pulmonary amyloidosis in primary Sjogren's syndrome. Eur J Intern Med. 2008 Dec;19(8):e97-8.
- 28. Aeberli D, Oertle S, Mauron H, et al. Inhibition of the TNF-pathway: use of infliximab and etanercept as remission-inducing agents in cases of therapy-resistant chronic inflammatory disorders. Swiss Med Wkly. 2002 Jul 27;132(29-30):414-22.
- 29. Aeberli D, Seitz M, Juni P, et al. Increase of peripheral CXCR3 positive T lymphocytes upon treatment of RA patients with TNF-alpha inhibitors. Rheumatology (Oxford). 2005 Feb;44(2):172-5.
- 30. Aerts NE, Ebo DG, Bridts CH, et al. Flow cytometric analysis of phospho-p38

- mitogen-activated kinase (MAPK): p38 MAPK does not mediate the effect of adalimumab on peripheral T cell cytokine production in rheumatoid arthritis. Cytokine. 2009 Sep;47(3):178-84.
- 31. Agarwal PK, Gallaghar M, Murphy E, et al. Endogenous endophthalmitis in a rheumatoid patient on tumor necrosis factor alpha blocker. Indian J Ophthalmol. 2007 May-Jun;55(3):230-2.
- 32. Agarwal S, Zaman T, Handa R. Retention rates of disease-modifying anti-rheumatic drugs in patients with rheumatoid arthritis. Singapore Med J 2009;50(7):686-92.
- 33. Agarwal SK, Maier AL, Chibnik LB, et al. Pattern of infliximab utilization in rheumatoid arthritis patients at an academic medical center. Arthritis Rheum. 2005 Dec 15;53(6):872-8.
- 34. Aggarwal A, Panda S, Misra R. Effect of etanercept on matrix metalloproteinases and angiogenic vascular endothelial growth factor: a time kinetic study. Ann Rheum Dis. 2004 Jul;63(7):891-2.
- 35. Aggarwal P, Naik S, Mishra KP, et al.
 Correlation between methotrexate efficacy
 & toxicity with C677T polymorphism of the
 methylenetetrahydrofolate gene in
 rheumatoid arthritis patients on folate
 supplementation. Indian J Med Res. 2006
 Nov;124(5):521-6.
- Agirbasli M, Inanc N, Baykan OA, et al.
 The effects of TNF alpha inhibition on plasma fibrinolytic balance in patients with chronic inflammatory rheumatical disorders.
 Clin Exp Rheumatol. 2006 Sep-Oct;24(5):580-3.
- 37. Ahmadi-Simab K, Lamprecht P, Nolle B, et al. Successful treatment of refractory anterior scleritis in primary Sjogren's syndrome with rituximab. Ann Rheum Dis. 2005 Jul;64(7):1087-8.
- 38. Ahmed M, Luggen M, Herman JH, et al. Hypertrophic pachymeningitis in rheumatoid arthritis after adalimumab administration. J Rheumatol. 2006 Nov;33(11):2344-6.

- 39. Ahmed MM, Mubashir E, Wolf RE, et al. Impact of treatment with infliximab on anticyclic citrullinated peptide antibody and rheumatoid factor in patients with rheumatoid arthritis. South Med J. 2006 Nov;99(11):1209-15.
- 40. Aida S, Okawa-Takatsuji M, Aotsuka S, et al. Calcitonin inhibits production of immunoglobulins, rheumatoid factor and interleukin-1 by mononuclear cells from patients with rheumatoid arthritis. Ann Rheum Dis. 1994 Apr;53(4):247-9.
- 41. Akai M, Ohno T, Kamura S, et al. Epidural abscess following septic arthritis in a rheumatoid patient. A case report. Spine. 1990 Jun;15(6):603-5.
- 42. Akay OM, Korkmaz C, Gulbas Z. Development of acute inflammatory arthritis by granulocyte-macrophage colonystimulating factor during autologous stem cell transplantation for cryoglobulinemia. Rheumatol Int. 2007 Oct;27(12):1167-9.
- 43. Akritidis N, Papadopoulos A, Pappas G. Long-term follow-up of patients with adultonset Still's disease. Scand J Rheumatol. 2006 Sep-Oct;35(5):395-7.
- 44. Alarcon GS. Early rheumatoid arthritis: combination therapy of doxycycline plus methotrexate versus methotrexate monotherapy. Nat Clin Pract Rheumatol. 2006 Jun;2(6):296-7.
- 45. Al-Arfaj AS, Al-Saleh S. Adult-Onset Still's disease in Saudi Arabia. Clin Rheumatol. 2001;20(3):197-200.
- 46. Alegre-Sancho JJ, Juanola X, Narvaez FJ, et al. Septic arthiritis due to Prevotella bivia in a patient with rheumatoid arthritis. Joint Bone Spine. 2000;67(3):228-9.
- 47. Alessandri C, Bombardieri M, Papa N, et al. Decrease of anti-cyclic citrullinated peptide antibodies and rheumatoid factor following anti-TNFalpha therapy (infliximab) in rheumatoid arthritis is associated with clinical improvement. Ann Rheum Dis. 2004 Oct;63(10):1218-21.

- 48. Aletaha D, Funovits J, Keystone EC, et al. Disease activity early in the course of treatment predicts response to therapy after one year in rheumatoid arthritis patients.

 Arthritis Rheum. 2007 Oct;56(10):3226-35.
- 49. Alex P, Szodoray P, Arthur E, et al. Influence of intraarticular corticosteroid administration on serum cytokines in rheumatoid arthritis. Clin Rheumatol. 2007 May;26(5):845-8.
- 50. Alex P, Szodoray P, Knowlton N, et al. Multiplex serum cytokine monitoring as a prognostic tool in rheumatoid arthritis. Clin Exp Rheumatol. 2007 Jul-Aug;25(4):584-92
- Alexander D, Friedrich B, Abruzzese T, et al. The active form of leflunomide,
 HMR1726, facilitates TNF-alpha and IL-17 induced MMP-1 and MMP-3 expression.
 Cell Physiol Biochem. 2006;17(1-2):69-78.
- 52. Ali AA, Moatter T, Baig JA, et al. Polymorphism of HLA-DR and HLA-DQ in rheumatoid arthritis patients and clinical response to methotrexate--a hospital-based study. J Pak Med Assoc. 2006 Oct;56(10):452-6.
- 53. Alivernini S, Mazzotta D, Zoli A, et al. Leflunomide treatment in elderly patients with rheumatoid or psoriatic arthritis: retrospective analysis of safety and adherence to treatment. Drugs Aging. 2009;26(5):395-402.
- 54. Alkassab F. Overlap of systemic sclerosis and rheumatoid arthritis. J Rheumatol. 2007 Jul;34(7):1593-4.
- 55. Allanore Y, Bremont C, Kahan A, et al. Transient hyperthyroidism in a patient with rheumatoid arthritis treated by etanercept. Clin Exp Rheumatol. 2001 May-Jun;19(3):356-7.
- 56. Allanore Y, Sellam J, Batteux F, et al. Induction of autoantibodies in refractory rheumatoid arthritis treated by infliximab. Clin Exp Rheumatol. 2004 Nov-Dec;22(6):756-8.

- 57. Allantaz F, Chaussabel D, Stichweh D, et al. Blood leukocyte microarrays to diagnose systemic onset juvenile idiopathic arthritis and follow the response to IL-1 blockade. J Exp Med. 2007 Sep 3;204(9):2131-44.
- 58. Almodovar R, Izquierdo M, Zarco P, et al. Pulmonary sarcoidosis in a patient with ankylosing spondylitis treated with infliximab. Clin Exp Rheumatol. 2007 Jan-Feb;25(1):99-101.
- 59. Almodovar R, Zarco P, Quiros FJ, et al. Infliximab treatment efficacy in lymphoedema associated with ankylosing spondylitis. Rheumatology (Oxford). 2004 Nov;43(11):1456.
- 60. al-Mughales J, Blyth TH, Hunter JA, et al. The chemoattractant activity of rheumatoid synovial fluid for human lymphocytes is due to multiple cytokines. Clin Exp Immunol. 1996 Nov;106(2):230-6.
- 61. Alonso-Bartolome P, Martinez-Taboada VM, Blanco R, et al. Insufficiency fractures of the tibia and fibula. Semin Arthritis Rheum. 1999 Jun;28(6):413-20.
- 62. Alshekhlee A, Basiri K, Miles JD, et al. Chronic inflammatory demyelinating polyneuropathy associated with tumor necrosis factor-alpha antagonists. Muscle Nerve. 2010 May;41(5):723-7.
- 63. Alstergren P, Larsson PT, Kopp S. Successful treatment with multiple intraarticular injections of infliximab in a patient with psoriatic arthritis. Scand J Rheumatol. 2008 Mar-Apr;37(2):155-7.
- 64. Altintop L, Cakar B, Hokelek M, et al. Strongyloides stercoralis hyperinfection in a patient with rheumatoid arthritis and bronchial asthma: a case report. Ann Clin Microbiol Antimicrob. 2010;9:27.
- 65. Alvarez-Rodriguez L, Carrasco-Marin E, Lopez-Hoyos M, et al. Interleukin-1RN gene polymorphisms in elderly patients with rheumatic inflammatory chronic conditions: Association of IL-1RN*2/2 genotype with polymyalgia rheumatica. Hum Immunol. 2009 Jan;70(1):49-54.

- 66. Aman S, Hakala M, Silvennoinen J, et al. Low incidence of osteoporosis in a two year follow-up of early community based patients with rheumatoid arthritis. Scand J Rheumatol. 1998;27(3):188-93.
- 67. Amenomori M, Migita K, Miyashita T, et al. Cytomegalovirus-associated hemophagocytic syndrome in a patient with adult onset Still's disease. Clin Exp Rheumatol. 2005 Jan-Feb;23(1):100-2.
- 68. Amichai B, Gat A, Grunwald MH.
 Cutaneous hyperpigmentation during
 therapy with hydroxychloroquine. J Clin
 Rheumatol. 2007 Apr;13(2):113.
- 69. Amital H, Aamar S, Rubinow A. Bilateral septic arthritis of the hip: does etanercept play a role? A case report. J Bone Joint Surg Am. 2003 Nov;85-A(11):2205-6.
- 70. Amital H, Arnson Y, Chodick G, et al. Hepatotoxicity rates do not differ in patients with rheumatoid arthritis and psoriasis treated with methotrexate. Rheumatology (Oxford). 2009 Sep;48(9):1107-10.
- 71. Anandacoomarasamy A, Kannangara S, Barnsley L. Cutaneous vasculitis associated with infliximab in the treatment of rheumatoid arthritis. Intern Med J. 2005 Oct;35(10):638-40.
- 72. Anandarajah AP, Schwarz EM, Totterman S, et al. The effect of etanercept on osteoclast precursor frequency and enhancing bone marrow oedema in patients with psoriatic arthritis. Ann Rheum Dis. 2008 Mar;67(3):296-301.
- 73. Ancuta C, Ancuta E, Miu S, et al. Adalimumab therapy in patients with active rheumatoid arthritis. Rev Med Chir Soc Med Nat Iasi. 2009 Jul-Sep;113(3):710-5.
- 74. Andonopoulos AP, Meimaris N, Daoussis D, et al. Intra-articular anti-tumor necrosis factor alpha antibody in recalcitrant arthritis of Behcet's disease. Clin Exp Rheumatol. 2003 Jul-Aug;21(4 Suppl 30):S57-8.
- 75. Andres E, Limbach FX, Goichot B, et al. Silent thyroiditis associated with etanercept

- in rheumatoid arthritis. Ann Rheum Dis. 2002 Jun;61(6):565.
- 76. Anelli MG, Torres DD, Manno C, et al. Improvement of renal function and disappearance of hepatitis B virus DNA in a patient with rheumatoid arthritis and renal amyloidosis following treatment with infliximab. Arthritis Rheum. 2005 Aug;52(8):2519-20.
- 77. Ang HT, Helfgott S. Do the clinical responses and complications following etanercept or infliximab therapy predict similar outcomes with the other tumor necrosis factor-alpha antagonists in patients with rheumatoid arthritis? J Rheumatol. 2003 Nov;30(11):2315-8.
- 78. Anis A, Zhang W, Emery P, et al. The effect of etanercept on work productivity in patients with early active rheumatoid arthritis: results from the COMET study. Rheumatology (Oxford) 2009;48(10):1283-9.
- 79. Anolik JH, Ravikumar R, Barnard J, et al. Cutting edge: anti-tumor necrosis factor therapy in rheumatoid arthritis inhibits memory B lymphocytes via effects on lymphoid germinal centers and follicular dendritic cell networks. J Immunol. 2008 Jan 15;180(2):688-92.
- 80. Antolin J, Azahara M, Hernandez C, et al. Tuberculous peritonitis after treatment with adalimumab. Scand J Infect Dis. 2008;40(8):677-8.
- 81. Antoni C, Dechant C, Hanns-Martin Lorenz PD, et al. Open-label study of infliximab treatment for psoriatic arthritis: clinical and magnetic resonance imaging measurements of reduction of inflammation. Arthritis Rheum. 2002 Oct 15;47(5):506-12.
- 82. Antoni C, Krueger GG, de Vlam K, et al. Infliximab improves signs and symptoms of psoriatic arthritis: results of the IMPACT 2 trial. Ann Rheum Dis. 2005
 Aug;64(8):1150-7.
- 83. Antoni CE, Kavanaugh A, Kirkham B, et al. Sustained benefits of infliximab therapy for dermatologic and articular manifestations of psoriatic arthritis: results from the

- infliximab multinational psoriatic arthritis controlled trial (IMPACT). Arthritis Rheum. 2005 Apr;52(4):1227-36.
- 84. Antoni CE, Kavanaugh A, van der Heijde D, et al. Two-year efficacy and safety of infliximab treatment in patients with active psoriatic arthritis: findings of the Infliximab Multinational Psoriatic Arthritis Controlled Trial (IMPACT). J Rheumatol. 2008 May;35(5):869-76.
- 85. Antoniou KM, Mamoulaki M, Malagari K, et al. Infliximab therapy in pulmonary fibrosis associated with collagen vascular disease. Clin Exp Rheumatol. 2007 Jan-Feb;25(1):23-8.
- 86. Antony T, Jose VM, Paul BJ, et al. Efficacy and safety of leflunomide alone and in combination with methotrexate in the treatment of refractory rheumatoid arthritis. Indian J Med Sci. 2006 Aug;60(8):318-26.
- 87. Aouba A, De Bandt M, Aslangul E, et al. Haemophagocytic syndrome in a rheumatoid arthritis patient treated with infliximab. Rheumatology (Oxford). 2003

 Jun;42(6):800-2.
- 88. Aparicio AG, Munoz-Fernandez S, Bonilla G, et al. Report of an additional case of antitumor necrosis factor therapy and Listeria monocytogenes infection: comment on the letter by Gluck et al. Arthritis Rheum. 2003 Jun;48(6):1764-5; author reply 5-6.
- 89. Appel da Silva F, Appel da Silva MC, Romagna ES. Clinical images: Psoriatic arthritis mutilans. Arthritis Rheum. 2010 Jul;62(7):2159.
- 90. Appenzeller S, Castro GR, Costallat LT, et al. Adult-onset Still disease in southeast Brazil. J Clin Rheumatol. 2005
 Apr;11(2):76-80.
- 91. Arabelovic S, Sam G, Dallal GE, et al. Preliminary evidence shows that folic acid fortification of the food supply is associated with higher methotrexate dosing in patients with rheumatoid arthritis. J Am Coll Nutr. 2007 Oct;26(5):453-5.

- 92. Aramaki T, Kawakami A, Iwamoto N, et al. Prediction of DAS28-CRP remission in patients with rheumatoid arthritis treated with tacrolimus at 6 months by baseline variables. Mod Rheumatol. 2009;19(6):652-6.
- 93. Ardalan MR, Shoja MM. Multiple myeloma presented as acute interstitial nephritis and rheumatoid arthritis-like polyarthritis. Am J Hematol. 2007 Apr;82(4):309-13.
- 94. Arend SM, Kuijper EJ, Allaart CF, et al. Cavitating pneumonia after treatment with infliximab and prednisone. Eur J Clin Microbiol Infect Dis. 2004 Aug;23(8):638-41
- 95. Argyropoulou MI, Glatzouni A, Voulgari PV, et al. Magnetic resonance imaging quantification of hand synovitis in patients with rheumatoid arthritis treated with infliximab. Joint Bone Spine. 2005 Dec;72(6):557-61.
- 96. Arif S, Cox P, Afzali B, et al. Anti-TNFalpha therapy--killing two birds with one stone? Lancet 2010;375(9733):2278.
- 97. Arkachaisri T, Lehman TJ. Use of biologics in the treatment of childhood rheumatic diseases. Curr Rheumatol Rep. 2000 Aug;2(4):330-6.
- 98. Arman A, Yilmaz B, Coker A, et al. Interleukin-1 receptor antagonist (IL-1RN) and interleukin-1B gene polymorphisms in Turkish patients with rheumatoid arthritis. Clin Exp Rheumatol. 2006 Nov-Dec;24(6):643-8.
- 99. Armstrong DJ, McCarron MT, Wright GD. Successful treatment of rheumatoid vasculitis-associated foot-drop with infliximab. J Rheumatol. 2005
 Apr;32(4):759; author reply -60.
- 100. Arnold EL, Khanna D, Paulus H, et al. Acute injection site reaction to intraarticular etanercept administration. Arthritis Rheum. 2003 Jul;48(7):2078-9.
- 101. Arvidson NG, Larsen A, Aaseth J, et al. Short-term effects of the TNFalpha antagonist infliximab on the acute phase

- reaction and activities of daily life in patients with rheumatoid arthritis. Scand J Clin Lab Invest. 2007;67(3):337-42.
- 102. Asanuma Y, Chung CP, Oeser A, et al. Serum osteoprotegerin is increased and independently associated with coronary-artery atherosclerosis in patients with rheumatoid arthritis. Atherosclerosis. 2007 Dec;195(2):e135-41.
- 103. Asherson RA, Pascoe L. Adult onset Still's disease: response to Enbrel. Ann Rheum Dis. 2002 Sep;61(9):859-60; author reply 60
- 104. Ashok D, Ayliffe WH, Kiely PD.

 Necrotizing scleritis associated with rheumatoid arthritis: long-term remission with high-dose infliximab therapy.

 Rheumatology (Oxford). 2005

 Jul;44(7):950-1.
- 105. Ashok D, Dubey S, Tomlinson I. C-ANCA positive systemic vasculitis in a patient with rheumatoid arthritis treated with infliximab. Clin Rheumatol. 2008 Feb;27(2):261-4.
- 106. Askling J, Fored CM, Brandt L, et al. Risk and case characteristics of tuberculosis in rheumatoid arthritis associated with tumor necrosis factor antagonists in Sweden.

 Arthritis Rheum. 2005 Jul;52(7):1986-92.
- 107. Askling J, van Vollenhoven RF, Granath F, et al. Cancer risk in patients with rheumatoid arthritis treated with anti-tumor necrosis factor alpha therapies: does the risk change with the time since start of treatment?

 Arthritis Rheum 2009;60(11):3180-9.
- 108. Aslangul E, Perrot S, Durand E, et al. Successful etanercept treatment of constrictive pericarditis complicating rheumatoid arthritis. Rheumatology (Oxford). 2005 Dec;44(12):1581-3.
- 109. Aslanidis S, Pyrpasopoulou A, Douma S, et al. Is it safe to readminister tumor necrosis factor alpha antagonists following tuberculosis flare? Arthritis Rheum. 2008 Jan;58(1):327-8.
- 110. Aslanidis S, Vassiliadis T, Pyrpasopoulou A, et al. Inhibition of TNFalpha does not

- induce viral reactivation in patients with chronic hepatitis C infection: two cases. Clin Rheumatol. 2007 Feb;26(2):261-4.
- 111. Asli B, Wechsler B, Lemaitre C. Inhibition of tumor necrosis factor alpha and ankylosing spondylitis. N Engl J Med. 2003 Jan 23;348(4):359-61; author reply -61.
- 112. Asplund MS, Hagberg H, Holmstrom M. Chemotherapy in severe nasal polyposis--a possible beneficial effect? A report of three cases. Rhinology. 2010 Sep;48(3):374-6.
- 113. Assimakopoulos SF, Michalopoulou S, Melachrinou M, et al. Primary Sjogren syndrome complicated by autoimmune hemolytic anemia and pure red cell aplasia. Am J Med Sci. 2007 Dec;334(6):493-6.
- 114. Assmann G, Pfreundschuh M, Voswinkel J. Rituximab in patients with rheumatoid arthritis and vasculitis-associated cutaneous ulcers. Clin Exp Rheumatol. 2010 Jan-Feb;28(1 Suppl 57):81-3.
- 115. Assous N, Gossec L, Dieude P, et al.
 Rituximab therapy in rheumatoid arthritis in daily practice. J Rheumatol. 2008
 Jan;35(1):31-4.
- 116. Atchia, II, Kidd CE, Bell RW. Rheumatoid arthritis-associated necrotizing scleritis and peripheral ulcerative keratitis treated successfully with infliximab. J Clin Rheumatol. 2006 Dec;12(6):291-3.
- 117. Atteno M, Peluso R, Costa L, et al.
 Comparison of effectiveness and safety of infliximab, etanercept, and adalimumab in psoriatic arthritis patients who experienced an inadequate response to previous disease-modifying antirheumatic drugs. Clin Rheumatol 2010;29(4):399-403.
- 118. Atzeni F, Doria A, Ghirardello A, et al. Organ-specific autoantibodies in patients with rheumatoid arthritis treated with adalimumab: a prospective long-term follow-up. Autoimmunity. 2008 Feb;41(1):87-91.
- 119. Atzeni F, Sarzi-Puttini P, DePortu S, et al. In etanercept-treated psoriatic arthritis patients clinical improvement correlated with an

- increase of serum cortisol relative to other adrenal hormones. Clin Exp Rheumatol. 2008 Jan-Feb;26(1):103-8.
- 120. Augustsson J, Eksborg S, Ernestam S, et al. Low-dose glucocorticoid therapy decreases risk for treatment-limiting infusion reaction to infliximab in patients with rheumatoid arthritis. Ann Rheum Dis. 2007
 Nov;66(11):1462-6.
- 121. Augustsson J, Neovius M, Cullinane-Carli C, et al. Patients with rheumatoid arthritis treated with tumour necrosis factor antagonists increase their participation in the workforce: potential for significant long-term indirect cost gains (data from a population-based registry). Ann Rheum Dis 2010;69(1):126-31.
- 122. Avancini-Dobrovic V, Vrbanic TS, Kukuljan M, et al. Spontaneous serial fractures of metatarsal bones in female patient with rheumatoid arthritis on long-term steroid therapy. Coll Antropol. 2010 Sep;34(3):1123-6.
- 123. Avriel A, Zeller L, Flusser D, et al. Coexistence of psoriatic arthritis and systemic lupus erythematosus. Isr Med Assoc J. 2007 Jan;9(1):48-9.
- 124. Ayaz NA, Demirkaya E, Bilginer Y, et al. Preventing tuberculosis in children receiving anti-TNF treatment. Clin Rheumatol. 2010 Apr;29(4):389-92.
- 125. Aydin T, Karacan I, Demir SE, et al. Bone loss in males with ankylosing spondylitis: its relation to sex hormone levels. Clin Endocrinol (Oxf). 2005 Oct;63(4):467-9.
- 126. Aydintug AO, D'Cruz D, Cervera R, et al. Low dose methotrexate treatment in adult Still's disease. J Rheumatol. 1992 Mar;19(3):431-5.
- 127. Aydog E, Yesilli O, Sever A, et al.
 Dermatitis herpetiformis and rheumatoid
 arthritis. Saudi Med J. 2006 Jun;27(6):8814.
- 128. Azuma T, Ishimaru H, Hatta K, et al. Improved response to infliximab after leukocytapheresis in a patent with

- rheumatoid arthritis. Mod Rheumatol. 2007;17(3):253-5.
- 129. Babacan T, Onat AM, Pehlivan Y, et al. Successful treatment of refractory adult Still's disease and membranous glomerulonephritis with infliximab. Clin Rheumatol. 2010 Apr;29(4):423-6.
- 130. Bacquet-Deschryver H, Jouen F, Quillard M, et al. Impact of three anti-TNFalpha biologics on existing and emergent autoimmunity in rheumatoid arthritis and spondylarthropathy patients. J Clin Immunol. 2008 Sep;28(5):445-55.
- 131. Bae SC, Corzillius M, Kuntz KM, et al. Cost-effectiveness of low dose corticosteroids versus non-steroidal anti-inflammatory drugs and COX-2 specific inhibitors in the long-term treatment of rheumatoid arthritis. Rheumatology (Oxford), 2003 Jan;42(1):46-53.
- 132. Baer AN, Dessypris EN, Krantz SB. The pathogenesis of anemia in rheumatoid arthritis: a clinical and laboratory analysis. Semin Arthritis Rheum. 1990 Feb;19(4):209-23.
- 133. Baeten D, De Keyser F, Veys EM, et al. Tumour necrosis factor alpha independent disease mechanisms in rheumatoid arthritis: a histopathological study on the effect of infliximab on rheumatoid nodules. Ann Rheum Dis. 2004 May;63(5):489-93.
- 134. Baeten D, Van Damme N, Van den Bosch F, et al. Impaired Th1 cytokine production in spondyloarthropathy is restored by anti-TNFalpha. Ann Rheum Dis. 2001 Aug;60(8):750-5.
- 135. Bagalas V, Kioumis I, Argyropoulou P, et al. Visceral leishmaniasis infection in a patient with rheumatoid arthritis treated with
 - etanercept. Clin Rheumatol. 2007 Aug;26(8):1344-5.
- 136. Baghai M, Osmon DR, Wolk DM, et al. Fatal sepsis in a patient with rheumatoid arthritis treated with etanercept. Mayo Clin Proc. 2001 Jun;76(6):653-6.

- 137. Baig MA, Aksoy T, McClain D, et al. Calciphylaxis in a hemodialysis patient on corticosteroids and etanercept for psoriatic arthritis. J Clin Rheumatol. 2010 Mar;16(2):92-3.
- 138. Bakewell C, Dugowson C. Images in clinical medicine. Baker's cyst in a patient with rheumatoid arthritis. N Engl J Med. 2009 Sep 10;361(11):1098.
- 139. Bakland G, Nossent H. Acute myelogenous leukaemia following etanercept therapy. Rheumatology (Oxford). 2003
 Jul;42(7):900-1.
- 140. Balandraud N, Guis S, Baptiste Meynard J, et al. Long-term treatment with methotrexate or tumor necrosis factor alpha inhibitors does not increase epstein-barr virus load in patients with rheumatoid arthritis. Arthritis Rheum. 2007 Jun 15;57(5):762-7.
- 141. Balanescu A, Radu E, Nat R, et al. Early and late effect of infliximab on circulating dendritic cells phenotype in rheumatoid arthritis patients. Int J Clin Pharmacol Res. 2005;25(1):9-18.
- 142. Balbir-Gurman A, Guralnik L, Best LA, et al. Accelerated pulmonary nodulosis and sterile pleural effusion in a patient with psoriatic arthropathy during methotrexate therapy: a case report. J Clin Rheumatol. 2009 Feb;15(1):29-30.
- 143. Bambery P, Thomas RJ, Malhotra HS, et al. Adult onset Still's disease: clinical experience with 18 patients over 15 years in northern India. Ann Rheum Dis. 1992 Apr;51(4):529-32.
- 144. Bandelier C, Guerne PA, Genevay S, et al. Clinical experience with mycophenolate mofetil in systemic autoimmune conditions refractory to common immunosuppressive therapies. Swiss Med Wkly. 2009 Jan 24;139(3-4):41-6.
- 145. Bang LM, Keating GM. Adalimumab: a review of its use in rheumatoid arthritis. BioDrugs. 2004;18(2):121-39.

- 146. Bankhurst AD. Etanercept and methotrexate combination therapy. Clin Exp Rheumatol. 1999 Nov-Dec;17(6 Suppl 18):S69-72.
- 147. Baraliakos X, Brandt J, Listing J, et al. Outcome of patients with active ankylosing spondylitis after two years of therapy with etanercept: clinical and magnetic resonance imaging data. Arthritis Rheum. 2005 Dec 15;53(6):856-63.
- 148. Baraliakos X, Davis J, Tsuji W, et al.

 Magnetic resonance imaging examinations of the spine in patients with ankylosing spondylitis before and after therapy with the tumor necrosis factor alpha receptor fusion protein etanercept. Arthritis Rheum. 2005

 Apr;52(4):1216-23.
- 149. Baraliakos X, Listing J, Rudwaleit M, et al. Radiographic progression in patients with ankylosing spondylitis after 2 years of treatment with the tumour necrosis factor alpha antibody infliximab. Ann Rheum Dis. 2005 Oct;64(10):1462-6.
- 150. Barber J, Sheeran T, Mulherin D. Antitumour necrosis factor treatment in a patient with anorexia nervosa and juvenile idiopathic arthritis. Ann Rheum Dis. 2003 May;62(5):490-1.
- 151. Bargagli E, Galeazzi M, Rottoli P. Infliximab treatment in a patient with rheumatoid arthritis and pulmonary fibrosis. Eur Respir J. 2004 Oct;24(4):708.
- 152. Barra L, Pope JE, Payne M. Real-world antitumor necrosis factor treatment in rheumatoid arthritis, psoriatic arthritis, and ankylosing spondylitis: cost-effectiveness based on number needed to treat to improve health assessment questionnaire. J Rheumatol. 2009 Jul;36(7):1421-8.
- 153. Barrera P, Oyen WJ, Boerman OC, et al. Scintigraphic detection of tumour necrosis factor in patients with rheumatoid arthritis. Ann Rheum Dis. 2003 Sep;62(9):825-8.
- 154. Barrera P, van der Laken CJ, Boerman OC, et al. Radiolabelled interleukin-1 receptor antagonist for detection of synovitis in patients with rheumatoid arthritis.

 Rheumatology (Oxford). 2000

 Aug;39(8):870-4.

- 155. Bartelds GM, Wijbrandts CA, Nurmohamed MT, et al. Clinical response to adalimumab: relationship to anti-adalimumab antibodies and serum adalimumab concentrations in rheumatoid arthritis. Ann Rheum Dis. 2007 Jul;66(7):921-6.
- 156. Barthel HR. Rapid remission of treatment-resistant ankylosing spondylitis with etanercept--a drug for refractory ankylosing spondylitis? Arthritis Rheum. 2001 Aug;45(4):404.
- 157. Bartke U, Venten I, Kreuter A, et al. Human immunodeficiency virus-associated psoriasis and psoriatic arthritis treated with infliximab. Br J Dermatol. 2004 Apr;150(4):784-6.
- 158. Bartolucci P, Ramanoelina J, Cohen P, et al. Efficacy of the anti-TNF-alpha antibody infliximab against refractory systemic vasculitides: an open pilot study on 10 patients. Rheumatology (Oxford). 2002 Oct;41(10):1126-32.
- 159. Barton A, Myerscough A, John S, et al. A single nucleotide polymorphism in exon 1 of cytotoxic T-lymphocyte-associated-4 (CTLA-4) is not associated with rheumatoid arthritis. Rheumatology (Oxford). 2000 Jan;39(1):63-6.
- 160. Barton P, Jobanputra P, Wilson J, et al. The use of modelling to evaluate new drugs for patients with a chronic condition: the case of antibodies against tumour necrosis factor in rheumatoid arthritis. Health Technol Assess. 2004 Mar;8(11):iii, 1-91.
- 161. Bartram D, Sheeran T, Price T, et al. Antitumour necrosis factor therapy in the West Midlands. Rheumatology (Oxford). 2004 Mar;43(3):400; author reply -1.
- 162. Bas S, Gauthier BR, Spenato U, et al. CD14 is an acute-phase protein. J Immunol. 2004 Apr 1;172(7):4470-9.
- 163. Baskan BM, Sivas F, Alemdaroglu E, et al. Association of bone mineral density and vertebral deformity in patients with rheumatoid arthritis. Rheumatol Int. 2007 Apr;27(6):579-84.

- 164. Bassetti S, Wasmer S, Hasler P, et al. Staphylococcus aureus in patients with rheumatoid arthritis under conventional and anti-tumor necrosis factor-alpha treatment. J Rheumatol. 2005 Nov;32(11):2125-9.
- 165. Bathon JM, Fleischmann RM, Van der Heijde D, et al. Safety and efficacy of etanercept treatment in elderly subjects with rheumatoid arthritis. J Rheumatol. 2006 Feb;33(2):234-43.
- 166. Bathon JM, Martin RW, Fleischmann RM, et al. A comparison of etanercept and methotrexate in patients with early rheumatoid arthritis. N Engl J Med. 2000 Nov 30;343(22):1586-93.
- 167. Batsis JA, Phy MP. West Nile virus meningitis in a chronic immunosuppressed patient with rheumatoid arthritis. Clin Rheumatol. 2005 Sep;24(5):548-50.
- 168. Bauer AS, Blazar PE, Earp BE, et al.
 Mycobacterial hand infections occurring
 postoperatively in patients treated with
 tumor necrosis factor-alpha inhibitors for
 inflammatory arthritis: report of three cases.
 J Hand Surg Am. 2010 Jan;35(1):104-8.
- 169. Baumgartner SW, Fleischmann RM, Moreland LW, et al. Etanercept (Enbrel) in patients with rheumatoid arthritis with recent onset versus established disease: improvement in disability. J Rheumatol. 2004 Aug;31(8):1532-7.
- 170. Bayer M, Stepan J, Nemcova D, et al. Juvenile chronic arthritis--bone mineral density in relation to corticosteroid therapy. Acta Univ Carol [Med] (Praha). 1994;40(1-4):33-5.
- 171. Bejarano V, Quinn M, Conaghan PG, et al. Effect of the early use of the anti-tumor necrosis factor adalimumab on the prevention of job loss in patients with early rheumatoid arthritis. Arthritis Rheum 2008;59(10):1467-74.
- 172. Bejot Y, Osseby GV, Ben Salem D, et al. Bilateral optic neuropathy revealing Sjogren's syndrome. Rev Neurol (Paris). 2008 Dec;164(12):1044-7.

- 173. Belknap R, Reves R, Burman W. Immune reconstitution to Mycobacterium tuberculosis after discontinuing infliximab. Int J Tuberc Lung Dis. 2005 Sep;9(9):1057-8
- 174. Bellisai F, Giannitti C, Donvito A, et al. Combination therapy with cyclosporine A and anti-TNF-alpha agents in the treatment of rheumatoid arthritis and concomitant hepatitis C virus infection. Clin Rheumatol. 2007 Jul;26(7):1127-9.
- 175. Belostocki K, Pricop L, Redecha PB, et al. Infliximab treatment shifts the balance between stimulatory and inhibitory Fcgamma receptor type II isoforms on neutrophils in patients with rheumatoid arthritis. Arthritis Rheum. 2008 Feb;58(2):384-8.
- 176. Bender NK, Heilig CE, Droll B, et al. Immunogenicity, efficacy and adverse events of adalimumab in RA patients. Rheumatol Int. 2007 Jan;27(3):269-74.
- 177. Ben-Horin S, Goldstein I, Koltakov A, et al. The effect of blockade of tumor necrosis factor alpha on VLA-1+ T-cells in rheumatoid arthritis patients. J Clin Immunol. 2007 Nov;27(6):580-8.
- 178. Benito-Garcia E, Heller JE, Chibnik LB, et al. Dietary caffeine intake does not affect methotrexate efficacy in patients with rheumatoid arthritis. J Rheumatol. 2006 Jul;33(7):1275-81.
- 179. Bennett AN, Peterson P, Zain A, et al. Adalimumab in clinical practice. Outcome in 70 rheumatoid arthritis patients, including comparison of patients with and without previous anti-TNF exposure. Rheumatology (Oxford). 2005 Aug;44(8):1026-31.
- 180. Bennett AN, Wong M, Zain A, et al. Adalimumab-induced asthma. Rheumatology (Oxford). 2005 Sep;44(9):1199-200.
- 181. Benucci M, Li GF, Del Rosso A, et al. Adalimumab (anti-TNF-alpha) therapy to improve the clinical course of adult-onset Still's disease: the first case report. Clin Exp Rheumatol. 2005 Sep-Oct;23(5):733.

- 182. Benucci M, Li Gobbi F, Fossi F, et al. Druginduced lupus after treatment with infliximab in rheumatoid arthritis. J Clin Rheumatol. 2005 Feb;11(1):47-9.
- 183. Benucci M, Li Gobbi F, Saviola G, et al. Improved rheumatoid digital vasculitis in a patient treated with TNFalpha agent blocking (infliximab). Rheumatol Int. 2008 Oct;28(12):1253-5.
- 184. Benucci M, Manfredi M, Mecocci L. Effect of etanercept plus lamivudine in a patient with rheumatoid arthritis and viral hepatitis B. J Clin Rheumatol. 2008 Aug;14(4):245-6.
- 185. Benucci M, Saviola G, Baiardi P, et al. Antinucleosome antibodies as prediction factor of development of autoantibodies during therapy with three different TNFalpha blocking agents in rheumatoid arthritis. Clin Rheumatol. 2008 Jan;27(1):91-5.
- 186. Berard A, Solomon DH, Avorn J. Patterns of drug use in rheumatoid arthritis. J Rheumatol. 2000 Jul;27(7):1648-55.
- 187. Berg L, Lampa J, Rogberg S, et al. Increased peripheral T cell reactivity to microbial antigens and collagen type II in rheumatoid arthritis after treatment with soluble TNFalpha receptors. Ann Rheum Dis. 2001 Feb;60(2):133-9.
- 188. Berger A, Edelsberg J, Li TT, et al. Dose intensification with infliximab in patients with rheumatoid arthritis. Ann Pharmacother. 2005 Dec;39(12):2021-5.
- 189. Bergman J, Schjott J. Hepatitis caused by Lotus-f3? Basic Clin Pharmacol Toxicol. 2009 May;104(5):414-6.
- 190. Bergstrom L, Yocum DE, Ampel NM, et al. Increased risk of coccidioidomycosis in patients treated with tumor necrosis factor alpha antagonists. Arthritis Rheum. 2004 Jun;50(6):1959-66.
- 191. Berkun Y, Abou Atta I, Rubinow A, et al. 2756GG genotype of methionine synthase reductase gene is more prevalent in rheumatoid arthritis patients treated with methotrexate and is associated with

- methotrexate-induced nodulosis. J Rheumatol. 2007 Aug;34(8):1664-9.
- 192. Bernatsky S, Ehrmann Feldman D.
 Discontinuation of methotrexate therapy in
 older patients with newly diagnosed
 rheumatoid arthritis: analysis of
 administrative health databases in Quebec,
 Canada. Drugs Aging. 2008;25(10):879-84.
- 193. Bernatsky S, Hudson M, Suissa S. Antirheumatic drug use and risk of serious infections in rheumatoid arthritis. Rheumatology (Oxford) 2007;46(7):1157-60.
- 194. Berookhim B, Fischer HD, Weinberg JM.
 Treatment of recalcitrant pemphigus
 vulgaris with the tumor necrosis factor alpha
 antagonist etanercept. Cutis. 2004
 Oct;74(4):245-7.
- 195. Berthelot C, Cather J, Jones D, et al. Atypical CD8+ cutaneous T-cell lymphoma after immunomodulatory therapy. Clin Lymphoma Myeloma. 2006 Jan;6(4):329-32.
- 196. Berthelot JM, De Bandt M, Goupille P, et al. Exposition to anti-TNF drugs during pregnancy: outcome of 15 cases and review of the literature. Joint Bone Spine. 2009 Jan;76(1):28-34.
- 197. Berthelot JM, Glemarec J, Maugars Y, et al. Lethal medium-vessel panarteritis mimicking deep sepsis following etanercept and minocycline therapy in a patient with severe rheumatoid arthritis. Rheumatology (Oxford). 2002 Jun;41(6):703-5.
- 198. Berthelot JM, Varin S, Cormier G, et al. 25 mg etanercept once weekly in rheumatoid arthritis and spondylarthropathy. Joint Bone Spine. 2007 Mar;74(2):144-7.
- 199. Bertoli AM, Strusberg I, Baravalle M, et al. Rate and causes of infliximab discontinuation in patients with rheumatoid arthritis in a private clinical practice. J Clin Rheumatol. 2008 Dec;14(6):313-7.
- 200. Beuthien W, Mellinghoff HU, von Kempis J. Skin reaction to adalimumab. Arthritis Rheum. 2004 May;50(5):1690-2.

- 201. Beyeler C, Frey BM, Bird HA. Urinary 6 beta-hydroxycortisol excretion in rheumatoid arthritis. Br J Rheumatol. 1997 Jan;36(1):54-8.
- 202. Bhagat S, Ostor AJ. Diagnosing joint pain in the older people. Practitioner. 2010 Jan;254(1725):17-21, 2.
- 203. Bibbo C, Goldberg JW. Infectious and healing complications after elective orthopaedic foot and ankle surgery during tumor necrosis factor-alpha inhibition therapy. Foot Ankle Int. 2004 May;25(5):331-5.
- 204. Bicer A, Tursen U, Cimen OB, et al. Prevalence of dermatophytosis in patients with rheumatoid arthritis. Rheumatol Int. 2003 Jan;23(1):37-40.
- 205. Biester S, Deuter C, Michels H, et al. Adalimumab in the therapy of uveitis in childhood. Br J Ophthalmol. 2007 Mar;91(3):319-24.
- 206. Bilsborough W, Keen H, Taylor A, et al. Anti-tumour necrosis factor-alpha therapy over conventional therapy improves endothelial function in adults with rheumatoid arthritis. Rheumatol Int. 2006 Oct;26(12):1125-31.
- 207. Biro T, Griger Z, Kiss E, et al. Abnormal cell-specific expressions of certain protein kinase C isoenzymes in peripheral mononuclear cells of patients with systemic lupus erythematosus: effect of corticosteroid application. Scand J Immunol. 2004 Oct;60(4):421-8.
- 208. Biyikoglu B, Buduneli N, Kardesler L, et al. Evaluation of t-PA, PAI-2, IL-1beta and PGE(2) in gingival crevicular fluid of rheumatoid arthritis patients with periodontal disease. J Clin Periodontol. 2006 Sep;33(9):605-11.
- 209. Biyikoglu B, Buduneli N, Kardesler L, et al. Gingival crevicular fluid MMP-8 and -13 and TIMP-1 levels in patients with rheumatoid arthritis and inflammatory periodontal disease. J Periodontol. 2009 Aug;80(8):1307-14.

- 210. Blackman MR, Muniyappa R, Wilson M, et al. Diurnal secretion of growth hormone, cortisol, and dehydroepiandrosterone in preand perimenopausal women with active rheumatoid arthritis: a pilot case-control study. Arthritis Res Ther. 2007:9(4):R73.
- 211. Blanco R, Martinez-Taboada VM, Rodriguez-Valverde V, et al. Successful therapy with danazol in refractory autoimmune thrombocytopenia associated with rheumatic diseases. Br J Rheumatol. 1997 Oct;36(10):1095-9.
- 212. Bleumink GS, ter Borg EJ, Ramselaar CG, et al. Etanercept-induced subacute cutaneous lupus erythematosus. Rheumatology (Oxford). 2001 Nov;40(11):1317-9.
- 213. Blom M, Kievit W, Fransen J, et al. The reason for discontinuation of the first tumor necrosis factor (TNF) blocking agent does not influence the effect of a second TNF blocking agent in patients with rheumatoid arthritis. J Rheumatol. 2009
 Oct;36(10):2171-7.
- 214. Blom M, Kievit W, Kuper HH, et al. Frequency and effectiveness of dose increase of adalimumab, etanercept, and infliximab in daily clinical practice. Arthritis Care Res (Hoboken). 2010 Sep;62(9):1335-41.
- 215. Blumberg SN, Fox DA. Rheumatoid arthritis: guidelines for emerging therapies. Am J Manag Care. 2001 Jun;7(6):617-26.
- 216. Blyth T, Hunter JA, Stirling A. Pain relief in the rheumatoid knee after steroid injection. A single-blind comparison of hydrocortisone succinate, and triamcinolone acetonide or hexacetonide. Br J Rheumatol. 1994 May;33(5):461-3.
- 217. Boatright MD, Wang BW. Clinical infection with Strongyloides sterocoralis following etanercept use for rheumatoid arthritis.

 Arthritis Rheum. 2005 Apr;52(4):1336-7.
- 218. Bobbio-Pallavicini F, Alpini C, Caporali R, et al. Autoantibody profile in rheumatoid arthritis during long-term infliximab treatment. Arthritis Res Ther. 2004;6(3):R264-72.

- 219. Bobbio-Pallavicini F, Caporali R, Alpini C, et al. High IgA rheumatoid factor levels are associated with poor clinical response to tumour necrosis factor alpha inhibitors in rheumatoid arthritis. Ann Rheum Dis. 2007 Mar;66(3):302-7.
- 220. Bodur H, Ataman S, Akbulut L, et al. Characteristics and medical management of patients with rheumatoid arthritis and ankylosing spondylitis. Clin Rheumatol. 2008 Sep;27(9):1119-25.
- 221. Bodur H, Seckin U, Eser F, et al.
 Coexistence of familial Mediterranean fever
 and psoriasis in a patient with seronegative
 spondyloarthropathy. Rheumatol Int. 2008
 Nov;29(1):107-10.
- 222. Boeger CA, Wittwer H, Schattenkirchner M, et al. Treatment of ankylosing spondylitis with infliximab. Ann Rheum Dis. 2001 Dec;60(12):1159-60.
- 223. Boers M, Verhoeven AC, Markusse HM, et al. Randomised comparison of combined step-down prednisolone, methotrexate and sulphasalazine with sulphasalazine alone in early rheumatoid arthritis. Lancet. 1997 Aug 2;350(9074):309-18.
- 224. Boesen M, Boesen L, Jensen KE, et al.
 Clinical outcome and imaging changes after
 intraarticular (IA) application of etanercept
 or methylprednisolone in rheumatoid
 arthritis: magnetic resonance imaging and
 ultrasound-Doppler show no effect of IA
 injections in the wrist after 4 weeks. J
 Rheumatol. 2008 Apr;35(4):584-91.
- 225. Boesen M, Jensen KE, Torp-Pedersen S, et al. Intra-articular distribution pattern after ultrasound-guided injections in wrist joints of patients with rheumatoid arthritis. Eur J Radiol. 2009 Feb;69(2):331-8.
- 226. Boey O, Van Hooland S, Woestenburg A, et al. Methotrexate should not be used for patients with end-stage kidney disease. Acta Clin Belg. 2006 Jul-Aug;61(4):166-9.
- 227. Bogoch E, Ouellette G, Hastings D. Failure of internal fixation of displaced femoral neck fractures in rheumatoid patients. J Bone Joint Surg Br. 1991 Jan;73(1):7-10.

- 228. Bogoch ER, Ouellette G, Hastings DE. Intertrochanteric fractures of the femur in rheumatoid arthritis patients. Clin Orthop Relat Res. 1993 Sep(294):181-6.
- 229. Bohanec Grabar P, Grabnar I, Rozman B, et al. Investigation of the influence of CYP1A2 and CYP2C19 genetic polymorphism on 2-Cyano-3-hydroxy-N-[4-(trifluoromethyl)phenyl]-2-butenamide (A77 1726) pharmacokinetics in leflunomidetreated patients with rheumatoid arthritis. Drug Metab Dispos. 2009 Oct;37(10):2061-8.
- 230. Bohanec Grabar P, Logar D, Lestan B, et al. Genetic determinants of methotrexate toxicity in rheumatoid arthritis patients: a study of polymorphisms affecting methotrexate transport and folate metabolism. Eur J Clin Pharmacol. 2008 Nov;64(11):1057-68.
- 231. Bohanec Grabar P, Rozman B, Tomsic M, et al. Genetic polymorphism of CYP1A2 and the toxicity of leflunomide treatment in rheumatoid arthritis patients. Eur J Clin Pharmacol. 2008 Sep;64(9):871-6.
- 232. Bolla G, Disdier P, Harle JR, et al.
 Concurrent acute megaloblastic anaemia and pneumonitis: a severe side-effect of low-dose methotrexate therapy during rheumatoid arthritis. Clin Rheumatol. 1993
 Dec;12(4):535-7.
- 233. Bollow M, Braun J, Taupitz M, et al. CT-guided intraarticular corticosteroid injection into the sacroiliac joints in patients with spondyloarthropathy: indication and follow-up with contrast-enhanced MRI. J Comput Assist Tomogr. 1996 Jul-Aug;20(4):512-21.
- 234. Bologna C, Jorgensen C, Sany J.
 Association of methotrexate and corticosteroids in the treatment of patients with rheumatoid arthritis. Clin Exp Rheumatol. 1996 Jul-Aug;14(4):401-6.
- 235. Bolstad AI, Eiken HG, Rosenlund B, et al. Increased salivary gland tissue expression of Fas, Fas ligand, cytotoxic T lymphocyte-associated antigen 4, and programmed cell death 1 in primary Sjogren's syndrome. Arthritis Rheum. 2003 Jan;48(1):174-85.

- 236. Bombardieri S, Ruiz AA, Fardellone P, et al. Effectiveness of adalimumab for rheumatoid arthritis in patients with a history of TNF-antagonist therapy in clinical practice. Rheumatology (Oxford). 2007
 Jul;46(7):1191-9.
- 237. Bongartz T, Harle P, Friedrich S, et al. Successful treatment of psoriatic onychopachydermo periostitis (POPP) with adalimumab. Arthritis Rheum. 2005 Jan;52(1):280-2.
- 238. Bongiorno MR, Pistone G, Doukaki S, et al. Adalimumab for treatment of moderate to severe psoriasis and psoriatic arthritis.

 Dermatol Ther. 2008 Oct;21 Suppl 2:S15-20
- 239. Book C, Karlsson M, Akesson K, et al. Disease activity and disability but probably not glucocorticoid treatment predicts loss in bone mineral density in women with early rheumatoid arthritis. Scand J Rheumatol. 2008 Jul-Aug;37(4):248-54.
- 240. Book C, Karlsson MK, Akesson K, et al. Early rheumatoid arthritis and body composition. Rheumatology (Oxford). 2009 Sep;48(9):1128-32.
- Book C, Saxne T, Jacobsson LT. Prediction of mortality in rheumatoid arthritis based on disease activity markers. J Rheumatol. 2005 Mar;32(3):430-4.
- 242. Boonen A, van der Heijde D, Severens JL, et al. Markov model into the cost-utility over five years of etanercept and infliximab compared with usual care in patients with active ankylosing spondylitis. Ann Rheum Dis. 2006 Feb;65(2):201-8.
- 243. Borowski LC, Lopes RP, Gonzalez TP, et al. Is steroid resistance related to multidrug resistance-I (MDR-I) in rheumatoid arthritis? Int Immunopharmacol. 2007 Jun;7(6):836-44.
- 244. Borras-Blasco J, Gracia-Perez A, Nunez-Cornejo C, et al. Exacerbation of psoriatic skin lesions in a patient with psoriatic arthritis receiving adalimumab. J Clin Pharm Ther. 2008 Jun;33(3):321-5.

- 245. Borras-Blasco J, Gracia-Perez A, Rosique-Robles JD, et al. Urticaria due to etanercept in a patient with psoriatic arthritis. South Med J. 2009 Mar;102(3):304-5.
- 246. Borras-Blasco J, Nunez-Cornejo C, Gracia-Perez A, et al. Parapharyngeal abscess in a patient receiving etanercept. Ann Pharmacother. 2007 Feb;41(2):341-4.
- 247. Bos WH, Bartelds GM, Vis M, et al. Preferential decrease in IgG4 anticitrullinated protein antibodies during treatment with tumour necrosis factor blocking agents in patients with rheumatoid arthritis. Ann Rheum Dis. 2009

 Apr;68(4):558-63.
- 248. Bos WH, Bartelds GM, Wolbink GJ, et al. Differential response of the rheumatoid factor and anticitrullinated protein antibodies during adalimumab treatment in patients with rheumatoid arthritis. J Rheumatol. 2008 Oct;35(10):1972-7.
- 249. Boscarino JA. Posttraumatic stress disorder and physical illness: results from clinical and epidemiologic studies. Ann N Y Acad Sci. 2004 Dec;1032:141-53.
- 250. Bosello S, Santoliquido A, Zoli A, et al. TNF-alpha blockade induces a reversible but transient effect on endothelial dysfunction in patients with long-standing severe rheumatoid arthritis. Clin Rheumatol. 2008 Jul;27(7):833-9.
- 251. Boss B, Neeck G, Engelhardt B, et al. Influence of corticosteroids on neutrophils, lymphocytes, their subsets, and T-cell activity markers in patients with active rheumatoid arthritis, compared to healthy controls. Ann N Y Acad Sci. 1999 Jun 22;876:198-200.
- 252. Bostrom EA, d'Elia HF, Dahlgren U, et al. Salivary resistin reflects local inflammation in Sjogren's syndrome. J Rheumatol. 2008 Oct;35(10):2005-11.
- 253. Botez SA, Herrmann DN. Prolonged remission of a demyelinating neuropathy in a patient with lymphoma and Sjogren's syndrome after Rituximab therapy. J Clin Neuromuscul Dis. 2010 Mar;11(3):127-31.

- 254. Bourgeois E, Caulier MT, Rose C, et al. Role of splenectomy in the treatment of myelodysplastic syndromes with peripheral thrombocytopenia: a report on six cases. Leukemia. 2001 Jun;15(6):950-3.
- 255. Boveri E, Castagnola C, Castello A, et al. Aberrant phenotype of plasmacytoid monocytes in acute myeloid leukemia. Am J Hematol. 2008 May;83(5):428-9.
- 256. Bowie VL, Snella KA, Gopalachar AS, et al. Listeria meningitis associated with infliximab. Ann Pharmacother. 2004 Jan;38(1):58-61.
- 257. Bozkurt FY, Berker E, Akkus S, et al. Relationship between interleukin-6 levels in gingival crevicular fluid and periodontal status in patients with rheumatoid arthritis and adult periodontitis. J Periodontol. 2000 Nov;71(11):1756-60.
- 258. Bramlage CP, Kaps C, Ungethum U, et al. Modulatory effects of inflammation and therapy on GDF-5 expression in rheumatoid arthritis synovium. Scand J Rheumatol. 2008 Nov-Dec;37(6):401-9.
- 259. Brandt J, Haibel H, Cornely D, et al. Successful treatment of active ankylosing spondylitis with the anti-tumor necrosis factor alpha monoclonal antibody infliximab. Arthritis Rheum. 2000 Jun;43(6):1346-52.
- 260. Brandt J, Khariouzov A, Listing J, et al. Sixmonth results of a double-blind, placebocontrolled trial of etanercept treatment in patients with active ankylosing spondylitis. Arthritis Rheum. 2003 Jun;48(6):1667-75.
- 261. Brandt J, Listing J, Haibel H, et al. Long-term efficacy and safety of etanercept after readministration in patients with active ankylosing spondylitis. Rheumatology (Oxford). 2005 Mar;44(3):342-8.
- 262. Brandt J, Listing J, Sieper J, et al.
 Development and preselection of criteria for short term improvement after anti-TNF alpha treatment in ankylosing spondylitis.
 Ann Rheum Dis. 2004 Nov;63(11):1438-44.

- 263. Brassard P, Kezouh A, Suissa S. Antirheumatic drugs and the risk of tuberculosis. Clin Infect Dis 2006;43(6):717-22.
- 264. Brassard P, Lowe AM, Bernatsky S, et al. Rheumatoid arthritis, its treatments, and the risk of tuberculosis in Quebec, Canada. Arthritis Rheum 2009;61(3):300-4.
- 265. Braun J, Baraliakos X, Brandt J, et al. Persistent clinical response to the anti-TNF-alpha antibody infliximab in patients with ankylosing spondylitis over 3 years. Rheumatology (Oxford). 2005

 May;44(5):670-6.
- 266. Braun J, Baraliakos X, Golder W, et al. Magnetic resonance imaging examinations of the spine in patients with ankylosing spondylitis, before and after successful therapy with infliximab: evaluation of a new scoring system. Arthritis Rheum. 2003 Apr;48(4):1126-36.
- 267. Braun J, Bollow M, Seyrekbasan F, et al. Computed tomography guided corticosteroid injection of the sacroiliac joint in patients with spondyloarthropathy with sacroiliitis: clinical outcome and followup by dynamic magnetic resonance imaging. J Rheumatol. 1996 Apr;23(4):659-64.
- 268. Braun J, Brandt J, Listing J, et al. Long-term efficacy and safety of infliximab in the treatment of ankylosing spondylitis: an open, observational, extension study of a three-month, randomized, placebocontrolled trial. Arthritis Rheum. 2003 Aug;48(8):2224-33.
- 269. Braun J, Brandt J, Listing J, et al. Two year maintenance of efficacy and safety of infliximab in the treatment of ankylosing spondylitis. Ann Rheum Dis. 2005 Feb;64(2):229-34.
- 270. Braun J, Brandt J, Listing J, et al. Treatment of active ankylosing spondylitis with infliximab: a randomised controlled multicentre trial. Lancet. 2002 Apr 6;359(9313):1187-93.
- 271. Braun J, Kastner P, Flaxenberg P, et al. Comparison of the clinical efficacy and safety of subcutaneous versus oral

- administration of methotrexate in patients with active rheumatoid arthritis: results of a six-month, multicenter, randomized, double-blind, controlled, phase IV trial. Arthritis Rheum. 2008 Jan;58(1):73-81.
- 272. Braun J, Landewe R, Hermann KG, et al. Major reduction in spinal inflammation in patients with ankylosing spondylitis after treatment with infliximab: results of a multicenter, randomized, double-blind, placebo-controlled magnetic resonance imaging study. Arthritis Rheum. 2006 May;54(5):1646-52.
- 273. Braun J, Sieper J, Breban M, et al. Antitumour necrosis factor alpha therapy for ankylosing spondylitis: international experience. Ann Rheum Dis. 2002 Dec;61 Suppl 3:iii51-60.
- 274. Braun J, van der Heijde D. Imaging and scoring in ankylosing spondylitis. Best Pract Res Clin Rheumatol. 2002 Sep;16(4):573-604.
- 275. Braun-Moscovici Y, Markovits D, Rozin A, et al. Anti-tumor necrosis factor therapy: 6 year experience of a single center in northern Israel and possible impact of health policy on results. Isr Med Assoc J. 2008 Apr;10(4):277-81.
- 276. Bravo Vergel Y, Hawkins NS, Claxton K, et al. The cost-effectiveness of etanercept and infliximab for the treatment of patients with psoriatic arthritis. Rheumatology (Oxford). 2007 Nov;46(11):1729-35.
- 277. Breban M, Vignon E, Claudepierre P, et al. Efficacy of infliximab in refractory ankylosing spondylitis: results of a sixmonth open-label study. Rheumatology (Oxford). 2002 Nov;41(11):1280-5.
- 278. Breedveld F, Agarwal S, Yin M, et al. Rituximab pharmacokinetics in patients with rheumatoid arthritis: B-cell levels do not correlate with clinical response. J Clin Pharmacol. 2007 Sep;47(9):1119-28.
- 279. Breedveld FC, Emery P, Keystone E, et al. Infliximab in active early rheumatoid arthritis. Ann Rheum Dis 2004;63(2):149-55.

- 280. Breedveld FC, Weisman MH, Kavanaugh AF, et al. The PREMIER study: A multicenter, randomized, double-blind clinical trial of combination therapy with adalimumab plus methotrexate versus methotrexate alone or adalimumab alone in patients with early, aggressive rheumatoid arthritis who had not had previous methotrexate treatment. Arthritis Rheum. 2006 Jan;54(1):26-37.
- 281. Breglia MD, Carter JD. Atypical insufficiency fracture of the tibia associated with long-term bisphosphonate therapy. J Clin Rheumatol. 2010 Mar;16(2):76-8.
- 282. Bremner R, Simpson E, White CR, et al. Palisaded neutrophilic and granulomatous dermatitis: an unusual cutaneous manifestation of immune-mediated disorders. Semin Arthritis Rheum. 2004 Dec;34(3):610-6.
- 283. Brennan A, Bansback N, Nixon R, et al. Modelling the cost effectiveness of TNF-alpha antagonists in the management of rheumatoid arthritis: results from the British Society for Rheumatology Biologics Registry. Rheumatology (Oxford). 2007 Aug;46(8):1345-54.
- 284. Brennan MT, Sankar V, Leakan RA, et al. Sex steroid hormones in primary Sjogren's syndrome. J Rheumatol. 2003
 Jun;30(6):1267-71.
- 285. Bresnihan B. Treating early rheumatoid arthritis in the younger patient. J Rheumatol Suppl. 2001 Jun;62:4-9.
- 286. Bresnihan B, Alvaro-Gracia JM, Cobby M, et al. Treatment of rheumatoid arthritis with recombinant human interleukin-1 receptor antagonist. Arthritis Rheum 1998;41(12):2196-204.
- 287. Bresnihan B, Newmark R, Robbins S, et al. Effects of anakinra monotherapy on joint damage in patients with rheumatoid arthritis. Extension of a 24-week randomized, placebo-controlled trial. J Rheumatol. 2004 Jun;31(6):1103-11.
- 288. Brocq O, Albert C, Roux C, et al.
 Adalimumab in rheumatoid arthritis after failed infliximab and/or etanercept therapy:

- experience with 18 patients. Joint Bone Spine. 2004 Nov;71(6):601-3.
- 289. Brocq O, Roux CH, Albert C, et al. TNFalpha antagonist continuation rates in 442 patients with inflammatory joint disease. Joint Bone Spine 2007;74(2):148-54.
- 290. Brooks H, Taylor HG, Nichol FE. The three week sulphasalazine syndrome. Clin Rheumatol. 1992 Dec;11(4):566-8.
- 291. Brophy RH, MacKenzie CR, Gamradt SC, et al. The diagnosis and management of psoriatic arthritis in a professional football player presenting with a knee effusion: a case report. Clin J Sport Med. 2008 Jul;18(4):369-71.
- 292. Broussais F, Kawashima M, Marotte H, et al. Chronic myeloid leukaemia and tuberculosis in a patient with rheumatoid arthritis treated with infliximab. Ann Rheum Dis. 2005 Mar;64(3):509-10.
- 293. Broussard JS, Jr. Derangement, osteoarthritis, and rheumatoid arthritis of the temporomandibular joint: implications, diagnosis, and management. Dent Clin North Am. 2005 Apr;49(2):327-42.
- 294. Brown A, Grubbs P, Mongey AB. Infection of total hip prosthesis by Mycobacterium tuberculosis and Mycobacterium chelonae in a patient with rheumatoid arthritis. Clin Rheumatol. 2008 Apr;27(4):543-5.
- 295. Brown ES, Frol A, Bobadilla L, et al. Effect of lamotrigine on mood and cognition in patients receiving chronic exogenous corticosteroids. Psychosomatics. 2003 May-Jun;44(3):204-8.
- 296. Brown ES, Woolston DJ, Frol AB. Amygdala volume in patients receiving chronic corticosteroid therapy. Biol Psychiatry. 2008 Apr 1;63(7):705-9.
- 297. Brown GT, Wright FV, Lang BA, et al.
 Clinical responsiveness of self-report
 functional assessment measures for children
 with juvenile idiopathic arthritis undergoing
 intraarticular corticosteroid injections.

- Arthritis Rheum. 2005 Dec 15;53(6):897-904.
- 298. Brown SL, Greene MH, Gershon SK, et al. Tumor necrosis factor antagonist therapy and lymphoma development: twenty-six cases reported to the Food and Drug Administration. Arthritis Rheum. 2002 Dec;46(12):3151-8.
- 299. Bruckle W, Eisenhut C, Goebel FD. Cerebral involvement in adult onset Still's disease. Clin Rheumatol. 1992
 Jun;11(2):276-9.
- 300. Brunasso AM, Massone C.
 Thrombocytopenia associated with the use of anti-tumor necrosis factor-alpha agents for psoriasis. J Am Acad Dermatol. 2009 May;60(5):781-5.
- 301. Bruns A, Nicaise-Roland P, Hayem G, et al. Prospective cohort study of effects of infliximab on rheumatoid factor, anti-cyclic citrullinated peptide antibodies and antinuclear antibodies in patients with long-standing rheumatoid arthritis. Joint Bone Spine. 2009 May;76(3):248-53.
- 302. Bruns H, Meinken C, Schauenberg P, et al. Anti-TNF immunotherapy reduces CD8+ T cell-mediated antimicrobial activity against Mycobacterium tuberculosis in humans. J Clin Invest. 2009 May;119(5):1167-77.
- 303. Bruyn GA, Tate G, Caeiro F, et al.
 Everolimus in patients with rheumatoid arthritis receiving concomitant methotrexate: a 3-month, double-blind, randomised, placebo-controlled, parallel-group, proof-of-concept study. Ann Rheum Dis. 2008 Aug;67(8):1090-5.
- 304. Bryl E, Vallejo AN, Matteson EL, et al. Modulation of CD28 expression with antitumor necrosis factor alpha therapy in rheumatoid arthritis. Arthritis Rheum. 2005 Oct;52(10):2996-3003.
- 305. Buccoliero G, Lonero G, Romanelli C, et al. Varicella zoster virus encephalitis during treatment with anti-tumor necrosis factoralpha agent in a psoriatic arthritis patient. New Microbiol. 2010 Jul;33(3):271-4.

- 306. Buccoliero R, Gambelli S, Sicurelli F, et al. Leukoencephalopathy as a rare complication of hepatitis C infection. Neurol Sci. 2006 Nov;27(5):360-3.
- 307. Buch MH, Bingham SJ, Bryer D, et al. Long-term infliximab treatment in rheumatoid arthritis: subsequent outcome of initial responders. Rheumatology (Oxford). 2007 Jul;46(7):1153-6.
- 308. Buch MH, Bingham SJ, Seto Y, et al. Lack of response to anakinra in rheumatoid arthritis following failure of tumor necrosis factor alpha blockade. Arthritis Rheum. 2004 Mar;50(3):725-8.
- 309. Buch MH, Boyle DL, Rosengren S, et al. Mode of action of abatacept in rheumatoid arthritis patients having failed tumour necrosis factor blockade: a histological, gene expression and dynamic magnetic resonance imaging pilot study. Ann Rheum Dis. 2009 Jul;68(7):1220-7.
- 310. Buch MH, Conaghan PG, Quinn MA, et al. True infliximab resistance in rheumatoid arthritis: a role for lymphotoxin alpha? Ann Rheum Dis. 2004 Oct;63(10):1344-6.
- 311. Buch MH, Reece RJ, Quinn MA, et al. The value of synovial cytokine expression in predicting the clinical response to TNF antagonist therapy (infliximab). Rheumatology (Oxford). 2008
 Oct;47(10):1469-75.
- 312. Buch MH, Seto Y, Bingham SJ, et al. Creactive protein as a predictor of infliximab treatment outcome in patients with rheumatoid arthritis: defining subtypes of nonresponse and subsequent response to etanercept. Arthritis Rheum. 2005

 Jan;52(1):42-8.
- 313. Buchbinder R, Barber M, Heuzenroeder L, et al. Incidence of melanoma and other malignancies among rheumatoid arthritis patients treated with methotrexate. Arthritis Rheum. 2008 Jun 15;59(6):794-9.
- 314. Buchs N, Silvestri T, di Giovine FS, et al. IL-4 VNTR gene polymorphism in chronic polyarthritis. The rare allele is associated with protection against destruction.

- Rheumatology (Oxford). 2000 Oct;39(10):1126-31.
- 315. Buckland GT, 3rd, Carlson JA, Meyer DR. Persistent periorbital and facial lymphedema associated with Group A beta-hemolytic streptococcal infection (erysipelas). Ophthal Plast Reconstr Surg. 2007 Mar-Apr;23(2):161-3.
- 316. Buckley LM, Leib ES, Cartularo KS, et al. Effects of low dose corticosteroids on the bone mineral density of patients with rheumatoid arthritis. J Rheumatol. 1995 Jun;22(6):1055-9.
- 317. Buckley LM, Leib ES, Cartularo KS, et al. Calcium and vitamin D3 supplementation prevents bone loss in the spine secondary to low-dose corticosteroids in patients with rheumatoid arthritis. A randomized, double-blind, placebo-controlled trial. Ann Intern Med. 1996 Dec 15;125(12):961-8.
- 318. Buckley LM, Leib ES, Cartularo KS, et al. Effects of low dose methotrexate on the bone mineral density of patients with rheumatoid arthritis. J Rheumatol. 1997 Aug;24(8):1489-94.
- 319. Buda-Okreglak EM, Drabick JJ, Delaney NR. Proinflammatory syndrome mimicking acute rheumatoid arthritis in a patient with Waldenstrom's macroglobulinemia treated with rituximab. Ann Hematol. 2004 Feb;83(2):117-9.
- 320. Bunescu A, Seideman P, Lenkei R, et al. Enhanced Fcgamma receptor I, alphaMbeta2 integrin receptor expression by monocytes and neutrophils in rheumatoid arthritis: interaction with platelets. J Rheumatol. 2004 Dec;31(12):2347-55.
- 321. Burge DJ, Bookbinder SA, Kivitz AJ, et al. Pharmacokinetic and pharmacodynamic properties of TRU-015, a CD20-directed small modular immunopharmaceutical protein therapeutic, in patients with rheumatoid arthritis: a Phase I, open-label, dose-escalation clinical study. Clin Ther. 2008 Oct;30(10):1806-16.
- 322. Burgos RA, Hancke JL, Bertoglio JC, et al. Efficacy of an Andrographis paniculata composition for the relief of rheumatoid

- arthritis symptoms: a prospective randomized placebo-controlled trial. Clin Rheumatol. 2009 Aug;28(8):931-46.
- 323. Burmester GR, Ferraccioli G, Flipo RM, et al. Clinical remission and/or minimal disease activity in patients receiving adalimumab treatment in a multinational, open-label, twelve-week study. Arthritis Rheum. 2008 Jan 15;59(1):32-41.
- 324. Burmester GR, Mariette X, Montecucco C, et al. Adalimumab alone and in combination with disease-modifying antirheumatic drugs for the treatment of rheumatoid arthritis in clinical practice: the Research in Active Rheumatoid Arthritis (ReAct) trial. Ann Rheum Dis 2007;66(6):732-9.
- 325. Burnham JM, Shults J, Dubner SE, et al. Bone density, structure, and strength in juvenile idiopathic arthritis: importance of disease severity and muscle deficits.

 Arthritis Rheum. 2008 Aug;58(8):2518-27.
- 326. Buttgereit F, Doering G, Schaeffler A, et al. Efficacy of modified-release versus standard prednisone to reduce duration of morning stiffness of the joints in rheumatoid arthritis (CAPRA-1): a double-blind, randomised controlled trial. Lancet. 2008 Jan 19;371(9608):205-14.
- 327. Buttgereit F, Doering G, Schaeffler A, et al. Targeting pathophysiological rhythms: prednisone chronotherapy shows sustained efficacy in rheumatoid arthritis. Ann Rheum Dis. 2010 Jul;69(7):1275-80.
- 328. Caballol Pons N, Montala N, Valverde J, et al. Isolated cerebral vasculitis associated with rheumatoid arthritis. Joint Bone Spine. 2010 Jul;77(4):361-3.
- 329. Cairns AP, Duncan MK, Hinder AE, et al. New onset systemic lupus erythematosus in a patient receiving etanercept for rheumatoid arthritis. Ann Rheum Dis. 2002
 Nov;61(11):1031-2.
- 330. Cairns AP, Taggart AJ. Anti-tumour necrosis factor therapy for severe inflammatory arthritis: two years of experience in Northern Ireland. Ulster Med J. 2002 Nov;71(2):101-5.

- 331. Calabrese LH. Rheumatoid arthritis and primary care: the case for early diagnosis and treatment. J Am Osteopath Assoc. 1999 Jun;99(6):313-21.
- 332. Calin A, Dijkmans BA, Emery P, et al.
 Outcomes of a multicentre randomised
 clinical trial of etanercept to treat ankylosing
 spondylitis. Ann Rheum Dis. 2004
 Dec;63(12):1594-600.
- 333. Callaly EL, FitzGerald O, Rogers S. Hydroxychloroquine-associated, photo-induced toxic epidermal necrolysis. Clin Exp Dermatol. 2008 Aug;33(5):572-4.
- 334. Cambridge G, Leandro MJ, Edwards JC, et al. Serologic changes following B lymphocyte depletion therapy for rheumatoid arthritis. Arthritis Rheum. 2003 Aug;48(8):2146-54.
- 335. Cambridge G, Stohl W, Leandro MJ, et al. Circulating levels of B lymphocyte stimulator in patients with rheumatoid arthritis following rituximab treatment: relationships with B cell depletion, circulating antibodies, and clinical relapse. Arthritis Rheum. 2006 Mar;54(3):723-32.
- 336. Campion GV, Lebsack ME, Lookabaugh J, et al. Dose-range and dose-frequency study of recombinant human interleukin-1 receptor antagonist in patients with rheumatoid arthritis. The IL-1Ra Arthritis Study Group. Arthritis Rheum. 1996 Jul;39(7):1092-101.
- 337. Campione E, Mazzotta A, Paterno EJ, et al. Effect of calcipotriol on etanercept partial responder psoriasis vulgaris and psoriatic arthritis patients. Acta Derm Venereol. 2009;89(3):288-91.
- 338. Cankaya H, Alpoz E, Karabulut G, et al. Effects of hydroxychloroquine on salivary flow rates and oral complaints of Sjogren patients: a prospective sample study. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 2010 Jul;110(1):62-7.
- 339. Cannon GW, Holden WL, Juhaeri J, et al. Adverse events with disease modifying antirheumatic drugs (DMARD): a cohort study of leflunomide compared with other DMARD. J Rheumatol. 2004 Oct;31(10):1906-11.

- 340. Cansu DU, Kalifoglu T, Korkmaz C. Short-term course of chronic hepatitis B and C under treatment with etanercept associated with different disease modifying antirheumatic drugs without antiviral prophylaxis. J Rheumatol. 2008

 Mar;35(3):421-4.
- 341. Cantarini L, Tinazzi I, Biasi D, et al. Sulfasalazine-induced immune thrombocytopenia. Postgrad Med J. 2007 Jun;83(980):e1.
- 342. Cantini F, Niccoli L, Benucci M, et al. Switching from infliximab to once-weekly administration of 50 mg etanercept in resistant or intolerant patients with ankylosing spondylitis: results of a fifty-four-week study. Arthritis Rheum. 2006 Oct 15;55(5):812-6.
- 343. Cantini F, Niccoli L, Nannini C, et al. Frequency and duration of clinical remission in patients with peripheral psoriatic arthritis requiring second-line drugs. Rheumatology (Oxford) 2008;47(6):872-6.
- 344. Capell H. Longterm maintenance therapy with disease modifying antirheumatic drugs. J Rheumatol Suppl. 2002 Nov;66:38-43.
- 345. Capell HA, Madhok R, Hunter JA, et al. Lack of radiological and clinical benefit over two years of low dose prednisolone for rheumatoid arthritis: results of a randomised controlled trial. Ann Rheum Dis. 2004 Jul;63(7):797-803.
- 346. Capell HA, Murphy EA, Hunter JA. Rheumatoid arthritis: workload and outcome over 10 years. Q J Med. 1991 Jun;79(290):461-76.
- 347. Caplan L, Wolfe F, Russell AS, et al.
 Corticosteroid use in rheumatoid arthritis:
 prevalence, predictors, correlates, and
 outcomes. J Rheumatol. 2007
 Apr;34(4):696-705.
- 348. Capria A, De Nardo D, Baffetti FR, et al. Long-term anti-TNF-alpha treatments reverse the endothelial dysfunction in rheumatoid arthritis: the biological coherence between synovial and endothelial inflammation. Int J Immunopathol Pharmacol. 2010 Jan-Mar;23(1):255-62.

- 349. Capsoni F, Sarzi-Puttini P, Atzeni F, et al. Effect of adalimumab on neutrophil function in patients with rheumatoid arthritis. Arthritis Res Ther. 2005;7(2):R250-5.
- 350. Caramaschi P, Biasi D, Carletto A, et al. A case of adult onset Still's disease treated with infliximab. Clin Exp Rheumatol. 2002 Jan-Feb;20(1):113.
- 351. Caramaschi P, Biasi D, Carletto A, et al. Orbital myositis in a rheumatoid arthritis patient during etanercept treatment. Clin Exp Rheumatol. 2003 Jan-Feb;21(1):136-7.
- 352. Caramaschi P, Ruzzenente O, Pieropan S, et al. Determination of ANA specificity using multiplexed fluorescent microsphere immunoassay in patients with ANA positivity at high titres after infliximab treatment: preliminary results. Rheumatol Int. 2007 May;27(7):649-54.
- 353. Caramella C, Avouac J, Sogni P, et al. Association between rheumatoid arthritis and primary biliary cirrhosis. Joint Bone Spine. 2007 May;74(3):279-81.
- 354. Cardillo C, Schinzari F, Mores N, et al. Intravascular tumor necrosis factor alpha blockade reverses endothelial dysfunction in rheumatoid arthritis. Clin Pharmacol Ther. 2006 Sep;80(3):275-81.
- 355. Carloni A, Piciucchi S, Giannakakis K, et al. Diffuse alveolar hemorrhage after leflunomide therapy in a patient with rheumatoid arthritis. J Thorac Imaging. 2008 Feb;23(1):57-9.
- 356. Carlson E, Rothfield N. Etanercept-induced lupus-like syndrome in a patient with rheumatoid arthritis. Arthritis Rheum. 2003 Apr;48(4):1165-6; author reply 6.
- 357. Carmona L, Gomez-Reino JJ, Rodriguez-Valverde V, et al. Effectiveness of recommendations to prevent reactivation of latent tuberculosis infection in patients treated with tumor necrosis factor antagonists. Arthritis Rheum. 2005 Jun;52(6):1766-72.
- 358. Caroyer JM, Manto MU, Steinfeld SD. Severe sensory neuronopathy responsive to

- infliximab in primary Sjogren's syndrome. Neurology. 2002 Oct 8:59(7):1113-4.
- 359. Carrasco R, Smith JA, Lovell D. Biologic agents for the treatment of juvenile rheumatoid arthritis: current status. Paediatr Drugs. 2004;6(3):137-46.
- 360. Carreira PE, Gonzalez-Crespo MR, Ciruelo E, et al. Polymorphism of the interleukin-1 receptor antagonist gene: a factor in susceptibility to rheumatoid arthritis in a Spanish population. Arthritis Rheum. 2005 Oct;52(10):3015-9.
- 361. Carrera C, Mascaro JM, Jr., Moreno-Romero JA, et al. Pyoderma vegetans associated with severe psoriatic arthritis: good response to etanercept. Dermatology. 2007;214(1):77-81.
- 362. Carroll MB, Bond MI. Use of tumor necrosis factor-alpha inhibitors in patients with chronic hepatitis B infection. Semin Arthritis Rheum. 2008 Dec;38(3):208-17.
- 363. Carter JD, Gerard HC, Hudson AP.
 Psoriasiform lesions induced by tumour
 necrosis factor antagonists: a skin-deep
 medical conundrum. Ann Rheum Dis. 2008
 Aug;67(8):1181-3.
- 364. Carter JD, Valeriano J, Vasey FB. Tumor necrosis factor-alpha inhibition and VATER association: a causal relationship. J Rheumatol. 2006 May;33(5):1014-7.
- 365. Caselli RJ, Scheithauer BW, Bowles CA, et al. The treatable dementia of Sjogren's syndrome. Ann Neurol. 1991 Jul;30(1):98-101.
- 366. Caselli RJ, Scheithauer BW, O'Duffy JD, et al. Chronic inflammatory meningoencephalitis should not be mistaken for Alzheimer's disease. Mayo Clin Proc. 1993 Sep;68(9):846-53.
- 367. Cash JM, Crofford LJ, Gallucci WT, et al. Pituitary-adrenal axis responsiveness to ovine corticotropin releasing hormone in patients with rheumatoid arthritis treated with low dose prednisone. J Rheumatol. 1992 Nov;19(11):1692-6.

- 368. Casoli P, Tumiati B. Rheumatoid arthritis, corticosteroid therapy and Kaposi's sarcoma: a coincidence? A case and review of literature. Clin Rheumatol. 1992 Sep;11(3):432-5.
- 369. Caspi D, Elkayam O, Eisinger M, et al. Clinical significance of low titer anti-nuclear antibodies in early rheumatoid arthritis: implications on the presentation and long-term course of the disease. Rheumatol Int. 2001 Feb;20(2):43-7.
- 370. Cassano N, Galluccio A, De Simone C, et al. Influence of body mass index, comorbidities and prior systemic therapies on the response of psoriasis to adalimumab: an exploratory analysis from the APHRODITE data. J Biol Regul Homeost Agents. 2008 Oct-Dec;22(4):233-7.
- 371. Cassano N, Loconsole F, Amoruso A, et al. Infliximab monotherapy for refractory psoriasis: preliminary results. Int J Immunopathol Pharmacol. 2004 Sep-Dec;17(3):373-80.
- 372. Castagnetta LA, Carruba G, Granata OM, et al. Increased estrogen formation and estrogen to androgen ratio in the synovial fluid of patients with rheumatoid arthritis. J Rheumatol. 2003 Dec;30(12):2597-605.
- 373. Castaneda O, Nair MG. Controlled trial of methotrexate versus CH-1504 in the treatment of rheumatoid arthritis. J Rheumatol. 2006 May;33(5):862-4.
- 374. Catananti C, Mastropaolo S, Calabrese C, et al. A case of normal-pressure hydrocephalus associated with rheumatoid arthritis. Aging Clin Exp Res. 2010 Apr;22(2):189-91.
- 375. Catley D, Kaell AT, Kirschbaum C, et al. A naturalistic evaluation of cortisol secretion in persons with fibromyalgia and rheumatoid arthritis. Arthritis Care Res. 2000 Feb;13(1):51-61.
- 376. Catrina AI, af Klint E, Ernestam S, et al. Anti-tumor necrosis factor therapy increases synovial osteoprotegerin expression in rheumatoid arthritis. Arthritis Rheum. 2006 Jan;54(1):76-81.

- 377. Catrina AI, Lampa J, Ernestam S, et al. Anti-tumour necrosis factor (TNF)-alpha therapy (etanercept) down-regulates serum matrix metalloproteinase (MMP)-3 and MMP-1 in rheumatoid arthritis. Rheumatology (Oxford). 2002 May;41(5):484-9.
- 378. Catrina AI, Trollmo C, af Klint E, et al. Evidence that anti-tumor necrosis factor therapy with both etanercept and infliximab induces apoptosis in macrophages, but not lymphocytes, in rheumatoid arthritis joints: extended report. Arthritis Rheum. 2005 Jan;52(1):61-72.
- 379. Catrina AI, Ulfgren AK, Lindblad S, et al. Low levels of apoptosis and high FLIP expression in early rheumatoid arthritis synovium. Ann Rheum Dis. 2002 Oct;61(10):934-6.
- 380. Cattalini M, Maduskuie V, Fawcett PT, et al. Predicting duration of beneficial effect of joint injection among children with chronic arthritis by measuring biomarkers concentration in synovial fluid at the time of injection. Clin Exp Rheumatol. 2008 Nov-Dec;26(6):1153-60.
- 381. Cauli A, Yanni G, Panayi GS. Interleukin-1, interleukin-1 receptor antagonist and macrophage populations in rheumatoid arthritis synovial membrane. Br J Rheumatol. 1997 Sep;36(9):935-40.
- 382. Cauza E, Cauza K, Hanusch-Enserer U, et al. Intravenous anti TNF-alpha antibody therapy leads to elevated triglyceride and reduced HDL-cholesterol levels in patients with rheumatoid and psoriatic arthritis. Wien Klin Wochenschr. 2002 Dec 30;114(23-24):1004-7.
- 383. Cauza E, Hanusch-Enserer U, Frischmuth K, et al. Short-term infliximab therapy improves symptoms of psoriatic arthritis and decreases concentrations of cartilage oligomeric matrix protein. J Clin Pharm Ther. 2006 Apr;31(2):149-52.
- 384. Cauza E, Spak M, Cauza K, et al. Treatment of psoriatic arthritis and psoriasis vulgaris with the tumor necrosis factor inhibitor infliximab. Rheumatol Int. 2002
 Nov;22(6):227-32.

- 385. Cavagna L, Caporali R, Epis O, et al. Infliximab in the treatment of adult Still's disease refractory to conventional therapy. Clin Exp Rheumatol. 2001 May-Jun;19(3):329-32.
- 386. Cavallasca JA, Caubet M, Helling CA, et al. Cryptogenic organizing pneumonia (COP), as presentation of rheumatoid arthritis. Rheumatol Int. 2008 Nov;29(1):99-101.
- 387. Cavazzana I, Bobbio-Pallavicini F, Franceschini F, et al. Anti-TNF-alpha treatment in rheumatoid arthritis with anti-Ro/SSA antibodies. Analysis of 17 cases among a cohort of 322 treated patients. Clin Exp Rheumatol. 2007 Sep-Oct;25(5):676-83
- 388. Cay HF, Gungor HA, Sezer I, et al. Adverse effect of TNF-alpha blocker? Demyelination in an ankylosing spondylitis patient: a case report. J Clin Pharm Ther. 2006
 Dec;31(6):645-8.
- 389. Cefle A. Leflunomide and azathioprine combination in refractory adult-onset Still's disease. Ann Pharmacother. 2005
 Apr;39(4):764-7.
- 390. Cepeda EJ, Williams FM, Ishimori ML, et al. The use of anti-tumour necrosis factor therapy in HIV-positive individuals with rheumatic disease. Ann Rheum Dis. 2008 May;67(5):710-2.
- 391. Chakraborty PP, Achar A. Spontaneous bleeding in a patient of rheumatoid arthritis: a complication after accidental overdose of methotrexate. J Assoc Physicians India. 2007 Jul;55:501.
- 392. Chakravarty EF, Sanchez-Yamamoto D, Bush TM. The use of disease modifying antirheumatic drugs in women with rheumatoid arthritis of childbearing age: a survey of practice patterns and pregnancy outcomes. J Rheumatol. 2003 Feb;30(2):241-6.
- 393. Chambers CD, Johnson DL, Robinson LK, et al. Birth outcomes in women who have taken leflunomide during pregnancy.
 Arthritis Rheum 2010;62(5):1494-503.

- 394. Chan AT, Cleeve V, Daymond TJ.
 Necrotising fasciitis in a patient receiving infliximab for rheumatoid arthritis. Postgrad Med J. 2002 Jan;78(915):47-8.
- 395. Chan JL, Davis-Reed L, Kimball AB.
 Counter-regulatory balance: atopic
 dermatitis in patients undergoing infliximab
 infusion therapy. J Drugs Dermatol. 2004
 May-Jun;3(3):315-8.
- 396. Chandra PA, Margulis Y, Schiff C. Rituximab is useful in the treatment of Felty's syndrome. Am J Ther. 2008 Jul-Aug;15(4):321-2.
- 397. Chandran V, Schentag CT, Gladman DD. Reappraisal of the effectiveness of methotrexate in psoriatic arthritis: results from a longitudinal observational cohort. J Rheumatol. 2008 Mar;35(3):469-71.
- 398. Chandran V, Siannis F, Rahman P, et al. Folate pathway enzyme gene polymorphisms and the efficacy and toxicity of methotrexate in psoriatic arthritis. J Rheumatol. 2010 Jul;37(7):1508-12.
- 399. Chang DM, Chang SY, Yeh MK, et al. The pharmacokinetics of interleukin-1 receptor antagonist in Chinese subjects with rheumatoid arthritis. Pharmacol Res. 2004 Sep;50(3):371-6.
- 400. Chang DM, Weinblatt ME, Schur PH. The effects of methotrexate on interleukin 1 in patients with rheumatoid arthritis. J Rheumatol. 1992 Nov;19(11):1678-82.
- 401. Chang HK, Park W, Ryu DS. Successful treatment of progressive rheumatoid interstitial lung disease with cyclosporine: a case report. J Korean Med Sci. 2002 Apr;17(2):270-3.
- 402. Chang J, Girgis L. Clinical use of anti-TNF-alpha biological agents--a guide for GPs.

 Aust Fam Physician. 2007 Dec;36(12):1035-8.
- 403. Chang WH, Katz BJ, Warner JE, et al. A novel method for screening the multifocal electroretonogram in patients using hydroxychloroquine. Retina. 2008 Nov-Dec;28(10):1478-86.

- 404. Chantler IW, Davie MW, Evans SF, et al. Oral corticosteroid prescribing in women over 50, use of fracture prevention therapy, and bone densitometry service. Ann Rheum Dis. 2003 Apr;62(4):350-2.
- 405. Chapman PT, O'Donnell JL, Moller PW. Rheumatoid pleural effusion: response to intrapleural corticosteroid. J Rheumatol. 1992 Mar;19(3):478-80.
- 406. Charabaty S, Shanmugam V. A 65-year-old man with longstanding seropositive rheumatoid arthritis and lower extremity ulceration. Arthritis Rheum. 2009 Sep 15;61(9):1275-80.
- 407. Charles PJ, Smeenk RJ, De Jong J, et al. Assessment of antibodies to double-stranded DNA induced in rheumatoid arthritis patients following treatment with infliximab, a monoclonal antibody to tumor necrosis factor alpha: findings in open-label and randomized placebo-controlled trials. Arthritis Rheum. 2000 Nov;43(11):2383-90.
- 408. Charles-Schoeman C, Watanabe J, Lee YY, et al. Abnormal function of high-density lipoprotein is associated with poor disease control and an altered protein cargo in rheumatoid arthritis. Arthritis Rheum. 2009 Oct;60(10):2870-9.
- 409. Chatterjee S. Severe interstitial pneumonitis associated with infliximab therapy. Scand J Rheumatol. 2004;33(4):276-7.
- 410. Chatzikyriakidou A, Georgiou I, Voulgari PV, et al. Transcription regulatory polymorphism -43T>C in the 5'-flanking region of SLC19A1 gene could affect rheumatoid arthritis patient response to methotrexate therapy. Rheumatol Int. 2007 Sep;27(11):1057-61.
- 411. Chauhan A, Mikulik Z, Hackshaw KV.
 Multicentric reticulohistiocytosis with
 positive anticyclic citrullinated antibodies. J
 Natl Med Assoc. 2007 Jun;99(6):678-80.
- 412. Chaveiro MA, Vieira R, Cardoso J, et al. Cutaneous infection due to Scedosporium apiospermum in an immunosuppressed patient. J Eur Acad Dermatol Venereol. 2003 Jan;17(1):47-9.

- 413. Chavez-Lopez MA, Delgado-Villafana J, Gallaga A, et al. Severe anaphylactic reaction during the second infusion of infliximab in a patient with psoriatic arthritis. Allergol Immunopathol (Madr). 2005 Sep-Oct;33(5):291-2.
- 414. Cheema GS, Quismorio FP, Jr. Pulmonary involvement in adult-onset Still's disease. Curr Opin Pulm Med. 1999 Sep;5(5):305-9.
- 415. Chen DY, Shen GH, Hsieh TY, et al. Effectiveness of the combination of a whole-blood interferon-gamma assay and the tuberculin skin test in detecting latent tuberculosis infection in rheumatoid arthritis patients receiving adalimumab therapy. Arthritis Rheum. 2008 Jun 15;59(6):800-6.
- 416. Chen HA, Lin KC, Chen CH, et al. The effect of etanercept on anti-cyclic citrullinated peptide antibodies and rheumatoid factor in patients with rheumatoid arthritis. Ann Rheum Dis. 2006 Jan;65(1):35-9.
- 417. Chen YC, Hsu SW. Tuberculous arthritis mimic arthritis of the Sjogren's syndrome: findings from sonography, computed tomography and magnetic resonance images. Eur J Radiol. 2001 Dec;40(3):232-5.
- 418. Chen YC, Yang WC, Yang AH, et al. Primary Sjogren's syndrome associated with Gitelman's syndrome presenting with muscular paralysis. Am J Kidney Dis. 2003 Sep;42(3):586-90.
- 419. Cheung KK, Chow KM, Szeto CC, et al. Fatal pancytopenia in a hemodialysis patient after treatment with low-dose methotrexate.

 J Clin Rheumatol. 2009 Jun;15(4):177-80.
- 420. Chevillotte-Maillard H, Ornetti P, Mistrih R, et al. Survival and safety of treatment with infliximab in the elderly population.
 Rheumatology (Oxford). 2005
 May;44(5):695-6.
- 421. Chew AL, Bennett A, Smith CH, et al. Successful treatment of severe psoriasis and psoriatic arthritis with adalimumab. Br J Dermatol. 2004 Aug;151(2):492-6.

- 422. Chikanza IC, Petrou P, Kingsley G, et al. Defective hypothalamic response to immune and inflammatory stimuli in patients with rheumatoid arthritis. Arthritis Rheum. 1992 Nov;35(11):1281-8.
- 423. Chikanza IC, Roux-Lombard P, Dayer JM, et al. Dysregulation of the in vivo production of interleukin-1 receptor antagonist in patients with rheumatoid arthritis. Pathogenetic implications. Arthritis Rheum. 1995 May;38(5):642-8.
- 424. Chikkamuniyappa S. Streptococcal toxic shock syndrome and sepsis manifesting in a patient with chronic rheumatoid arthritis.

 Dermatol Online J. 2004;10(1):7.
- 425. Chikura B, Sathi N, Lane S, et al. Variation of immunological response in methotrexate-induced pneumonitis. Rheumatology (Oxford). 2008 Nov;47(11):1647-50.
- 426. Chilton F, Collett RA. Treatment choices, preferences and decision-making by patients with rheumatoid arthritis. Musculoskeletal Care. 2008 Mar;6(1):1-14.
- 427. Chim CS, Pang YY, Ooi GC, et al. EBV-associated synovial lymphoma in a chronically inflamed joint in rheumatoid arthritis receiving prolonged methotrexate treatment. Haematologica. 2006 Aug;91(8 Suppl):ECR31.
- 428. Chiou CF, Sherbourne CD, Cornelio I, et al. Revalidation of the original Cedars-Sinai health-related quality of life in rheumatoid arthritis questionnaire. J Rheumatol. 2006 Feb;33(2):256-62.
- 429. Cho I, Mori S, Imamura F, et al.

 Methotrexate pneumonia lacking dyspnea
 and radiographic interstitial patterns during
 treatment for early rheumatoid arthritis:
 bronchoalveolar lavage and transbronchial
 lung biopsy in a differential diagnosis. Mod
 Rheumatol. 2007;17(3):256-61.
- 430. Choi SW, Ahn JJ, Hwang YT, et al. A case of tuberculous arthritis following the use of etanercept. Korean J Intern Med. 2009 Dec;24(4):397-401.

- 431. Chomarat P, Vannier E, Dechanet J, et al. Balance of IL-1 receptor antagonist/IL-1 beta in rheumatoid synovium and its regulation by IL-4 and IL-10. J Immunol. 1995 Feb 1:154(3):1432-9.
- 432. Chopin F, Garnero P, le Henanff A, et al. Long-term effects of infliximab on bone and cartilage turnover markers in patients with rheumatoid arthritis. Ann Rheum Dis. 2008 Mar;67(3):353-7.
- 433. Chopra A, Saluja M, Lagu-Joshi V, et al. Leflunomide (Arava) is a useful DMARD in Indian (Asian) patients: a clinic-based observational study of 1-year treatment. Clin Rheumatol 2008;27(8):1039-44.
- 434. Chou CT. The clinical application of etanercept in Chinese patients with rheumatic diseases. Mod Rheumatol. 2006;16(4):206-13.
- 435. Choy EH, Isenberg DA, Garrood T, et al. Therapeutic benefit of blocking interleukin-6 activity with an anti-interleukin-6 receptor monoclonal antibody in rheumatoid arthritis: a randomized, double-blind, placebocontrolled, dose-escalation trial. Arthritis Rheum. 2002 Dec;46(12):3143-50.
- 436. Choy EH, Smith CM, Farewell V, et al. Factorial randomised controlled trial of glucocorticoids and combination disease modifying drugs in early rheumatoid arthritis. Ann Rheum Dis 2008;67(5):656-63
- 437. Chung CP, Oeser A, Solus JF, et al. Inflammation-associated insulin resistance: differential effects in rheumatoid arthritis and systemic lupus erythematosus define potential mechanisms. Arthritis Rheum. 2008 Jul;58(7):2105-12.
- 438. Chung CP, Russell AS, Segami MI, et al. The effect of low-dose prednisone on bone mineral density in Peruvian rheumatoid arthritis patients. Rheumatol Int. 2005 Mar;25(2):114-7.
- 439. Ciboddo G, Idone C. Treatment of renal amyloidosis in rheumatoid arthritis requires further investigation: comment on the case report by Elkayam et al. Arthritis Rheum. 2003 Nov;48(11):3299; author reply -300.

- 440. Cisternas M, Gutierrez M, Jacobelli S. Successful rechallenge with anti-tumor necrosis factor alpha for psoriatic arthritis after development of demyelinating nervous system disease during initial treatment: comment on the article by Mohan et al. Arthritis Rheum. 2002 Nov;46(11):3107-8; author reply 8-9.
- 441. Clark W, Jobanputra P, Barton P, et al. The clinical and cost-effectiveness of anakinra for the treatment of rheumatoid arthritis in adults: a systematic review and economic analysis. Health Technol Assess. 2004 May;8(18):iii-iv, ix-x, 1-105.
- 442. Clarke LE, Junkins-Hopkins J, Seykora JT, et al. Methotrexate-associated lymphoproliferative disorder in a patient with rheumatoid arthritis presenting in the skin. J Am Acad Dermatol. 2007 Apr;56(4):686-90.
- 443. Cleland LG, Caughey GE, James MJ, et al. Reduction of cardiovascular risk factors with longterm fish oil treatment in early rheumatoid arthritis. J Rheumatol. 2006 Oct;33(10):1973-9.
- 444. Clelland S, Hunek JR. Etanercept injection site reaction. Dermatol Nurs. 2005 Oct;17(5):375-.
- 445. Clementine RR, Lyman J, Zakem J, et al. Tumor necrosis factor-alpha antagonist-induced sarcoidosis. J Clin Rheumatol. 2010 Sep;16(6):274-9.
- 446. Clifford LJ, Rossiter JD. Peripheral visual field loss following treatment with etanercept. Br J Ophthalmol. 2004 Jun;88(6):842.
- 447. Clunie G, Voules S, Watts R. Dose reduction of etanercept--can we treat more patients using a fixed budget?
 Rheumatology (Oxford). 2003
 Apr;42(4):600-1.
- 448. Coates LC, Cawkwell LS, Ng NW, et al. Sustained response to long-term biologics and switching in psoriatic arthritis: results from real life experience. Ann Rheum Dis. 2008 May;67(5):717-9.

- 449. Cobo Ibanez T, Yehia Tayel M, Balsa Criado A, et al. Safety and efficacy of leflunomide and infliximab versus methotrexate and infliximab combination therapy in rheumatoid arthritis. Rheumatology (Oxford). 2005 Nov;44(11):1467-8.
- 450. Coca A, Sanz I. B cell depletion in lupus and Sjogren's syndrome: an update. Curr Opin Rheumatol. 2009 Sep;21(5):483-8.
- 451. Cocito D, Bergamasco B, Tavella A, et al. Multifocal motor neuropathy during treatment with infliximab. J Peripher Nerv Syst. 2005 Dec;10(4):386-7.
- 452. Cohen CD, Horster S, Sander CA, et al. Kaposi's sarcoma associated with tumour necrosis factor alpha neutralising therapy. Ann Rheum Dis. 2003 Jul;62(7):684.
- 453. Cohen G, Courvoisier N, Cohen JD, et al. The efficiency of switching from infliximab to etanercept and vice-versa in patients with rheumatoid arthritis. Clin Exp Rheumatol. 2005 Nov-Dec;23(6):795-800.
- 454. Cohen J. Still looking for the cause of fever? Crit Care Resusc. 2006 Jun;8(2):155-6.
- 455. Cohen JD, Bournerias I, Buffard V, et al. Psoriasis induced by tumor necrosis factoralpha antagonist therapy: a case series. J Rheumatol. 2007 Feb;34(2):380-5.
- 456. Cohen JD, Zaltni S, Kaiser MJ, et al. Secondary addition of methotrexate to partial responders to etanercept alone is effective in severe rheumatoid arthritis. Ann Rheum Dis. 2004 Feb;63(2):209-10.
- 457. Cohen MD, Conn DL. Benefits of low-dose corticosteroids in rheumatoid arthritis. Bull Rheum Dis. 1997 Jun;46(4):4-7.
- 458. Cohen S, Hurd E, Cush J, et al. Treatment of rheumatoid arthritis with anakinra, a recombinant human interleukin-1 receptor antagonist, in combination with methotrexate: results of a twenty-four-week, multicenter, randomized, double-blind, placebo-controlled trial. Arthritis Rheum. 2002 Mar;46(3):614-24.

- 459. Cohen SB, Cheng TT, Chindalore V, et al. Evaluation of the efficacy and safety of pamapimod, a p38 MAP kinase inhibitor, in a double-blind, methotrexate-controlled study of patients with active rheumatoid arthritis. Arthritis Rheum. 2009 Feb;60(2):335-44.
- 460. Cohen SB, Dore RK, Lane NE, et al.
 Denosumab treatment effects on structural damage, bone mineral density, and bone turnover in rheumatoid arthritis: a twelvemonth, multicenter, randomized, doubleblind, placebo-controlled, phase II clinical trial. Arthritis Rheum. 2008
 May;58(5):1299-309.
- 461. Cohen SB, Keystone E, Genovese MC, et al. Continued inhibition of structural damage over 2 years in patients with rheumatoid arthritis treated with rituximab in combination with methotrexate. Ann Rheum Dis 2010;69(6):1158-61.
- 462. Cohen SB, Moreland LW, Cush JJ, et al. A multicentre, double blind, randomised, placebo controlled trial of anakinra (Kineret), a recombinant interleukin 1 receptor antagonist, in patients with rheumatoid arthritis treated with background methotrexate. Ann Rheum Dis. 2004 Sep;63(9):1062-8.
- 463. Cohen SB, Strand V, Aguilar D, et al. Patient- versus physician-reported outcomes in rheumatoid arthritis patients treated with recombinant interleukin-1 receptor antagonist (anakinra) therapy. Rheumatology (Oxford). 2004
 Jun;43(6):704-11.
- 464. Cohen SB, Woolley JM, Chan W. Interleukin 1 receptor antagonist anakinra improves functional status in patients with rheumatoid arthritis. J Rheumatol. 2003 Feb;30(2):225-31.
- 465. Cole J, Busti A, Kazi S. The incidence of new onset congestive heart failure and heart failure exacerbation in Veteran's Affairs patients receiving tumor necrosis factor alpha antagonists. Rheumatol Int 2007;27(4):369-73.
- 466. Cole JC, Li T, Lin P, et al. Treatment impact on estimated medical expenditure and job

- loss likelihood in rheumatoid arthritis: reexamining quality of life outcomes from a randomized placebo-controlled clinical trial with abatacept. Rheumatology (Oxford). 2008 Jul;47(7):1044-50.
- 467. Coluccia D, Wolf OT, Kollias S, et al. Glucocorticoid therapy-induced memory deficits: acute versus chronic effects. J Neurosci. 2008 Mar 26;28(13):3474-8.
- 468. Colwell CW, Jr., Robinson CA, Stevenson DD, et al. Osteonecrosis of the femoral head in patients with inflammatory arthritis or asthma receiving corticosteroid therapy. Orthopedics. 1996 Nov;19(11):941-6.
- 469. Combe B, Codreanu C, Fiocco U, et al. Efficacy, safety and patient-reported outcomes of combination etanercept and sulfasalazine versus etanercept alone in patients with rheumatoid arthritis: a double-blind randomised 2-year study. Ann Rheum Dis 2009;68(7):1146-52.
- 470. Comby E, Tanaff P, Mariotte D, et al. Evolution of antinuclear antibodies and clinical patterns in patients with active rheumatoid arthritis with longterm infliximab therapy. J Rheumatol. 2006 Jan;33(1):24-30.
- 471. Conaghan PG, O'Connor P, McGonagle D, et al. Elucidation of the relationship between synovitis and bone damage: a randomized magnetic resonance imaging study of individual joints in patients with early rheumatoid arthritis. Arthritis Rheum. 2003 Jan;48(1):64-71.
- 472. Constantinescu F, Goucher S, Weinstein A, et al. Racial disparities in treatment preferences for rheumatoid arthritis. Med Care. 2009 Mar;47(3):350-5.
- 473. Constantinou M, Jhanji V, Tao LW, et al. Clinical review of corneal ulcers resulting in evisceration and enucleation in elderly population. Graefes Arch Clin Exp Ophthalmol. 2009 Oct;247(10):1389-93.
- 474. Conti A, Sartorio A, Ferrero S, et al. Modifications of biochemical markers of bone and collagen turnover during corticosteroid therapy. J Endocrinol Invest. 1996 Feb;19(2):127-30.

- 475. Conti F, Ceccarelli F, Marocchi E, et al. Switching tumour necrosis factor alpha antagonists in patients with ankylosing spondylitis and psoriatic arthritis: an observational study over a 5-year period. Ann Rheum Dis. 2007 Oct;66(10):1393-7.
- 476. Conti F, Priori R, Chimenti MS, et al. Successful treatment with intraarticular infliximab for resistant knee monarthritis in a patient with spondylarthropathy: a role for scintigraphy with 99mTc-infliximab.

 Arthritis Rheum. 2005 Apr;52(4):1224-6.
- 477. Contreras-Yanez I, Ponce De Leon S, Cabiedes J, et al. Inadequate therapy behavior is associated to disease flares in patients with rheumatoid arthritis who have achieved remission with disease-modifying antirheumatic drugs. Am J Med Sci. 2010 Oct;340(4):282-90.
- 478. Cooper C, Coupland C, Mitchell M. Rheumatoid arthritis, corticosteroid therapy and hip fracture. Ann Rheum Dis. 1995
 Jan;54(1):49-52.
- 479. Cordero-Coma M, Anzaar F, Sobrin L, et al. Systemic immunomodulatory therapy in severe dry eye secondary to inflammation. Ocul Immunol Inflamm. 2007 Mar-Apr;15(2):99-104.
- 480. Cordiali-Fei P, Trento E, D'Agosto G, et al. Effective therapy with anti-TNF-alpha in patients with psoriatic arthritis is associated with decreased levels of metalloproteinases and angiogenic cytokines in the sera and skin lesions. Ann N Y Acad Sci. 2007 Sep;1110:578-89.
- 481. Corrao S, Pistone G, Arnone S, et al. Safety of etanercept therapy in rheumatoid patients undergoing surgery: preliminary report. Clin Rheumatol. 2007 Sep;26(9):1513-5.
- 482. Corsi F, Previde P, Colombo F, et al. Two cases of intestinal perforation in patients on anti-rheumatic treatment with etanercept. Clin Exp Rheumatol. 2006 Jan-Feb;24(1):113.
- 483. Cortet B, Flipo RM, Pigny P, et al. How useful are bone turnover markers in rheumatoid arthritis? Influence of disease

- activity and corticosteroid therapy. Rev Rhum Engl Ed. 1997 Mar;64(3):153-9.
- 484. Cortet B, Guyot MH, Solau E, et al. Factors influencing bone loss in rheumatoid arthritis: a longitudinal study. Clin Exp Rheumatol. 2000 Nov-Dec;18(6):683-90.
- 485. Cortot AB, Cottin V, Miossec P, et al. Improvement of refractory rheumatoid arthritis-associated constrictive bronchiolitis with etanercept. Respir Med. 2005 Apr;99(4):511-4.
- 486. Courtney PA, Alderdice J, Whitehead EM. Comment on methotrexate pneumonitis after initiation of infliximab therapy for rheumatoid arthritis. Arthritis Rheum. 2003 Aug 15;49(4):617; author reply -8.
- 487. Coury F, Ferraro-Peyret C, Le Cam S, et al. Peripheral blood lymphocytes from patients with rheumatoid arthritis are differentially sensitive to apoptosis induced by antitumour necrosis factor-alpha therapy. Clin Exp Rheumatol. 2008 Mar-Apr;26(2):234-9.
- 488. Covelli M, Scioscia C, Iannone F, et al. Repeated infusions of low-dose infliximab plus methotrexate in psoriatic arthritis: immediate benefits are not maintained after discontinuation of infliximab. Clin Exp Rheumatol. 2005 Mar-Apr;23(2):145-51.
- 489. Coyle CM, Weiss LM, Rhodes LV, 3rd, et al. Fatal myositis due to the microsporidian Brachiola algerae, a mosquito pathogen. N Engl J Med. 2004 Jul 1;351(1):42-7.
- 490. Cracchiolo A, 3rd, Severt R, Moreland J. Uncemented total hip arthroplasty in rheumatoid arthritis diseases. A two- to sixyear follow-up study. Clin Orthop Relat Res. 1992 Apr(277):166-74.
- 491. Creamer P, Keen M, Zananiri F, et al. Quantitative magnetic resonance imaging of the knee: a method of measuring response to intra-articular treatments. Ann Rheum Dis. 1997 Jun;56(6):378-81.
- 492. Creemers MC, Franssen MJ, van de Putte LB, et al. Methotrexate in severe ankylosing spondylitis: an open study. J Rheumatol. 1995 Jun;22(6):1104-7.

- 493. Crellin AM, Shareef DS, Maher EJ.
 Opportunistic Listeria pericardial effusion.
 Postgrad Med J. 1990 Mar;66(773):203-4.
- 494. Crilly A, Maiden N, Capell HA, et al. Predictive value of interleukin 1 gene polymorphisms for surgery. Ann Rheum Dis. 2000 Sep;59(9):695-9.
- 495. Criswell LA, Lum RF, Turner KN, et al. The influence of genetic variation in the HLA-DRB1 and LTA-TNF regions on the response to treatment of early rheumatoid arthritis with methotrexate or etanercept. Arthritis Rheum. 2004 Sep;50(9):2750-6.
- 496. Crnkic M, Mansson B, Larsson L, et al. Serum cartilage oligomeric matrix protein (COMP) decreases in rheumatoid arthritis patients treated with infliximab or etanercept. Arthritis Res Ther. 2003;5(4):R181-5.
- 497. Croce A, Firuzi O, Altieri F, et al. Effect of infliximab on the glycosylation of IgG of patients with rheumatoid arthritis. J Clin Lab Anal. 2007;21(5):303-14.
- 498. Crofford LJ, Kalogeras KT, Mastorakos G, et al. Circadian relationships between interleukin (IL)-6 and hypothalamic-pituitary-adrenal axis hormones: failure of IL-6 to cause sustained hypercortisolism in patients with early untreated rheumatoid arthritis. J Clin Endocrinol Metab. 1997 Apr;82(4):1279-83.
- 499. Crowson CS, Rahman MU, Matteson EL. Which measure of inflammation to use? A comparison of erythrocyte sedimentation rate and C-reactive protein measurements from randomized clinical trials of golimumab in rheumatoid arthritis. J Rheumatol. 2009 Aug;36(8):1606-10.
- 500. Cruse LM, Valeriano J, Vasey FB, et al. Prevalence of evaluation and treatment of glucocorticoid-induced osteoporosis in men. J Clin Rheumatol. 2006 Oct;12(5):221-5.
- 501. Cuchacovich M, Catalan D, Wainstein E, et al. Basal anti-cyclic citrullinated peptide (anti-CCP) antibody levels and a decrease in anti-CCP titres are associated with clinical response to adalimumab in rheumatoid

- arthritis. Clin Exp Rheumatol. 2008 Nov-Dec;26(6):1067-73.
- 502. Cuchacovich M, Ferreira L, Aliste M, et al. Tumour necrosis factor-alpha (TNF-alpha) levels and influence of -308 TNF-alpha promoter polymorphism on the responsiveness to infliximab in patients with rheumatoid arthritis. Scand J Rheumatol. 2004;33(4):228-32.
- 503. Cuchacovich M, Soto L, Edwardes M, et al. Tumour necrosis factor (TNF)alpha -308 G/G promoter polymorphism and TNFalpha levels correlate with a better response to adalimumab in patients with rheumatoid arthritis. Scand J Rheumatol. 2006 Nov-Dec;35(6):435-40.
- 504. Cuchacovich R, Espinoza CG, Virk Z, et al. Biologic therapy (TNF-alpha antagonists)-induced psoriasis: a cytokine imbalance between TNF-alpha and IFN-alpha? J Clin Rheumatol. 2008 Dec;14(6):353-6.
- 505. Cuchacovich R, Espinoza LR. Does TNF-alpha blockade play any role in cardiovascular risk among rheumatoid arthritis (RA) patients? Clin Rheumatol. 2009 Oct;28(10):1217-20.
- 506. Cui J, Saevarsdottir S, Thomson B, et al. Rheumatoid arthritis risk allele PTPRC is also associated with response to anti-tumor necrosis factor alpha therapy. Arthritis Rheum 2010;62(7):1849-61.
- 507. Culy CR, Keating GM. Etanercept: an updated review of its use in rheumatoid arthritis, psoriatic arthritis and juvenile rheumatoid arthritis. Drugs. 2002;62(17):2493-537.
- 508. Cunnane G, Madigan A, Murphy E, et al.
 The effects of treatment with interleukin-1
 receptor antagonist on the inflamed synovial
 membrane in rheumatoid arthritis.
 Rheumatology (Oxford). 2001 Jan;40(1):629.
- 509. Cunnane G, Warnock M, Fye KH, et al. Accelerated nodulosis and vasculitis following etanercept therapy for rheumatoid arthritis. Arthritis Rheum. 2002 Aug;47(4):445-9.

- 510. Curkendall S, Patel V, Gleeson M, et al. Compliance with biologic therapies for rheumatoid arthritis: do patient out-of-pocket payments matter? Arthritis Rheum. 2008 Oct 15:59(10):1519-26.
- 511. Cursiefen C, Grunke M, Dechant C, et al. Multiple bilateral eyelid molluscum contagiosum lesions associated with TNFalpha-antibody and methotrexate therapy. Am J Ophthalmol. 2002 Aug;134(2):270-1.
- 512. Curtis JR, Kramer JM, Martin C, et al. Heart failure among younger rheumatoid arthritis and Crohn's patients exposed to TNF-alpha antagonists. Rheumatology (Oxford) 2007;46(11):1688-93.
- 513. Curtis JR, Martin C, Saag KG, et al.
 Confirmation of administrative claimsidentified opportunistic infections and other
 serious potential adverse events associated
 with tumor necrosis factor alpha antagonists
 and disease-modifying antirheumatic drugs.
 Arthritis Rheum. 2007 Mar 15:57(2):343-6.
- 514. Curtis JR, Patkar N, Xie A, et al. Risk of serious bacterial infections among rheumatoid arthritis patients exposed to tumor necrosis factor alpha antagonists. Arthritis Rheum 2007;56(4):1125-33.
- 515. Curtis JR, Xi J, Patkar N, et al. Drugspecific and time-dependent risks of bacterial infection among patients with rheumatoid arthritis who were exposed to tumor necrosis factor alpha antagonists. Arthritis Rheum 2007;56(12):4226-7.
- 516. Cutolo M, Balleari E, Giusti M, et al. Androgen replacement therapy in male patients with rheumatoid arthritis. Arthritis Rheum. 1991 Jan;34(1):1-5.
- 517. Cutolo M, Bisso A, Sulli A, et al.
 Antiproliferative and antiinflammatory
 effects of methotrexate on cultured
 differentiating myeloid monocytic cells
 (THP-1) but not on synovial macrophages
 from patients with rheumatoid arthritis. J
 Rheumatol. 2000 Nov;27(11):2551-7.
- 518. Cutolo M, Foppiani L, Minuto F. Hypothalamic-pituitary-adrenal axis impairment in the pathogenesis of

- rheumatoid arthritis and polymyalgia rheumatica. J Endocrinol Invest. 2002;25(10 Suppl):19-23.
- 519. Cutolo M, Foppiani L, Prete C, et al. Hypothalamic-pituitary-adrenocortical axis function in premenopausal women with rheumatoid arthritis not treated with glucocorticoids. J Rheumatol. 1999 Feb;26(2):282-8.
- 520. Cutolo M, Maestroni GJ, Otsa K, et al. Circadian melatonin and cortisol levels in rheumatoid arthritis patients in winter time: a north and south Europe comparison. Ann Rheum Dis. 2005 Feb;64(2):212-6.
- 521. Cutolo M, Villaggio B, Pizzorni C, et al. Inflammatory gene profile in early rheumatoid arthritis and modulation by leflunomide and prednisone treatment. Ann N Y Acad Sci. 2010 Apr;1193(1):15-21.
- 522. Cvetkovic JT, Wallberg-Jonsson S, Stegmayr B, et al. Susceptibility for and clinical manifestations of rheumatoid arthritis are associated with polymorphisms of the TNF-alpha, IL-1beta, and IL-1Ra genes. J Rheumatol. 2002 Feb;29(2):212-9.
- 523. Cypiene A, Laucevicius A, Venalis A, et al. Non-invasive assessment of arterial stiffness indices by applanation tonometry and pulse wave analysis in patients with rheumatoid arthritis treated with TNF-alpha blocker remicade (infliximab). Proc West Pharmacol Soc. 2007;50:119-22.
- 524. D'Acquisto F, Paschalidis N, Raza K, et al. Glucocorticoid treatment inhibits annexin-1 expression in rheumatoid arthritis CD4+ T cells. Rheumatology (Oxford). 2008 May;47(5):636-9.
- 525. Dagci H, Zeyrek F, Gerzile YK, et al. A case of myiasis in a patient with psoriasis from Turkey. Parasitol Int. 2008
 Jun;57(2):239-41.
- 526. Dahlqvist SR, Engstrand S, Berglin E, et al. Conversion towards an atherogenic lipid profile in rheumatoid arthritis patients during long-term infliximab therapy. Scand J Rheumatol. 2006 Mar-Apr;35(2):107-11.

- 527. Dahlqvist SR, Olsson T. Interference with the cortisol axis by the microtubule antagonist, CPH82. Br J Rheumatol. 1993 Sep;32(9):804-6.
- 528. Dain L, Braun-Moscovici Y, Baum E, et al. Modification of neutrophil function by plasma of rheumatoid arthritis patients treated with infliximab. Clin Exp Rheumatol. 2006 Jan-Feb;24(1):38-44.
- 529. Dalrymple JM, Stamp LK, O'Donnell JL, et al. Pharmacokinetics of oral methotrexate in patients with rheumatoid arthritis. Arthritis Rheum. 2008 Nov;58(11):3299-308.
- 530. Damjanov N, Kauffman RS, Spencer-Green GT. Efficacy, pharmacodynamics, and safety of VX-702, a novel p38 MAPK inhibitor, in rheumatoid arthritis: results of two randomized, double-blind, placebocontrolled clinical studies. Arthritis Rheum. 2009 May;60(5):1232-41.
- 531. Danko JR, Gilliland WR, Miller RS, et al. Disseminated Mycobacterium marinum infection in a patient with rheumatoid arthritis receiving infliximab therapy. Scand J Infect Dis. 2009;41(4):252-5.
- 532. Dans M, Hivnor C, van Voorhees AS.
 Psoriatic onychopachydermoperiostitis:
 improvement with etanercept. Br J
 Dermatol. 2005 Oct;153(4):858-9.
- 533. Darabi K, Jaiswal R, Hostetler S, et al. Infectious complications in patients with psoriasis and rheumatoid arthritis treated with antitumor necrosis factor agents and methotrexate. J Drugs Dermatol. 2009 Feb;8(2):175-8.
- 534. Darmawan J, Muirden KD, Valkenburg HA, et al. The epidemiology of rheumatoid arthritis in Indonesia. Br J Rheumatol. 1993 Jul;32(7):537-40.
- 535. Das P, Raghu P, Amit Kumar D, et al. Strongyloides hyperinfection in rheumatoid arthritis. Int J Surg Pathol. 2007 Oct;15(4):391-2.
- 536. Das SK, Pareek A, Mathur DS, et al. Efficacy and safety of hydroxychloroquine sulphate in rheumatoid arthritis: a

- randomized, double-blind, placebo controlled clinical trial--an Indian experience. Curr Med Res Opin. 2007 Sep;23(9):2227-34.
- 537. Dascalu C, Mrejen-Shakin K, Bandagi S. Adalimumab-induced acute pneumonitis in a patient with rheumatoid arthritis. J Clin Rheumatol. 2010 Jun;16(4):172-4.
- 538. Dass S, Bowman SJ, Vital EM, et al. Reduction of fatigue in Sjogren syndrome with rituximab: results of a randomised, double-blind, placebo-controlled pilot study. Ann Rheum Dis. 2008 Nov;67(11):1541-4.
- 539. Dauendorffer JN, Rivet J, Allard A, et al. Sezary syndrome in a patient receiving infliximab for ankylosing spondylitis. Br J Dermatol. 2007 Apr;156(4):742-3.
- 540. D'Auria F, Rovere-Querini P, Giazzon M, et al. Accumulation of plasma nucleosomes upon treatment with anti-tumour necrosis factor-alpha antibodies. J Intern Med. 2004 Mar;255(3):409-18.
- 541. Davaine AC, Saraux A, Prigent S, et al. Cutaneous events during treatment of chronic inflammatory joint disorders with anti-tumour necrosis factor alpha: a cross-sectional study. J Eur Acad Dermatol Venereol. 2008 Dec;22(12):1471-7.
- 542. Davey M, Buchbinder R. Glucocorticoids in early rheumatoid arthritis. Aust Fam Physician. 2008 Jan-Feb;37(1-2):31-2.
- 543. Davies K, Stiehm ER, Woo P, et al. Juvenile idiopathic polyarticular arthritis and IgA deficiency in the 22q11 deletion syndrome. J Rheumatol. 2001 Oct;28(10):2326-34.
- 544. Davis JC, Jr. The role of etanercept in ankylosing spondylitis. Clin Exp Rheumatol. 2002 Nov-Dec;20(6 Suppl 28):S111-5.
- 545. Davis JC, Jr., Van Der Heijde D, Braun J, et al. Recombinant human tumor necrosis factor receptor (etanercept) for treating ankylosing spondylitis: a randomized, controlled trial. Arthritis Rheum. 2003 Nov;48(11):3230-6.

- 546. Davis JC, van der Heijde D, Dougados M, et al. Reductions in health-related quality of life in patients with ankylosing spondylitis and improvements with etanercept therapy. Arthritis Rheum. 2005 Aug 15;53(4):494-501
- 547. Davis JC, van der Heijde DM, Braun J, et al. Sustained durability and tolerability of etanercept in ankylosing spondylitis for 96 weeks. Ann Rheum Dis. 2005
 Nov;64(11):1557-62.
- 548. Davis JC, Jr., Van der Heijde DM, Dougados M, et al. Baseline factors that influence ASAS 20 response in patients with ankylosing spondylitis treated with etanercept. J Rheumatol. 2005 Sep;32(9):1751-4.
- 549. Davis JM, 3rd, Maradit Kremers H, Crowson CS, et al. Glucocorticoids and cardiovascular events in rheumatoid arthritis: a population-based cohort study. Arthritis Rheum. 2007 Mar;56(3):820-30.
- 550. Davis MC, Zautra AJ, Younger J, et al. Chronic stress and regulation of cellular markers of inflammation in rheumatoid arthritis: implications for fatigue. Brain Behav Immun. 2008 Jan;22(1):24-32.
- 551. Day R. Adverse reactions to TNF-alpha inhibitors in rheumatoid arthritis. Lancet. 2002 Feb 16;359(9306):540-1.
- 552. Daza L, Martin-Jimenez R, De la Torre PX, et al. Improvement of ACTH response to insulin tolerance test in female patients with rheumatoid arthritis due to tumor necrosis factor inhibition. Eur J Endocrinol. 2007 Jul;157(1):47-51.
- 553. De A, Blotta HM, Mamoni RL, et al. Effects of dexamethasone on lymphocyte proliferation and cytokine production in rheumatoid arthritis. J Rheumatol. 2002 Jan;29(1):46-51.
- 554. De Bandt M, Kahn MF. Takayasu's arteritis associated with Still's disease in an adult. Clin Exp Rheumatol. 1991 Nov-Dec;9(6):639-40.

- 555. De Bandt M, Sibilia J, Le Loet X, et al. Systemic lupus erythematosus induced by anti-tumour necrosis factor alpha therapy: a French national survey. Arthritis Res Ther. 2005;7(3):R545-51.
- 556. De Bandt M, Vittecoq O, Descamps V, et al. Anti-TNF-alpha-induced systemic lupus syndrome. Clin Rheumatol. 2003 Feb;22(1):56-61.
- 557. De Benedetti F. Targeting interleukin-6 in pediatric rheumatic diseases. Curr Opin Rheumatol. 2009 Sep;21(5):533-7.
- 558. De Benedetti F, Pignatti P, Gerloni V, et al. Differences in synovial fluid cytokine levels between juvenile and adult rheumatoid arthritis. J Rheumatol. 1997 Jul;24(7):1403-9.
- 559. de' Clari F, Salani I, Safwan E, et al. Sudden death in a patient without heart failure after a single infusion of 200 mg infliximab: does TNF-alpha have protective effects on the failing heart, or does infliximab have direct harmful cardiovascular effects? Circulation. 2002 May 28;105(21):E183.
- 560. De Felice C, Mazzotta A, Esposito M, et al. High-dose initiation of etanercept in psoriatic arthritis and plaque psoriasis: efficacy, safety and impact on patients' quality of life. J Dermatolog Treat. 2006;17(6):355-8.
- 561. de Jong JW, van Altena R. Non-respiratory tuberculosis with Mycobacterium tuberculosis after penetrating lesions of the skin: five case histories. Int J Tuberc Lung Dis. 2000 Dec;4(12):1184-7.
- 562. de la Torre B, Hedman M, Nilsson E, et al. Relationship between blood and joint tissue DHEAS levels in rheumatoid arthritis and osteoarthritis. Clin Exp Rheumatol. 1993 Nov-Dec;11(6):597-601.
- 563. De Leonardis F, Govoni M, Lo Monaco A, et al. Visceral leishmaniasis and anti-TNF-alpha therapy: case report and review of the literature. Clin Exp Rheumatol. 2009 May-Jun;27(3):503-6.

- 564. De Miguel S, Jover JA, Vadillo C, et al. B cell activation in rheumatoid arthritis patients under infliximab treatment. Clin Exp Rheumatol. 2003 Nov-Dec;21(6):726-32.
- 565. de Nijs RN, Jacobs JW, Bijlsma JW, et al. Prevalence of vertebral deformities and symptomatic vertebral fractures in corticosteroid treated patients with rheumatoid arthritis. Rheumatology (Oxford). 2001 Dec;40(12):1375-83.
- 566. de Paz B, Alperi-Lopez M, Ballina-Garcia FJ, et al. Interleukin 10 and tumor necrosis factor-alpha genotypes in rheumatoid arthritis--association with clinical response to glucocorticoids. J Rheumatol. 2010 Mar;37(3):503-11.
- 567. De Rosa FG, Shaz D, Campagna AC, et al. Invasive pulmonary aspergillosis soon after therapy with infliximab, a tumor necrosis factor-alpha-neutralizing antibody: a possible healthcare-associated case? Infect Control Hosp Epidemiol. 2003

 Jul;24(7):477-82.
- 568. De Rycke L, Baeten D, Foell D, et al. Differential expression and response to anti-TNFalpha treatment of infiltrating versus resident tissue macrophage subsets in autoimmune arthritis. J Pathol. 2005
 May;206(1):17-27.
- 569. De Rycke L, Baeten D, Kruithof E, et al. Infliximab, but not etanercept, induces IgM anti-double-stranded DNA autoantibodies as main antinuclear reactivity: biologic and clinical implications in autoimmune arthritis. Arthritis Rheum. 2005
 Jul;52(7):2192-201.
- 570. De Rycke L, Kruithof E, Van Damme N, et al. Antinuclear antibodies following infliximab treatment in patients with rheumatoid arthritis or spondylarthropathy. Arthritis Rheum. 2003 Apr;48(4):1015-23.
- 571. De Rycke L, Vandooren B, Kruithof E, et al. Tumor necrosis factor alpha blockade treatment down-modulates the increased systemic and local expression of Toll-like receptor 2 and Toll-like receptor 4 in spondylarthropathy. Arthritis Rheum. 2005 Jul;52(7):2146-58.

- 572. De Rycke L, Verhelst X, Kruithof E, et al. Rheumatoid factor, but not anti-cyclic citrullinated peptide antibodies, is modulated by infliximab treatment in rheumatoid arthritis. Ann Rheum Dis. 2005 Feb;64(2):299-302.
- 573. de Seze J, Delalande S, Fauchais AL, et al. Myelopathies secondary to Sjogren's syndrome: treatment with monthly intravenous cyclophosphamide associated with corticosteroids. J Rheumatol. 2006 Apr;33(4):709-11.
- 574. De Stefano R, Frati E, Nargi F, et al.
 Comparison of combination therapies in the treatment of rheumatoid arthritis:
 leflunomide-anti-TNF-alpha versus methotrexate-anti-TNF-alpha. Clin Rheumatol 2010;29(5):517-24.
- 575. de Thurah A, Norgaard M, Johansen M, et al. Time to methotrexate treatment in patients with rheumatoid arthritis referred to hospital. Scand J Rheumatol. 2010;39(1):19-25.
- 576. de Thurah A, Norgaard M, Johansen MB, et al. Methotrexate compliance among patients with rheumatoid arthritis: the influence of disease activity, disease duration, and comorbidity in a 10-year longitudinal study. Scand J Rheumatol. 2010 May;39(3):197-205.
- 577. De Vita S, Zaja F, Sacco S, et al. Efficacy of selective B cell blockade in the treatment of rheumatoid arthritis: evidence for a pathogenetic role of B cells. Arthritis Rheum. 2002 Aug;46(8):2029-33.
- 578. de Vries-Bouwstra JK, Goekoop-Ruiterman YP, Verpoort KN, et al. Progression of joint damage in early rheumatoid arthritis: association with HLA-DRB1, rheumatoid factor, and anti-citrullinated protein antibodies in relation to different treatment strategies. Arthritis Rheum. 2008 May;58(5):1293-8.
- 579. de Vries-Bouwstra JK, Goekoop-Ruiterman YP, Wesoly J, et al. Ex vivo interleukin 1 receptor antagonist production on lipopolysaccharide stimulation is associated with rheumatoid arthritis and with joint

- damage. Ann Rheum Dis. 2007 Aug;66(8):1033-7.
- 580. de Winter S, van Buchem MA, Vermeer MH. Annular erythema of Sjogren's syndrome. Lancet. 2006 May 13;367(9522):1604.
- 581. Debiais S, Maillot F, Luca L, et al. Efficacy of anakinra in a case of refractory Still disease. J Clin Rheumatol. 2008
 Dec;14(6):357-8.
- 582. Deighton CM, Watson MJ, Walker DJ. Sex hormones in postmenopausal HLA-identical rheumatoid arthritis discordant sibling pairs. J Rheumatol. 1992 Nov;19(11):1663-7.
- 583. Dekkers JC, Geenen R, Godaert GL, et al. Experimentally challenged reactivity of the hypothalamic pituitary adrenal axis in patients with recently diagnosed rheumatoid arthritis. J Rheumatol. 2001 Jul;28(7):1496-504.
- 584. del Porto F, Aloe L, Lagana B, et al. Nerve growth factor and brain-derived neurotrophic factor levels in patients with rheumatoid arthritis treated with TNF-alpha blockers. Ann N Y Acad Sci. 2006 Jun;1069:438-43.
- 585. Del Porto F, Lagana B, Lai S, et al.
 Response to anti-tumour necrosis factor
 alpha blockade is associated with reduction
 of carotid intima-media thickness in patients
 with active rheumatoid arthritis.
 Rheumatology (Oxford). 2007
 Jul;46(7):1111-5.
- 586. Delabaye I, De Keyser F. 74-week followup of safety of infliximab in patients with refractory rheumatoid arthritis. Arthritis Res Ther. 2010;12(3):R121.
- 587. Delaunay C, Farrenq V, Marini-Portugal A, et al. Infliximab to etanercept switch in patients with spondyloarthropathies and psoriatic arthritis: preliminary data. J Rheumatol. 2005 Nov;32(11):2183-5.
- 588. Delmez JA, Dusso AS, Slatopolsky E, et al. Modulation of renal osteodystrophy by extrarenal production of calcitriol. Am J Nephrol. 1995;15(1):85-9.

- 589. Demir H, Kelestimur F, Tunc M, et al. Hypothalamo-pituitary-adrenal axis and growth hormone axis in patients with rheumatoid arthritis. Scand J Rheumatol. 1999;28(1):41-6.
- 590. den Broeder A, van de Putte L, Rau R, et al. A single dose, placebo controlled study of the fully human anti-tumor necrosis factoralpha antibody adalimumab (D2E7) in patients with rheumatoid arthritis. J Rheumatol. 2002 Nov;29(11):2288-98.
- 591. den Broeder AA, Assmann KJ, van Riel PL, et al. Nephrotic syndrome as a complication of anti-TNFalpha in a patient with rheumatoid arthritis. Neth J Med. 2003 Apr;61(4):137-41.
- 592. den Broeder AA, Creemers MC, Fransen J, et al. Risk factors for surgical site infections and other complications in elective surgery in patients with rheumatoid arthritis with special attention for anti-tumor necrosis factor: a large retrospective study. J Rheumatol 2007;34(4):689-95.
- 593. Den Broeder AA, Creemers MC, van Gestel AM, et al. Dose titration using the Disease Activity Score (DAS28) in rheumatoid arthritis patients treated with anti-TNF-alpha. Rheumatology (Oxford). 2002 Jun;41(6):638-42.
- 594. den Broeder AA, Joosten LA, Saxne T, et al. Long term anti-tumour necrosis factor alpha monotherapy in rheumatoid arthritis: effect on radiological course and prognostic value of markers of cartilage turnover and endothelial activation. Ann Rheum Dis. 2002 Apr;61(4):311-8.
- 595. den Broeder AA, Wanten GJ, Oyen WJ, et al. Neutrophil migration and production of reactive oxygen species during treatment with a fully human anti-tumor necrosis factor-alpha monoclonal antibody in patients with rheumatoid arthritis. J Rheumatol. 2003 Feb;30(2):232-7.
- 596. Denault A, Dimopoulos MA, Fitzcharles MA. Meningoencephalitis and peripheral neuropathy complicating adult Still's disease. J Rheumatol. 1990 May;17(5):698-700.

- 597. Deng A, Harvey V, Sina B, et al. Interstitial granulomatous dermatitis associated with the use of tumor necrosis factor alpha inhibitors. Arch Dermatol. 2006 Feb;142(2):198-202.
- 598. Denis B, Lefort A, Flipo RM, et al. Longterm follow-up of patients with tuberculosis as a complication of tumour necrosis factor (TNF)-alpha antagonist therapy: safe reinitiation of TNF-alpha blockers after appropriate anti-tuberculous treatment. Clin Microbiol Infect. 2008 Feb;14(2):183-6.
- 599. Deodhar A, Allen E, Daoud K, et al. Vasculitis secondary to staphylococcal Protein A immunoadsorption (Prosorba column) treatment in rheumatoid arthritis. Semin Arthritis Rheum. 2002 Aug;32(1):3-9.
- 600. Dequeker J, Borghs H, Van Cleemput J, et al. Transplantation osteoporosis and corticosteroid-induced osteoporosis in autoimmune diseases: experience with alfacalcidol. Z Rheumatol. 2000;59 Suppl 1:53-7.
- 601. Dereure O, Guillot B, Jorgensen C, et al. Psoriatic lesions induced by antitumour necrosis factor-alpha treatment: two cases. Br J Dermatol. 2004 Aug;151(2):506-7.
- 602. Derot G, Marini-Portugal A, Maitre B, et al. Marked regression of pulmonary rheumatoid nodules under etanercept therapy. J Rheumatol. 2009 Feb;36(2):437-9.
- 603. Dervieux T, Greenstein N, Kremer J. Pharmacogenomic and metabolic biomarkers in the folate pathway and their association with methotrexate effects during dosage escalation in rheumatoid arthritis. Arthritis Rheum. 2006 Oct;54(10):3095-103.
- 604. Desai D, Goldbach-Mansky R, Milner JD, et al. Anaphylactic reaction to anakinra in a rheumatoid arthritis patient intolerant to multiple nonbiologic and biologic disease-modifying antirheumatic drugs. Ann Pharmacother. 2009 May;43(5):967-72.
- 605. Despaux J, Manzoni P, Toussirot E, et al. Prospective study of the prevalence of bronchiectasis in rheumatoid arthritis using

- high-resolution computed tomography. Rev Rhum Engl Ed. 1998 Jul-Sep;65(7-9):453-61.
- 606. Dessein PH, Joffe BI. Suppression of circulating interleukin-6 concentrations is associated with decreased endothelial activation in rheumatoid arthritis. Clin Exp Rheumatol. 2006 Mar-Apr;24(2):161-7.
- 607. Dessein PH, Joffe BI, Stanwix AE, et al. Hyposecretion of the adrenal androgen dehydroepiandrosterone sulfate and its relation to clinical variables in inflammatory arthritis. Arthritis Res. 2001;3(3):183-8.
- 608. Dessein PH, Woodiwiss AJ, Joffe BI, et al. Aminotransferases are associated with insulin resistance and atherosclerosis in rheumatoid arthritis. BMC Cardiovasc Disord. 2007;7:31.
- 609. Devauchelle-Pensec V, Pennec Y, Morvan J, et al. Improvement of Sjogren's syndrome after two infusions of rituximab (anti-CD20). Arthritis Rheum. 2007 Mar 15;57(2):310-7.
- 610. Devos SA, Van Den Bossche N, De Vos M, et al. Adverse skin reactions to anti-TNF-alpha monoclonal antibody therapy. Dermatology. 2003;206(4):388-90.
- 611. Dhaille F, Viseux V, Caudron A, et al. Cutaneous sarcoidosis occurring during anti-TNF-alpha treatment: report of two cases. Dermatology. 2010;220(3):234-7.
- 612. di Comite G, Marinosci A, Di Matteo P, et al. Neuroendocrine modulation induced by selective blockade of TNF-alpha in rheumatoid arthritis. Ann N Y Acad Sci. 2006 Jun;1069:428-37.
- 613. Di Poi E, Perin A, Morassi MP, et al. Switching to etanercept in patients with rheumatoid arthritis with no response to infliximab. Clin Exp Rheumatol. 2007 Jan-Feb;25(1):85-7.
- 614. Dichamp I, Bourgeois A, Dirand C, et al.
 Increased nuclear factor-kappaB activation
 in peripheral blood monocytes of patients
 with rheumatoid arthritis is mediated

- primarily by tumor necrosis factor-alpha. J Rheumatol. 2007 Oct;34(10):1976-83.
- of sulphasalazine on urinary excretion of the hydroxypyridinium crosslinks of collagen in patients with rheumatoid arthritis. Yonsei Med J. 2002 Aug;43(4):435-40.
- 616. Dilhuydy MS, Vatan R, Etienne G, et al. Prolonged efficacy of infliximab for refractory adult-onset Still's disease. Clin Exp Rheumatol. 2005 Jan-Feb;23(1):121-2.
- 617. Dimakou K, Papaioannides D, Latsi P, et al. Disseminated tuberculosis complicating anti-TNF-alpha treatment. Int J Clin Pract. 2004 Nov;58(11):1052-5.
- 618. Diskin CJ, Stokes TJ, Dansby LM, et al. Removal of methotrexate by peritoneal dialysis and hemodialysis in a single patient with end-stage renal disease. Am J Med Sci. 2006 Sep;332(3):156-8.
- 619. Dockery KM, Sismanis A, Abedi E. Rheumatoid arthritis of the larynx: the importance of early diagnosis and corticosteroid therapy. South Med J. 1991 Jan;84(1):95-6.
- 620. Doggrell SA. Triamcinolone: new and old indications. Expert Opin Pharmacother. 2001 Jul;2(7):1177-86.
- 621. Doggrell SA. Is tocilizumab an option for the treatment of arthritis? Expert Opin Pharmacother. 2008 Aug;9(11):2009-13.
- 622. Dohn UM, Skjodt H, Hetland ML, et al. No erosive progression revealed by MRI in rheumatoid arthritis patients treated with etanercept, even in patients with persistent MRI and clinical signs of joint inflammation. Clin Rheumatol. 2007 Nov;26(11):1857-61.
- 623. Dombrecht EJ, Aerts NE, Schuerwegh AJ, et al. Influence of anti-tumor necrosis factor therapy (Adalimumab) on regulatory T cells and dendritic cells in rheumatoid arthritis. Clin Exp Rheumatol. 2006 Jan-Feb;24(1):31-7.

- 624. Domiciano DS, de Carvalho JF, Macedo AR, et al. Central diabetes insipidus induced by tuberculosis in a rheumatoid arthritis patient. Acta Reumatol Port. 2010 Apr-Jun;35(2):232-5.
- 625. Domm A. A patient's reaction to infliximab. Ann Allergy Asthma Immunol. 2003 Mar;90(3):298-301.
- 626. Donahue KE, Gartlehner G, Jonas DE, et al. Systematic review: comparative effectiveness and harms of disease-modifying medications for rheumatoid arthritis. Ann Intern Med. 2008 Jan 15;148(2):124-34.
- 627. Doran MF, Crowson CS, Pond GR, et al. Predictors of infection in rheumatoid arthritis. Arthritis Rheum. 2002 Sep;46(9):2294-300.
- 628. Doran MF, Crowson CS, Pond GR, et al. Frequency of infection in patients with rheumatoid arthritis compared with controls: a population-based study. Arthritis Rheum. 2002 Sep;46(9):2287-93.
- 629. Dore RK, Mathews S, Schechtman J, et al. The immunogenicity, safety, and efficacy of etanercept liquid administered once weekly in patients with rheumatoid arthritis. Clin Exp Rheumatol. 2007 Jan-Feb;25(1):40-6.
- 630. Doria AS, Kiss MH, Sallum AM, et al.
 Correlation between osteochondral changes
 depicted by magnetic resonance imaging
 and disease progression. Rev Hosp Clin Fac
 Med Sao Paulo. 2001 Jul-Aug;56(4):107-14.
- 631. Doshi JA, Li P, Puig A. Impact of the Medicare Modernization Act of 2003 on utilization and spending for medicare part B-covered biologics in rheumatoid arthritis. Arthritis Care Res (Hoboken). 2010 Mar;62(3):354-61.
- 632. Douglas G, Bird K, Flume P, et al. Wegener's granulomatosis in patients with rheumatoid arthritis. J Rheumatol. 2003 Sep;30(9):2064-9.
- 633. Doulton TW, Tucker B, Reardon J, et al. Antineutrophil cytoplasmic antibody-associated necrotizing crescentic

- glomerulonephritis in a patient receiving treatment with etanercept for severe rheumatoid arthritis. Clin Nephrol. 2004 Sep;62(3):234-8.
- 634. Drosos A. Methotrexate intolerance in elderly patients with rheumatoid arthritis: what are the alternatives? Drugs Aging. 2003;20(10):723-36.
- 635. Drouin J, Haraoui B. Predictors of clinical response and radiographic progression in patients with rheumatoid arthritis treated with methotrexate monotherapy. J Rheumatol. 2010 Jul;37(7):1405-10.
- 636. Drozdzik M, Rudas T, Pawlik A, et al. Reduced folate carrier-1 80G>A polymorphism affects methotrexate treatment outcome in rheumatoid arthritis. Pharmacogenomics J. 2007 Dec;7(6):404-7.
- 637. Drozdzik M, Rudas T, Pawlik A, et al. The effect of 3435C>T MDR1 gene polymorphism on rheumatoid arthritis treatment with disease-modifying antirheumatic drugs. Eur J Clin Pharmacol. 2006 Nov;62(11):933-7.
- 638. Drynda S, Kuhne C, Kekow J. Soluble tumour necrosis factor receptor treatment does not affect raised transforming growth factor beta levels in rheumatoid arthritis.

 Ann Rheum Dis. 2002 Mar;61(3):254-6.
- 639. Dubois T, Bisagni-Faure A, Coste J, et al. High levels of antibodies to annexins V and VI in patients with rheumatoid arthritis. J Rheumatol. 1995 Jul;22(7):1230-4.
- 640. Ducharme J, Pelletier C, Zacharias R. The safety of infliximab infusions in the community setting. Can J Gastroenterol 2010;24(5):307-11.
- 641. Duclos M, Gossec L, Ruyssen-Witrand A, et al. Retention rates of tumor necrosis factor blockers in daily practice in 770 rheumatic patients. J Rheumatol 2006;33(12):2433-8.
- 642. Ducoulombier V, Solau E, Coquerelle P, et al. Long-term results of infliximab therapy in rheumatoid arthritis: experience acquired by the North-Pas-de-Calais hospital

- network. Joint Bone Spine. 2007 Jan;74(1):56-9.
- 643. Duftner C, Dejaco C, Larcher H, et al. Biologicals in rheumatology: Austrian experiences from a rheumatic outpatient clinic. Rheumatol Int. 2008 Nov;29(1):69-73.
- 644. Dumont-Berset M, Laffitte E, Gerber C, et al. Eczematous drug eruption after infliximab. Br J Dermatol. 2004
 Dec:151(6):1272-3.
- 645. Dunne CA, Moran CJ, Thompson PW. The effect of regular intramuscular corticosteroid therapy on bone mineral density in rheumatoid patients. Scand J Rheumatol. 1995;24(1):48-9.
- 646. Durez P, Malghem J, Nzeusseu Toukap A, et al. Treatment of early rheumatoid arthritis: a randomized magnetic resonance imaging study comparing the effects of methotrexate alone, methotrexate in combination with infliximab, and methotrexate in combination with intravenous pulse methylprednisolone. Arthritis Rheum 2007;56(12):3919-27.
- 647. Durez P, Nzeusseu Toukap A, Lauwerys BR, et al. A randomised comparative study of the short term clinical and biological effects of intravenous pulse methylprednisolone and infliximab in patients with active rheumatoid arthritis despite methotrexate treatment. Ann Rheum Dis. 2004 Sep;63(9):1069-74.
- 648. Durez P, Van den Bosch F, Corluy L, et al. A dose adjustment in patients with rheumatoid arthritis not optimally responding to a standard dose of infliximab of 3 mg/kg every 8 weeks can be effective: a Belgian prospective study. Rheumatology (Oxford). 2005 Apr;44(4):465-8.
- 649. Dursun AB, Kalac N, Ozkan B, et al. Pulmonary tuberculosis in patients with rheumatoid arthritis (four case reports). Rheumatol Int. 2002 Jan;21(4):153-7.
- 650. Dweik M, Baethge BA, Duarte AG.
 Coccidioidomycosis pneumonia in a
 nonendemic area associated with infliximab.
 South Med J. 2007 May;100(5):517-8.

- 651. Eberhardt K, Rydgren L, Fex E, et al. D-penicillamine in early rheumatoid arthritis: experience from a 2-year double blind placebo controlled study. Clin Exp Rheumatol. 1996 Nov-Dec;14(6):625-31.
- 652. Eberhardt K, Sandqvist G, Geborek P. Hand function tests are important and sensitive tools for assessment of treatment response in patients with rheumatoid arthritis. Scand J Rheumatol. 2008 Mar-Apr;37(2):109-12.
- 653. Eberhardt R, Kruger K, Reiter W, et al. Long-term therapy with the new glucocorticosteroid deflazacort in rheumatoid arthritis. Double-blind controlled randomized 12-months study against prednisone. Arzneimittelforschung. 1994 May;44(5):642-7.
- 654. Eder L, Chandran V, Gladman DD. From ankylosis to pencil-in-cup deformity in psoriatic arthritis: a case report. Clin Exp Rheumatol. 2009 Jul-Aug;27(4):661-3.
- 655. Edwards CJ, Cooper C, Fisher D, et al. The importance of the disease process and disease-modifying antirheumatic drug treatment in the development of septic arthritis in patients with rheumatoid arthritis. Arthritis Rheum 2007;57(7):1151-7.
- 656. Edwards JC, Szczepanski L, Szechinski J, et al. Efficacy of B-cell-targeted therapy with rituximab in patients with rheumatoid arthritis. N Engl J Med. 2004 Jun 17;350(25):2572-81.
- 657. Edwards KR, Mowad CM, Tyler WB. Worsening injection site reactions with continued use of etanercept. J Drugs Dermatol. 2003 Apr;2(2):184-7.
- 658. Efde MN, Houtman PM, Spoorenberg JP, et al. Tonsillar tuberculosis in a rheumatoid arthritis patient receiving anti-TNFalpha (adalimumab) treatment. Neth J Med. 2005 Mar;63(3):112-4.
- 659. Efthimiou P, Georgy S. Pathogenesis and management of adult-onset Still's disease. Semin Arthritis Rheum. 2006
 Dec;36(3):144-52.

- 660. Eggert M, Kluter A, Rusch D, et al. Expression analysis of the glucocorticoid receptor and the nuclear factor-kB subunit p50 in lymphocytes from patients with rheumatoid arthritis. J Rheumatol. 2002 Dec;29(12):2500-6.
- 661. Egnatios G, Warthan MM, Pariser R, et al. Pustular psoriasis following treatment of rheumatoid arthritis with TNF-alpha inhibitors. J Drugs Dermatol. 2008 Oct;7(10):975-7.
- 662. Eijsbouts AM, van den Hoogen FH, Laan RF, et al. Hypothalamic-pituitary-adrenal axis activity in patients with rheumatoid arthritis. Clin Exp Rheumatol. 2005 Sep-Oct;23(5):658-64.
- 663. Eklow C, Makrygiannakis D, Backdahl L, et al. Cellular distribution of the C-type II lectin dendritic cell immunoreceptor (DCIR) and its expression in the rheumatic joint: identification of a subpopulation of DCIR+ T cells. Ann Rheum Dis. 2008
 Dec:67(12):1742-9.
- 664. Eklund KK, Leirisalo-Repo M, Ranta P, et al. Serum IL-1beta levels are associated with the presence of erosions in recent onset rheumatoid arthritis. Clin Exp Rheumatol. 2007 Sep-Oct;25(5):684-9.
- 665. Eklund KK, Peltomaa R, Leirisalo-Repo M. Occurrence of pulmonary thromboembolism during infliximab therapy. Clin Exp Rheumatol. 2003 Sep-Oct;21(5):679.
- 666. El Maghraoui A, Do Santos Zounon AA, Jroundi I, et al. Reproducibility of bone mineral density measurements using dual X-ray absorptiometry in daily clinical practice. Osteoporos Int. 2005 Dec;16(12):1742-8.
- 667. Elkayam O, Burke M, Vardinon N, et al. Autoantibodies profile of rheumatoid arthritis patients during treatment with infliximab. Autoimmunity. 2005

 Mar; 38(2):155-60.
- 668. Elkayam O, Caspi D. Infliximab induced lupus in patients with rheumatoid arthritis. Clin Exp Rheumatol. 2004 Jul-Aug;22(4):502-3.

- 669. Elkayam O, Caspi D, Reitblatt T, et al. The effect of tumor necrosis factor blockade on the response to pneumococcal vaccination in patients with rheumatoid arthritis and ankylosing spondylitis. Semin Arthritis Rheum. 2004 Feb;33(4):283-8.
- 670. Elkayam O, Hawkins PN, Lachmann H, et al. Rapid and complete resolution of proteinuria due to renal amyloidosis in a patient with rheumatoid arthritis treated with infliximab. Arthritis Rheum. 2002 Oct;46(10):2571-3.
- 671. Elkayam O, Paran D, Flusser G, et al.
 Insufficiency fractures in rheumatic patients:
 misdiagnosis and underlying characteristics.
 Clin Exp Rheumatol. 2000 MayJun;18(3):369-74.
- 672. Elkayam O, Yaron I, Shirazi I, et al. Serum levels of IL-10, IL-6, IL-1ra, and sIL-2R in patients with psoriatic arthritis. Rheumatol Int. 2000;19(3):101-5.
- 673. ElKayam O, Yaron M, Caspi D. From wheels to feet: a dramatic response of severe chronic psoriatic arthritis to etanercept. Ann Rheum Dis. 2000 Oct;59(10):839.
- 674. Ellerton ML. When parents and children disagree about care. Can Nurse. 2000 Aug;96(7):35-6.
- 675. Ellingsen T, Hornung N, Moller BK, et al. In active chronic rheumatoid arthritis, dipeptidyl peptidase IV density is increased on monocytes and CD4(+) T lymphocytes. Scand J Immunol. 2007 Oct;66(4):451-7.
- 676. Ellingsen T, Hornung N, Moller BK, et al.
 Differential effect of methotrexate on the
 increased CCR2 density on circulating CD4
 T lymphocytes and monocytes in active
 chronic rheumatoid arthritis, with a down
 regulation only on monocytes in responders.
 Ann Rheum Dis. 2007 Feb;66(2):151-7.
- 677. Elliott MJ, Maini RN, Feldmann M, et al. Randomised double-blind comparison of chimeric monoclonal antibody to tumour necrosis factor alpha (cA2) versus placebo in rheumatoid arthritis. Lancet. 1994 Oct 22;344(8930):1105-10.

- 678. Emery P, Breedveld F, van der Heijde D, et al. Two-year clinical and radiographic results with combination etanerceptmethotrexate therapy versus monotherapy in early rheumatoid arthritis: a two-year, double-blind, randomized study. Arthritis Rheum 2010;62(3):674-82.
- 679. Emery P, Breedveld FC, Hall S, et al. Comparison of methotrexate monotherapy with a combination of methotrexate and etanercept in active, early, moderate to severe rheumatoid arthritis (COMET): a randomised, double-blind, parallel treatment trial. Lancet 2008;372(9636):375-82.
- 680. Emery P, Deodhar A, Rigby WF, et al. Efficacy and safety of different doses and retreatment of rituximab: a randomised, placebo-controlled trial in patients who are biological naive with active rheumatoid arthritis and an inadequate response to methotrexate (Study Evaluating Rituximab's Efficacy in MTX iNadequate rEsponders (SERENE)). Ann Rheum Dis 2010;69(9):1629-35.
- 681. Emery P, Fleischmann RM, Moreland LW, et al. Golimumab, a human anti-tumor necrosis factor alpha monoclonal antibody, injected subcutaneously every four weeks in methotrexate-naive patients with active rheumatoid arthritis: twenty-four-week results of a phase III, multicenter, randomized, double-blind, placebocontrolled study of golimumab before methotrexate as first-line therapy for early-onset rheumatoid arthritis. Arthritis Rheum 2009;60(8):2272-83.
- 682. Emery P, Keystone E, Tony HP, et al. IL-6 receptor inhibition with tocilizumab improves treatment outcomes in patients with rheumatoid arthritis refractory to antitumour necrosis factor biologicals: results from a 24-week multicentre randomised placebo-controlled trial. Ann Rheum Dis 2008;67(11):1516-23.
- 683. Emery P, Kosinski M, Li T, et al. Treatment of rheumatoid arthritis patients with abatacept and methotrexate significantly improved health-related quality of life. J Rheumatol. 2006 Apr;33(4):681-9.

- 684. Emkey RD, Lindsay R, Lyssy J, et al. The systemic effect of intraarticular administration of corticosteroid on markers of bone formation and bone resorption in patients with rheumatoid arthritis. Arthritis Rheum. 1996 Feb;39(2):277-82.
- 685. Emlen W, Niebur J, Kadera R. Accelerated in vitro apoptosis of lymphocytes from patients with systemic lupus erythematosus. J Immunol. 1994 Apr 1;152(7):3685-92.
- 686. Engels EA, Cerhan JR, Linet MS, et al. Immune-related conditions and immune-modulating medications as risk factors for non-Hodgkin's lymphoma: a case-control study. Am J Epidemiol. 2005 Dec 15;162(12):1153-61.
- 687. Epler GR. Bronchiolitis obliterans organizing pneumonia. Semin Respir Infect. 1995 Jun;10(2):65-77.
- 688. Eriksson C, Engstrand S, Sundqvist KG, et al. Autoantibody formation in patients with rheumatoid arthritis treated with anti-TNF alpha. Ann Rheum Dis. 2005
 Mar;64(3):403-7.
- 689. Eriksson C, Rantapaa-Dahlqvist S, Sundqvist KG. T-cell expression of CD91 a marker of unresponsiveness to anti-TNF therapy in rheumatoid arthritis. APMIS. 2010 Nov;118(11):837-45.
- 690. Ernestam S, Hafstrom I, Werner S, et al. Increased DHEAS levels in patients with rheumatoid arthritis after treatment with tumor necrosis factor antagonists: evidence for improved adrenal function. J Rheumatol. 2007 Jul;34(7):1451-8.
- 691. Escalante A, Kaufman RL, Quismorio FP, Jr., et al. Cardiac compression in rheumatoid pericarditis. Semin Arthritis Rheum. 1990 Dec;20(3):148-63.
- 692. Esmailzadeh A, Yousefi P, Farhi D, et al. Predictive factors of eczema-like eruptions among patients without cutaneous psoriasis receiving infliximab: a cohort study of 92 patients. Dermatology. 2009;219(3):263-7.
- 693. Esser AC, Abril A, Fayne S, et al. Acute development of multiple keratoacanthomas

- and squamous cell carcinomas after treatment with infliximab. J Am Acad Dermatol. 2004 May;50(5 Suppl):S75-7.
- 694. Estradas J, Pascual-Ramos V, Martinez B, et al. Autoimmune hepatitis with giant-cell transformation. Ann Hepatol. 2009 Jan-Mar;8(1):68-70.
- 695. Etemad L, Yu EB, Wanke LA. Dose adjustment over time of etanercept and infliximab in patients with rheumatoid arthritis. Manag Care Interface. 2005 Apr;18(4):21-7.
- 696. Ettefagh L, Nedorost S, Mirmirani P.
 Alopecia areata in a patient using infliximab: new insights into the role of tumor necrosis factor on human hair follicles. Arch Dermatol. 2004
 Aug;140(8):1012.
- 697. Evans CH, Robbins PD, Ghivizzani SC, et al. Gene transfer to human joints: progress toward a gene therapy of arthritis. Proc Natl Acad Sci U S A. 2005 Jun 14;102(24):8698-703.
- 698. Eyigor S, Karapolat H, Kirazli Y. Efficacy of etanercept and complete decongestive physical therapy in bilateral lower-limb lymphoedema associated with rheumatoid arthritis: a case report. Adv Ther. 2008 Jan;25(1):23-8.
- 699. Fabre S, Dupuy AM, Dossat N, et al. Protein biochip array technology for cytokine profiling predicts etanercept responsiveness in rheumatoid arthritis. Clin Exp Immunol. 2008 Aug;153(2):188-95.
- 700. Fabre S, Gibert C, Lechiche C, et al. Visceral leishmaniasis infection in a rheumatoid arthritis patient treated with infliximab. Clin Exp Rheumatol. 2005 Nov-Dec;23(6):891-2.
- 701. Fabre S, Gibert C, Lechiche C, et al. Primary cutaneous Nocardia otitidiscaviarum infection in a patient with rheumatoid arthritis treated with infliximab. J Rheumatol. 2005 Dec:32(12):2432-3.
- 702. Fabre S, Guisset C, Tatem L, et al. Protein biochip array technology to monitor

- rituximab in rheumatoid arthritis. Clin Exp Immunol. 2009 Mar;155(3):395-402.
- 703. Familian A, Voskuyl AE, van Mierlo GJ, et al. Infliximab treatment reduces complement activation in patients with rheumatoid arthritis. Ann Rheum Dis. 2005
 Jul;64(7):1003-8.
- 704. Fantasia JE. Bisphosphonates--what the dentist needs to know: practical considerations. J Oral Maxillofac Surg. 2009 May;67(5 Suppl):53-60.
- 705. Fantini F, Gallazzi M, Gattinara M, et al. Monitoring bone mineralization in chronic rheumatic children on steroid treatment.

 Acta Univ Carol [Med] (Praha). 1994;40(1-4):17-22.
- 706. Fantini F, Gallazzi M, Gattinara M, et al. Monitoring osteopenia by dual-photon absorptiometry in chronically ill children treated with steroids. Acta Univ Carol [Med] (Praha). 1991;37(1-2):68-72.
- 707. Farah RE, Shay MD. Pulmonary sarcoidosis associated with etanercept therapy. Pharmacotherapy. 2007 Oct;27(10):1446-8.
- 708. Farahani P, Levine M, Gaebel K, et al. Clinical data gap between phase III clinical trials (pre-marketing) and phase IV (post-marketing) studies: evaluation of etanercept in rheumatoid arthritis. Can J Clin Pharmacol. 2005 Fall;12(3):e254-63.
- 709. Farahani P, Levine M, Gaebel K, et al. Community-based evaluation of etanercept in patients with rheumatoid arthritis. J Rheumatol. 2006 Apr;33(4):665-70.
- 710. Farukhi FI, Bollinger K, Ruggieri P, et al. Infliximab-associated third nerve palsy. Arch Ophthalmol. 2006 Jul;124(7):1055-7.
- 711. Fautrel B, Borget C, Rozenberg S, et al.
 Corticosteroid sparing effect of low dose
 methotrexate treatment in adult Still's
 disease. J Rheumatol. 1999 Feb;26(2):373-8.
- 712. Fautrel B, Flipo RM, Saraux A. Eligibility of rheumatoid arthritis patients for anti-TNF-alpha therapy according to the 2005 recommendations of the French and British

- Societies for Rheumatology. Rheumatology (Oxford). 2008 Nov;47(11):1698-703.
- 713. Fautrel B, Foltz V, Frances C, et al.
 Regression of subacute cutaneous lupus
 erythematosus in a patient with rheumatoid
 arthritis treated with a biologic tumor
 necrosis factor alpha-blocking agent:
 comment on the article by Pisetsky and the
 letter from Aringer et al. Arthritis Rheum.
 2002 May;46(5):1408-9; author reply 9.
- 714. Fautrel B, Sibilia J, Mariette X, et al. Tumour necrosis factor alpha blocking agents in refractory adult Still's disease: an observational study of 20 cases. Ann Rheum Dis. 2005 Feb;64(2):262-6.
- 715. Fautrel B, Woronoff-Lemsi MC, Ethgen M, et al. Impact of medical practices on the costs of management of rheumatoid arthritis by anti-TNFalpha biological therapy in France. Joint Bone Spine. 2005 Dec;72(6):550-6.
- 716. Favalli EG, Arreghini M, Arnoldi C, et al. Anti-tumor necrosis factor alpha switching in rheumatoid arthritis and juvenile chronic arthritis. Arthritis Rheum. 2004 Apr 15;51(2):301-2.
- 717. Favalli EG, Marchesoni A, Colombo GL, et al. Pattern of use, economic burden and vial optimization of infliximab for rheumatoid arthritis in Italy. Clin Exp Rheumatol. 2008 Jan-Feb;26(1):45-51.
- 718. Favalli EG, Sinigaglia L, Varenna M, et al. Drug-induced lupus following treatment with infliximab in rheumatoid arthritis. Lupus. 2002;11(11):753-5.
- 719. Favero M, Schiavon F, Riato L, et al. Rheumatoid arthritis is the major risk factor for septic arthritis in rheumatological settings. Autoimmun Rev. 2008 Oct;8(1):59-61.
- 720. Feijoo M, Tunez I, Tasset I, et al. Infliximab reduces myeloperoxidase concentration in chronic inflammatory joint diseases.
 Pharmacology. 2009;83(4):211-6.
- 721. Felder M, Ruegsegger P. Bone loss in patients with rheumatoid arthritis--effect of

- steroids measured by low dose quantitative computed tomography. Rheumatol Int. 1991:11(1):41-4.
- 722. Feldman SR, Gottlieb AB, Bala M, et al. Infliximab improves health-related quality of life in the presence of comorbidities among patients with moderate-to-severe psoriasis. Br J Dermatol. 2008 Sep;159(3):704-10.
- 723. Feldstein AC, Elmer PJ, Nichols GA, et al. Practice patterns in patients at risk for glucocorticoid-induced osteoporosis.

 Osteoporos Int. 2005 Dec;16(12):2168-74.
- 724. Feletar M, Brockbank JE, Schentag CT, et al. Treatment of refractory psoriatic arthritis with infliximab: a 12 month observational study of 16 patients. Ann Rheum Dis. 2004 Feb;63(2):156-61.
- 725. Feltelius N, Fored CM, Blomqvist P, et al. Results from a nationwide postmarketing cohort study of patients in Sweden treated with etanercept. Ann Rheum Dis. 2005 Feb;64(2):246-52.
- 726. Fernandes M, Vemuganti GK, Rao GN. Bilateral periocular psoriasis: an initial manifestation of acute generalized pustular psoriasis with coexistent Sjogren's syndrome. Clin Experiment Ophthalmol. 2007 Nov;35(8):763-6.
- 727. Fernandes NF, Martin RR, Schenker S. Trazodone-induced hepatotoxicity: a case report with comments on drug-induced hepatotoxicity. Am J Gastroenterol. 2000 Feb;95(2):532-5.
- 728. Fernandez-Castro M, Andreu JL, Munoz P, et al. Sepsis of a prosthetic joint and biological therapies. Rheumatology (Oxford). 2005 Aug;44(8):1076-7; author reply 5.
- 729. Fernandez-Nebro A, Irigoyen MV, Urena I, et al. Effectiveness, predictive response factors, and safety of anti-tumor necrosis factor (TNF) therapies in anti-TNF-naive rheumatoid arthritis. J Rheumatol 2007;34(12):2334-42.

- 730. Fernandez-Nebro A, Tomero E, Ortiz-Santamaria V, et al. Treatment of rheumatic inflammatory disease in 25 patients with secondary amyloidosis using tumor necrosis factor alpha antagonists. Am J Med. 2005 May;118(5):552-6.
- 731. Ferraccioli G, Casatta L, Bartoli E. Increase of bone mineral density and anabolic variables in patients with rheumatoid arthritis resistant to methotrexate after cyclosporin A therapy. J Rheumatol. 1996 Sep;23(9):1539-42.
- 732. Ferraccioli G, Guerra P, Rizzi V, et al. Cyclosporin A increases somatomedin C insulin-like growth factor I levels in chronic rheumatic diseases. J Rheumatol. 1995
 Jun;22(6):1060-4.
- 733. Ferraccioli G, Mecchia F, Di Poi E, et al. Anticardiolipin antibodies in rheumatoid patients treated with etanercept or conventional combination therapy: direct and indirect evidence for a possible association with infections. Ann Rheum Dis. 2002 Apr;61(4):358-61.
- 734. Ferraccioli G, Zoli A, Alivernini S, et al. Lupus anticoagulant and ischemic myocardial microangiopathy in rheumatoid arthritis. Nat Clin Pract Cardiovasc Med. 2006 Jun;3(6):339-43; quiz following 43.
- 735. Ferraccioli GF, Assaloni R, Di Poi E, et al. Rescue of combination therapy failures using infliximab, while maintaining the combination or monotherapy with methotrexate: results of an open trial. Rheumatology (Oxford). 2002
 Oct;41(10):1109-12.
- 736. Ferri C, Ferraccioli G, Ferrari D, et al. Safety of anti-tumor necrosis factor-alpha therapy in patients with rheumatoid arthritis and chronic hepatitis C virus infection. J Rheumatol. 2008 Oct;35(10):1944-9.
- 737. Fidalgo A, Baptista J, Rocha Paris F, et al. Etanercept for psoriasis: two case reports. Int J Clin Pharmacol Res. 2005;25(4):159-63.
- 738. Fiedorczyk M, Klimiuk PA, Sierakowski S, et al. Serum matrix metalloproteinases and tissue inhibitors of metalloproteinases in

- patients with early rheumatoid arthritis. J Rheumatol. 2006 Aug;33(8):1523-9.
- 739. Fiehn C, Andrassy K. Case number 29: hitting three with one strike: rapid improvement of psoriatic arthritis, psoriatic erythroderma, and secondary renal amyloidosis by treatment with infliximab (Remicade). Ann Rheum Dis. 2004 Mar;63(3):232.
- 740. Fiehn C, Jacki S, Heilig B, et al. Eight versus 16-week re-evaluation period in rheumatoid arthritis patients treated with leflunomide or methotrexate accompanied by moderate dose prednisone. Rheumatol Int. 2007 Aug;27(10):975-9.
- 741. Figueiredo IT, Morel J, Sany J, et al. Maintenance and tolerability of infliximab in a cohort of 152 patients with rheumatoid arthritis. Clin Exp Rheumatol. 2008 Jan-Feb;26(1):18-23.
- 742. Finckh A, Ciurea A, Brulhart L, et al. B cell depletion may be more effective than switching to an alternative anti-tumor necrosis factor agent in rheumatoid arthritis patients with inadequate response to anti-tumor necrosis factor agents. Arthritis Rheum 2007;56(5):1417-23.
- 743. Finckh A, Ciurea A, Brulhart L, et al. Which subgroup of patients with rheumatoid arthritis benefits from switching to rituximab versus alternative anti-tumour necrosis factor (TNF) agents after previous failure of an anti-TNF agent? Ann Rheum Dis 2010;69(2):387-93.
- 744. Finckh A, Dehler S, Gabay C. The effectiveness of leflunomide as a co-therapy of tumour necrosis factor inhibitors in rheumatoid arthritis: a population-based study. Ann Rheum Dis 2009;68(1):33-9.
- 745. Finckh A, Dudler J, Wermelinger F, et al. Influence of anti-infliximab antibodies and residual infliximab concentrations on the occurrence of acquired drug resistance to infliximab in rheumatoid arthritis patients. Joint Bone Spine. 2010 Jul;77(4):313-8.
- 746. Finckh A, Simard JF, Duryea J, et al. The effectiveness of anti-tumor necrosis factor therapy in preventing progressive

- radiographic joint damage in rheumatoid arthritis: a population-based study. Arthritis Rheum. 2006 Jan;54(1):54-9.
- 747. Finlay DG, Szauter K, Raju GS, et al. Tuberculous peritonitis. Am J Gastroenterol. 2005 Jul;100(7):1624-5.
- 748. Fiocco U, Ferro F, Vezzu M, et al. Rheumatoid and psoriatic knee synovitis: clinical, grey scale, and power Doppler ultrasound assessment of the response to etanercept. Ann Rheum Dis. 2005 Jun;64(6):899-905.
- 749. Firestein GS, Paine MM, Littman BH. Gene expression (collagenase, tissue inhibitor of metalloproteinases, complement, and HLA-DR) in rheumatoid arthritis and osteoarthritis synovium. Quantitative analysis and effect of intraarticular corticosteroids. Arthritis Rheum. 1991 Sep;34(9):1094-105.
- 750. Firth J, Helliwell P, Hale C, et al. The predictors of foot ulceration in patients with rheumatoid arthritis: a preliminary investigation. Clin Rheumatol. 2008
 Nov;27(11):1423-8.
- 751. Fischer P. Resolution of treatment-related arthralgias and serologic findings with a switch of TNF antagonist therapies in a patient with psoriatic arthritis. J Clin Rheumatol. 2007 Oct;13(5):294-5.
- 752. Fiter J, Nolla JM, Navarro MA, et al. Weak androgen levels, glucocorticoid therapy, and bone mineral density in postmenopausal women with rheumatoid arthritis. Joint Bone Spine. 2000;67(3):199-203.
- 753. Fitzgerald AA, Leclercq SA, Yan A, et al. Rapid responses to anakinra in patients with refractory adult-onset Still's disease. Arthritis Rheum. 2005 Jun;52(6):1794-803.
- 754. Flaisler F, Hedon B, Sany J, et al. A study of ovarian function in rheumatoid arthritis. Rev Rhum Engl Ed. 1995 Oct;62(9):549-54.
- 755. Fleischmann R. The clinical efficacy and safety of certolizumab pegol in rheumatoid arthritis. Expert Opin Biol Ther. 2010 May;10(5):773-86.

- 756. Fleischmann R, Baumgartner SW, Weisman MH, et al. Long term safety of etanercept in elderly subjects with rheumatic diseases.

 Ann Rheum Dis 2006;65(3):379-84.
- 757. Fleischmann R, Stern R, Iqbal I. Anakinra: an inhibitor of IL-1 for the treatment of rheumatoid arthritis. Expert Opin Biol Ther. 2004 Aug;4(8):1333-44.
- 758. Fleischmann R, Vencovsky J, van Vollenhoven RF, et al. Efficacy and safety of certolizumab pegol monotherapy every 4 weeks in patients with rheumatoid arthritis failing previous disease-modifying antirheumatic therapy: the FAST4WARD study. Ann Rheum Dis. 2009 Jun;68(6):805-11.
- 759. Fleischmann RM. Safety of anakinra, a recombinant interleukin-1 receptor antagonist (r-metHuIL-1ra), in patients with rheumatoid arthritis and comparison to anti-TNF-alpha agents. Clin Exp Rheumatol. 2002 Sep-Oct;20(5 Suppl 27):S35-41.
- 760. Fleischmann RM. Addressing the safety of anakinra in patients with rheumatoid arthritis. Rheumatology (Oxford). 2003
 May;42 Suppl 2:ii29-35.
- 761. Fleischmann RM. Progressive multifocal leukoencephalopathy following rituximab treatment in a patient with rheumatoid arthritis. Arthritis Rheum. 2009 Nov;60(11):3225-8.
- 762. Fleischmann RM, Cohen SB, Moreland LW, et al. Methotrexate dosage reduction in patients with rheumatoid arthritis beginning therapy with infliximab: the Infliximab Rheumatoid Arthritis Methotrexate Tapering (iRAMT) trial. Curr Med Res Opin. 2005 Aug;21(8):1181-90.
- 763. Fleischmann RM, Schechtman J, Bennett R, et al. Anakinra, a recombinant human interleukin-1 receptor antagonist (r-metHuIL-1ra), in patients with rheumatoid arthritis: A large, international, multicenter, placebo-controlled trial. Arthritis Rheum. 2003 Apr;48(4):927-34.
- 764. Flenaugh EL, Kolawole FO, Allen R. Dyspnea and dry cough in a patient with

- rheumatoid arthritis. Am Fam Physician. 2007 Jan 1;75(1):103-5.
- 765. Flendrie M, Creemers MC, van Riel PL. Titration of infliximab treatment in rheumatoid arthritis patients based on response patterns. Rheumatology (Oxford). 2007 Jan;46(1):146-9.
- 766. Flendrie M, Creemers MC, Welsing PM, et al. Survival during treatment with tumour necrosis factor blocking agents in rheumatoid arthritis. Ann Rheum Dis. 2003 Nov;62 Suppl 2:ii30-3.
- 767. Flendrie M, Creemers MC, Welsing PM, et al. The influence of previous and concomitant leflunomide on the efficacy and safety of infliximab therapy in patients with rheumatoid arthritis; a longitudinal observational study. Rheumatology (Oxford). 2005 Apr;44(4):472-8.
- 768. Foell D, Wittkowski H, Hammerschmidt I, et al. Monitoring neutrophil activation in juvenile rheumatoid arthritis by \$100A12 serum concentrations. Arthritis Rheum. 2004 Apr;50(4):1286-95.
- 769. Fomin I, Caspi D, Levy V, et al. Vaccination against influenza in rheumatoid arthritis: the effect of disease modifying drugs, including TNF alpha blockers. Ann Rheum Dis. 2006 Feb;65(2):191-4.
- 770. Fonollosa A, Segura A, Giralt J, et al. Tuberculous uveitis after treatment with etanercept. Graefes Arch Clin Exp Ophthalmol. 2007 Sep;245(9):1397-9.
- 771. Fonseca A, Wagner J, Yamaga LI, et al. (18) F-FDG PET imaging of rheumatoid articular and extraarticular synovitis. J Clin Rheumatol. 2008 Oct;14(5):307.
- 772. Fonseca JE, Canhao H, Tavares NJ, et al. Persistent low grade synovitis without erosive progression in magnetic resonance imaging of rheumatoid arthritis patients treated with infliximab over 1 year. Clin Rheumatol. 2009 Oct;28(10):1213-6.
- 773. Fonseca JE, Carvalho T, Cruz M, et al. Polymorphism at position -308 of the tumour necrosis factor alpha gene and

- rheumatoid arthritis pharmacogenetics. Ann Rheum Dis. 2005 May;64(5):793-4.
- 774. Font J, Ramos-Casals M, de la Red G, et al. Pure sensory neuropathy in primary Sjogren's syndrome. Longterm prospective followup and review of the literature. J Rheumatol. 2003 Jul;30(7):1552-7.
- 775. Foppiani L, Cutolo M, Sessarego P, et al. Desmopressin and low-dose ACTH test in rheumatoid arthritis. Eur J Endocrinol. 1998 Mar;138(3):294-301.
- 776. Forsblad d'Elia H, Pullerits R, Carlsten H, et al. Resistin in serum is associated with higher levels of IL-1Ra in post-menopausal women with rheumatoid arthritis. Rheumatology (Oxford). 2008
 Jul;47(7):1082-7.
- 777. Forsblad-d'Elia H, Carlsten H, Labrie F, et al. Low serum levels of sex steroids are associated with disease characteristics in primary Sjogren's syndrome; supplementation with dehydroepiandrosterone restores the concentrations. J Clin Endocrinol Metab. 2009 Jun;94(6):2044-51.
- 778. Forslind K, Boonen A, Albertsson K, et al. Hand bone loss measured by digital X-ray radiogrammetry is a predictor of joint damage in early rheumatoid arthritis. Scand J Rheumatol. 2009 Nov-Dec;38(6):431-8.
- 779. Forslind K, Hafstrom I, Ahlmen M, et al. Sex: a major predictor of remission in early rheumatoid arthritis? Ann Rheum Dis. 2007 Jan;66(1):46-52.
- 780. Forslund T, Hannonen P, Reitamo S, et al. Hypertension in cyclosporin A-treated patients is independent of circulating endothelin levels. J Intern Med. 1995 Jul;238(1):71-5.
- 781. Fortna RR, Gudjonsson JE, Seidel G, et al. Persistent pruritic papules and plaques: a characteristic histopathologic presentation seen in a subset of patients with adult-onset and juvenile Still's disease. J Cutan Pathol. 2010 Sep;37(9):932-7.

- 782. Fossaluzza V, De Vita S. Clinical differences between ANA/anti-ENA positive or negative primary Sjogren's syndrome. Clin Rheumatol. 1992 Sep;11(3):385-7.
- 783. Foster CS, Barrett F. Cataract development and cataract surgery in patients with juvenile rheumatoid arthritis-associated iridocyclitis. Ophthalmology. 1993 Jun;100(6):809-17.
- 784. Foster EN, Nguyen KK, Sheikh RA, et al. Crohn's disease associated with Sweet's syndrome and Sjogren's syndrome treated with infliximab. Clin Dev Immunol. 2005 Jun;12(2):145-9.
- 785. Fox RI, Stern M, Michelson P. Update in Sjogren syndrome. Curr Opin Rheumatol. 2000 Sep;12(5):391-8.
- 786. Fraenkel L, Bogardus ST, Concato J, et al. Patient preferences for treatment of rheumatoid arthritis. Ann Rheum Dis. 2004 Nov;63(11):1372-8.
- 787. Franchini S, Dagna L, Salvo F, et al. Efficacy of traditional and biologic agents in different clinical phenotypes of adult-onset Still's disease. Arthritis Rheum. 2010 Aug;62(8):2530-5.
- 788. Franck H, Gottwalt J. Peripheral bone density in patients with rheumatoid arthritis. Clin Rheumatol. 2009 Oct;28(10):1141-5.
- 789. Franklin CM. Clinical experience with soluble TNF p75 receptor in rheumatoid arthritis. Semin Arthritis Rheum. 1999 Dec;29(3):172-81.
- 790. Franklin J, Lunt M, Bunn D, et al. Risk and predictors of infection leading to hospitalisation in a large primary-carederived cohort of patients with inflammatory polyarthritis. Ann Rheum Dis. 2007 Mar;66(3):308-12.
- 791. Fransen J, Moens HB, Speyer I, et al. Effectiveness of systematic monitoring of rheumatoid arthritis disease activity in daily practice: a multicentre, cluster randomised controlled trial. Ann Rheum Dis. 2005 Sep;64(9):1294-8.

- 792. Fransen J, Stucki G, Twisk J, et al. Effectiveness of a measurement feedback system on outcome in rheumatoid arthritis: a controlled clinical trial. Ann Rheum Dis. 2003 Jul;62(7):624-9.
- 793. Fraser DA, Thoen J, Djoseland O, et al. Serum levels of interleukin-6 and dehydroepiandrosterone sulphate in response to either fasting or a ketogenic diet in rheumatoid arthritis patients. Clin Exp Rheumatol. 2000 May-Jun;18(3):357-62.
- 794. Fraser DA, Thoen J, Selvaag AM, et al. A preliminary study of circadian serum cortisol concentrations in response to a 72-hour fast in rheumatoid arthritis patients not previously treated with corticosteroids. Clin Rheumatol. 2001;20(2):85-7.
- 795. Frediani B, Falsetti P, Baldi F, et al. Effects of 4-year treatment with once-weekly clodronate on prevention of corticosteroid-induced bone loss and fractures in patients with arthritis: evaluation with dual-energy X-ray absorptiometry and quantitative ultrasound. Bone. 2003 Oct;33(4):575-81.
- 796. Frediani B, Falsetti P, Bisogno S, et al. Effects of high dose methylprednisolone pulse therapy on bone mass and biochemical markers of bone metabolism in patients with active rheumatoid arthritis: a 12-month randomized prospective controlled study. J Rheumatol. 2004 Jun;31(6):1083-7.
- 797. Fries JF, Bruce B. Rates of serious gastrointestinal events from low dose use of acetylsalicylic acid, acetaminophen, and ibuprofen in patients with osteoarthritis and rheumatoid arthritis. J Rheumatol. 2003 Oct;30(10):2226-33.
- 798. Fries JF, Miller SR, Spitz PW, et al. Identification of patients at risk for gastropathy associated with NSAID use. J Rheumatol Suppl. 1990 Feb;20:12-9.
- 799. Fries W, Giofre MR, Catanoso M, et al. Treatment of acute uveitis associated with Crohn's disease and sacroileitis with infliximab. Am J Gastroenterol. 2002 Feb;97(2):499-500.
- 800. Fu A, Bertouch JV, McNeil HP.
 Disseminated Salmonella typhimurium

- infection secondary to infliximab treatment. Arthritis Rheum. 2004 Sep;50(9):3049.
- 801. Fucci JC, Nightengale ML. Primary esophageal histoplasmosis. Am J Gastroenterol. 1997 Mar;92(3):530-1.
- 802. Fuchs I, Avnon L, Freud T, et al. Repeated tuberculin skin testing following therapy with TNF-alpha inhibitors. Clin Rheumatol. 2009 Feb;28(2):167-72.
- 803. Fuerst M, Mohl H, Baumgartel K, et al. Leflunomide increases the risk of early healing complications in patients with rheumatoid arthritis undergoing elective orthopedic surgery. Rheumatol Int 2006;26(12):1138-42.
- 804. Fujikawa S. Non-steroidal antiinflammatory drugs and slow-acting antirheumatic drugs in juvenile rheumatoid arthritis. Acta Paediatr Jpn. 1993 Oct;35(5):447-53.
- 805. Fujita K, Tanaka E, Hatta K, et al. An autopsy case of Mycobacterium abscessus pulmonary infection complicated with rheumatoid arthritis. Intern Med. 2008;47(13):1273-6.
- 806. Fujita Y, Fujii T, Takeda N, et al. Successful treatment of primary Sjogren's syndrome with chronic natural killer lymphocytosis by high-dose prednisolone and indomethacin farnesil. Intern Med. 2007;46(5):251-4.
- 807. Fujiwara H, Nishimoto N, Hamano Y, et al. Masked early symptoms of pneumonia in patients with rheumatoid arthritis during tocilizumab treatment: a report of two cases. Mod Rheumatol. 2009;19(1):64-8.
- 808. Fukino K, Kawashima T, Suzuki M, et al. Methylenetetrahydrofolate reductase and reduced folate carrier-1 genotypes and methotrexate serum concentrations in patients with rheumatoid arthritis. J Toxicol Sci. 2007 Oct;32(4):449-52.
- 809. Fukuchi M, Mizushima Y, Hori T, et al. Cryptococcal pleural effusion in a patient with chronic renal failure receiving long-term corticosteroid therapy for rheumatoid arthritis. Intern Med. 1998 Jun;37(6):534-7.

- 810. Fulchiero GJ, Jr., Salvaggio H, Drabick JJ, et al. Eruptive latent metastatic melanomas after initiation of antitumor necrosis factor therapies. J Am Acad Dermatol. 2007 May;56(5 Suppl):S65-7.
- 811. Fumagalli M, Incorvaia C, Nitti F, et al. The assessment of quality of life as a measure of gold salts treatment efficacy in rheumatoid arthritis. Minerva Med. 2002 Jun;93(3):199-202.
- 812. Funahashi K, Koyano S, Miura T, et al. Efficacy of tocilizumab and evaluation of clinical remission as determined by CDAI and MMP-3 level. Mod Rheumatol. 2009;19(5):507-12.
- 813. Funovits J, Aletaha D, Bykerk V, et al. The 2010 American College of Rheumatology/European League Against Rheumatism classification criteria for rheumatoid arthritis: methodological report phase I. Ann Rheum Dis. 2010 Sep;69(9):1589-95.
- 814. Furfaro N, Mease PJ. Nursing considerations for infusion therapy in rheumatoid arthritis versus malignancy. J Infus Nurs. 2008 Nov-Dec;31(6):350-60.
- 815. Furse RK, Rossetti RG, Seiler CM, et al.
 Oral administration of gammalinolenic acid,
 an unsaturated fatty acid with antiinflammatory properties, modulates
 interleukin-1 beta production by human
 monocytes. J Clin Immunol. 2002
 Mar;22(2):83-91.
- 816. Furst DE. Anakinra: review of recombinant human interleukin-I receptor antagonist in the treatment of rheumatoid arthritis. Clin Ther. 2004 Dec;26(12):1960-75.
- 817. Furst DE, Gaylis N, Bray V, et al. Openlabel, pilot protocol of patients with rheumatoid arthritis who switch to infliximab after an incomplete response to etanercept: the opposite study. Ann Rheum Dis 2007;66(7):893-9.
- 818. Furst DE, Schiff MH, Fleischmann RM, et al. Adalimumab, a fully human anti tumor necrosis factor-alpha monoclonal antibody, and concomitant standard antirheumatic therapy for the treatment of rheumatoid

- arthritis: results of STAR (Safety Trial of Adalimumab in Rheumatoid Arthritis). J Rheumatol. 2003 Dec;30(12):2563-71.
- 819. Furtado RN, Oliveira LM, Natour J. Polyarticular corticosteroid injection versus systemic administration in treatment of rheumatoid arthritis patients: a randomized controlled study. J Rheumatol. 2005 Sep;32(9):1691-8.
- 820. Furukawa K, Ohtani T, Furukawa F, et al. Infectious mononucleosis-like syndrome induced by salazosulfapyridine in a patient with rheumatoid arthritis. Mod Rheumatol. 2007;17(6):492-5.
- 821. Gadadhar H, Hawkins S, Huffstutter JE, et al. Cutaneous mucormycosis complicating methotrexate, prednisone, and infliximab therapy. J Clin Rheumatol. 2007 Dec;13(6):361-2.
- 822. Gadsby K, Deighton C. Characteristics and treatment responses of patients satisfying the BSR guidelines for anti-TNF in ankylosing spondylitis. Rheumatology (Oxford). 2007 Mar;46(3):439-41.
- 823. Gal I, Toth L, Szegedi L, et al. Gastric bleeding in a patient with rheumatoid arthritis complicated by immune thrombocytopenic purpura. Joint Bone Spine. 2008 May;75(3):350-2.
- 824. Galaria NA, Werth VP, Schumacher HR. Leukocytoclastic vasculitis due to etanercept. J Rheumatol. 2000 Aug;27(8):2041-4.
- 825. Galarraga B, Belch JJ, Pullar T, et al.
 Clinical improvement in rheumatoid arthritis
 is associated with healthier microvascular
 function in patients who respond to
 antirheumatic therapy. J Rheumatol. 2010
 Mar;37(3):521-8.
- 826. Galarraga B, Khan F, Kumar P, et al. Etanercept improves inflammation-associated arterial stiffness in rheumatoid arthritis. Rheumatology (Oxford). 2009 Nov;48(11):1418-23.
- 827. Galindo M, Pablos JL, Gomez-Reino JJ. Internuclear ophthalmoplegia in systemic

- lupus erythematosus. Semin Arthritis Rheum. 1998 Dec;28(3):179-86.
- 828. Ganeshan A, Quen L, Smith D. Occurrence of vesicocolic fistula with a use of etanercept: a cautionary tale. J Clin Rheumatol. 2005 Oct;11(5):290-1.
- 829. Garcia-Gomez C, Nolla JM, Valverde J, et al. High HDL-cholesterol in women with rheumatoid arthritis on low-dose glucocorticoid therapy. Eur J Clin Invest. 2008 Sep;38(9):686-92.
- 830. Garcia-Porrua C, Gonzalez-Gay MA.
 Successful treatment of refractory
 mononeuritis multiplex secondary to
 rheumatoid arthritis with the anti-tumour
 necrosis factor alpha monoclonal antibody
 infliximab. Rheumatology (Oxford). 2002
 Feb;41(2):234-5.
- 831. Garcia-Porrua C, Gonzalez-Gay MA, Quevedo V. Should anti-tumor necrosis factor-alpha be the first therapy for rheumatoid vasculitis? J Rheumatol. 2006 Feb;33(2):433; author reply -4.
- 832. Gardiner PV, Bell AL, Taggart AJ, et al. A potential pitfall in the use of the Disease Activity Score (DAS28) as the main response criterion in treatment guidelines for patients with rheumatoid arthritis. Ann Rheum Dis. 2005 Mar;64(3):506-7.
- 833. Garfield BE, Krahl T, Appel S, et al. Regulation of p38 MAP kinase in CD4+ lymphocytes by infliximab therapy in patients with rheumatoid arthritis. Clin Immunol. 2005 Aug;116(2):101-7.
- 834. Garnero P, Gineyts E, Christgau S, et al. Association of baseline levels of urinary glucosyl-galactosyl-pyridinoline and type II collagen C-telopeptide with progression of joint destruction in patients with early rheumatoid arthritis. Arthritis Rheum. 2002 Jan;46(1):21-30.
- 835. Garnero P, Tabassi NC, Voorzanger-Rousselot N. Circulating dickkopf-1 and radiological progression in patients with early rheumatoid arthritis treated with etanercept. J Rheumatol. 2008

 Dec;35(12):2313-5.

- 836. Gartlehner G, Hansen RA, Nissman D, et al. A simple and valid tool distinguished efficacy from effectiveness studies. J of Clinical Epidemiology. 2006 Aug 4;59(10):1040-8.
- 837. Garton MJ, Reid DM. Bone mineral density of the hip and of the anteroposterior and lateral dimensions of the spine in men with rheumatoid arthritis. Effects of low-dose corticosteroids. Arthritis Rheum. 1993 Feb;36(2):222-8.
- 838. Gaujoux-Viala C, Smolen JS, Landewe R, et al. Current evidence for the management of rheumatoid arthritis with synthetic disease-modifying antirheumatic drugs: a systematic literature review informing the EULAR recommendations for the management of rheumatoid arthritis. Ann Rheum Dis. 2010 Jun;69(6):1004-9.
- 839. Gaylis NB, Needell SD, Rudensky D.
 Comparison of in-office magnetic resonance imaging versus conventional radiography in detecting changes in erosions after one year of infliximab therapy in patients with rheumatoid arthritis. Mod Rheumatol. 2007;17(4):273-8.
- 840. Geborek P, Bladstrom A, Turesson C, et al. Tumour necrosis factor blockers do not increase overall tumour risk in patients with rheumatoid arthritis, but may be associated with an increased risk of lymphomas. Ann Rheum Dis. 2005 May;64(5):699-703.
- 841. Geborek P, Crnkic M, Petersson IF, et al. Etanercept, infliximab, and leflunomide in established rheumatoid arthritis: clinical experience using a structured follow up programme in southern Sweden. Ann Rheum Dis. 2002 Sep;61(9):793-8.
- 842. Geborek P, Mansson B, Wollheim FA, et al. Intraarticular corticosteroid injection into rheumatoid arthritis knees improves extensor muscles strength. Rheumatol Int. 1990;9(6):265-70.
- 843. Geenen R, Godaert GL, Heijnen CJ, et al. Experimentally induced stress in rheumatoid arthritis of recent onset: effects on peripheral blood lymphocytes. Clin Exp Rheumatol. 1998 Sep-Oct;16(5):553-9.

- 844. Gelinck LB, van der Bijl AE, Beyer WE, et al. The effect of anti-tumour necrosis factor alpha treatment on the antibody response to influenza vaccination. Ann Rheum Dis. 2008 May;67(5):713-6.
- 845. Genc H, Duyur Cakit B, Nacir B, et al. The effects of sulfasalazine treatment on enthesal abnormalities of inflammatory rheumatic diseases. Clin Rheumatol. 2007 Jul;26(7):1104-10.
- 846. Gengenbacher M, Sebald HJ, Villiger PM, et al. Infliximab inhibits bone resorption by circulating osteoclast precursor cells in patients with rheumatoid arthritis and ankylosing spondylitis. Ann Rheum Dis. 2008 May;67(5):620-4.
- 847. Genovese MC, Bathon JM, Fleischmann RM, et al. Longterm safety, efficacy, and radiographic outcome with etanercept treatment in patients with early rheumatoid arthritis. J Rheumatol. 2005 Jul;32(7):1232-42.
- 848. Genovese MC, Bathon JM, Martin RW, et al. Etanercept versus methotrexate in patients with early rheumatoid arthritis: two-year radiographic and clinical outcomes.

 Arthritis Rheum. 2002 Jun;46(6):1443-50.
- 849. Genovese MC, Becker JC, Schiff M, et al. Abatacept for rheumatoid arthritis refractory to tumor necrosis factor alpha inhibition. N Engl J Med. 2005 Sep 15;353(11):1114-23.
- 850. Genovese MC, Cohen S, Moreland L, et al. Combination therapy with etanercept and anakinra in the treatment of patients with rheumatoid arthritis who have been treated unsuccessfully with methotrexate. Arthritis Rheum. 2004 May;50(5):1412-9.
- 851. Genovese MC, Schiff M, Luggen M, et al. Efficacy and safety of the selective costimulation modulator abatacept following 2 years of treatment in patients with rheumatoid arthritis and an inadequate response to anti-tumour necrosis factor therapy. Ann Rheum Dis. 2008 Apr;67(4):547-54.
- 852. Genovese MC, Van den Bosch F, Roberson SA, et al. LY2439821, a humanized anti-interleukin-17 monoclonal antibody, in the

- treatment of patients with rheumatoid arthritis: A phase I randomized, double-blind, placebo-controlled, proof-of-concept study. Arthritis Rheum. 2010 Apr;62(4):929-39.
- 853. Geoghegan JM, Clark DI, Bainbridge LC, et al. Risk factors in carpal tunnel syndrome. J Hand Surg [Br]. 2004 Aug;29(4):315-20.
- 854. George D, Kadlubek P, Batra D, et al. Infliximab dose and charge escalation patterns in managed care. Manag Care Interface. 2004;Suppl A:5-8.
- 855. Georgescu C. Sulphasalazine therapy in rheumatoid arthritis. A two-year study and follow-up of clinical results. Rom J Intern Med. 1992 Apr-Jun;30(2):127-32.
- 856. Georgiadis AN, Papavasiliou EC, Lourida ES, et al. Atherogenic lipid profile is a feature characteristic of patients with early rheumatoid arthritis: effect of early treatment—a prospective, controlled study. Arthritis Res Ther. 2006;8(3):R82.
- 857. Georgiadis AN, Voulgari PV, Argyropoulou MI, et al. Early treatment reduces the cardiovascular risk factors in newly diagnosed rheumatoid arthritis patients.

 Semin Arthritis Rheum. 2008 Aug;38(1):13-9.
- 858. Geraghty EM, Ristow B, Gordon SM, et al. Overwhelming parasitemia with Plasmodium falciparum infection in a patient receiving infliximab therapy for rheumatoid arthritis. Clin Infect Dis. 2007 May 15;44(10):e82-4.
- 859. Gergely P, Jr., Blazsek A, Danko K, et al. Detection of TT virus in patients with idiopathic inflammatory myopathies. Ann N Y Acad Sci. 2005 Jun;1050:304-13.
- 860. Gerlag DM, Boyle DL, Rosengren S, et al. Real-time quantitative PCR to detect changes in synovial gene expression in rheumatoid arthritis after corticosteroid treatment. Ann Rheum Dis. 2007 Apr;66(4):545-7.
- 861. Gerli R, Bertotto A, Agea E, et al. Basis for defective proliferation of peripheral blood T

- cells to anti-CD2 antibodies in primary Sjogren's syndrome. J Clin Invest. 1990 Dec;86(6):1870-7.
- 862. Gerli R, Lunardi C, Bocci EB, et al. Antitumor necrosis factor-alpha response in rheumatoid arthritis is associated with an increase in serum soluble CD30. J Rheumatol. 2008 Jan;35(1):14-9.
- 863. Gerli R, Schillaci G, Giordano A, et al. CD4+CD28- T lymphocytes contribute to early atherosclerotic damage in rheumatoid arthritis patients. Circulation. 2004 Jun 8;109(22):2744-8.
- 864. Gerloni V, Pontikaki I, Gattinara M, et al. Focus on adverse events of tumour necrosis factor alpha blockade in juvenile idiopathic arthritis in an open monocentric long-term prospective study of 163 patients. Ann Rheum Dis. 2008 Aug;67(8):1145-52.
- 865. Germano V, Picchianti Diamanti A, Baccano G, et al. Autoimmune hepatitis associated with infliximab in a patient with psoriatic arthritis. Ann Rheum Dis. 2005 Oct;64(10):1519-20.
- 866. Gerster JC, Dudler J. Cellulitis caused by Capnocytophaga cynodegmi associated with etanercept treatment in a patient with rheumatoid arthritis. Clin Rheumatol. 2004 Dec;23(6):570-1.
- 867. Geusens P, Dequeker J, Vanhoof J, et al. Cyclical etidronate increases bone density in the spine and hip of postmenopausal women receiving long term corticosteroid treatment. A double blind, randomised placebo controlled study. Ann Rheum Dis. 1998 Dec;57(12):724-7.
- 868. Gevers G, Dequeker J, van Holsbeeck M, et al. A high dose (up to 200 mg) tolerance and efficacy study of intra-articular rimexolone (Org 6216) in rheumatoid synovitis of the knee. Clin Rheumatol. 1994 Mar;13(1):103-
- 869. Ghavami A, Genevay S, Fulpius T, et al. Etanercept in treatment of Felty's syndrome. Ann Rheum Dis. 2005 Jul;64(7):1090-1.

- 870. Giagounidis AA, Haase S, Germing U, et al. Autoimmune disorders in two patients with myelodysplastic syndrome and 5q deletion. Acta Haematol. 2005;113(2):146-9.
- 871. Gianella S, Schaer DJ, Schwarz U, et al. Retinal microangiopathy and rapidly fatal cerebral edema in a patient with adult-onset Still's disease and concurrent macrophage activation syndrome. Am J Hematol. 2008 May;83(5):424-7.
- 872. Giannelli G, Iannone F, Marinosci F, et al. Infliximab therapy does not modify MMP-2 and MMP-9 serum concentrations in chronic arthritis. Clin Exp Rheumatol. 2005 Nov-Dec;23(6):867-72.
- 873. Giardina AR, Accardo-Palumbo A, Ciccia F, et al. Blocking TNF in vitro with infliximab determines the inhibition of expansion and interferon gamma production of Vgamma9/Vdelta2 T lymphocytes from patients with active rheumatoid arthritis. A role in the susceptibility to tuberculosis? Reumatismo. 2009 Jan-Mar;61(1):21-6.
- 874. Gibofsky A, Palmer WR, Goldman JA, et al. Real-world utilization of DMARDs and biologics in rheumatoid arthritis: the RADIUS (Rheumatoid Arthritis Disease-Modifying Anti-Rheumatic Drug Intervention and Utilization Study) study. Curr Med Res Opin. 2006 Jan;22(1):169-83.
- 875. Gibson JN, Poyser NL, Morrison WL, et al. Muscle protein synthesis in patients with rheumatoid arthritis: effect of chronic corticosteroid therapy on prostaglandin F2 alpha availability. Eur J Clin Invest. 1991 Aug;21(4):406-12.
- 876. Gilbert ME, Savino PJ. Missing the bull's eye. Surv Ophthalmol. 2007 Jul-Aug;52(4):440-2.
- 877. Gilbert TD, Jr., Smith D, Ollendorf DA. Patterns of use, dosing, and economic impact of biologic agent use in patients with rheumatoid arthritis: a retrospective cohort study. BMC Musculoskelet Disord. 2004 Oct 14;5(1):36.
- 878. Gilboe IM, Kvien TK, Haugeberg G, et al.
 Bone mineral density in systemic lupus
 erythematosus: comparison with rheumatoid

- arthritis and healthy controls. Ann Rheum Dis. 2000 Feb;59(2):110-5.
- 879. Giles JT, Bartlett SJ, Gelber AC, et al. Tumor necrosis factor inhibitor therapy and risk of serious postoperative orthopedic infection in rheumatoid arthritis. Arthritis Rheum. 2006 Apr 15;55(2):333-7.
- 880. Giles JT, Fernandes V, Lima JA, et al. Myocardial dysfunction in rheumatoid arthritis: epidemiology and pathogenesis. Arthritis Res Ther. 2005;7(5):195-207.
- 881. Gill JB. Fat suppression imaging in epidural lipomatosis: case report. J Surg Orthop Adv. 2007 Fall;16(3):144-7.
- 882. Giltay EJ, Popp-Snijders C, van Schaardenburg D, et al. Serum testosterone levels are not elevated in patients with ankylosing spondylitis. J Rheumatol. 1998 Dec;25(12):2389-94.
- 883. Gladman DD, Mease PJ, Choy EH, et al.
 Risk factors for radiographic progression in
 psoriatic arthritis: subanalysis of the
 randomized controlled trial ADEPT.
 Arthritis Res Ther. 2010;12(3):R113.
- 884. Glass GE, Greig AV, Weir J, et al. Nasal tip necrosis--an unusual presentation of rheumatoid vasculitis. Clin Rheumatol. 2007 Nov;26(11):1943-5.
- 885. Gleissner C, Willershausen B, Kaesser U, et al. The role of risk factors for periodontal disease in patients with rheumatoid arthritis. Eur J Med Res. 1998 Aug 18;3(8):387-92.
- 886. Gluck T, Linde HJ, Scholmerich J, et al. Anti-tumor necrosis factor therapy and Listeria monocytogenes infection: report of two cases. Arthritis Rheum. 2002 Aug;46(8):2255-7; author reply 7.
- 887. Go RS, Li CY, Tefferi A, et al. Acquired pure red cell aplasia associated with lymphoproliferative disease of granular T lymphocytes. Blood. 2001 Jul 15;98(2):483-5.
- 888. Godaert GL, Hartkamp A, Geenen R, et al. Fatigue in daily life in patients with primary Sjogren's syndrome and systemic lupus

- erythematosus. Ann N Y Acad Sci. 2002 Jun;966:320-6.
- 889. Godinho F, Godfrin B, El Mahou S, et al. Safety of leflunomide plus infliximab combination therapy in rheumatoid arthritis. Clin Exp Rheumatol. 2004 May-Jun;22(3):328-30.
- 890. Goeb V, Buch MH, Vital EM, et al. Costimulation blockade in rheumatic diseases: where we are? Curr Opin Rheumatol. 2009 May;21(3):244-50.
- 891. Goedkoop AY, Kraan MC, Picavet DI, et al. Deactivation of endothelium and reduction in angiogenesis in psoriatic skin and synovium by low dose infliximab therapy in combination with stable methotrexate therapy: a prospective single-centre study. Arthritis Res Ther. 2004;6(4):R326-34.
- 892. Goedkoop AY, Kraan MC, Teunissen MB, et al. Early effects of tumour necrosis factor alpha blockade on skin and synovial tissue in patients with active psoriasis and psoriatic arthritis. Ann Rheum Dis. 2004 Jul;63(7):769-73.
- 893. Goekoop-Ruiterman YP, de Vries-Bouwstra JK, Allaart CF, et al. Patient preferences for treatment: report from a randomised comparison of treatment strategies in early rheumatoid arthritis (BeSt trial). Ann Rheum Dis. 2007 Sep;66(9):1227-32.
- 894. Goekoop-Ruiterman YP, de Vries-Bouwstra JK, Allaart CF, et al. Clinical and radiographic outcomes of four different treatment strategies in patients with early rheumatoid arthritis (the BeSt study): a randomized, controlled trial. Arthritis Rheum. 2005 Nov;52(11):3381-90.
- 895. Goekoop-Ruiterman YP, de Vries-Bouwstra JK, Allaart CF, et al. Clinical and radiographic outcomes of four different treatment strategies in patients with early rheumatoid arthritis (the BeSt study): A randomized, controlled trial. Arthritis Rheum. 2008 Feb;58(2 Suppl):S126-35.
- 896. Goerres GW, Forster A, Uebelhart D, et al. F-18 FDG whole-body PET for the assessment of disease activity in patients

- with rheumatoid arthritis. Clin Nucl Med. 2006 Jul;31(7):386-90.
- 897. Goerttler E, Kutzner H, Peter HH, et al. Methotrexate-induced papular eruption in patients with rheumatic diseases: a distinctive adverse cutaneous reaction produced by methotrexate in patients with collagen vascular diseases. J Am Acad Dermatol. 1999 May;40(5 Pt 1):702-7.
- 898. Goksugur N, Yilmaz F. Medical image. Extensive oral ulcerations. N Z Med J. 2006;119(1242):U2236.
- 899. Golan TD, Keren D, Elias N, et al. Severe reversible cardiomyopathy associated with systemic vasculitis in primary Sjogren's syndrome. Lupus. 1997;6(6):505-8.
- 900. Golda N, Feldman M. Histoplasmosis clinically imitating cutaneous malignancy. J Cutan Pathol. 2008 Oct;35 Suppl 1:26-8.
- 901. Goldbach-Mansky R, Wilson M, Fleischmann R, et al. Comparison of Tripterygium wilfordii Hook F versus sulfasalazine in the treatment of rheumatoid arthritis: a randomized trial. Ann Intern Med. 2009 Aug 18;151(4):229-40, W49-51.
- 902. Goldberger C, Dulak J, Duftner C, et al. Vascular endothelial growth factor (VEGF) in ankylosing spondylitis--a pilot study. Wien Med Wochenschr. 2002;152(9-10):223-5.
- 903. Goldenberg MM. Etanercept, a novel drug for the treatment of patients with severe, active rheumatoid arthritis. Clin Ther. 1999 Jan;21(1):75-87; discussion 1-2.
- 904. Gomez-Reino JJ, Carmona L, Valverde VR, et al. Treatment of rheumatoid arthritis with tumor necrosis factor inhibitors may predispose to significant increase in tuberculosis risk: a multicenter active-surveillance report. Arthritis Rheum. 2003 Aug;48(8):2122-7.
- 905. Gonnet-Gracia C, Barnetche T, Richez C, et al. Anti-nuclear antibodies, anti-DNA and C4 complement evolution in rheumatoid arthritis and ankylosing spondylitis treated

- with TNF-alpha blockers. Clin Exp Rheumatol. 2008 May-Jun;26(3):401-7.
- 906. Gonzalez-Alvaro I, Ortiz AM, Tomero EG, et al. Baseline serum RANKL levels may serve to predict remission in rheumatoid arthritis patients treated with TNF antagonists. Ann Rheum Dis. 2007 Dec;66(12):1675-8.
- 907. Gonzalez-Chavez JR, Berlingeri-Ramos AC, Sanchez Casiano MA. Puerto Rico psoriasis study group: efficacy and safety of etanercept. J Drugs Dermatol. 2005 Nov-Dec;4(6):735-9.
- 908. Gonzalez-Gay MA, De Matias JM, Gonzalez-Juanatey C, et al. Anti-tumor necrosis factor-alpha blockade improves insulin resistance in patients with rheumatoid arthritis. Clin Exp Rheumatol. 2006 Jan-Feb;24(1):83-6.
- 909. Gonzalez-Gay MA, Garcia-Unzueta MT, Berja A, et al. Anti-TNF-alpha therapy does not modulate leptin in patients with severe rheumatoid arthritis. Clin Exp Rheumatol. 2009 Mar-Apr;27(2):222-8.
- 910. Gonzalez-Gay MA, Garcia-Unzueta MT, Berja A, et al. Short-term effect of anti-TNF-alpha therapy on nitric oxide production in patients with severe rheumatoid arthritis. Clin Exp Rheumatol. 2009 May-Jun;27(3):452-8.
- 911. Gonzalez-Gay MA, Garcia-Unzueta MT, De Matias JM, et al. Influence of anti-TNF-alpha infliximab therapy on adhesion molecules associated with atherogenesis in patients with rheumatoid arthritis. Clin Exp Rheumatol. 2006 Jul-Aug;24(4):373-9.
- 912. Gonzalez-Gay MA, Garcia-Unzueta MT, Gonzalez-Juanatey C, et al. Anti-TNF-alpha therapy modulates resistin in patients with rheumatoid arthritis. Clin Exp Rheumatol. 2008 Mar-Apr;26(2):311-6.
- 913. Gonzalez-Gay MA, Llorca J, Garcia-Unzueta MT, et al. High-grade inflammation, circulating adiponectin concentrations and cardiovascular risk factors in severe rheumatoid arthritis. Clin Exp Rheumatol. 2008 Jul-Aug;26(4):596-603.

- 914. Gonzalez-Gay MA, Vazquez-Rodriguez TR, Garcia-Unzueta MT, et al. Visfatin is not associated with inflammation or metabolic syndrome in patients with severe rheumatoid arthritis undergoing anti-TNF-alpha therapy. Clin Exp Rheumatol. 2010 Jan-Feb;28(1):56-62.
- 915. Gonzalez-Juanatey C, Llorca J, Sanchez-Andrade A, et al. Short-term adalimumab therapy improves endo-thelial function in patients with rheumatoid arthritis refractory to infliximab. Clin Exp Rheumatol. 2006 May-Jun;24(3):309-12.
- 916. Gonzalez-Juanatey C, Llorca J, Vazquez-Rodriguez TR, et al. Short-term improvement of endothelial function in rituximab-treated rheumatoid arthritis patients refractory to tumor necrosis factor alpha blocker therapy. Arthritis Rheum. 2008 Dec 15;59(12):1821-4.
- 917. Gonzalez-Juanatey C, Testa A, Garcia-Castelo A, et al. Active but transient improvement of endothelial function in rheumatoid arthritis patients undergoing long-term treatment with anti-tumor necrosis factor alpha antibody. Arthritis Rheum. 2004 Jun 15;51(3):447-50.
- 918. Gonzalez-Lopez MA, Martinez-Taboada VM, Gonzalez-Vela MC, et al. Recall injection-site reactions associated with etanercept therapy: report of two new cases with immunohistochemical analysis. Clin Exp Dermatol. 2007 Nov;32(6):672-4.
- 919. Goossens PH, Heemskerk B, van Tongeren J, et al. Reliability and sensitivity to change of various measures of hand function in relation to treatment of synovitis of the metacarpophalangeal joint in rheumatoid arthritis. Rheumatology (Oxford). 2000 Aug;39(8):909-13.
- 920. Gorman JD, Sack KE, Davis JC, Jr.
 Treatment of ankylosing spondylitis by
 inhibition of tumor necrosis factor alpha. N
 Engl J Med. 2002 May 2;346(18):1349-56.
- 921. Gosset P, Perez T, Lassalle P, et al. Increased TNF-alpha secretion by alveolar macrophages from patients with rheumatoid arthritis. Am Rev Respir Dis. 1991 Mar;143(3):593-7.

- 922. Gottenberg JE, Guillevin L, Lambotte O, et al. Tolerance and short term efficacy of rituximab in 43 patients with systemic autoimmune diseases. Ann Rheum Dis. 2005 Jun;64(6):913-20.
- 923. Gottenberg JE, Miceli-Richard C, Ducot B, et al. Markers of B-lymphocyte activation are elevated in patients with early rheumatoid arthritis and correlated with disease activity in the ESPOIR cohort.

 Arthritis Res Ther. 2009;11(4):R114.
- 924. Gottenberg JE, Ravaud P, Bardin T, et al. Risk factors for severe infections in patients with rheumatoid arthritis treated with rituximab in the autoimmunity and rituximab registry. Arthritis Rheum. 2010 Sep;62(9):2625-32.
- 925. Gottlieb AB, Kircik L, Eisen D, et al. Use of etanercept for psoriatic arthritis in the dermatology clinic: the Experience Diagnosing, Understanding Care, and Treatment with Etanercept (EDUCATE) study. J Dermatolog Treat. 2006;17(6):343-52.
- 926. Gottlieb AB, Mease PJ, Mark Jackson J, et al. Clinical characteristics of psoriatic arthritis and psoriasis in dermatologists' offices. J Dermatolog Treat. 2006;17(5):279-87.
- 927. Gough A, Sheeran T, Arthur V, et al. Adverse interaction between intramuscular methylprednisolone and sulphasalazine in patients with early rheumatoid arthritis. A pilot study. Scand J Rheumatol. 1994;23(1):46-8.
- 928. Graf C, Cardoso G, Silva MB, et al. Intra ocular pressure in chronic users of oral glucocorticoids for rheumatoid arthritis. Acta Reumatol Port. 2006 Apr-Jun;31(2):151-5, 83.
- 929. Gran JT, Myklebust G. Toxicity of sulphasalazine in rheumatoid arthritis. Possible protective effect of rheumatoid factors and corticosteroids. Scand J Rheumatol. 1993;22(5):229-32.
- 930. Grange L, Nissen MJ, Garambois K, et al. Infliximab-induced cerebral

- thrombophlebitis. Rheumatology (Oxford). 2005 Feb;44(2):260-1.
- 931. Granjo E, Lima M, Correia T, et al. Cd8(+)/V beta 5.1(+) large granular lymphocyte leukemia associated with autoimmune cytopenias, rheumatoid arthritis and vascular mammary skin lesions: successful response to 2-deoxycoformycin. Hematol Oncol. 2002 Jun;20(2):87-93.
- 932. Grassi W, De Angelis R, Cervini C.
 Corticosteroid prescribing in rheumatoid arthritis and psoriatic arthritis. Clin
 Rheumatol. 1998;17(3):223-6.
- 933. Grassi W, Lamanna G, Farina A, et al. Synovitis of small joints: sonographic guided diagnostic and therapeutic approach. Ann Rheum Dis. 1999 Oct;58(10):595-7.
- 934. Gratacos J, Casado E, Real J, et al.
 Prediction of major clinical response
 (ACR50) to infliximab in psoriatic arthritis
 refractory to methotrexate. Ann Rheum Dis.
 2007 Apr;66(4):493-7.
- 935. Gray RE, Doherty SM, Galloway J, et al. A double-blind study of deflazacort and prednisone in patients with chronic inflammatory disorders. Arthritis Rheum. 1991 Mar;34(3):287-95.
- 936. Greenberg JD, Kishimoto M, Strand V, et al. Tumor necrosis factor antagonist responsiveness in a United States rheumatoid arthritis cohort. Am J Med. 2008 Jun;121(6):532-8.
- 937. Greenwood MC, Hakim AJ, Doyle DV. A simple extension to the Rheumatoid Arthritis Quality of Life Questionnaire (RAQol) to explore individual patient concerns and monitor group outcome in clinical practice. Rheumatology (Oxford). 2006 Jan;45(1):61-5.
- 938. Grijalva CG, Chung CP, Arbogast PG, et al. Assessment of adherence to and persistence on disease-modifying antirheumatic drugs (DMARDs) in patients with rheumatoid arthritis. Med Care 2007;45(10 Supl 2):S66-76.

- 939. Grijalva CG, Chung CP, Stein CM, et al. Changing patterns of medication use in patients with rheumatoid arthritis in a Medicaid population. Rheumatology (Oxford). 2008 Jul;47(7):1061-4.
- 940. Grijalva CG, Kaltenbach L, Arbogast PG, et al. Adherence to disease-modifying antirheumatic drugs and the effects of exposure misclassification on the risk of hospital admission. Arthritis Care Res (Hoboken) 2010;62(5):730-4.
- 941. Grinblat B, Scheinberg M. Unexpected onset of psoriasis during infliximab treatment: comment on the article by Beuthien et al. Arthritis Rheum. 2005 Apr;52(4):1333-4; author reply 4.
- 942. Grinblat B, Scheinberg M. The enigmatic development of psoriasis and psoriasiform lesions during anti-TNF therapy: a review. Semin Arthritis Rheum. 2008 Feb;37(4):251-5.
- 943. Grisar J, Aletaha D, Steiner CW, et al. Endothelial progenitor cells in active rheumatoid arthritis: effects of tumour necrosis factor and glucocorticoid therapy. Ann Rheum Dis. 2007 Oct;66(10):1284-8.
- 944. Guarneri C, Polimeni G. Nicolau syndrome following etanercept administration. Am J Clin Dermatol. 2010;11 Suppl 1:51-2.
- 945. Guarneri C, Polimeni G, Nunnari G. Pityriasis rosea during etanercept therapy. Eur Rev Med Pharmacol Sci. 2009 Sep-Oct;13(5):383-7.
- 946. Guarnieri MV, Rosenberg L, Scheinberg MA. Intractable pain in a rheumatoid wrist. J Rheumatol. 2003 Dec;30(12):2718-9.
- 947. Gubinelli E, Angelo C, Pacifico V. A case of dystrophic epidermolysis bullosa improved with etanercept for concomitant psoriatic arthritis. Am J Clin Dermatol. 2010;11 Suppl 1:53-4.
- 948. Gudbjornsson B, Skogseid B, Oberg K, et al. Intact adrenocorticotropic hormone secretion but impaired cortisol response in patients with active rheumatoid arthritis.

- Effect of glucocorticoids. J Rheumatol. 1996 Apr;23(4):596-602.
- 949. Gudbrandsdottir S, Bliddal H, Petri A, et al. Plasma TNF binding capacity profiles during treatment with etanercept in rheumatoid arthritis. Scand J Rheumatol. 2004;33(6):385-8.
- 950. Guignard S, Dien G, Dougados M. Severe systemic inflammatory response syndrome in a patient with adult onset Still's disease treated with the anti-IL1 drug anakinra: a case report. Clin Exp Rheumatol. 2007 Sep-Oct;25(5):758-9.
- 951. Guignard S, Gossec L, Bandinelli F, et al.
 Comparison of the clinical characteristics of
 vasculitis occurring during anti-tumor
 necrosis factor treatment or not in
 rheumatoid arthritis patients. A systematic
 review of 2707 patients, 18 vasculitis. Clin
 Exp Rheumatol 2008;26(3 Suppl 49):S23-9.
- 952. Guillot X, Solau-Gervais E, Coulon A, et al. Sjogren's syndrome with ANCA-associated crescentic extramembranous glomerulonephritis. Joint Bone Spine. 2009 Mar;76(2):188-9.
- 953. Guion TL, Sculco TP. Pasteurella multocida infection in total knee arthroplasty. Case report and literature review. J Arthroplasty. 1992 Jun;7(2):157-60.
- 954. Guis S, Balandraud N, Bouvenot J, et al. Influence of -308 A/G polymorphism in the tumor necrosis factor alpha gene on etanercept treatment in rheumatoid arthritis. Arthritis Rheum. 2007 Dec 15;57(8):1426-30
- 955. Gul U, Gonul M, Kilic A, et al. Treatment of psoriatic arthritis with etanercept, methotrexate, and cyclosporin A. Clin Ther. 2006 Feb;28(2):251-4.
- 956. Guler-Yuksel M, Allaart CF, Goekoop-Ruiterman YP, et al. Changes in hand and generalised bone mineral density in patients with recent-onset rheumatoid arthritis. Ann Rheum Dis. 2009 Mar;68(3):330-6.
- 957. Guler-Yuksel M, Bijsterbosch J, Goekoop-Ruiterman YP, et al. Changes in bone

- mineral density in patients with recent onset, active rheumatoid arthritis. Ann Rheum Dis. 2008 Jun;67(6):823-8.
- 958. Guler-Yuksel M, Bijsterbosch J, Goekoop-Ruiterman YP, et al. Bone mineral density in patients with recently diagnosed, active rheumatoid arthritis. Ann Rheum Dis. 2007 Nov;66(11):1508-12.
- 959. Guler-Yuksel M, Klarenbeek NB, Goekoop-Ruiterman YP, et al. Accelerated hand bone mineral density loss is associated with progressive joint damage in hands and feet in recent-onset rheumatoid arthritis. Arthritis Res Ther. 2010;12(3):R96.
- 960. Gupta A, Bansal RK, Bambery P. Posterior scleritis related fundal mass in a patient with rheumatoid arthritis. Scand J Rheumatol. 1992;21(5):254-6.
- 961. Gupta N, Fox CM, Grisolano SW.
 Disseminated histoplasmosis with colonic ulcers in a patient receiving infliximab.
 Gastrointest Endosc. 2009 Sep;70(3):597-8.
- 962. Gutierrez MA, Garcia ME, Rodriguez JA, et al. Hypothalamic-pituitary-adrenal axis function in patients with active rheumatoid arthritis: a controlled study using insulin hypoglycemia stress test and prolactin stimulation. J Rheumatol. 1999 Feb;26(2):277-81.
- 963. Guzman-Clark JR, Fang MA, Sehl ME, et al. Barriers in the management of glucocorticoid-induced osteoporosis.

 Arthritis Rheum. 2007 Feb 15;57(1):140-6.
- 964. Gwak GY, Koh KC, Kim HY. Fatal hepatic failure associated with hepatitis B virus reactivation in a hepatitis B surface antigennegative patient with rheumatoid arthritis receiving low dose methotrexate. Clin Exp Rheumatol. 2007 Nov-Dec;25(6):888-9.
- 965. Habib GS, Haj S. Bone mineral density in patients with early rheumatoid arthritis treated with corticosteroids. Clin Rheumatol. 2005 Apr;24(2):129-33.
- 966. Hadi A, Hickling P, Brown M, et al. Scintigraphic evidence of effect of infliximab on disease activity in ankylosing

- spondylitis. Rheumatology (Oxford). 2002 Jan;41(1):114-6.
- 967. Hadj Kacem H, Kaddour N, Adyel FZ, et al. HLA-DQB1 CAR1/CAR2, TNFa IR2/IR4 and CTLA-4 polymorphisms in Tunisian patients with rheumatoid arthritis and Sjogren's syndrome. Rheumatology (Oxford). 2001 Dec;40(12):1370-4.
- 968. Haerden J, Coolen L, Dequeker J. The effect of D-penicillamine on lung function parameters (diffusion capacity) in rheumatoid arthritis. Clin Exp Rheumatol. 1993 Sep-Oct;11(5):509-13.
- 969. Hafstrom I, Albertsson K, Boonen A, et al. Remission achieved after 2 years treatment with low-dose prednisolone in addition to disease-modifying anti-rheumatic drugs in early rheumatoid arthritis is associated with reduced joint destruction still present after 4 years: an open 2-year continuation study. Ann Rheum Dis. 2009 Apr;68(4):508-13.
- 970. Hafstrom I, Rohani M, Deneberg S, et al. Effects of low-dose prednisolone on endothelial function, atherosclerosis, and traditional risk factors for atherosclerosis in patients with rheumatoid arthritis--a randomized study. J Rheumatol. 2007 Sep;34(9):1810-6.
- 971. Hage CA, Wood KL, Winer-Muram HT, et al. Pulmonary cryptococcosis after initiation of anti-tumor necrosis factor-alpha therapy. Chest. 2003 Dec;124(6):2395-7.
- 972. Hagiwara K, Sato T, Takagi-Kobayashi S, et al. Acute exacerbation of preexisting interstitial lung disease after administration of etanercept for rheumatoid arthritis. J Rheumatol. 2007 May;34(5):1151-4.
- 973. Hahtola PA, Jarvenpaa RE, Lounatmaa K, et al. Hard metal alveolitis accompanied by rheumatoid arthritis. Respiration. 2000;67(2):209-12.
- 974. Haibel H, Rudwaleit M, Brandt HC, et al. Adalimumab reduces spinal symptoms in active ankylosing spondylitis: clinical and magnetic resonance imaging results of a fifty-two-week open-label trial. Arthritis Rheum. 2006 Feb;54(2):678-81.

- 975. Haibel H, Rudwaleit M, Listing J, et al. Open label trial of anakinra in active ankylosing spondylitis over 24 weeks. Ann Rheum Dis. 2005 Feb;64(2):296-8.
- 976. Haigh RC, McCabe CS, Halligan PW, et al. Joint stiffness in a phantom limb: evidence of central nervous system involvement in rheumatoid arthritis. Rheumatology (Oxford). 2003 Jul;42(7):888-92.
- 977. Hall GM, Daniels M, Doyle DV, et al. Effect of hormone replacement therapy on bone mass in rheumatoid arthritis patients treated with and without steroids. Arthritis Rheum. 1994 Oct;37(10):1499-505.
- 978. Hall GM, Peerbhoy D, Shenkin A, et al. Hip and knee arthroplasty: a comparison and the endocrine, metabolic and inflammatory responses. Clin Sci (Lond). 2000
 Jan;98(1):71-9.
- 979. Hall GM, Perry LA, Spector TD. Depressed levels of dehydroepiandrosterone sulphate in postmenopausal women with rheumatoid arthritis but no relation with axial bone density. Ann Rheum Dis. 1993

 Mar;52(3):211-4.
- 980. Hall GM, Spector TD, Delmas PD. Markers of bone metabolism in postmenopausal women with rheumatoid arthritis. Effects of corticosteroids and hormone replacement therapy. Arthritis Rheum. 1995
 Jul;38(7):902-6.
- 981. Hall GM, Spector TD, Griffin AJ, et al. The effect of rheumatoid arthritis and steroid therapy on bone density in postmenopausal women. Arthritis Rheum. 1993
 Nov;36(11):1510-6.
- 982. Hall HA, Zimmermann B. Evolution of dermatomyositis during therapy with a tumor necrosis factor alpha inhibitor.
 Arthritis Rheum. 2006 Dec 15;55(6):982-4.
- 983. Hall J, Morand EF, Medbak S, et al. Abnormal hypothalamic-pituitary-adrenal axis function in rheumatoid arthritis. Effects of nonsteroidal antiinflammatory drugs and water immersion. Arthritis Rheum. 1994 Aug;37(8):1132-7.

- 984. Hall SJ, Hickling P. Failure of etanercept to control extra-articular manifestations of rheumatoid arthritis. J Clin Rheumatol. 2007 Feb;13(1):54.
- 985. Halpern MT, Cifaldi MA, Kvien TK. Impact of adalimumab on work participation in rheumatoid arthritis: comparison of an openlabel extension study and a registry-based control group. Ann Rheum Dis. 2009 Jun;68(6):930-7.
- 986. Halvorsen EH, Haavardsholm EA, Pollmann S, et al. Serum IgG antibodies to peptidylarginine deiminase 4 predict radiographic progression in patients with rheumatoid arthritis treated with tumour necrosis factor-alpha blocking agents. Ann Rheum Dis. 2009 Feb;68(2):249-52.
- 987. Hamada H, Kohno N, Yokoyama A, et al. KL-6 as a serologic indicator of Pneumocystis carinii pneumonia in immunocompromised hosts. Intern Med. 1998 Mar;37(3):307-10.
- 988. Hamadeh MA, Atkinson J, Smith LJ. Sulfasalazine-induced pulmonary disease. Chest. 1992 Apr;101(4):1033-7.
- 989. Hamalainen H, Arkela-Kautiainen M, Kautiainen H, et al. Bone mineral content in young adults with active or inactive juvenile idiopathic arthritis and in controls. Scand J Rheumatol. 2010 May;39(3):219-22.
- 990. Hamilton TK. Treatment of psoriatic arthritis and recalcitrant skin disease with combination therapy. J Drugs Dermatol. 2008 Nov;7(11):1089-93.
- 991. Hammer HB, Sveinsson M, Kongtorp AK, et al. A 78-joints ultrasonographic assessment is associated with clinical assessments and is highly responsive to improvement in a longitudinal study of patients with rheumatoid arthritis starting adalimumab treatment. Ann Rheum Dis. 2010 Jul;69(7):1349-51.
- 992. Hammoudeh M. Infliximab treatment in a patient with rheumatoid arthritis on haemodialysis. Rheumatology (Oxford). 2006 Mar;45(3):357-9.

- 993. Hammoudeh M. Recurrent postpartum episodic rheumatoid arthritis. J Clin Rheumatol. 2006 Aug;12(4):196-8.
- 994. Han C, Rahman MU, Doyle MK, et al. Association of anemia and physical disability among patients with rheumatoid arthritis. J Rheumatol. 2007
 Nov;34(11):2177-82.
- 995. Han C, Smolen J, Kavanaugh A, et al. Comparison of employability outcomes among patients with early or long-standing rheumatoid arthritis. Arthritis Rheum. 2008 Apr 15;59(4):510-4.
- 996. Hanauer SB. Review article: safety of infliximab in clinical trials. Aliment Pharmacol Ther. 1999 Sep;13 Suppl 4:16-22; discussion 38.
- 997. Hanna B, Holdeman NR, Tang RA, et al. Retinal toxicity secondary to Plaquenil therapy. Optometry. 2008 Feb;79(2):90-4.
- 998. Hansel S, Lassig G, Pistrosch F, et al. Endothelial dysfunction in young patients with long-term rheumatoid arthritis and low disease activity. Atherosclerosis. 2003 Sep;170(1):177-80.
- 999. Hansen IB, Ellingsen T, Hornung N, et al. Plasma level of CXC-chemokine CXCL12 is increased in rheumatoid arthritis and is independent of disease activity and methotrexate treatment. J Rheumatol. 2006 Sep;33(9):1754-9.
- 1000. Hansen KE, Cush J, Singhal A, et al. The safety and efficacy of leflunomide in combination with infliximab in rheumatoid arthritis. Arthritis Rheum. 2004 Apr 15;51(2):228-32.
- 1001. Hansen KE, Hildebrand JP, Genovese MC, et al. The efficacy of switching from etanercept to infliximab in patients with rheumatoid arthritis. J Rheumatol. 2004 Jun;31(6):1098-102.
- 1002. Hansen M, Florescu A, Stoltenberg M, et al. Bone loss in rheumatoid arthritis. Influence of disease activity, duration of the disease, functional capacity, and corticosteroid

- treatment. Scand J Rheumatol. 1996;25(6):367-76.
- 1003. Harada K, Akai Y, Koyama S, et al. A case of autoimmune hepatitis exacerbated by the administration of etanercept in the patient with rheumatoid arthritis. Clin Rheumatol. 2008 Aug;27(8):1063-6.
- 1004. Harada S, Mitsunobu F, Kodama F, et al. Giant cell arteritis associated with rheumatoid arthritis monitored by magnetic resonance angiography. Intern Med. 1999 Aug;38(8):675-8.
- 1005. Haraoui B, Cameron L, Ouellet M, et al. Anti-infliximab antibodies in patients with rheumatoid arthritis who require higher doses of infliximab to achieve or maintain a clinical response. J Rheumatol. 2006 Jan;33(1):31-6.
- 1006. Haraoui B, Keystone EC, Thorne JC, et al. Clinical outcomes of patients with rheumatoid arthritis after switching from infliximab to etanercept. J Rheumatol. 2004 Dec;31(12):2356-9.
- 1007. Harboe E, Tjensvoll AB, Vefring HK, et al. Fatigue in primary Sjogren's syndrome--a link to sickness behaviour in animals? Brain Behav Immun. 2009 Nov;23(8):1104-8.
- 1008. Harbuz MS, Korendowych E, Jessop DS, et al. Hypothalamo-pituitary-adrenal axis dysregulation in patients with rheumatoid arthritis after the dexamethasone/corticotrophin releasing factor test. J Endocrinol. 2003

 Jul;178(1):55-60.
- 1009. Hardy R, Rabbitt EH, Filer A, et al. Local and systemic glucocorticoid metabolism in inflammatory arthritis. Ann Rheum Dis. 2008 Sep;67(9):1204-10.
- 1010. Hargreaves MR, Mowat AG, Benson MK. Acute pneumonitis associated with low dose methotrexate treatment for rheumatoid arthritis: report of five cases and review of published reports. Thorax. 1992 Aug;47(8):628-33.
- 1011. Harle P, Pongratz G, Weidler C, et al. Possible role of leptin in hypoandrogenicity

- in patients with systemic lupus erythematosus and rheumatoid arthritis. Ann Rheum Dis. 2004 Jul;63(7):809-16.
- 1012. Harle P, Straub RH, Wiest R, et al. Increase of sympathetic outflow measured by neuropeptide Y and decrease of the hypothalamic-pituitary-adrenal axis tone in patients with systemic lupus erythematosus and rheumatoid arthritis: another example of uncoupling of response systems. Ann Rheum Dis. 2006 Jan;65(1):51-6.
- 1013. Harley CR, Frytak JR, Tandon N. Treatment compliance and dosage administration among rheumatoid arthritis patients receiving infliximab, etanercept, or methotrexate. Am J Manag Care. 2003 Oct;9(6 Suppl):S136-43.
- 1014. Harner KC, Jackson LW, Drabick JJ.
 Normalization of anticardiolipin antibodies
 following rituximab therapy for marginal
 zone lymphoma in a patient with Sjogren's
 syndrome. Rheumatology (Oxford). 2004
 Oct;43(10):1309-10.
- 1015. Harney S, O'Shea FD, FitzGerald O. Peptostreptococcal pericarditis complicating anti-tumour necrosis factor alpha treatment in rheumatoid arthritis. Ann Rheum Dis. 2002 Jul;61(7):653-4.
- 1016. Haroon M, Bond U, Phelan M. Sinusitis: a possible link with adalimumab. Clin Rheumatol. 2008 Sep;27(9):1189-90.
- 1017. Haroon N, Srivastava R, Misra R, et al. A novel predictor of clinical response to methotrexate in patients with rheumatoid arthritis: a pilot study of in vitro T cell cytokine suppression. J Rheumatol. 2008 Jun;35(6):975-8.
- 1018. Harrison DJ, Huang X, Globe D. Dosing patterns and costs of tumor necrosis factor inhibitor use for rheumatoid arthritis. Am J Health Syst Pharm. 2010 Aug;67(15):1281-7.
- 1019. Harrison MJ, Dixon WG, Watson KD, et al.
 Rates of new-onset psoriasis in patients with
 rheumatoid arthritis receiving anti-tumour
 necrosis factor alpha therapy: results from
 the British Society for Rheumatology

- Biologics Register. Ann Rheum Dis 2009;68(2):209-15.
- 1020. Harrison MJ, Kim CA, Silverberg M, et al. Does age bias the aggressive treatment of elderly patients with rheumatoid arthritis? J Rheumatol. 2005 Jul;32(7):1243-8.
- 1021. Hartkamp A, Geenen R, Godaert GL, et al. Effect of dehydroepiandrosterone administration on fatigue, well-being, and functioning in women with primary Sjogren syndrome: a randomised controlled trial. Ann Rheum Dis. 2008 Jan;67(1):91-7.
- 1022. Hashiramoto A, Shiozawa K, Tanaka Y, et al. Prospective study of methotrexate treatment for rheumatoid arthritis treated legitimately according to the government recommended 8 mg/week dose. Mod Rheumatol. 2009;19(6):637-42.
- 1023. Hassell AB, Davis MJ, Fowler PD, et al. The relationship between serial measures of disease activity and outcome in rheumatoid arthritis. Q J Med. 1993 Sep;86(9):601-7.
- 1024. Hassett AL, Li T, Buyske S, et al. The multi-faceted assessment of independence in patients with rheumatoid arthritis: preliminary validation from the ATTAIN study. Curr Med Res Opin 2008;24(5):1443-53.
- 1025. Hassikou H, El Haouri M, Tabache F, et al. Leflunomide-induced toxic epidermal necrolysis in a patient with rheumatoid arthritis. Joint Bone Spine. 2008
 Oct;75(5):597-9.
- 1026. Hatemi G, Melikoglu M, Fresko I, et al. Infliximab does not suppress the tuberculin skin test (purified protein derivative). J Rheumatol. 2007 Mar;34(3):474-80.
- 1027. Hau M, Kneitz C, Tony HP, et al. High resolution ultrasound detects a decrease in pannus vascularisation of small finger joints in patients with rheumatoid arthritis receiving treatment with soluble tumour necrosis factor alpha receptor (etanercept). Ann Rheum Dis. 2002 Jan;61(1):55-8.
- 1028. Haugeberg G, Orstavik RE, Uhlig T, et al. Clinical decision rules in rheumatoid

- arthritis: do they identify patients at high risk for osteoporosis? Testing clinical criteria in a population based cohort of patients with rheumatoid arthritis recruited from the Oslo Rheumatoid Arthritis Register. Ann Rheum Dis. 2002 Dec;61(12):1085-9.
- 1029. Haugeberg G, Orstavik RE, Uhlig T, et al. Bone loss in patients with rheumatoid arthritis: results from a population-based cohort of 366 patients followed up for two years. Arthritis Rheum. 2002

 Jul;46(7):1720-8.
- 1030. Haugeberg G, Orstavik RE, Uhlig T, et al. Comparison of ultrasound and X-ray absorptiometry bone measurements in a case control study of female rheumatoid arthritis patients and randomly selected subjects in the population. Osteoporos Int. 2003

 Jun;14(4):312-9.
- 1031. Haugeberg G, Uhlig T, Falch JA, et al. Bone mineral density and frequency of osteoporosis in female patients with rheumatoid arthritis: results from 394 patients in the Oslo County Rheumatoid Arthritis register. Arthritis Rheum. 2000 Mar;43(3):522-30.
- 1032. Haugen M, Lien G, Flato B, et al. Young adults with juvenile arthritis in remission attain normal peak bone mass at the lumbar spine and forearm. Arthritis Rheum. 2000 Jul;43(7):1504-10.
- 1033. Haugen MA, Lien G, Flato B, et al. Minor impact of juvenile arthritis on nutritional status in young adult patients. Arthritis Rheum. 2002 Dec 15;47(6):623-9.
- 1034. Hauselmann HJ, Caravatti M, Seifert B, et al. Can collagen type II sustain a methotrexate-induced therapeutic effect in patients with long-standing rheumatoid arthritis? A double-blind, randomized trial. Br J Rheumatol. 1998 Oct;37(10):1110-7.
- 1035. Havel J, Aboutalebi S, Doughty L, et al. Development of systemic lupus erythematosus in a patient with rheumatoid arthritis following treatment conversion of infliximab to adalimumab. J Drugs Dermatol. 2008 Aug;7(8):796-8.

- 1036. Havelka S, Vavrincova P, Stepan J. Metabolic bone status in young women with juvenile chronic arthritis. J Rheumatol Suppl. 1993 Apr;37:14-6.
- 1037. Havelka S, Vavrincova P, Stepan J, et al. Metabolic bone status in young women with JCA. Acta Univ Carol [Med] (Praha). 1994;40(1-4):65-7.
- 1038. Hawboldt J, Bader M. Intramuscular methotrexate-induced aseptic meningitis.

 Ann Pharmacother. 2007 Nov;41(11):1906-
- 1039. Hayashi H, Fujimaki C, Daimon T, et al. Genetic polymorphisms in folate pathway enzymes as a possible marker for predicting the outcome of methotrexate therapy in Japanese patients with rheumatoid arthritis. J Clin Pharm Ther. 2009 Jun;34(3):355-61.
- 1040. He Y, Lu A, Zha Y, et al. Differential effect on symptoms treated with traditional Chinese medicine and western combination therapy in RA patients. Complement Ther Med. 2008 Aug;16(4):206-11.
- 1041. He Y, Lu A, Zha Y, et al. Correlations between symptoms as assessed in traditional chinese medicine (TCM) and ACR20 efficacy response: a comparison study in 396 patients with rheumatoid arthritis treated with TCM or Western medicine. J Clin Rheumatol. 2007 Dec:13(6):317-21.
- 1042. Healy PJ, Groves C, Chandramohan M, et al. MRI changes in psoriatic dactylitis-extent of pathology, relationship to tenderness and correlation with clinical indices. Rheumatology (Oxford). 2008

 Jan;47(1):92-5.
- 1043. Healy PJ, Helliwell PS. Measuring dactylitis in clinical trials: which is the best instrument to use? J Rheumatol. 2007 Jun;34(6):1302-6.
- 1044. Healy PJ, Helliwell PS. Measuring clinical enthesitis in psoriatic arthritis: assessment of existing measures and development of an instrument specific to psoriatic arthritis.

 Arthritis Rheum. 2008 May 15;59(5):686-91.

- 1045. Hebbar M, Hebbar-Savean K, Hachulla E, et al. Participation of cryoglobulinaemia in the severe peripheral neuropathies of primary Sjogren's syndrome. Ann Med Interne (Paris). 1995;146(4):235-8.
- 1046. Hedman M, Nilsson E, de la Torre B. Low blood and synovial fluid levels of sulphoconjugated steroids in rheumatoid arthritis. Clin Exp Rheumatol. 1992 Jan-Feb;10(1):25-30.
- 1047. Heiberg MS, Koldingsnes W, Mikkelsen K, et al. The comparative one-year performance of anti-tumor necrosis factor alpha drugs in patients with rheumatoid arthritis, psoriatic arthritis, and ankylosing spondylitis: results from a longitudinal, observational, multicenter study. Arthritis Rheum. 2008 Feb 15;59(2):234-40.
- 1048. Heiberg MS, Nordvag BY, Mikkelsen K, et al. The comparative effectiveness of tumor necrosis factor-blocking agents in patients with rheumatoid arthritis and patients with ankylosing spondylitis: a six-month, longitudinal, observational, multicenter study. Arthritis Rheum. 2005
 Aug;52(8):2506-12.
- 1049. Heikkila R, Aho K, Heliovaara M, et al. Serum androgen-anabolic hormones and the risk of rheumatoid arthritis. Ann Rheum Dis. 1998 May;57(5):281-5.
- 1050. Helliwell PS, Taylor WJ. Treatment of psoriatic arthritis and rheumatoid arthritis with disease modifying drugs -- comparison of drugs and adverse reactions. J Rheumatol. 2008 Mar;35(3):472-6.
- 1051. Henke PK, Sukheepod P, Proctor MC, et al. Clinical relevance of peripheral vascular occlusive disease in patients with rheumatoid arthritis and systemic lupus erythematosus. J Vasc Surg. 2003

 Jul;38(1):111-5.
- 1052. Henrickson M, Reiff A. Prolonged efficacy of etanercept in refractory enthesitis-related arthritis. J Rheumatol. 2004
 Oct;31(10):2055-61.
- 1053. Hepburn AL, Mason JC, Davies KA. Expression of Fcgamma and complement receptors on peripheral blood monocytes in

- systemic lupus erythematosus and rheumatoid arthritis. Rheumatology (Oxford). 2004 May;43(5):547-54.
- 1054. Herenius MM, Hoving JL, Sluiter JK, et al. Improvement of work ability, quality of life, and fatigue in patients with rheumatoid arthritis treated with adalimumab. J Occup Environ Med. 2010 Jun;52(6):618-21.
- 1055. Hermann J, Mueller T, Fahrleitner A, et al. Early onset and effective inhibition of bone resorption in patients with rheumatoid arthritis treated with the tumour necrosis factor alpha antibody infliximab. Clin Exp Rheumatol. 2003 Jul-Aug;21(4):473-6.
- 1056. Herrera-Esparza R, Avalos-Diaz E. Infliximab treatment in a case of rheumatoid scleromalacia perforans. Reumatismo. 2009 Jul-Sep;61(3):212-5.
- 1057. Hetland ML, Stengaard-Pedersen K, Junker P, et al. Combination treatment with methotrexate, cyclosporine, and intraarticular betamethasone compared with methotrexate and intraarticular betamethasone in early active rheumatoid arthritis: an investigator-initiated, multicenter, randomized, double-blind, parallel-group, placebo-controlled study. Arthritis Rheum. 2006 May;54(5):1401-9.
- 1058. Hetland ML, Stengaard-Pedersen K, Junker P, et al. Aggressive combination therapy with intra-articular glucocorticoid injections and conventional disease-modifying anti-rheumatic drugs in early rheumatoid arthritis: second-year clinical and radiographic results from the CIMESTRA study. Ann Rheum Dis. 2008 Jun;67(6):815-22.
- 1059. Hetland ML, Stengaard-Pedersen K, Junker P, et al. Radiographic progression and remission rates in early rheumatoid arthritis MRI bone oedema and anti-CCP predicted radiographic progression in the 5-year extension of the double-blind randomised CIMESTRA trial. Ann Rheum Dis. 2010 Oct;69(10):1789-95.
- 1060. Heytman M, Ahern MJ, Smith MD, et al. The longterm effect of pulsed corticosteroids on the efficacy and toxicity

- of chrysotherapy in rheumatoid arthritis. J Rheumatol. 1994 Mar;21(3):435-41.
- 1061. Hider SL, Thomson W, Mack LF, et al. Polymorphisms within the adenosine receptor 2a gene are associated with adverse events in RA patients treated with MTX. Rheumatology (Oxford). 2008

 Aug;47(8):1156-9.
- 1062. Higashida J, Wun T, Schmidt S, et al. Safety and efficacy of rituximab in patients with rheumatoid arthritis refractory to disease modifying antirheumatic drugs and antitumor necrosis factor-alpha treatment. J Rheumatol. 2005 Nov;32(11):2109-15.
- 1063. High WA, Muldrow ME, Fitzpatrick JE. Cutaneous lupus erythematosus induced by infliximab. J Am Acad Dermatol. 2005 Apr;52(4):E5.
- 1064. Hilliquin P, Houbaba H, Aissa J, et al. Correlations between PAF-acether and tumor necrosis factor in rheumatoid arthritis. Influence of parenteral corticosteroids. Scand J Rheumatol. 1995;24(3):169-73.
- 1065. Hirabayashi Y, Shimizu H, Kobayashi N, et al. Leflunomide-induced pneumonitis in a patient with rheumatoid arthritis. Intern Med. 2006;45(10):689-91.
- 1066. Hirano D, Nagashima M, Ogawa R, et al. Serum levels of interleukin 6 and stress related substances indicate mental stress condition in patients with rheumatoid arthritis. J Rheumatol. 2001 Mar;28(3):490-5.
- 1067. Hirano Y, Kishimoto H, Hagino H, et al. The change of bone mineral density in secondary osteoporosis and vertebral fracture incidence. J Bone Miner Metab. 1999;17(2):119-24.
- 1068. Hirano Y, Kojima T, Kanayama Y, et al. Influences of anti-tumour necrosis factor agents on postoperative recovery in patients with rheumatoid arthritis. Clin Rheumatol 2010;29(5):495-500.
- 1069. Hirayama T, Danks L, Sabokbar A, et al.
 Osteoclast formation and activity in the
 pathogenesis of osteoporosis in rheumatoid

- arthritis. Rheumatology (Oxford). 2002 Nov;41(11):1232-9.
- 1070. Hirche D, Rubbert A, Lunau L, et al. Successful treatment of refractory rheumatoid arthritis-associated leg ulcerations with adalimumab. Br J Dermatol. 2005 May;152(5):1062-4.
- 1071. Hirohata M, Yasukawa Y, Ishida C, et al. Reversible cortical lesions in primary Sjogren's syndrome presenting with meningoencephalitis as an initial manifestation. J Neurol Sci. 2005 May 15;232(1-2):111-3.
- 1072. Hirohata S, Yanagida T, Tomita T, et al. Differential influences of bucillamine and methotrexate on the generation of fibroblast-like cells from bone marrow CD34+ cells of rheumatoid arthritis patients. Int Immunopharmacol. 2009 Jan;9(1):86-90.
- 1073. Hirose W, Nishikawa K, Hirose M, et al. Response of early active rheumatoid arthritis to tumor necrosis factor inhibitors: evaluation by magnetic resonance imaging. Mod Rheumatol. 2009;19(1):20-6.
- 1074. Hjardem E, Ostergaard M, Podenphant J, et al. Do rheumatoid arthritis patients in clinical practice benefit from switching from infliximab to a second tumor necrosis factor alpha inhibitor? Ann Rheum Dis 2007;66(9):1184-9.
- 1075. Ho YV, Briganti EM, Duan Y, et al. Polymorphism of the vitamin D receptor gene and corticosteroid-related osteoporosis. Osteoporos Int. 1999;9(2):134-8.
- 1076. Hochberg MC, Johnston SS, John AK. The incidence and prevalence of extra-articular and systemic manifestations in a cohort of newly-diagnosed patients with rheumatoid arthritis between 1999 and 2006. Curr Med Res Opin. 2008 Feb;24(2):469-80.
- 1077. Hoff M, Kvien TK, Kalvesten J, et al. Adalimumab therapy reduces hand bone loss in early rheumatoid arthritis: explorative analyses from the PREMIER study. Ann Rheum Dis 2009;68(7):1171-6.

- 1078. Holman AJ, Ng E. Heart rate variability predicts anti-tumor necrosis factor therapy response for inflammatory arthritis. Auton Neurosci. 2008 Dec 5;143(1-2):58-67.
- 1079. Homsi S, Alexandrescu DT, Milojkovic N, et al. Diffuse large B-cell lymphoma with lung involvement in a psoriatic arthritis patient treated with methotrexate. Dermatol Online J. 2010;16(5):1.
- 1080. Hong BK, Kumar C, Marottoli RA. "MAC" attack. Am J Med. 2009 Dec;122(12):1096-8.
- 1081. Hong S, Kim T, Chung SH, et al.
 Recurrence after topical nonpreserved
 methylprednisolone therapy for
 keratoconjunctivitis sicca in Sjogren's
 syndrome. J Ocul Pharmacol Ther. 2007
 Feb;23(1):78-82.
- 1082. Hooper DR, Tarnopolsky MA, Baker SK. Lewis-Sumner syndrome associated with infliximab therapy in rheumatoid arthritis. Muscle Nerve. 2008 Oct;38(4):1318-25.
- 1083. Hoppe E, Masson C, Audran M, et al. Whipple's disease diagnosed during biological treatment for joint disease. Joint Bone Spine. 2010 Jul;77(4):335-9.
- 1084. Hornung N, Ellingsen T, Attermann J, et al. Patients with rheumatoid arthritis treated with methotrexate (MTX): concentrations of steady-state erythrocyte MTX correlate to plasma concentrations and clinical efficacy. J Rheumatol. 2008 Sep;35(9):1709-15.
- 1085. Hosaka K, Ryu J, Saitoh S, et al. The combined effects of anti-TNFalpha antibody and IL-1 receptor antagonist in human rheumatoid arthritis synovial membrane. Cytokine. 2005 Dec 21;32(6):263-9.
- 1086. Hoshida Y, Xu JX, Fujita S, et al. Lymphoproliferative disorders in rheumatoid arthritis: clinicopathological analysis of 76 cases in relation to methotrexate medication. J Rheumatol. 2007 Feb;34(2):322-31.
- 1087. Hoshida Y, Yamamoto S, Wada N, et al. Infliximab-associated lymphoproliferative

- disorders. Int J Hematol. 2005 May;81(4):356-7.
- 1088. Hot A, Toh ML, Coppere B, et al. Reactive hemophagocytic syndrome in adult-onset Still disease: clinical features and long-term outcome: a case-control study of 8 patients. Medicine (Baltimore). 2010 Jan;89(1):37-46.
- 1089. Housden MM, Bell G, Heycock CR, et al. How to reduce morbidity and mortality from chest infections in rheumatoid arthritis. Clin Med. 2010 Aug;10(4):326-9.
- 1090. Houtman PM. Septic monarthritis due to Pasteurella multocida after a cat scratch in a patient with rheumatoid arthritis. Neth J Med. 1990 Apr;36(3-4):207-8.
- 1091. Hrycaj P, Korczowska I, Lacki JK. Severe Parkinson's disease in rheumatoid arthritis patient treated with infliximab. Rheumatology (Oxford). 2003 May;42(5):702-3.
- 1092. Hrycaj P, Lacki JK. Treatment resistant ankylosing spondylitis with peripheral joint involvement a case for infliximab? J Rheumatol. 2003 Jan;30(1):204-6; author reply 6.
- 1093. Hsieh TY, Lan JL, Chen DY. Primary Sjogren's syndrome with protein-losing gastroenteropathy: report of two cases. J Formos Med Assoc. 2002 Jul;101(7):519-22.
- 1094. Hsu CT, Lin YT, Yang YH, et al. Factors affecting clinical and therapeutic outcomes of patients with juvenile rheumatoid arthritis. Scand J Rheumatol. 2004;33(5):312-7.
- 1095. Hsu PC, Lan JL, Hsieh TY, et al. Methotrexate pneumonitis in a patient with rheumatoid arthritis. J Microbiol Immunol Infect. 2003 Jun;36(2):137-40.
- 1096. Hu D, Bao C, Chen S, et al. A comparison study of a recombinant tumor necrosis factor receptor:Fc fusion protein (rhTNFR:Fc) and methotrexate in treatment of patients with active rheumatoid arthritis in China. Rheumatol Int. 2009 Jan;29(3):297-303.

- 1097. Hu S, Cohen D, Murphy G, et al. Interstitial granulomatous dermatitis in a patient with rheumatoid arthritis on etanercept. Cutis. 2008 Apr;81(4):336-8.
- 1098. Huang F, Zhu J, Zhang L, et al. Response to one infusion predicts subsequent improvement as well as the rate of relapse of ankylosing spondylitis infused with three pulses of infliximab. Clin Rheumatol. 2007 Jun;26(6):920-6.
- 1099. Huang X, Gu NY, Fox KM, et al.
 Comparison of methods for measuring dose
 escalation of the subcutaneous TNF
 antagonists for rheumatoid arthritis patients
 treated in routine clinical practice. Curr Med
 Res Opin. 2010 Jul;26(7):1637-45.
- 1100. Hubscher O, Re R, Iotti R. Pulmonary rheumatoid nodules in an etanercept-treated patient. Arthritis Rheum. 2003
 Jul;48(7):2077-8.
- 1101. Hughes LB, Criswell LA, Beasley TM, et al. Genetic risk factors for infection in patients with early rheumatoid arthritis. Genes Immun. 2004 Dec;5(8):641-7.
- 1102. Hurlimann D, Forster A, Noll G, et al. Antitumor necrosis factor-alpha treatment improves endothelial function in patients with rheumatoid arthritis. Circulation. 2002 Oct 22;106(17):2184-7.
- 1103. Huscher D, Thiele K, Gromnica-Ihle E, et al. Dose-related patterns of glucocorticoid-induced side effects. Ann Rheum Dis. 2009 Jul;68(7):1119-24.
- 1104. Husni ME, Maier AL, Mease PJ, et al. Etanercept in the treatment of adult patients with Still's disease. Arthritis Rheum. 2002 May;46(5):1171-6.
- 1105. Hussar DA. New drugs: abatacept, sorafenib, and nelarabine. J Am Pharm Assoc (Wash DC). 2006 Mar-Apr;46(2):300-3.
- 1106. Hutas G. Golimumab, a fully human monoclonal antibody against TNFalpha.

 Curr Opin Mol Ther. 2008 Aug;10(4):393-406.

- 1107. Huwait H, Wang B, Shustik C, et al. Composite cutaneous lymphoma in a patient with rheumatoid arthritis treated with methotrexate. Am J Dermatopathol. 2010 Feb;32(1):65-70.
- 1108. Hyon JY, Lee YJ, Yun PY. Management of ocular surface inflammation in Sjogren syndrome. Cornea. 2007 Oct;26(9 Suppl 1):S13-5.
- 1109. Hyrich KL, Deighton C, Watson KD, et al. Benefit of anti-TNF therapy in rheumatoid arthritis patients with moderate disease activity. Rheumatology (Oxford) 2009;48(10):1323-7.
- 1110. Hyrich KL, Lunt M, Dixon WG, et al. Effects of switching between anti-TNF therapies on HAQ response in patients who do not respond to their first anti-TNF drug. Rheumatology (Oxford). 2008

 Jul;47(7):1000-5.
- 1111. Hyrich KL, Lunt M, Watson KD, et al. Outcomes after switching from one antitumor necrosis factor alpha agent to a second anti-tumor necrosis factor alpha agent in patients with rheumatoid arthritis: results from a large UK national cohort study. Arthritis Rheum 2007;56(1):13-20.
- 1112. Iagnocco A, Filippucci E, Perella C, et al. Clinical and ultrasonographic monitoring of response to adalimumab treatment in rheumatoid arthritis. J Rheumatol. 2008 Jan;35(1):35-40.
- 1113. Iagnocco A, Perella C, Naredo E, et al. Etanercept in the treatment of rheumatoid arthritis: clinical follow-up over one year by ultrasonography. Clin Rheumatol. 2008 Apr;27(4):491-6.
- 1114. Iannone F, Trotta F, Montecucco C, et al. Etanercept maintains the clinical benefit achieved by infliximab in patients with rheumatoid arthritis who discontinued infliximab because of side effects. Ann Rheum Dis. 2007 Feb;66(2):249-52.
- 1115. Ichikawa T, Kageyama Y, Kobayashi H, et al. Etanercept treatment reduces the serum levels of interleukin-15 and interferongamma inducible protein-10 in patients with

- rheumatoid arthritis. Rheumatol Int. 2010 Apr;30(6):725-30.
- 1116. Ideguchi H, Ohno S, Ishigatsubo Y. Risk factors associated with the cumulative survival of low-dose methotrexate in 273 Japanese patients with rheumatoid arthritis. J Clin Rheumatol. 2007 Apr;13(2):73-8.
- 1117. Iglesias J, Sathiraju S, Marik PE. Severe systemic inflammatory response syndrome with shock and ARDS resulting from Still's disease: clinical response with high-dose pulse methylprednisolone therapy. Chest. 1999 Jun;115(6):1738-40.
- 1118. Iikuni N, Inoue E, Tanaka E, et al. Low disease activity state with corticosteroid may not represent 'true' low disease activity state in patients with rheumatoid arthritis. Rheumatology (Oxford). 2008

 Apr;47(4):519-21.
- 1119. Ikegawa S, Urano F, Suzuki S, et al. Three cases of pustulotic arthro-osteitis associated with episcleritis. J Am Acad Dermatol. 1999 Nov;41(5 Pt 2):845-6.
- 1120. Ikonomidis I, Lekakis JP, Nikolaou M, et al. Inhibition of interleukin-1 by anakinra improves vascular and left ventricular function in patients with rheumatoid arthritis. Circulation. 2008 May 20;117(20):2662-9.
- 1121. Ikonomidis I, Tzortzis S, Lekakis J, et al. Lowering interleukin-1 activity with anakinra improves myocardial deformation in rheumatoid arthritis. Heart. 2009 Sep;95(18):1502-7.
- 1122. Ilias I, Mastorakos G, Mavrikakis M, et al. Thyroid disease associated with rheumatoid arthritis is not adequately screened with a sensitive chemiluminescence thyrotrophin assay. Acta Med Austriaca. 1999;26(1):26-8.
- 1123. Imaizumi K, Sugishita M, Usui M, et al. Pulmonary infectious complications associated with anti-TNFalpha therapy (infliximab) for rheumatoid arthritis. Intern Med. 2006;45(10):685-8.

- 1124. Imrich R, Rovensky J, Malis F, et al. Low levels of dehydroepiandrosterone sulphate in plasma, and reduced sympathoadrenal response to hypoglycaemia in premenopausal women with rheumatoid arthritis. Ann Rheum Dis. 2005 Feb;64(2):202-6.
- 1125. Imrich R, Rovensky J, Zlnay M, et al. Hypothalamic-pituitary-adrenal axis function in ankylosing spondylitis. Ann Rheum Dis. 2004 Jun;63(6):671-4.
- 1126. Imrich R, Vigas M, Rovensky J, et al. Adrenal plasma steroid relations in glucocorticoid-naive premenopausal rheumatoid arthritis patients during insulininduced hypoglycemia test compared to matched normal control females. Endocr Regul. 2009 Apr;43(2):65-73.
- 1127. Imrich R, Vlcek M, Aldag JC, et al. An endocrinologist's view on relative adrenocortical insufficiency in rheumatoid arthritis. Ann N Y Acad Sci. 2010 Apr;1193(1):134-8.
- 1128. Inanc N, Direskeneli H. Serious infections under treatment with TNF-alpha antagonists compared to traditional DMARDs in patients with rheumatoid arthritis.

 Rheumatol Int. 2006 Nov;27(1):67-71.
- 1129. Infante R, Lahita RG. Rheumatoid arthritis. New disease-modifying and antiinflammatory drugs. Geriatrics. 2000 Mar;55(3):30-2, 5-6, 9-40.
- 1130. Ingegnoli F, Fantini F, Favalli EG, et al. Inflammatory and prothrombotic biomarkers in patients with rheumatoid arthritis: effects of tumor necrosis factor-alpha blockade. J Autoimmun. 2008 Sep;31(2):175-9.
- 1131. Ingegnoli F, Fantini F, Griffini S, et al. Antitumor necrosis factor alpha therapy normalizes fibrinolysis impairment in patients with active rheumatoid arthritis. Clin Exp Rheumatol. 2010 Mar-Apr;28(2):254-7.
- 1132. Ingegnoli F, Sciascera A, Galbiati V, et al. Bronchus-associated lymphoid tissue lymphoma in a patient with primary Sjogren's syndrome. Rheumatol Int. 2008 Dec;29(2):207-9.

- 1133. Inokuma S, Sato T, Sagawa A, et al.
 Proposals for leflunomide use to avoid lung injury in patients with rheumatoid arthritis.
 Mod Rheumatol. 2008;18(5):442-6.
- 1134. Inoue K, Takano H, Yanagisawa R, et al. Effects of tumor necrosis factor-alpha inhibitors on lung lesions with rheumatoid arthritis. Chest. 2003 Jul;124(1):413-4; author reply 4.
- 1135. Inoue S, Hashiguchi M, Kawai S, et al. Erythrocyte methotrexate-polyglutamate assay using fluorescence polarization immunoassay technique: application to the monitoring of patients with rheumatoid arthritis. Yakugaku Zasshi. 2009
 Aug;129(8):1001-5.
- 1136. Inoue S, Hashiguchi M, Takagi K, et al. Preliminary study to identify the predictive factors for the response to methotrexate therapy in patients with rheumatoid arthritis. Yakugaku Zasshi. 2009 Jul;129(7):843-9.
- 1137. Iobst W, Ingraham K. Sneddon-Wilkinson disease in a patient with rheumatoid arthritis. Arthritis Rheum. 2005
 Dec;52(12):3771.
- 1138. Ippolito JA, Palmer L, Spector S, et al. Bronchiolitis obliterans organizing pneumonia and rheumatoid arthritis. Semin Arthritis Rheum. 1993 Aug;23(1):70-8.
- 1139. Irwin LR, Beckett R, Suman RK. Steroid injection for carpal tunnel syndrome. J Hand Surg [Br]. 1996 Jun;21(3):355-7.
- 1140. Ishiguro T, Takayanagi N, Kurashima K, et al. Development of sarcoidosis during etanercept therapy. Intern Med. 2008;47(11):1021-5.
- 1141. Ishii H, Nagashima M, Tanno M, et al. Does being easily moved to tears as a response to psychological stress reflect response to treatment and the general prognosis in patients with rheumatoid arthritis? Clin Exp Rheumatol. 2003 Sep-Oct;21(5):611-6.
- 1142. Ishikawa Y, Yukawa N, Ohmura K, et al. Etanercept-induced anti-Jo-1-antibody-positive polymyositis in a patient with rheumatoid arthritis: a case report and

- review of the literature. Clin Rheumatol. 2010 May;29(5):563-6.
- 1143. Itonaga I, Fujikawa Y, Sabokbar A, et al. Rheumatoid arthritis synovial macrophage-osteoclast differentiation is osteoprotegerin ligand-dependent. J Pathol. 2000 Sep;192(1):97-104.
- 1144. Iwamoto N, Kawakami A, Fujikawa K, et al. Prediction of DAS28-ESR remission at 6 months by baseline variables in patients with rheumatoid arthritis treated with etanercept in Japanese population. Mod Rheumatol 2009;19(5):488-92.
- 1145. Iwatani M, Inoue E, Nakamura T, et al. Efficacy profile of bucillamine in rheumatoid arthritis patients in a large observational cohort study, IORRA. Mod Rheumatol 2006;16(6):376-80.
- 1146. Iyer S, Yamauchi P, Lowe NJ. Etanercept for severe psoriasis and psoriatic arthritis: observations on combination therapy. Br J Dermatol. 2002 Jan;146(1):118-21.
- 1147. Izumi A. Varicella zoster virus infection in patients taking the TNF-alpha inhibitor, etanercept: coincidence or causal? Hawaii Med J. 2009 Dec;68(11):277-8.
- 1148. Izumi M, Eguchi K, Nakamura H, et al. Corticosteroid irrigation of parotid gland for treatment of xerostomia in patients with Sjogren's syndrome. Ann Rheum Dis. 1998 Aug;57(8):464-9.
- 1149. Jacobs JW, Geenen R, Evers AW, et al.
 Short term effects of corticosteroid pulse treatment on disease activity and the wellbeing of patients with active rheumatoid arthritis. Ann Rheum Dis. 2001
 Jan;60(1):61-4.
- 1150. Jacobsson LT, Turesson C, Gulfe A, et al. Treatment with tumor necrosis factor blockers is associated with a lower incidence of first cardiovascular events in patients with rheumatoid arthritis. J Rheumatol. 2005 Jul;32(7):1213-8.
- 1151. James HM, Gillis D, Hissaria P, et al.

 Common polymorphisms in the folate pathway predict efficacy of combination

- regimens containing methotrexate and sulfasalazine in early rheumatoid arthritis. J Rheumatol. 2008 Apr;35(4):562-71.
- 1152. Jamnitski A, Visman IM, Peters MJ, et al. Beneficial effect of 1-year etanercept treatment on the lipid profile in responding patients with rheumatoid arthritis: the ETRA study. Ann Rheum Dis. 2010 Nov;69(11):1929-33.
- 1153. Jarrett SJ, Cunnane G, Conaghan PG, et al. Anti-tumor necrosis factor-alpha therapyinduced vasculitis: case series. J Rheumatol. 2003 Oct;30(10):2287-91.
- 1154. Jenkins EA, Walker-Bone KE, Wood A, et al. The prevention of corticosteroid-induced bone loss with intermittent cyclical etidronate. Scand J Rheumatol. 1999;28(3):152-6.
- 1155. Jenks KA, Stamp LK, O'Donnell JL, et al. Leflunomide-associated infections in rheumatoid arthritis. J Rheumatol. 2007 Nov;34(11):2201-3.
- 1156. Jeurissen ME, Boerbooms AM, van de Putte LB, et al. Methotrexate versus azathioprine in the treatment of rheumatoid arthritis. A forty-eight-week randomized, double-blind trial. Arthritis Rheum. 1991 Aug;34(8):961-72.
- 1157. Jia J, Wang Q, Zhang T, et al. Treatment of ankylosing spondylitis with medicated moxibustion plus salicylazosulfapyridine and methotrexate--a report of 30 cases. J Tradit Chin Med. 2006 Mar;26(1):26-8.
- 1158. Jian X, Guo G, Ruan Y, et al. Severe cutaneous adverse drug reaction to leflunomide: a report of two cases. Cutan Ocul Toxicol. 2008;27(1):5-9.
- 1159. Jiang Y, Genant HK, Watt I, et al. A multicenter, double-blind, dose-ranging, randomized, placebo-controlled study of recombinant human interleukin-1 receptor antagonist in patients with rheumatoid arthritis: radiologic progression and correlation of Genant and Larsen scores. Arthritis Rheum. 2000 May;43(5):1001-9.

- 1160. Jimenez FG, Colmenero JD, Irigoyen MV. Reactivation of brucellosis after treatment with infliximab in a patient with rheumatoid arthritis. J Infect. 2005 May;50(4):370-1.
- 1161. Jin T, Bokarewa M, Amu S, et al. Impact of short-term therapies with biologics on prothrombotic biomarkers in rheumatoid arthritis. Clin Exp Rheumatol. 2009 May-Jun;27(3):491-4.
- 1162. Jinno S, Pulido S, Pien BC. First reported United States case of Legionella pneumophila serogroup 1 pneumonia in a patient receiving anti-tumor necrosis factoralpha therapy. Hawaii Med J. 2009 Jun;68(5):109-12.
- 1163. Jo SJ, Park JY, Yoon HS, et al. Case of acrodermatitis continua accompanied by psoriatic arthritis. J Dermatol. 2006 Nov;33(11):787-91.
- 1164. Jobanputra P, Amarasena R, Maggs F, et al. Hepatotoxicity associated with sulfasalazine in inflammatory arthritis: A case series from a local surveillance of serious adverse events. BMC Musculoskelet Disord. 2008;9:48.
- 1165. Johns KR, Littlejohn GO. The safety and efficacy of cyclosporine (Neoral) in rheumatoid arthritis. J Rheumatol. 1999 Oct;26(10):2110-3.
- 1166. Johnsen AK, Schiff MH, Mease PJ, et al. Comparison of 2 doses of etanercept (50 vs 100 mg) in active rheumatoid arthritis: a randomized double blind study. J Rheumatol. 2006 Apr;33(4):659-64.
- 1167. Johnson EO, Vlachoyiannopoulos PG, Skopouli FN, et al. Hypofunction of the stress axis in Sjogren's syndrome. J Rheumatol. 1998 Aug;25(8):1508-14.
- 1168. Jois RN, Masding A, Somerville M, et al. Rituximab therapy in patients with resistant rheumatoid arthritis: real-life experience. Rheumatology (Oxford). 2007
 Jun;46(6):980-2.
- 1169. Jones G. The AMBITION trial: tocilizumab monotherapy for rheumatoid arthritis. Expert Rev Clin Immunol 2010;6(2):189-95.

- 1170. Jones SM, Bhalla AK. Osteoporosis in rheumatoid arthritis. Clin Exp Rheumatol. 1993 Sep-Oct;11(5):557-62.
- 1171. Jonsdottir T, Forslid J, van Vollenhoven A, et al. Treatment with tumour necrosis factor alpha antagonists in patients with rheumatoid arthritis induces anticardiolipin antibodies. Ann Rheum Dis. 2004 Sep;63(9):1075-8.
- 1172. Jorgensen C, Bressot N, Bologna C, et al. Dysregulation of the hypothalamo-pituitary axis in rheumatoid arthritis. J Rheumatol. 1995 Oct;22(10):1829-33.
- 1173. Josefina M, Ana CJ, Ariel V, et al. Development of pseudogout during etanercept treatment. J Clin Rheumatol. 2007 Jun;13(3):177.
- 1174. Josipovic B. Levels of dehydroepiandrosterone sulfate in female patients with early stage of rheumatoid arthritis. Ann N Y Acad Sci. 1999 Jun 22;876:145-7.
- 1175. Josipovic B. Adrenal secretion of cortisol in patients with short-lasting rheumatoid arthritis. Z Rheumatol. 2000;59 Suppl 2:II/136.
- 1176. Ju JH, Kim SI, Lee JH, et al. Risk of interstitial lung disease associated with leflunomide treatment in Korean patients with rheumatoid arthritis. Arthritis Rheum 2007;56(6):2094-6.
- 1177. Juillard-Condat B, Constantin A, Cambon-Thomsen A, et al. Impact of etanercept on the costs of rheumatoid arthritis (RA): results from a French observational study. Joint Bone Spine. 2008 Jan;75(1):25-8.
- 1178. Julkunen H. Hormone replacement therapy in women with rheumatic diseases. Scand J Rheumatol. 2000;29(3):146-53.
- 1179. Jung N, Hellmann M, Hoheisel R, et al. An open-label pilot study of the efficacy and safety of anakinra in patients with psoriatic arthritis refractory to or intolerant of methotrexate (MTX). Clin Rheumatol. 2010 Oct;29(10):1169-73.

- 1180. Kaaja R, Julkunen H, Ammala P, et al.
 Congenital heart block: successful
 prophylactic treatment with intravenous
 gamma globulin and corticosteroid therapy.
 Am J Obstet Gynecol. 1991 Nov;165(5 Pt
 1):1333-4.
- 1181. Kadar J, Petrovicz E. Adult-onset Still's disease. Best Pract Res Clin Rheumatol. 2004 Oct;18(5):663-76.
- 1182. Kadota J, Kusano S, Kawakami K, et al. Usual interstitial pneumonia associated with primary Sjogren's syndrome. Chest. 1995 Dec;108(6):1756-8.
- 1183. Kageyama Y, Kobayashi H, Kato N. Infliximab treatment reduces the serum levels of interleukin-23 in patients with rheumatoid arthritis. Mod Rheumatol. 2009;19(6):657-62.
- 1184. Kageyama Y, Kobayashi H, Kato N, et al. Etanercept reduces the serum levels of macrophage chemotactic protein-1 in patients with rheumatoid arthritis. Mod Rheumatol. 2009;19(4):372-8.
- 1185. Kageyama Y, Takahashi M, Ichikawa T, et al. Reduction of oxidative stress marker levels by anti-TNF-alpha antibody, infliximab, in patients with rheumatoid arthritis. Clin Exp Rheumatol. 2008 Jan-Feb;26(1):73-80.
- 1186. Kageyama Y, Torikai E, Nagano A. Antitumor necrosis factor-alpha antibody treatment reduces serum CXCL16 levels in patients with rheumatoid arthritis.

 Rheumatol Int. 2007 Mar;27(5):467-72.
- 1187. Kahan A, Modder G, Menkes CJ, et al. 169Erbium-citrate synoviorthesis after failure of local corticosteroid injections to treat rheumatoid arthritis-affected finger joints. Clin Exp Rheumatol. 2004 Nov-Dec;22(6):722-6.
- 1188. Kahn KL, MacLean CH, Liu H, et al.
 Application of explicit process of care
 measurement to rheumatoid arthritis:
 Moving from evidence to practice. Arthritis
 Rheum. 2006 Dec 15;55(6):884-91.

- 1189. Kahn P, Weiss M, Imundo LF, et al. Favorable response to high-dose infliximab for refractory childhood uveitis. Ophthalmology. 2006 May;113(5):864 e1-2.
- 1190. Kaipiainen-Seppanen O, Leino M. Recurrent uveitis in a patient with juvenile spondyloarthropathy associated with tumour necrosis factor alpha inhibitors. Ann Rheum Dis. 2003 Jan;62(1):88-9.
- 1191. Kaiser J. Clinical trials. Gene transfer an unlikely contributor to patient's death. Science. 2007 Dec 7;318(5856):1535.
- 1192. Kaiser J. Gene therapy. Questions remain on cause of death in arthritis trial. Science. 2007 Sep 21;317(5845):1665.
- 1193. Kaiser MJ, Bozonnat MC, Jorgensen C, et al. Effect of etanercept on tenosynovitis and nodules in rheumatoid arthritis. Arthritis Rheum. 2002 Feb;46(2):559-60.
- 1194. Kaiser MJ, Sany J. Efficacy of infliximab (Remicade) in the treatment of spondyloarthropathies. two case reports. Joint Bone Spine. 2001 Dec;68(6):525-7.
- 1195. Kakkassery V, Mergler S, Pleyer U. Anti-TNF-alpha treatment: a possible promoter in endogenous uveitis? observational report on six patients: occurrence of uveitis following etanercept treatment. Curr Eye Res. 2010 Aug;35(8):751-6.
- 1196. Kalden JR, Nusslein HG, Wollenhaupt J, et al. Combination treatment with infliximab and leflunomide in patients with active rheumatoid arthritis: safety and efficacy in an open-label clinical trial. Clin Exp Rheumatol. 2008 Sep-Oct;26(5):834-40.
- 1197. Kalla AA, Bewerunge L, Langley A, et al. Trabecular bone density in premenopausal rheumatoid arthritis patients. S Afr Med J. 2002 Jan;92(1):62-8.
- 1198. Kalla AA, Brown GM, Meyers OL. Nutritional status in rheumatoid arthritis. Effects of disease activity, corticosteroid therapy and functional impairment. S Afr Med J. 1992 Dec;82(6):411-4.

- 1199. Kalla AA, Meyers OL, Kotze TJ, et al. Corticosteroid therapy and bone mass-comparison of rheumatoid arthritis and systemic lupus erythematosus. S Afr Med J. 1994 Jul;84(7):404-9.
- 1200. Kalyoncu U, Karadag O, Akdogan A, et al. Pneumocystis carinii pneumonia in a rheumatoid arthritis patient treated with adalimumab. Scand J Infect Dis. 2007;39(5):475-8.
- 1201. Kamal KM, Madhavan SS, Hornsby JA, et al. Use of tumor necrosis factor inhibitors in rheumatoid arthritis: a national survey of practicing United States rheumatologists.

 Joint Bone Spine. 2006 Dec;73(6):718-24.
- 1202. Kamarashev J, Lor P, Forster A, et al. Generalised pustular psoriasis induced by cyclosporin a withdrawal responding to the tumour necrosis factor alpha inhibitor etanercept. Dermatology. 2002;205(2):213-6.
- 1203. Kameda H, Okuyama A, Tamaru J, et al. Lymphomatoid granulomatosis and diffuse alveolar damage associated with methotrexate therapy in a patient with rheumatoid arthritis. Clin Rheumatol. 2007 Sep;26(9):1585-9.
- 1204. Kameda T, Dobashi H, Kittaka K, et al. A case of rheumatoid arthritis complicated by demyelination in both cerebral cortex and spinal cord during etanercept therapy. Mod Rheumatol. 2008;18(4):399-402.
- 1205. Kamili QA, Menter A. Atypical presentation of histoplasmosis in a patient with psoriasis and psoriatic arthritis on infliximab therapy.

 J Drugs Dermatol. 2010 Jan;9(1):57-60.
- 1206. Kamper AM, Malbrain M, Zachee P, et al. Parvovirus infection causing red cell aplasia and leukopenia in rheumatoid arthritis. Clin Rheumatol. 1994 Mar;13(1):129-31.
- 1207. Kanakoudi-Tsakalidou F, Tzimouli V, Pratsidou-Gertsi P, et al. The significance of persistent newly developed autoantibodies in JIA patients under long-term anti-TNF treatment. Cytokine. 2008 Jun;42(3):293-7.

- 1208. Kanbe K, Inoue Y, Inoue Y, et al. Histological analysis of synovium in cases of effect attenuation associated with infliximab therapy in rheumatoid arthritis. Clin Rheumatol. 2008 Jun;27(6):777-81.
- 1209. Kanbe K, Inoue K, Inoue Y, et al. Histological changes in bone marrow after treatment of infliximab for rheumatoid arthritis. Clin Rheumatol. 2008

 Apr;27(4):497-501.
- 1210. Kaneko K, Nonomura Y, Watanabe K, et al. Infected abdominal aortic aneurysm caused by nontyphoid Salmonella in an immunocompromised patient with rheumatoid arthritis. J Infect Chemother. 2009 Oct;15(5):312-5.
- 1211. Kaneko Y, Suwa A, Ikeda Y, et al. Pneumocystis jiroveci pneumonia associated with low-dose methotrexate treatment for rheumatoid arthritis: report of two cases and review of the literature. Mod Rheumatol. 2006;16(1):36-8.
- 1212. Kanekura T, Terasaki K, Higashi Y, et al. Improvement of adult Still's disease with granulocyte and monocyte adsorption apheresis. Clin Exp Dermatol. 2004 Jul;29(4):410-2.
- 1213. Kang CP, Lee KW, Yoo DH, et al. The influence of a polymorphism at position 857 of the tumour necrosis factor alpha gene on clinical response to etanercept therapy in rheumatoid arthritis. Rheumatology (Oxford). 2005 Apr;44(4):547-52.
- 1214. Kang MJ, Kim MS, Choi EH, et al. Adenoviral pneumonia during etanercept treatment in a patient with rheumatoid arthritis. Korean J Intern Med. 2007 Mar;22(1):63-6.
- 1215. Kang MJ, Lee YH, Lee J. Etanerceptinduced systemic lupus erythematosus in a patient with rheumatoid arthritis. J Korean Med Sci. 2006 Oct;21(5):946-9.
- 1216. Kanik KS, Chrousos GP, Schumacher HR, et al. Adrenocorticotropin, glucocorticoid, and androgen secretion in patients with new onset synovitis/rheumatoid arthritis: relations with indices of inflammation. J

- Clin Endocrinol Metab. 2000 Apr;85(4):1461-6.
- 1217. Kanis JA, Borgstrom F, De Laet C, et al. Assessment of fracture risk. Osteoporos Int. 2005 Jun;16(6):581-9.
- 1218. Kao CD, Liao KK. A flow chart proposed for early diagnosis of cryptococcal infection as a cause of stroke. Acta Neurol Taiwan. 2009 Mar;18(1):30-3.
- 1219. Kapetanovic MC, Larsson L, Truedsson L, et al. Predictors of infusion reactions during infliximab treatment in patients with arthritis. Arthritis Res Ther. 2006;8(4):R131.
- 1220. Kapetanovic MC, Saxne T, Sjoholm A, et al. Influence of methotrexate, TNF blockers and prednisolone on antibody responses to pneumococcal polysaccharide vaccine in patients with rheumatoid arthritis. Rheumatology (Oxford). 2006

 Jan;45(1):106-11.
- 1221. Kaplan MJ. Do tumor-necrosis-factor inhibitors prevent first cardiovascular events in patients with rheumatoid arthritis? Nat Clin Pract Rheumatol. 2005 Dec;1(2):74-5.
- 1222. Kaplan RM, Groessl EJ, Sengupta N, et al. Comparison of measured utility scores and imputed scores from the SF-36 in patients with rheumatoid arthritis. Med Care. 2005 Jan;43(1):79-87.
- 1223. Karabacakoglu A, Karakose S, Ozerbil OM, et al. Fluoroscopy-guided intraarticular corticosteroid injection into the sacroiliac joints in patients with ankylosing spondylitis. Acta Radiol. 2002

 Jul;43(4):425-7.
- 1224. Karaca-Mandic P, Joyce GF, Goldman DP, et al. Cost sharing, family health care burden, and the use of specialty drugs for rheumatoid arthritis. Health Serv Res. 2010 Oct;45(5 Pt 1):1227-50.
- 1225. Karagiannis S, Papaioannou D, Goulas S, et al. Intestinal tuberculosis in a patient on infliximab treatment. Gastrointest Endosc. 2008 Jun;67(7):1178-9; discussion 9.

- 1226. Karanikolas G, Charalambopoulos D,
 Vaiopoulos G, et al. Adjunctive anakinra in
 patients with active rheumatoid arthritis
 despite methotrexate, or leflunomide, or
 cyclosporin-A monotherapy: a 48-week,
 comparative, prospective study.
 Rheumatology (Oxford) 2008;47(9):1384-8.
- 1227. Karie S, Gandjbakhch F, Janus N, et al. Kidney disease in RA patients: prevalence and implication on RA-related drugs management: the MATRIX study. Rheumatology (Oxford). 2008

 Mar;47(3):350-4.
- 1228. Karlsson JA, Kristensen LE, Kapetanovic MC, et al. Treatment response to a second or third TNF-inhibitor in RA: results from the South Swedish Arthritis Treatment Group Register. Rheumatology (Oxford) 2008;47(4):507-13.
- 1229. Karstila KL, Rantalaiho VM, Mustonen JT, et al. Renal safety of initial combination versus single DMARD therapy in patients with early rheumatoid arthritis: an 11-year experience from the FIN-RACo Trial. Clin Exp Rheumatol 2010;28(1):73-8.
- 1230. Kary S, Worm M, Audring H, et al. New onset or exacerbation of psoriatic skin lesions in patients with definite rheumatoid arthritis receiving tumour necrosis factor alpha antagonists. Ann Rheum Dis. 2006 Mar;65(3):405-7.
- 1231. Kasama T, Wakabayashi K, Odai T, et al. Effects of low-dose mizoribine pulse therapy in combination with methotrexate in rheumatoid arthritis patients with an insufficient response to methotrexate. Mod Rheumatol. 2009;19(4):395-400.
- 1232. Kasser UR, Gleissner C, Dehne F, et al. Risk for periodontal disease in patients with longstanding rheumatoid arthritis. Arthritis Rheum. 1997 Dec;40(12):2248-51.
- 1233. Kassimos D, Choy EH, Grossman AB, et al. Endogenous opioid tone in patients with rheumatoid arthritis. Br J Rheumatol. 1996 May;35(5):436-40.
- 1234. Kastanek L. Using anakinra for adult rheumatoid arthritis. Nurse Pract. 2002 Apr;27(4):62-5.

- 1235. Kastbom A, Bratt J, Ernestam S, et al. Fcgamma receptor type IIIA genotype and response to tumor necrosis factor alphablocking agents in patients with rheumatoid arthritis. Arthritis Rheum. 2007 Feb;56(2):448-52.
- 1236. Kastrinaki MC, Sidiropoulos P, Roche S, et al. Functional, molecular and proteomic characterisation of bone marrow mesenchymal stem cells in rheumatoid arthritis. Ann Rheum Dis. 2008
 Jun;67(6):741-9.
- 1237. Kasukawa R, Shio K, Kanno Y, et al.
 Doppler ultrasound measurements of knee
 joint synovitis in rheumatoid arthritis
 patients treated with infliximab. Mod
 Rheumatol. 2007;17(5):376-9.
- 1238. Katayama K, Matsuno T. Effects of bisphosphonates on fracture incidence and bone metabolism in rheumatoid arthritis patients in general practice taking long-term corticosteroid therapy: a retrospective study. Clin Drug Investig. 2008;28(3):149-58.
- 1239. Katayama K, Matsuno T. Long-term efficacy of leflunomide on disease activity and inhibition of joint damage: retrospective comparison with methotrexate for Japanese rheumatoid arthritis patients. Mod Rheumatol. 2009;19(5):513-21.
- 1240. Katayama Y, Kohriyama K, Kirizuka K, et al. Sjogren's syndrome complicated with autoimmune hepatitis and antiphospholipid antibody syndrome. Intern Med. 2000 Jan;39(1):73-6.
- 1241. Katchamart W, Trudeau J, Phumethum V, et al. Methotrexate monotherapy versus methotrexate combination therapy with non-biologic disease modifying anti-rheumatic drugs for rheumatoid arthritis. Cochrane Database Syst Rev. 2010;4:CD008495.
- 1242. Kato T, Hoshi K, Sekijima Y, et al. Rheumatoid meningitis: an autopsy report and review of the literature. Clin Rheumatol. 2003 Dec;22(6):475-80.
- 1243. Kato T, Kiire A, Yamagata H, et al. Hypersensitivity reaction against influenza vaccine in a patient with rheumatoid arthritis

- after the initiation of etanercept injections. Mod Rheumatol. 2006;16(5):327-9.
- 1244. Katoulis AC, Kanelleas A, Zambacos G, et al. Development of two primary malignant melanomas after treatment with adalimumab: a case report and review of the possible link between biological therapy with TNF-alpha antagonists and melanocytic proliferation. Dermatology. 2010 Aug;221(1):9-12.
- 1245. Katz JA, Antoni C, Keenan GF, et al.
 Outcome of pregnancy in women receiving infliximab for the treatment of Crohn's disease and rheumatoid arthritis. Am J Gastroenterol. 2004 Dec;99(12):2385-92.
- 1246. Katz P, Yelin E, Patel V, et al. Patient-reported outcomes following biologic therapy in a sample of adults with rheumatoid arthritis recruited from community-based rheumatologists. Arthritis Rheum. 2009 May 15;61(5):593-9.
- 1247. Kaufman I, Schwartz D, Caspi D, et al. Sjogren's syndrome - not just Sicca: renal involvement in Sjogren's syndrome. Scand J Rheumatol. 2008 May-Jun;37(3):213-8.
- 1248. Kaufman KR. Etanercept, anticytokines and mania. Int Clin Psychopharmacol. 2005 Jul;20(4):239-41.
- 1249. Kaur N, Mahl TC. Pneumocystis jiroveci (carinii) pneumonia after infliximab therapy: a review of 84 cases. Dig Dis Sci. 2007 Jun;52(6):1481-4.
- 1250. Kaur PP, Chan VC, Berney SN. Successful etanercept use in an HIV-positive patient with rheumatoid arthritis. J Clin Rheumatol. 2007 Apr;13(2):79-80.
- 1251. Kaur PP, Chan VC, Berney SN. Histological evaluation of liver in two rheumatoid arthritis patients with chronic hepatitis B and C treated with TNF-alpha blockade: case reports. Clin Rheumatol. 2008

 Aug;27(8):1069-71.
- 1252. Kaur PP, Derk CT, Chatterji M, et al. Septic arthritis caused by Actinobacillus ureae in a patient with rheumatoid arthritis receiving

- anti-tumor necrosis factor-alpha therapy. J Rheumatol. 2004 Aug;31(8):1663-5.
- 1253. Kaushik P, Cooper ES, Banda VR, et al. Bronchiolitis obliterans with organizing pneumonia in rheumatoid arthritis--a fatal case and short review of literature. Rheumatol Int. 2005 Jun;25(5):391-3.
- 1254. Kavalar R, Skok P, Kramberger KG.
 Phlegmonous gastritis in a patient with
 rheumatoid arthritis. Wien Klin
 Wochenschr. 2005 May;117(9-10):364-8.
- 1255. Kavanaugh A, Antoni C, Krueger GG, et al. Infliximab improves health related quality of life and physical function in patients with psoriatic arthritis. Ann Rheum Dis. 2006 Apr;65(4):471-7.
- 1256. Kavanaugh A, Klareskog L, van der Heijde D, et al. Improvements in clinical response between 12 and 24 weeks in patients with rheumatoid arthritis on etanercept therapy with or without methotrexate. Ann Rheum Dis 2008;67(10):1444-7.
- 1257. Kavanaugh A, Lee SJ, Weng HH, et al. Patient-derived joint counts are a potential alternative for determining Disease Activity Score. J Rheumatol 2010;37(5):1035-41.
- 1258. Kavanaugh A, McInnes I, Mease P, et al. Golimumab, a new human tumor necrosis factor alpha antibody, administered every four weeks as a subcutaneous injection in psoriatic arthritis: Twenty-four-week efficacy and safety results of a randomized, placebo-controlled study. Arthritis Rheum 2009;60(4):976-86.
- 1259. Kavanaugh A, Rosengren S, Lee SJ, et al. Assessment of rituximab's immunomodulatory synovial effects (ARISE trial). 1: clinical and synovial biomarker results. Ann Rheum Dis. 2008
 Mar;67(3):402-8.
- 1260. Kavanaugh A, Smolen JS, Emery P, et al. Effect of certolizumab pegol with methotrexate on home and work place productivity and social activities in patients with active rheumatoid arthritis. Arthritis Rheum 2009;61(11):1592-600.

- 1261. Kavanaugh A, St Clair EW, McCune WJ, et al. Chimeric anti-tumor necrosis factor-alpha monoclonal antibody treatment of patients with rheumatoid arthritis receiving methotrexate therapy. J Rheumatol. 2000 Apr;27(4):841-50.
- 1262. Kawano M, Okada K, Muramoto H, et al. Simultaneous, clonally identical T cell expansion in tonsil and synovium in a patient with rheumatoid arthritis and chronic tonsillitis. Arthritis Rheum. 2003 Sep;48(9):2483-8.
- 1263. Kawano M, Seya T, Koni I, et al. Elevated serum levels of soluble membrane cofactor protein (CD46, MCP) in patients with systemic lupus erythematosus (SLE). Clin Exp Immunol. 1999 Jun;116(3):542-6.
- 1264. Kawashima M, Miossec P. Effect of treatment of rheumatoid arthritis with infliximab on IFN gamma, IL4, T-bet, and GATA-3 expression: link with improvement of systemic inflammation and disease activity. Ann Rheum Dis. 2005

 Mar;64(3):415-8.
- 1265. Kawashima N, Shindo R, Kohno M. Primary Sjogren's syndrome with subcortical dementia. Intern Med. 1993 Jul;32(7):561-4.
- 1266. Kawashiri SY, Kawakami A, Iwamoto N, et al. Proinflammatory cytokines synergistically enhance the production of chemokine ligand 20 (CCL20) from rheumatoid fibroblast-like synovial cells in vitro and serum CCL20 is reduced in vivo by biologic disease-modifying antirheumatic drugs. J Rheumatol. 2009 Nov;36(11):2397-402.
- 1267. Kay J, Matteson EL, Dasgupta B, et al. Golimumab in patients with active rheumatoid arthritis despite treatment with methotrexate: a randomized, double-blind, placebo-controlled, dose-ranging study. Arthritis Rheum 2008;58(4):964-75.
- 1268. Kay LJ, Holland TM, Platt PN. Stress fractures in rheumatoid arthritis: a case series and case-control study. Ann Rheum Dis. 2004 Dec;63(12):1690-2.

- 1269. Kaya S, Kaptanoglu E, Elden H, et al. Coexistence of familial Mediterranean fever and juvenile idiopathic arthritis with osteoporosis successfully treated with etanercept. Intern Med. 2010;49(6):619-22.
- 1270. Kazkaz L, Marotte H, Hamwi M, et al. Rheumatoid arthritis and genetic markers in Syrian and French populations: different effect of the shared epitope. Ann Rheum Dis. 2007 Feb;66(2):195-201.
- 1271. Keane J, Gershon S, Wise RP, et al. Tuberculosis associated with infliximab, a tumor necrosis factor alpha-neutralizing agent. N Engl J Med. 2001 Oct 11;345(15):1098-104.
- 1272. Kedzia A, Boldys A, Krysiak R, et al.
 Potential benefit of paracetamol
 administration in adult-onset Still's disease.
 Pol Arch Med Wewn. 2009 Sep;119(9):5958.
- 1273. Kekow J, Welte T, Kellner U, et al.
 Development of rheumatoid nodules during anti-tumor necrosis factor alpha therapy with etanercept. Arthritis Rheum. 2002
 Mar;46(3):843-4.
- 1274. Kelaidi C, Tulliez M, Lecoq-Lafon C, et al. Long-term remission of an EBV-positive B cell lymphoproliferative disorder associated with rheumatoid arthritis under methotrexate with anti-CD20 monoclonal antibody (Rituximab) monotherapy. Leukemia. 2002 Oct;16(10):2173-4.
- 1275. Kelesidis T, Salhotra A, Fleisher J, et al. Listeria endocarditis in a patient with psoriatic arthritis on infliximab: are biologic agents as treatment for inflammatory arthritis increasing the incidence of Listeria infections? J Infect. 2010 May;60(5):386-96.
- 1276. Kellner H, Bornholdt K, Hein G.
 Leflunomide in the treatment of patients
 with early rheumatoid arthritis--results of a
 prospective non-interventional study. Clin
 Rheumatol. 2010 Aug;29(8):913-20.
- 1277. Kelsey JL, Lamster IB. Influence of musculoskeletal conditions on oral health among older adults. Am J Public Health. 2008 Jul;98(7):1177-83.

- 1278. Kemp E, Nielsen H, Petersen LJ, et al. Newer immunomodulating drugs in rheumatoid arthritis may precipitate glomerulonephritis. Clin Nephrol. 2001 Jan;55(1):87-8.
- 1279. Kennedy JW, Wong LK, Kalantarian B, et al. An unusual presentation of methotrexate-induced B-cell lymphoma of the metacarpophalangeal joint: a case report and literature review. J Hand Surg Am. 2006 Sep;31(7):1193-6.
- 1280. Kent PD, Davis JM, 3rd, Davis MD, et al. Bullous skin lesions following infliximab infusion in a patient with rheumatoid arthritis. Arthritis Rheum. 2002 Aug;46(8):2257-8; author reply 9.
- 1281. Keren Z, Braun-Moscovici Y, Markovits D, et al. Depletion of B lymphocytes in rheumatoid arthritis patients modifies IL-8-anti-IL-8 autoantibody network. Clin Immunol. 2009 Oct;133(1):108-16.
- 1282. Kesteman T, Yombi JC, Gigi J, et al. Listeria infections associated with infliximab: case reports. Clin Rheumatol. 2007 Dec;26(12):2173-5.
- 1283. Keystone E, Burmester GR, Furie R, et al. Improvement in patient-reported outcomes in a rituximab trial in patients with severe rheumatoid arthritis refractory to anti-tumor necrosis factor therapy. Arthritis Rheum 2008;59(6):785-93.
- 1284. Keystone E, Emery P, Peterfy CG, et al. Rituximab inhibits structural joint damage in patients with rheumatoid arthritis with an inadequate response to tumour necrosis factor inhibitor therapies. Ann Rheum Dis 2009;68(2):216-21.
- 1285. Keystone E, Fleischmann R, Emery P, et al. Safety and efficacy of additional courses of rituximab in patients with active rheumatoid arthritis: an open-label extension analysis. Arthritis Rheum. 2007 Dec;56(12):3896-908.
- 1286. Keystone E, Freundlich B, Schiff M, et al. Patients with moderate rheumatoid arthritis (RA) achieve better disease activity states with etanercept treatment than patients with severe RA. J Rheumatol 2009;36(3):522-31.

- 1287. Keystone E, Heijde D, Mason D, Jr., et al. Certolizumab pegol plus methotrexate is significantly more effective than placebo plus methotrexate in active rheumatoid arthritis: findings of a fifty-two-week, phase III, multicenter, randomized, double-blind, placebo-controlled, parallel-group study. Arthritis Rheum 2008;58(11):3319-29.
- 1288. Keystone EC, Genovese MC, Klareskog L, et al. Golimumab, a human antibody to tumour necrosis factor {alpha} given by monthly subcutaneous injections, in active rheumatoid arthritis despite methotrexate therapy: the GO-FORWARD Study. Ann Rheum Dis 2009;68(6):789-96.
- 1289. Keystone EC, Kavanaugh AF, Sharp JT, et al. Radiographic, clinical, and functional outcomes of treatment with adalimumab (a human anti-tumor necrosis factor monoclonal antibody) in patients with active rheumatoid arthritis receiving concomitant methotrexate therapy: a randomized, placebo-controlled, 52-week trial. Arthritis Rheum. 2004 May;50(5):1400-11.
- 1290. Keystone EC, Schiff MH, Kremer JM, et al. Once-weekly administration of 50 mg etanercept in patients with active rheumatoid arthritis: results of a multicenter, randomized, double-blind, placebocontrolled trial. Arthritis Rheum. 2004 Feb;50(2):353-63.
- 1291. Khan IH, Krishnan VV, Ziman M, et al. A comparison of multiplex suspension array large-panel kits for profiling cytokines and chemokines in rheumatoid arthritis patients. Cytometry B Clin Cytom. 2009

 May;76(3):159-68.
- 1292. Khanna M, Shirodkar MA, Gottlieb AB. Etanercept therapy in patients with autoimmunity and hepatitis C. J Dermatolog Treat. 2003 Dec;14(4):229-32.
- 1293. Kho LK, Kermode AG. Leflunomideinduced peripheral neuropathy. J Clin Neurosci. 2007 Feb;14(2):179-81.
- 1294. Khosla P, Aroaa N, Jain S. Tubercular pyomyositis in a case of rheumatoid arthritis being treated with infliximab. Int J Rheum Dis. 2010 Feb 1;13(1):82-5.

- 1295. Kielhorn A, Porter D, Diamantopoulos A, et al. UK cost-utility analysis of rituximab in patients with rheumatoid arthritis that failed to respond adequately to a biologic disease-modifying antirheumatic drug. Curr Med Res Opin. 2008 Sep;24(9):2639-50.
- 1296. Kiely PD, Johnson DM. Infliximab and leflunomide combination therapy in rheumatoid arthritis: an open-label study. Rheumatology (Oxford). 2002
 Jun;41(6):631-7.
- 1297. Kietz DA, Pepmueller PH, Moore TL. Clinical response to etanercept in polyarticular course juvenile rheumatoid arthritis. J Rheumatol. 2001 Feb;28(2):360-2.
- 1298. Kietz DA, Pepmueller PH, Moore TL. Therapeutic use of etanercept in polyarticular course juvenile idiopathic arthritis over a two year period. Ann Rheum Dis. 2002 Feb;61(2):171-3.
- 1299. Kievit W, Adang EM, Fransen J, et al. The effectiveness and medication costs of three anti-tumour necrosis factor alpha agents in the treatment of rheumatoid arthritis from prospective clinical practice data. Ann Rheum Dis 2008;67(9):1229-34.
- 1300. Kievit W, Fransen J, Oerlemans AJ, et al. The efficacy of anti-TNF in rheumatoid arthritis, a comparison between randomised controlled trials and clinical practice. Ann Rheum Dis. 2007 Nov;66(11):1473-8.
- 1301. Kim SK, Jun JB, El-Sohemy A, et al. Costeffectiveness analysis of MTHFR polymorphism screening by polymerase chain reaction in Korean patients with rheumatoid arthritis receiving methotrexate. J Rheumatol. 2006 Jul;33(7):1266-74.
- 1302. Kim TH, Stone M, Payne U, et al. Cartilage biomarkers in ankylosing spondylitis: relationship to clinical variables and treatment response. Arthritis Rheum. 2005 Mar;52(3):885-91.
- 1303. Kimball AB, Jackson JM, Sobell JM, et al.
 Reductions in healthcare resource utilization
 in psoriatic arthritis patients receiving
 etanercept therapy: results from the educate

- trial. J Drugs Dermatol. 2007 Mar;6(3):299-306.
- 1304. Kimel M, Cifaldi M, Chen N, et al. Adalimumab plus methotrexate improved SF-36 scores and reduced the effect of rheumatoid arthritis (RA) on work activity for patients with early RA. J Rheumatol 2008;35(2):206-15.
- 1305. Kimura E, Oga S, Pereira RM. Comparative study of the pharmacokinetics of MTX in juvenile idiopathic arthritis patients receiving long-term MTX monotherapy or MTX plus chloroquine. J Clin Pharm Ther. 2007 Dec;32(6):579-84.
- 1306. Kimura Y, Fieldston E, Devries-Vandervlugt B, et al. High dose, alternate day corticosteroids for systemic onset juvenile rheumatoid arthritis. J Rheumatol. 2000 Aug;27(8):2018-24.
- 1307. Kimura Y, Pinho P, Walco G, et al. Etanercept treatment in patients with refractory systemic onset juvenile rheumatoid arthritis. J Rheumatol. 2005 May;32(5):935-42.
- 1308. Kinder A, Stephens S, Mortimer N, et al. Severe herpes zoster after infliximab infusion. Postgrad Med J. 2004 Jan;80(939):26.
- 1309. Kinder AJ, Edwards J, Samanta A, et al. Pregnancy in a rheumatoid arthritis patient on infliximab and methotrexate. Rheumatology (Oxford). 2004 Sep;43(9):1195-6.
- 1310. Kinjo M, Setoguchi S, Solomon DH. Bone mineral density in older adult patients with rheumatoid arthritis: an analysis of NHANES III. J Rheumatol. 2007 Oct;34(10):1971-5.
- 1311. Kiortsis DN, Mavridis AK, Vasakos S, et al. Effects of infliximab treatment on insulin resistance in patients with rheumatoid arthritis and ankylosing spondylitis. Ann Rheum Dis. 2005 May;64(5):765-6.
- 1312. Kiortsis DN, Mavridis AK, Vasakos S, et al. Effects of infliximab treatment on lipoprotein profile in patients with

- rheumatoid arthritis and ankylosing spondylitis. J Rheumatol. 2006 May;33(5):921-3.
- 1313. Kirchgatterer A, Weber T, Hinterreiter M, et al. Haemorrhagic colitis due to Escherichia coli O103:H2 associated with infliximab therapy in a patient with rheumatoid arthritis. Rheumatology (Oxford). 2002 Mar;41(3):355-6.
- 1314. Kirino Y, Takeno M, Murakami S, et al. Tumor necrosis factor alpha acceleration of inflammatory responses by down-regulating heme oxygenase 1 in human peripheral monocytes. Arthritis Rheum. 2007 Feb;56(2):464-75.
- 1315. Kirshen C, Kanigsberg N. Alopecia areata following adalimumab. J Cutan Med Surg. 2009 Jan-Feb;13(1):48-50.
- 1316. Kirwan J. Early rheumatoid arthritis: combination therapy with disease-modifying antirheumatic drugs and low-dose glucocorticoids? Nat Clin Pract Rheumatol. 2006 Apr;2(4):182-3.
- 1317. Kirwan JR. The effect of glucocorticoids on joint destruction in rheumatoid arthritis. The Arthritis and Rheumatism Council Low-Dose Glucocorticoid Study Group. N Engl J Med. 1995 Jul 20;333(3):142-6.
- 1318. Klaasen R, Thurlings RM, Wijbrandts CA, et al. The relationship between synovial lymphocyte aggregates and the clinical response to infliximab in rheumatoid arthritis: a prospective study. Arthritis Rheum. 2009 Nov;60(11):3217-24.
- 1319. Klareskog L, van der Heijde D, de Jager JP, et al. Therapeutic effect of the combination of etanercept and methotrexate compared with each treatment alone in patients with rheumatoid arthritis: double-blind randomised controlled trial. Lancet. 2004 Feb 28;363(9410):675-81.
- 1320. Klein A, Buskila D, Gladman D, et al. Cortisol catabolism by lymphocytes of patients with systemic lupus erythematosus and rheumatoid arthritis. J Rheumatol. 1990 Jan;17(1):30-3.

- 1321. Klein R, Rosenbach M, Kim EJ, et al. Tumor necrosis factor inhibitor-associated dermatomyositis. Arch Dermatol. 2010 Jul;146(7):780-4.
- 1322. Klimiuk PA, Kita J, Chwiecko J, et al. The changes in serum chemokines following leflunomide therapy in patients with rheumatoid arthritis. Clin Rheumatol. 2009 Jan;28(1):17-21.
- 1323. Klimiuk PA, Sierakowski S, Domyslawska I, et al. Effect of repeated infliximab therapy on serum matrix metalloproteinases and tissue inhibitors of metalloproteinases in patients with rheumatoid arthritis. J Rheumatol. 2004 Feb;31(2):238-42.
- 1324. Klimiuk PA, Sierakowski S, Domyslawska I, et al. Regulation of serum chemokines following infliximab therapy in patients with rheumatoid arthritis. Clin Exp Rheumatol. 2006 Sep-Oct;24(5):529-33.
- 1325. Klimiuk PA, Sierakowski S, Domyslawska I, et al. Effect of etanercept on serum levels of soluble cell adhesion molecules (sICAM-1, sVCAM-1, and sE-selectin) and vascular endothelial growth factor in patients with rheumatoid arthritis. Scand J Rheumatol. 2009 Nov-Dec;38(6):439-44.
- 1326. Kneitz C, Suerbaum S, Beer M, et al. Exacerbation of Whipple's disease associated with infliximab treatment. Scand J Rheumatol. 2005 Mar-Apr;34(2):148-51.
- 1327. Kneitz C, Wilhelm M, Tony HP.
 Improvement of refractory rheumatoid
 arthritis after depletion of B cells. Scand J
 Rheumatol. 2004;33(2):82-6.
- 1328. Kobak S. Osteonecrosis and monoarticular rheumatoid arthritis treated with intra-articular adalimumab. Mod Rheumatol. 2008;18(3):290-2.
- 1329. Kobak S, Deveci H. Retinopathy due to antimalarial drugs in patients with connective tissue diseases: are they so innocent? A single center retrospective study. Int J Rheum Dis. 2010 Aug;13(3):e11-5.

- 1330. Kobayashi K, Okamoto Y, Inoue H, et al. Leukoencephalopathy with cognitive impairment following tocilizumab for the treatment of rheumatoid arthritis (RA). Intern Med. 2009;48(15):1307-9.
- 1331. Kobelt G, Andlin-Sobocki P, Brophy S, et al. The burden of ankylosing spondylitis and the cost-effectiveness of treatment with infliximab (Remicade). Rheumatology (Oxford). 2004 Sep;43(9):1158-66.
- 1332. Kobelt G, Eberhardt K, Geborek P. TNF inhibitors in the treatment of rheumatoid arthritis in clinical practice: costs and outcomes in a follow up study of patients with RA treated with etanercept or infliximab in southern Sweden. Ann Rheum Dis. 2004 Jan;63(1):4-10.
- 1333. Kobelt G, Jonsson L, Young A, et al. The cost-effectiveness of infliximab (Remicade) in the treatment of rheumatoid arthritis in Sweden and the United Kingdom based on the ATTRACT study. Rheumatology (Oxford). 2003 Feb;42(2):326-35.
- 1334. Kobelt G, Lindgren P, Singh A, et al. Cost effectiveness of etanercept (Enbrel) in combination with methotrexate in the treatment of active rheumatoid arthritis based on the TEMPO trial. Ann Rheum Dis. 2005 Aug;64(8):1174-9.
- 1335. Kobelt G, Sobocki P, Sieper J, et al.
 Comparison of the cost-effectiveness of
 infliximab in the treatment of ankylosing
 spondylitis in the United Kingdom based on
 two different clinical trials. Int J Technol
 Assess Health Care. 2007
 Summer;23(3):368-75.
- 1336. Koch AE, Kunkel SL, Chensue SW, et al. Expression of interleukin-1 and interleukin-1 receptor antagonist by human rheumatoid synovial tissue macrophages. Clin Immunol Immunopathol. 1992 Oct;65(1):23-9.
- 1337. Kocharla L, Taylor J, Weiler T, et al.

 Monitoring methotrexate toxicity in juvenile idiopathic arthritis. J Rheumatol. 2009

 Dec;36(12):2813-8.
- 1338. Koczan D, Drynda S, Hecker M, et al.

 Molecular discrimination of responders and
 nonresponders to anti-TNF alpha therapy in

- rheumatoid arthritis by etanercept. Arthritis Res Ther. 2008;10(3):R50.
- 1339. Koffeman EC, Genovese M, Amox D, et al. Epitope-specific immunotherapy of rheumatoid arthritis: clinical responsiveness occurs with immune deviation and relies on the expression of a cluster of molecules associated with T cell tolerance in a double-blind, placebo-controlled, pilot phase II trial. Arthritis Rheum. 2009 Nov;60(11):3207-16.
- 1340. Kogure T, Tatsumi T, Sato H, et al.
 Traditional herbal medicines (Kampo) for patients with rheumatoid arthritis receiving concomitant methotrexate: a preliminary study. Altern Ther Health Med. 2010 Jan-Feb;16(1):46-51.
- 1341. Koh ET. New disease modifying agents in adult rheumatoid arthritis. Ann Acad Med Singapore. 2001 Mar;30(2):170-3.
- 1342. Koh MS, Leng PH, Eng P, et al. An unusual cause of pulmonary haemorrhage in a patient with rheumatoid arthritis. Ann Acad Med Singapore. 2004 May;33(3):365-7.
- 1343. Kohno M, Tsutsumi A, Matsui H, et al. Interleukin-17 gene expression in patients with rheumatoid arthritis. Mod Rheumatol. 2008;18(1):15-22.
- 1344. Koide R, Isoo A, Ishii K, et al. Rheumatoid leptomeningitis: rare complication of rheumatoid arthritis. Clin Rheumatol. 2009 Sep;28(9):1117-9.
- 1345. Koike T, Harigai M, Inokuma S, et al. Postmarketing surveillance of the safety and effectiveness of etanercept in Japan. J Rheumatol. 2009 May;36(5):898-906.
- 1346. Kojima M, Itoh H, Hirabayashi K, et al. Methtrexate-associated lymphoproliferative disorders. A clinicopathological study of 13 Japanese cases. Pathol Res Pract. 2006;202(9):679-85.
- 1347. Kokkinos A, Iliopoulos A, Greka P, et al. Successful treatment of refractory adultonset Still's disease with infliximab. A prospective, non-comparative series of four patients. Clin Rheumatol. 2004 Feb;23(1):45-9.

- 1348. Kolokotronis A, Avramidou E, Zaraboukas T, et al. Oral tuberculosis associated with a treatment with anti-rheumatic drugs. J Oral Pathol Med. 2006 Feb;35(2):123-5.
- 1349. Komai N, Morita Y, Sakuta T, et al. Antitumor necrosis factor therapy increases serum adiponectin levels with the improvement of endothelial dysfunction in patients with rheumatoid arthritis. Mod Rheumatol. 2007;17(5):385-90.
- 1350. Komano Y, Harigai M, Koike R, et al. Pneumocystis jiroveci pneumonia in patients with rheumatoid arthritis treated with infliximab: a retrospective review and case-control study of 21 patients. Arthritis Rheum. 2009 Mar 15;61(3):305-12.
- 1351. Komatsuda A, Okamoto Y, Hatakeyama T, et al. Sulfasalazine-induced hypersensitivity syndrome and hemophagocytic syndrome associated with reactivation of Epstein-Barr virus. Clin Rheumatol. 2008 Mar;27(3):395-7.
- 1352. Komatsuda A, Wakui H, Nimura T, et al. Reversible infliximab-related lymphoproliferative disorder associated with Epstein-Barr virus in a patient with rheumatoid arthritis. Mod Rheumatol. 2008;18(3):315-8.
- 1353. Konai MS, Vilar Furtado RN, Dos Santos MF, et al. Monoarticular corticosteroid injection versus systemic administration in the treatment of rheumatoid arthritis patients: a randomized double-blind controlled study. Clin Exp Rheumatol. 2009 Mar-Apr;27(2):214-21.
- 1354. Kong XD, Xu D, Zhang W, et al. Clinical features and prognosis in adult-onset Still's disease: a study of 104 cases. Clin Rheumatol. 2010 Sep;29(9):1015-9.
- 1355. Kononoff A, Heiskanen J, Lumiaho J, et al. Intensifying treatment of rheumatoid arthritis with combinations of traditional disease-modifying anti-rheumatic drugs among patients with persistent disease did not reduce the need for large joint surgery. Scand J Rheumatol. 2007 Nov-Dec;36(6):424-7.

- 1356. Konttinen YT, Ramsay H, Hietanen J, et al. Otitis externa sicca/fibrotising external otitis (FEO) as a complication of Sjogren's syndrome. Clin Exp Rheumatol. 2000 Nov-Dec;18(6):746-8.
- 1357. Kontzias A, Efthimiou P. Adult-onset Still's disease: pathogenesis, clinical manifestations and therapeutic advances. Drugs. 2008;68(3):319-37.
- 1358. Kopp S, Alstergren P, Ernestam S, et al. Interleukin-1beta influences the effect of infliximab on temporomandibular joint pain in rheumatoid arthritis. Scand J Rheumatol. 2006 May-Jun;35(3):182-8.
- 1359. Kopp S, Alstergren P, Ernestam S, et al. Reduction of temporomandibular joint pain after treatment with a combination of methotrexate and infliximab is associated with changes in synovial fluid and plasma cytokines in rheumatoid arthritis. Cells Tissues Organs. 2005;180(1):22-30.
- 1360. Korah S, Kuriakose T. Optical coherence tomography in a patient with chloroquine-induced maculopathy. Indian J Ophthalmol. 2008 Nov-Dec;56(6):511-3.
- 1361. Korczowska I, Olewicz-Gawlik A, Trefler J, et al. Does low-dose and short-term glucocorticoids treatment increase the risk of osteoporosis in rheumatoid arthritis female patients? Clin Rheumatol. 2008 May;27(5):565-72.
- 1362. Korkmaz C, Kasifoglu T, Yasar B.
 Acceleration of left-ventricular diastolic dysfunction and pulmonary hypertension after TNF-alpha blocker. Ann Pharmacother. 2005 Jun;39(6):1138-9.
- 1363. Kosinski M, Kujawski SC, Martin R, et al. Health-related quality of life in early rheumatoid arthritis: impact of disease and treatment response. Am J Manag Care. 2002 Mar;8(3):231-40.
- 1364. Kotaniemi K, Penttila H. Intraocular lens implantation in patients with juvenile idiopathic arthritis-associated uveitis.

 Ophthalmic Res. 2006;38(6):318-23.

- 1365. Kotha P, McGreevy MJ, Kotha A, et al. Early deaths with thrombolytic therapy for acute myocardial infarction in corticosteroid-dependent rheumatoid arthritis. Clin Cardiol. 1998
 Nov;21(11):853-6.
- 1366. Kothapalli R, Nyland SB, Kusmartseva I, et al. Constitutive production of proinflammatory cytokines RANTES, MIP-1beta and IL-18 characterizes LGL leukemia. Int J Oncol. 2005 Feb;26(2):529-35.
- 1367. Kotter I, Wacker A, Koch S, et al. Anakinra in patients with treatment-resistant adult-onset Still's disease: four case reports with serial cytokine measurements and a review of the literature. Semin Arthritis Rheum. 2007 Dec;37(3):189-97.
- 1368. Kovacs A, Szekeres E, Berek L, et al.
 Relationship between the occurrence of antiSSA, anti-SSB autoantibodies and HLA
 class II alleles from the aspect of in vitro
 inhibitory effect of glucocorticosteroid on
 the antibody-dependent cellular cytotoxicity
 in patients with primary Sjogren's syndrome.
 Acta Microbiol Immunol Hung.
 2000;47(4):421-31.
- 1369. Kozaci DL, Chernajovsky Y, Chikanza IC. The differential expression of corticosteroid receptor isoforms in corticosteroid-resistant and -sensitive patients with rheumatoid arthritis. Rheumatology (Oxford). 2007 Apr;46(4):579-85.
- 1370. Kozora E, Laudenslager M, Lemieux A, et al. Inflammatory and hormonal measures predict neuropsychological functioning in systemic lupus erythematosus and rheumatoid arthritis patients. J Int Neuropsychol Soc. 2001 Sep;7(6):745-54.
- 1371. Kraetsch HG, Antoni C, Kalden JR, et al. Successful treatment of a small cohort of patients with adult onset of Still's disease with infliximab: first experiences. Ann Rheum Dis. 2001 Nov;60 Suppl 3:iii55-7.
- 1372. Kramer N, Chuzhin Y, Kaufman LD, et al. Methotrexate pneumonitis after initiation of infliximab therapy for rheumatoid arthritis. Arthritis Rheum. 2002 Dec 15;47(6):670-1.

- 1373. Kreitzer T, Saoud A. Bacillary angiomatosis following the use of long-term methotrexate therapy: a case report. W V Med J. 2006 Jan-Feb;102(1):317-8.
- 1374. Kremer J, Ritchlin C, Mendelsohn A, et al. Golimumab, a new human anti-tumor necrosis factor alpha antibody, administered intravenously in patients with active rheumatoid arthritis: Forty-eight-week efficacy and safety results of a phase III randomized, double-blind, placebocontrolled study. Arthritis Rheum 2010;62(4):917-28.
- 1375. Kremer JM, Bloom BJ, Breedveld FC, et al. The safety and efficacy of a JAK inhibitor in patients with active rheumatoid arthritis: Results of a double-blind, placebocontrolled phase IIa trial of three dosage levels of CP-690,550 versus placebo. Arthritis Rheum. 2009 Jul;60(7):1895-905.
- 1376. Kremer JM, Genant HK, Moreland LW, et al. Results of a two-year followup study of patients with rheumatoid arthritis who received a combination of abatacept and methotrexate. Arthritis Rheum. 2008 Apr;58(4):953-63.
- 1377. Kremer JM, Habros JS, Kolba KS, et al. Tacrolimus in rheumatoid arthritis patients receiving concomitant methotrexate: a sixmonth, open-label study. Arthritis Rheum. 2003 Oct;48(10):2763-8.
- 1378. Kremer JM, Weinblatt ME, Bankhurst AD, et al. Etanercept added to background methotrexate therapy in patients with rheumatoid arthritis: continued observations. Arthritis Rheum. 2003 Jun;48(6):1493-9.
- 1379. Kremer JM, Westhovens R, Leon M, et al. Treatment of rheumatoid arthritis by selective inhibition of T-cell activation with fusion protein CTLA4Ig. N Engl J Med 2003;349(20):1907-15.
- 1380. Kremers HM, Nicola P, Crowson CS, et al. Therapeutic strategies in rheumatoid arthritis over a 40-year period. J Rheumatol. 2004 Dec;31(12):2366-73.
- 1381. Kreuter A, Rose C, Zillikens D, et al. Bullous rheumatoid neutrophilic dermatosis.

- J Am Acad Dermatol. 2005 May;52(5):916-8.
- 1382. Krishnamurthy R, Dincer HE, Whittemore D. Strongyloides stercoralis hyperinfection in a patient with rheumatoid arthritis after anti-TNF-alpha therapy. J Clin Rheumatol. 2007 Jun;13(3):150-2.
- 1383. Kriss TC, Kriss VM. Neck pain. Primary care work-up of acute and chronic symptoms. Geriatrics. 2000 Jan;55(1):47-8, 51-4, 7.
- 1384. Kristensen LE, Gulfe A, Saxne T, et al. Efficacy and tolerability of anti-tumour necrosis factor therapy in psoriatic arthritis patients: results from the South Swedish Arthritis Treatment Group register. Ann Rheum Dis 2008;67(3):364-9.
- 1385. Kristensen LE, Kapetanovic MC, Gulfe A, et al. Predictors of response to anti-TNF therapy according to ACR and EULAR criteria in patients with established RA: results from the South Swedish Arthritis Treatment Group Register. Rheumatology (Oxford). 2008 Apr;47(4):495-9.
- 1386. Kristensen LE, Saxne T, Geborek P. The LUNDEX, a new index of drug efficacy in clinical practice: results of a five-year observational study of treatment with infliximab and etanercept among rheumatoid arthritis patients in southern Sweden.

 Arthritis Rheum. 2006 Feb;54(2):600-6.
- 1387. Kristensen LE, Saxne T, Nilsson JA, et al. Impact of concomitant DMARD therapy on adherence to treatment with etanercept and infliximab in rheumatoid arthritis. Results from a six-year observational study in southern Sweden. Arthritis Res Ther 2006;8(6):R174.
- 1388. Kritikos K, Haritatos E, Tsigkos S, et al. An atypical presentation of visceral leishmaniasis infection in a patient with rheumatoid arthritis treated with infliximab. J Clin Rheumatol. 2010 Jan;16(1):38-9.
- 1389. Kroesen S, Widmer AF, Tyndall A, et al. Serious bacterial infections in patients with rheumatoid arthritis under anti-TNF-alpha therapy. Rheumatology (Oxford). 2003 May;42(5):617-21.

- 1390. Kroger H, Honkanen R, Saarikoski S, et al. Decreased axial bone mineral density in perimenopausal women with rheumatoid arthritis--a population based study. Ann Rheum Dis. 1994 Jan;53(1):18-23.
- 1391. Kroot EJ, van Gestel AM, Swinkels HL, et al. Chronic comorbidity in patients with early rheumatoid arthritis: a descriptive study. J Rheumatol. 2001 Jul;28(7):1511-7.
- 1392. Kruithof E, Baeten D, De Rycke L, et al. Synovial histopathology of psoriatic arthritis, both oligo- and polyarticular, resembles spondyloarthropathy more than it does rheumatoid arthritis. Arthritis Res Ther. 2005;7(3):R569-80.
- 1393. Kruize AA, Hene RJ, van der Heide A, et al. Long-term followup of patients with Sjogren's syndrome. Arthritis Rheum. 1996 Feb;39(2):297-303.
- 1394. Kucharekova M, Winnepenninckx V, Frank J, et al. Generalized pustulosis induced by adalimumab in a patient with rheumatoid arthritis a therapeutic challenge. Int J Dermatol. 2008 Nov;47 Suppl 1:25-8.
- 1395. Kucharz EJ, Gozdzik J, Kopec M, et al. A single infusion of infliximab increases the serum endostatin level in patients with rheumatoid arthritis. Clin Exp Rheumatol. 2003 Mar-Apr;21(2):273-4.
- 1396. Kuek A, Hazleman BL, Gaston JH, et al. Successful treatment of refractory polyarticular juvenile idiopathic arthritis with rituximab. Rheumatology (Oxford). 2006 Nov;45(11):1448-9.
- 1397. Kumar D, Bouldin TW, Berger RG. A case of progressive multifocal leukoencephalopathy in a patient treated with infliximab. Arthritis Rheum. 2010 Nov;62(11):3191-5.
- 1398. Kumar N, Sandroni P, Steensma DP, et al. Polyradiculopathy due to methotrexate-induced ebv-associated lymphoproliferative disorder. Neurology. 2008 Nov 11;71(20):1644-5.
- 1399. Kumar S, Gupta N, Jhamb R, et al. Celiac disease: association with adult-onset Still's

- disease: apropos of a clinical case. Indian J Med Sci. 2007 Jul;61(7):414-7.
- 1400. Kumari R, Uppal SS. Prolonged remission in adult-onset Still's disease with etanercept. Clin Rheumatol. 2006 Feb;25(1):106-8.
- 1401. Kumeda Y, Inaba M, Goto H, et al.
 Increased thickness of the arterial intimamedia detected by ultrasonography in patients with rheumatoid arthritis. Arthritis Rheum. 2002 Jun;46(6):1489-97.
- 1402. Kumon Y, Kakigi A, Sugiura T. Clinical images: Otalgia, an unusual complication of Sjogren's syndrome. Arthritis Rheum. 2009 Aug;60(8):2542.
- 1403. Kurasawa M, Kotani K, Kurasawa G, et al. Adult-onset Still's disease in a patient over 80 years old successfully treated with low-dose methotrexate therapy. Age Ageing. 2007 Jan;36(1):104-6.
- 1404. Kuriya B, Arkema EV, Bykerk VP, et al. Efficacy of initial methotrexate monotherapy versus combination therapy with a biological agent in early rheumatoid arthritis: a meta-analysis of clinical and radiographic remission. Ann Rheum Dis 2010;69(7):1298-304.
- 1405. Kurmann PT, Van Linthoudt D, So AK. Miller-Fisher syndrome in a patient with rheumatoid arthritis treated with adalimumab. Clin Rheumatol. 2009 Jan;28(1):93-4.
- 1406. Kuroda T, Otaki Y, Sato H, et al. A case of AA amyloidosis associated with rheumatoid arthritis effectively treated with Infliximab. Rheumatol Int. 2008 Sep;28(11):1155-9.
- 1407. Kuroda T, Wada Y, Kobayashi D, et al. Effective anti-TNF-alpha therapy can induce rapid resolution and sustained decrease of gastroduodenal mucosal amyloid deposits in reactive amyloidosis associated with rheumatoid arthritis. J Rheumatol. 2009 Nov;36(11):2409-15.
- 1408. Kurschat P, Rubbert A, Poswig A, et al. Treatment of psoriatic arthritis with etanercept. J Am Acad Dermatol. 2001 Jun;44(6):1052.

- 1409. Kurtais Y, Tur BS, Elhan AH, et al. Hypothalamic-pituitary-adrenal hormonal responses to exercise stress test in patients with rheumatoid arthritis compared to healthy controls. J Rheumatol. 2006 Aug;33(8):1530-7.
- 1410. Kuruvilla J, Leitch HA, Vickars LM, et al. Aplastic anemia following administration of a tumor necrosis factor-alpha inhibitor. Eur J Haematol. 2003 Nov;71(5):396-8.
- 1411. Kur-Zalewska J, Swarowska-Knap J,
 Tlustochowicz W. Neurological disorders
 with demyelinating brain white matter
 lesions in a patient with rheumatoid arthritis
 treated with etanercept. Pol Arch Med
 Wewn. 2008 Apr;118(4):234-7.
- 1412. Kurzawski M, Pawlik A, Safranow K, et al. 677C>T and 1298A>C MTHFR polymorphisms affect methotrexate treatment outcome in rheumatoid arthritis. Pharmacogenomics. 2007 Nov;8(11):1551-9
- 1413. Kusabe T, Waguri-Nagaya Y, Tanikawa T, et al. The inhibitory effect of disease-modifying anti-rheumatic drugs and steroids on gliostatin/platelet-derived endothelial cell growth factor production in human fibroblast-like synoviocytes. Rheumatol Int. 2005 Oct;25(8):625-30.
- 1414. Kuuliala A, Nissinen R, Kautiainen H, et al. Low circulating soluble interleukin 2 receptor level predicts rapid response in patients with refractory rheumatoid arthritis treated with infliximab. Ann Rheum Dis. 2006 Jan;65(1):26-9.
- 1415. Kuzmanova SI. Arthroscopic treatment of rheumatoid synovitis. Folia Med (Plovdiv). 2003;45(3):48-54.
- 1416. Kvalvik AG, Aadland HA, Hoyeraal HM, et al. Were the patterns of treatment for rheumatoid arthritis during 1977-1992 consistent with modern clinical guidelines? Scand J Rheumatol. 2001;30(2):61-8.
- 1417. Kvalvik AG, Lefsaker L, Dyvik S, et al.
 Anti-tumor necrosis factor-alpha therapy in
 the ordinary clinical setting: Three-year
 effectiveness in patients with rheumatoid

- arthritis. Joint Bone Spine. 2007 Dec;74(6):606-11.
- 1418. Kvien TK, Haugeberg G, Uhlig T, et al. Data driven attempt to create a clinical algorithm for identification of women with rheumatoid arthritis at high risk of osteoporosis. Ann Rheum Dis. 2000 Oct;59(10):805-11.
- 1419. Kwak JJ, Chang JE, Lee J, et al. Chronic eosinophilic pneumonia associated with an initiation of rheumatoid arthritis. Clin Rheumatol. 2003 Sep;22(3):240-3.
- 1420. Kwon HH, Baek SH, Park SH. Miliary tuberculosis and necrotizing tuberculous fasciitis--an unusual coexistence in a rheumatoid arthritis patient. Int J Rheum Dis. 2010 May;13(2):171-4.
- 1421. Kwon HJ, Cote TR, Cuffe MS, et al. Case reports of heart failure after therapy with a tumor necrosis factor antagonist. Ann Intern Med. 2003 May 20;138(10):807-11.
- 1422. La Montagna G, Cacciapuoti F, Buono R, et al. Insulin resistance is an independent risk factor for atherosclerosis in rheumatoid arthritis. Diab Vasc Dis Res. 2007
 Jun;4(2):130-5.
- 1423. La Montagna G, Valentini G. Listeria monocytogenes meningitis in a patient receiving etanercept for Still's disease. Clin Exp Rheumatol. 2005 Jan-Feb;23(1):121.
- 1424. Laas K, Peltomaa R, Kautiainen H, et al. Clinical impact of switching from infliximab to etanercept in patients with rheumatoid arthritis. Clin Rheumatol. 2008

 Jul;27(7):927-32.
- 1425. Labbe P, Hardouin P. Epidemiology and optimal management of polymyalgia rheumatica. Drugs Aging. 1998 Aug;13(2):109-18.
- 1426. Lacaille D, Guh DP, Abrahamowicz M, et al. Use of nonbiologic disease-modifying antirheumatic drugs and risk of infection in patients with rheumatoid arthritis. Arthritis Rheum 2008;59(8):1074-81.

- 1427. Lacroix BD, Lovern MR, Stockis A, et al. A pharmacodynamic Markov mixed-effects model for determining the effect of exposure to certolizumab pegol on the ACR20 score in patients with rheumatoid arthritis. Clin Pharmacol Ther. 2009 Oct;86(4):387-95.
- 1428. Lafforgue P, Monjanel-Mouterde S, Durand A, et al. Is there an interaction between low doses of corticosteroids and methotrexate in patients with rheumatoid arthritis? A pharmacokinetic study in 33 patients. J Rheumatol. 1993 Feb;20(2):263-7.
- 1429. Lafforgue P, Toussirot E, Bille F, et al. Astasia-abasia revealing a primary Sjogren's syndrome. Clin Rheumatol. 1993 Jun;12(2):261-4.
- 1430. Lagana B, Picchianti Diamanti A, Ferlito C, et al. Imaging progression despite clinical remission in early rheumatoid arthritis patients after etanercept interruption. Int J Immunopathol Pharmacol. 2009 Apr-Jun;22(2):447-54.
- 1431. Lahiff C, Khiaron OB, Nolan N, et al. Pneumocystis carinii pneumonia in a patient on etanercept for psoriatic arthritis. Ir J Med Sci. 2007 Dec;176(4):309-11.
- 1432. Lahiri M, Teng GG. A case of refractory adult-onset Still's disease treated with anakinra. Int J Rheum Dis. 2010 Aug;13(3):e36-41.
- 1433. Lahners WJ, Hardten DR, Lindstrom RL. Peripheral keratitis following laser in situ keratomileusis. J Refract Surg. 2003 Nov-Dec;19(6):671-5.
- 1434. Lai TY, Ngai JW, Chan WM, et al. Visual field and multifocal electroretinography and their correlations in patients on hydroxychloroquine therapy. Doc Ophthalmol. 2006 May;112(3):177-87.
- 1435. Laine L, Bombardier C, Hawkey CJ, et al. Stratifying the risk of NSAID-related upper gastrointestinal clinical events: results of a double-blind outcomes study in patients with rheumatoid arthritis. Gastroenterology. 2002 Oct;123(4):1006-12.

- 1436. Laine L, Connors LG, Reicin A, et al.
 Serious lower gastrointestinal clinical events
 with nonselective NSAID or coxib use.
 Gastroenterology. 2003 Feb;124(2):288-92.
- 1437. Laine M, Porola P, Udby L, et al. Low salivary dehydroepiandrosterone and androgen-regulated cysteine-rich secretory protein 3 levels in Sjogren's syndrome.

 Arthritis Rheum. 2007 Aug;56(8):2575-84.
- 1438. Lainez B, Fernandez-Real JM, Romero X, et al. Identification and characterization of a novel spliced variant that encodes human soluble tumor necrosis factor receptor 2. Int Immunol. 2004 Jan;16(1):169-77.
- 1439. Lakatos P, Nagy Z, Kiss L, et al. Prevention of corticosteroid-induced osteoporosis by alfacalcidol. Z Rheumatol. 2000;59 Suppl 1:48-52.
- 1440. Lam A, Toma W, Schlesinger N. Mycobacterium marinum arthritis mimicking rheumatoid arthritis. J Rheumatol. 2006 Apr;33(4):817-9.
- 1441. Lamazza L, Guerra F, Pezza M, et al. The use of etanercept as a non-surgical treatment for temporomandibular joint psoriatric arthritis: a case report. Aust Dent J. 2009 Jun;54(2):161-5.
- 1442. Lan JL, Chou SJ, Chen DY, et al. A comparative study of etanercept plus methotrexate and methotrexate alone in Taiwanese patients with active rheumatoid arthritis: a 12-week, double-blind, randomized, placebo-controlled study. J Formos Med Assoc. 2004 Aug;103(8):618-23
- 1443. Landewe RB, Boers M, Verhoeven AC, et al. COBRA combination therapy in patients with early rheumatoid arthritis: long-term structural benefits of a brief intervention.

 Arthritis Rheum. 2002 Feb;46(2):347-56.
- 1444. Lane NE, Pressman AR, Star VL, et al. Rheumatoid arthritis and bone mineral density in elderly women. The Study of Osteoporotic Fractures Research Group. J Bone Miner Res. 1995 Feb;10(2):257-63.

- 1445. Lange U, Boss B, Teichmann J, et al. Bone mineral density and biochemical markers of bone metabolism in late onset rheumatoid arthritis and polymyalgia rheumatica--a prospective study on the influence of glucocorticoid therapy. Z Rheumatol. 2000;59 Suppl 2:II/137-41.
- 1446. Lange U, Teichmann J, Muller-Ladner U, et al. Increase in bone mineral density of patients with rheumatoid arthritis treated with anti-TNF-alpha antibody: a prospective open-label pilot study. Rheumatology (Oxford). 2005 Dec;44(12):1546-8.
- 1447. Langer HE, Missler-Karger B. Kineret: efficacy and safety in daily clinical practice: an interim analysis of the Kineret response assessment initiative (kreative) protocol. Int J Clin Pharmacol Res. 2003;23(4):119-28.
- 1448. Lassoued S, Sire S, Farny M, et al. Pulmonary aspergillosis in a patient with rheumatoid arthritis treated by etanercept. Clin Exp Rheumatol. 2004 Mar-Apr;22(2):267-8.
- 1449. Lassoued S, Zabraniecki L, Marin F, et al. Toxoplasmic chorioretinitis and antitumor necrosis factor treatment in rheumatoid arthritis. Semin Arthritis Rheum. 2007 Feb;36(4):262-3.
- 1450. Laurberg TB, Frystyk J, Ellingsen T, et al. Plasma adiponectin in patients with active, early, and chronic rheumatoid arthritis who are steroid- and disease-modifying antirheumatic drug-naive compared with patients with osteoarthritis and controls. J Rheumatol. 2009 Sep;36(9):1885-91.
- 1451. Lavie F, Miceli-Richard C, Ittah M, et al. Increase of B cell-activating factor of the TNF family (BAFF) after rituximab treatment: insights into a new regulating system of BAFF production. Ann Rheum Dis. 2007 May;66(5):700-3.
- 1452. Lazzerini PE, Acampa M, Hammoud M, et al. Arrhythmic risk during acute infusion of infliximab: a prospective, single-blind, placebo-controlled, crossover study in patients with chronic arthritis. J Rheumatol. 2008 Oct;35(10):1958-65.

- 1453. Le Loet X, Nordstrom D, Rodriguez M, et al. Effect of anakinra on functional status in patients with active rheumatoid arthritis receiving concomitant therapy with traditional disease modifying antirheumatic drugs: evidence from the OMEGA Trial. J Rheumatol. 2008 Aug;35(8):1538-44.
- 1454. Leandro MJ, Cambridge G, Ehrenstein MR, et al. Reconstitution of peripheral blood B cells after depletion with rituximab in patients with rheumatoid arthritis. Arthritis Rheum. 2006 Feb;54(2):613-20.
- 1455. Leandro MJ, Cooper N, Cambridge G, et al. Bone marrow B-lineage cells in patients with rheumatoid arthritis following rituximab therapy. Rheumatology (Oxford). 2007 Jan;46(1):29-36.
- 1456. Leandro MJ, Edwards JC, Cambridge G. Clinical outcome in 22 patients with rheumatoid arthritis treated with B lymphocyte depletion. Ann Rheum Dis. 2002 Oct;61(10):883-8.
- 1457. Lebwohl M, Blum R, Berkowitz E, et al. No evidence for increased risk of cutaneous squamous cell carcinoma in patients with rheumatoid arthritis receiving etanercept for up to 5 years. Arch Dermatol. 2005 Jul;141(7):861-4.
- 1458. Ledingham J, Deighton C. Update on the British Society for Rheumatology guidelines for prescribing TNFalpha blockers in adults with rheumatoid arthritis (update of previous guidelines of April 2001). Rheumatology (Oxford). 2005 Feb;44(2):157-63.
- 1459. Ledwich LJ, Clarke K. Screening and treatment of glucocorticoid-induced osteoporosis in rheumatoid arthritis patients in an urban multispecialty practice. J Clin Rheumatol. 2009 Mar;15(2):61-4.
- 1460. Lee CK, Lee EY, Cho YS, et al. Increased expression of glucocorticoid receptor beta messenger RNA in patients with ankylosing spondylitis. Korean J Intern Med. 2005 Jun;20(2):146-51.
- 1461. Lee EB, Shin KC, Lee YJ, et al. 188Re-tincolloid as a new therapeutic agent for rheumatoid arthritis. Nucl Med Commun. 2003 Jun;24(6):689-96.

- 1462. Lee H, Kimko HC, Rogge M, et al. Population pharmacokinetic and pharmacodynamic modeling of etanercept using logistic regression analysis. Clin Pharmacol Ther. 2003 Apr;73(4):348-65.
- 1463. Lee HJ, Waller RD, Stebbings S, et al. The effects of an orally administered probiotic on sulfasalazine metabolism in individuals with rheumatoid arthritis: a preliminary study. Int J Rheum Dis. 2010 Feb 1:13(1):48-54.
- 1464. Lee J, Noh JW, Hwang JW, et al. Extended dosing of etanercept 25 mg can be effective in patients with ankylosing spondylitis: a retrospective analysis. Clin Rheumatol. 2010 Oct;29(10):1149-54.
- 1465. Lee JH, Slifman NR, Gershon SK, et al. Life-threatening histoplasmosis complicating immunotherapy with tumor necrosis factor alpha antagonists infliximab and etanercept. Arthritis Rheum. 2002 Oct;46(10):2565-70.
- 1466. Lee SS, Park YW, Park JJ, et al.
 Combination treatment with leflunomide and methotrexate for patients with active rheumatoid arthritis. Scand J Rheumatol. 2009 Jan-Feb;38(1):11-4.
- 1467. Lee YC, Cui J, Costenbader KH, et al. Investigation of candidate polymorphisms and disease activity in rheumatoid arthritis patients on methotrexate. Rheumatology (Oxford). 2009 Jun;48(6):613-7.
- 1468. Lee YH, Choi SJ, Ji JD, et al. No association of polymorphisms of the CTLA-4 exon 1(+49) and promoter(-318) genes with rheumatoid arthritis in the Korean population. Scand J Rheumatol. 2002;31(5):266-70.
- 1469. Lee YH, Kim HJ, Rho YH, et al. Interleukin-1 receptor antagonist gene polymorphism and rheumatoid arthritis. Rheumatol Int. 2004 May;24(3):133-6.
- 1470. Lehman TJ. Clinical trials for the treatment of systemic onset juvenile rheumatoid arthritis-juvenile idiopathic arthritis. Curr Rheumatol Rep. 2000 Aug;2(4):313-5.

- 1471. Lehnen M, Franckson T, Knab J, et al. Successful infliximab therapy of psoriasis vulgaris and psoriatic arthritis in a patient with cirrhosis. Br J Dermatol. 2005 Jul;153(1):212-4.
- 1472. Lehnen M, Franckson T, Korber A, et al. Etanercept therapy of psoriatic arthritis in a patient with liver cirrhosis. Acta Derm Venereol. 2005;85(4):351-2.
- 1473. Leitch R, Walker SE, Hillard AE. The rheumatoid knee before and after arthrocentesis and prednisolone injection: evaluation by Gd-enhanced MRI. Clin Rheumatol. 1996 Jul;15(4):358-66.
- 1474. Lems WF, Gerrits MI, Jacobs JW, et al. Changes in (markers of) bone metabolism during high dose corticosteroid pulse treatment in patients with rheumatoid arthritis. Ann Rheum Dis. 1996 May;55(5):288-93.
- 1475. Lems WF, Jacobs JW, van den Brink HR, et al. Transient decrease in osteocalcin and markers of type 1 collagen turnover during high-dose corticosteroid pulse therapy in rheumatoid arthritis. Br J Rheumatol. 1993 Sep;32(9):787-9.
- 1476. Lems WF, Jahangier ZN, Jacobs JW, et al. Vertebral fractures in patients with rheumatoid arthritis treated with corticosteroids. Clin Exp Rheumatol. 1995 May-Jun;13(3):293-7.
- 1477. Lems WF, Jahangier ZN, Raymakers JA, et al. Methods to score vertebral deformities in patients with rheumatoid arthritis. Br J Rheumatol. 1997 Feb;36(2):220-4.
- 1478. Leonardou A, Giali S, Daoussis D, et al. Moraxella catarrhalis-induced septic arthritis of a prosthetic knee joint in a patient with rheumatoid arthritis treated with anakinra: comment on the article by Schiff et al. Arthritis Rheum. 2005 Apr;52(4):1337; author reply 8.
- 1479. Lequerre T, Gauthier-Jauneau AC, Bansard C, et al. Gene profiling in white blood cells predicts infliximab responsiveness in rheumatoid arthritis. Arthritis Res Ther. 2006;8(4):R105.

- 1480. Lequerre T, Jouen F, Brazier M, et al. Autoantibodies, metalloproteinases and bone markers in rheumatoid arthritis patients are unable to predict their responses to infliximab. Rheumatology (Oxford). 2007 Mar;46(3):446-53.
- 1481. Lequerre T, Quartier P, Rosellini D, et al. Interleukin-1 receptor antagonist (anakinra) treatment in patients with systemic-onset juvenile idiopathic arthritis or adult onset Still disease: preliminary experience in France. Ann Rheum Dis. 2008

 Mar; 67(3):302-8.
- 1482. Lesnik A, Bolivar J, Morel J, et al. On the AJR viewbox. Pseudotumoral colonic tuberculosis complicating rheumatoid arthritis treated with a tumor necrosis factor antagonist. AJR Am J Roentgenol. 2006 Jun;186(6):1799-800.
- 1483. Levalampi T, Korpela M, Vuolteenaho K, et al. Infliximab treatment in patients with rheumatoid arthritis and spondyloarthropathies in clinical practice: adverse events and other reasons for discontinuation of treatment. Scand J Rheumatol. 2008 Jan-Feb;37(1):6-12.
- 1484. Levy Y, Uziel Y, Zandman GG, et al. Intravenous immunoglobulins in peripheral neuropathy associated with vasculitis. Ann Rheum Dis. 2003 Dec;62(12):1221-3.
- 1485. Lewiecki EM. Denosumab for joints and bones. Curr Rheumatol Rep. 2009
 Jul;11(3):196-201.
- 1486. Li Gobbi F, Benucci M, Del Rosso A.
 Pneumonitis caused by Legionella
 pneumoniae in a patient with rheumatoid
 arthritis treated with anti-TNF-alpha therapy
 (infliximab). J Clin Rheumatol. 2005
 Apr;11(2):119-20.
- 1487. Li JY, Lai PH, Lam HC, et al. Hypertrophic cranial pachymeningitis and lymphocytic hypophysitis in Sjogren's syndrome. Neurology. 1999 Jan 15;52(2):420-3.
- 1488. Li P, Blum MA, Von Feldt J, et al. Adherence, discontinuation, and switching of biologic therapies in medicaid enrollees with rheumatoid arthritis. Value Health 2010;13(6):805-12.

- 1489. Li St, Kaur PP, Berney SN. Effects of methotrexate use in a patient with rheumatoid arthritis and multiple sclerosis. J Clin Rheumatol. 2008 Aug;14(4):241-2.
- 1490. Li T, Gignac M, Wells G, et al. Decreased external home help use with improved clinical status in rheumatoid arthritis: an exploratory analysis of the Abatacept in Inadequate responders to Methotrexate (AIM) trial. Clin Ther 2008;30(4):734-48.
- 1491. Lian EC, Tzakis AG, Andrews D. Response of factor V inhibitor to rituximab in a patient who received liver transplantation for primary biliary cirrhosis. Am J Hematol. 2004 Dec;77(4):363-5.
- 1492. Liberopoulos EN, Drosos AA, Elisaf MS. Exacerbation of tuberculosis enteritis after treatment with infliximab. Am J Med. 2002 Nov;113(7):615.
- 1493. Lieberman-Maran L, Orzano IM, Passero MA, et al. Bronchiectasis in rheumatoid arthritis: report of four cases and a review of the literature--implications for management with biologic response modifiers. Semin Arthritis Rheum. 2006 Jun;35(6):379-87.
- 1494. Lin YT, Tsai MJ, Wang LH, et al. Efficacy and safety of methotrexate therapy for juvenile rheumatoid arthritis. J Formos Med Assoc. 2000 Aug;99(8):623-9.
- 1495. Linardaki G, Katsarou O, Ioannidou P, et al. Effective etanercept treatment for psoriatic arthritis complicating concomitant human immunodeficiency virus and hepatitis C virus infection. J Rheumatol. 2007 Jun;34(6):1353-5.
- 1496. Lindberg J, af Klint E, Catrina AI, et al. Effect of infliximab on mRNA expression profiles in synovial tissue of rheumatoid arthritis patients. Arthritis Res Ther. 2006;8(6):R179.
- 1497. Lindberg J, Wijbrandts CA, van Baarsen LG, et al. The gene expression profile in the synovium as a predictor of the clinical response to infliximab treatment in rheumatoid arthritis. PLoS One. 2010;5(6):e11310.

- 1498. Linde L, Hetland ML, Ostergaard M. Drug survival and reasons for discontinuation of intramuscular methotrexate: a study of 212 consecutive patients switching from oral methotrexate. Scand J Rheumatol. 2006 Mar-Apr;35(2):102-6.
- 1499. Lindgren P, Geborek P, Kobelt G. Modeling the cost-effectiveness of treatment of rheumatoid arthritis with rituximab using registry data from Southern Sweden. Int J Technol Assess Health Care. 2009 Apr;25(2):181-9.
- 1500. Lindsay K, Fraser AD, Layton A, et al. Liver fibrosis in patients with psoriasis and psoriatic arthritis on long-term, high cumulative dose methotrexate therapy. Rheumatology (Oxford). 2009
 May;48(5):569-72.
- 1501. Ling S, Lewanczuk RZ, Russell AS, et al. Influence of controlled rheumatoid arthritis on the action and disposition of verapamil: focus on infliximab. J Clin Pharmacol. 2009 Mar;49(3):301-11.
- 1502. Lingg GM, Soltesz I, Kessler S, et al. Insufficiency and stress fractures of the long bones occurring in patients with rheumatoid arthritis and other inflammatory diseases, with a contribution on the possibilities of computed tomography. Eur J Radiol. 1997 Dec:26(1):54-63.
- 1503. Liote H, Liote F, Lenique F, et al. Adultonset Still's disease revealed by a pleuropericarditis. Eur Respir J. 1990 Oct;3(9):1064-6.
- 1504. Liou LB. Serum and in vitro production of IL-1 receptor antagonist correlate with C-reactive protein levels in newly diagnosed, untreated lupus patients. Clin Exp Rheumatol. 2001 Sep-Oct;19(5):515-23.
- 1505. Lipsky PE, van der Heijde DM, St Clair EW, et al. Infliximab and methotrexate in the treatment of rheumatoid arthritis. Anti-Tumor Necrosis Factor Trial in Rheumatoid Arthritis with Concomitant Therapy Study Group. N Engl J Med. 2000 Nov 30;343(22):1594-602.
- 1506. Lisbona MP, Maymo J, Perich J, et al. Rapid reduction in tenosynovitis of the wrist and

- fingers evaluated by MRI in patients with rheumatoid arthritis after treatment with etanercept. Ann Rheum Dis 2010;69(6):1117-22.
- 1507. Lisbona MP, Maymo J, Perich J, et al. Etanercept reduces synovitis as measured by magnetic resonance imaging in patients with active rheumatoid arthritis after only 6 weeks. J Rheumatol 2008;35(3):394-7.
- 1508. Listing J, Brandt J, Rudwaleit M, et al. Impact of anti-tumour necrosis factor alpha treatment on admissions to hospital and days of sick leave in patients with ankylosing spondylitis. Ann Rheum Dis. 2004 Dec;63(12):1670-2.
- 1509. Listing J, Strangfeld A, Kary S, et al.
 Infections in patients with rheumatoid
 arthritis treated with biologic agents.
 Arthritis Rheum. 2005 Nov;52(11):3403-12.
- 1510. Listing J, Strangfeld A, Kekow J, et al. Does tumor necrosis factor alpha inhibition promote or prevent heart failure in patients with rheumatoid arthritis? Arthritis Rheum 2008;58(3):667-77.
- 1511. Liu FC, Chiang SY, Chang DM, et al. Purtscher's-like retinopathy as an initial presentation of adult-onset Still's disease: a case report and review of the literature. Clin Rheumatol. 2007 Jul;26(7):1204-6.
- 1512. Liu MF, Yang CY, Li JS, et al. Increased expression of down-regulatory CTLA-4 molecule on T lymphocytes from rheumatoid synovial compartment. Scand J Immunol. 1999 Jul;50(1):68-72.
- 1513. Li-Yu J, Clayburne GM, Sieck MS, et al. Calcium apatite crystals in synovial fluid rice bodies. Ann Rheum Dis. 2002 May;61(5):387-90.
- 1514. Ljung L, Olsson T, Engstrand S, et al. Interleukin-1 receptor antagonist is associated with both lipid metabolism and inflammation in rheumatoid arthritis. Clin Exp Rheumatol. 2007 Jul-Aug;25(4):617-20.
- 1515. Lloyd ME, Davitt S, Hall JR. Bilateral tibia and fibula fractures in a patient with

- rheumatoid arthritis. Clin Rheumatol. 2001;20(4):270-2.
- 1516. Lodder MC, de Jong Z, Kostense PJ, et al. Bone mineral density in patients with rheumatoid arthritis: relation between disease severity and low bone mineral density. Ann Rheum Dis. 2004 Dec;63(12):1576-80.
- 1517. Lodder MC, Haugeberg G, Lems WF, et al. Radiographic damage associated with low bone mineral density and vertebral deformities in rheumatoid arthritis: the Oslo-Truro-Amsterdam (OSTRA) collaborative study. Arthritis Rheum. 2003 Apr 15;49(2):209-15.
- 1518. Lonardo A, Neri P, Mascia MT, et al. Hereditary hemochromatosis masquerading as rheumatoid arthritis. Ann Ital Med Int. 2001 Jan-Mar;16(1):46-9.
- 1519. Long JA, Husted JA, Gladman DD, et al. The relationship between patient satisfaction with health and clinical measures of function and disease status in patients with psoriatic arthritis. J Rheumatol. 2000 Apr;27(4):958-66.
- 1520. Loos T, Dekeyzer L, Struyf S, et al. TLR ligands and cytokines induce CXCR3 ligands in endothelial cells: enhanced CXCL9 in autoimmune arthritis. Lab Invest. 2006 Sep;86(9):902-16.
- 1521. Lopes RV, Furtado RN, Parmigiani L, et al. Accuracy of intra-articular injections in peripheral joints performed blindly in patients with rheumatoid arthritis. Rheumatology (Oxford). 2008
 Dec;47(12):1792-4.
- 1522. Lopez-Hoyos M, Rodrigo E, Fernandez-Fresnedo G, et al. Lack of effect of rapamycin in anti-CCP antibody production in a rheumatoid arthritis kidney allograft recipient. Clin Exp Rheumatol. 2005 Jul-Aug;23(4):529-31.
- 1523. Lorenzi AR, Morgan TA, Anderson A, et al. Thymic function in juvenile idiopathic arthritis. Ann Rheum Dis. 2009
 Jun;68(6):983-90.

- 1524. Lories RJ, Derese I, Luyten FP, et al. Activation of nuclear factor kappa B and mitogen activated protein kinases in psoriatic arthritis before and after etanercept treatment. Clin Exp Rheumatol. 2008 Jan-Feb;26(1):96-102.
- 1525. Louis M, Rauch J, Armstrong M, et al. Induction of autoantibodies during prolonged treatment with infliximab. J Rheumatol. 2003 Dec;30(12):2557-62.
- 1526. Louthrenoo W, Kongtawelert P, Sivasomboon C, et al. Correlation between serum hyaluronan and disease activity and severity in Thai patients with rheumatoid arthritis. J Med Assoc Thai. 2001 May;84(5):622-7.
- 1527. Louthrenoo W, Zager EL, Freundlich B, et al. Intravenous corticosteroid therapy of cervical cord compression in rheumatoid arthritis. Clin Exp Rheumatol. 1992 Mar-Apr;10(2):173-5.
- 1528. Lozeron P, Denier C, Lacroix C, et al. Long-term course of demyelinating neuropathies occurring during tumor necrosis factoralpha-blocker therapy. Arch Neurol. 2009 Apr;66(4):490-7.
- 1529. Lu LJ, Bao CD, Dai M, et al. Multicenter, randomized, double-blind, controlled trial of treatment of active rheumatoid arthritis with T-614 compared with methotrexate.

 Arthritis Rheum. 2009 Jul 15;61(7):979-87.
- 1530. Lubbe S, Tikly M, van der Merwe L, et al. Interleukin-1 receptor antagonist gene polymorphisms are associated with disease severity in Black South Africans with rheumatoid arthritis. Joint Bone Spine. 2008 Jul;75(4):422-5.
- 1531. Lubrano E, D'Angelo S, Parsons WJ, et al. Effects of a combination treatment of an intensive rehabilitation program and etanercept in patients with ankylosing spondylitis: a pilot study. J Rheumatol. 2006 Oct;33(10):2029-34.
- 1532. Luessenhop CP, Higgins LD, Brause BD, et al. Multiple prosthetic infections after total joint arthroplasty. Risk factor analysis. J Arthroplasty. 1996 Oct;11(7):862-8.

- 1533. Lun SW, Wong CK, Tam LS, et al.
 Decreased ex vivo production of TNF-alpha and IL-8 by peripheral blood cells of patients with rheumatoid arthritis after infliximab therapy. Int Immunopharmacol. 2007 Dec 15:7(13):1668-77.
- 1534. Lurati A, Pontikaki I, Teruzzi B, et al. A comparison of response criteria to evaluate therapeutic response in patients with juvenile idiopathic arthritis treated with methotrexate and/or anti-tumor necrosis factor alpha agents. Arthritis Rheum. 2006 May;54(5):1602-7.
- 1535. Luukkainen R, Hakala M, Sajanti E, et al. Predictive value of synovial fluid analysis in estimating the efficacy of intra-articular corticosteroid injections in patients with rheumatoid arthritis. Ann Rheum Dis. 1992 Jul;51(7):874-6.
- 1536. Luzi G, Lagana B, Salemi S, et al. Are glucocorticoids a consistent risk factor for infections in rheumatoid arthritis patients under treatment with methotrexate and etanercept? Clin Ter. 2009 Mar-Apr;160(2):121-3.
- 1537. Lyman J, Serebro L. Efalizumab-induced inflammatory polyarthritis: what are the implications? South Med J. 2010 Apr;103(4):357-60.
- 1538. Lyngberg KK, Harreby M, Bentzen H, et al. Elderly rheumatoid arthritis patients on steroid treatment tolerate physical training without an increase in disease activity. Arch Phys Med Rehabil. 1994 Nov;75(11):1189-95.
- 1539. Lyons JS, Severns ML. Detection of early hydroxychloroquine retinal toxicity enhanced by ring ratio analysis of multifocal electroretinography. Am J Ophthalmol. 2007 May;143(5):801-9.
- 1540. Ma Y, Lin BR, Lin B, et al.
 Pharmacokinetics of CTLA4Ig fusion
 protein in healthy volunteers and patients
 with rheumatoid arthritis. Acta Pharmacol
 Sin. 2009 Mar;30(3):364-71.
- 1541. Machado P, Santos A, Pereira C, et al.
 Increased prevalence of allergic sensitisation in rheumatoid arthritis patients treated with

- anti-TNFalpha. Joint Bone Spine 2009;76(5):508-13.
- 1542. Macias I, Garcia-Perez S, Ruiz-Tudela M, et al. Modification of pro- and antiinflammatory cytokines and vascular-related molecules by tumor necrosis factor-a blockade in patients with rheumatoid arthritis. J Rheumatol. 2005
 Nov;32(11):2102-8.
- 1543. Mackie GC, Pohlen JM. Methotrexateinduced pulmonary non-Hodgkin lymphoma. Clin Nucl Med. 2006 May;31(5):272-4.
- 1544. MacLean CH, Mojica WA, Morton SC, et al. Effects of omega-3 fatty acids on lipids and glycemic control in type II diabetes and the metabolic syndrome and on inflammatory bowel disease, rheumatoid arthritis, renal disease, systemic lupus erythematosus, and osteoporosis. Evid Rep Technol Assess (Summ). 2004 Mar(89):1-4.
- 1545. Maenpaa HM, Soini I, Lehto MU, et al. Insufficiency fractures in patients with chronic inflammatory joint diseases. Clin Exp Rheumatol. 2002 Jan-Feb;20(1):77-9.
- 1546. Magaro M, Tricerri A, Piane D, et al. Generalized osteoporosis in non-steroid treated rheumatoid arthritis. Rheumatol Int. 1991;11(2):73-6.
- 1547. Magliocco MA, Gottlieb AB. Etanercept therapy for patients with psoriatic arthritis and concurrent hepatitis C virus infection: report of 3 cases. J Am Acad Dermatol. 2004 Oct;51(4):580-4.
- 1548. Magnusson SE, Engstrom M, Jacob U, et al. High synovial expression of the inhibitory FcgammaRIIb in rheumatoid arthritis. Arthritis Res Ther. 2007;9(3):R51.
- 1549. Maillard H, Ornetti P, Grimault L, et al. Severe pyogenic infections in patients taking infliximab: a regional cohort study. Joint Bone Spine. 2005 Jul;72(4):330-4.
- 1550. Maimon N, Brunton J, Chan AK, et al. Fatal pulmonary Mycobacterium xenopi in a patient with rheumatoid arthritis receiving etanercept. Thorax. 2007 Aug;62(8):739-40.

- 1551. Maini R, St Clair EW, Breedveld F, et al. Infliximab (chimeric anti-tumour necrosis factor alpha monoclonal antibody) versus placebo in rheumatoid arthritis patients receiving concomitant methotrexate: a randomised phase III trial. ATTRACT Study Group. Lancet. 1999 Dec 4;354(9194):1932-9.
- 1552. Maini RN, Breedveld FC, Kalden JR, et al. Therapeutic efficacy of multiple intravenous infusions of anti-tumor necrosis factor alpha monoclonal antibody combined with low-dose weekly methotrexate in rheumatoid arthritis. Arthritis Rheum. 1998 Sep;41(9):1552-63.
- 1553. Maini RN, Breedveld FC, Kalden JR, et al. Sustained improvement over two years in physical function, structural damage, and signs and symptoms among patients with rheumatoid arthritis treated with infliximab and methotrexate. Arthritis Rheum. 2004 Apr;50(4):1051-65.
- 1554. Maini RN, Taylor PC, Szechinski J, et al. Double-blind randomized controlled clinical trial of the interleukin-6 receptor antagonist, tocilizumab, in European patients with rheumatoid arthritis who had an incomplete response to methotrexate. Arthritis Rheum 2006;54(9):2817-29.
- 1555. Mainman H, McClaren E, Heycock C, et al. When should we use parenteral methotrexate? Clin Rheumatol. 2010 Oct;29(10):1093-8.
- 1556. Maki-Petaja KM, Hall FC, Booth AD, et al. Rheumatoid arthritis is associated with increased aortic pulse-wave velocity, which is reduced by anti-tumor necrosis factoralpha therapy. Circulation. 2006 Sep 12;114(11):1185-92.
- 1557. Maksymowych WP. Ankylosing spondylitis. Not just another pain in the back. Can Fam Physician. 2004 Feb;50:257-62.
- 1558. Maksymowych WP, Blackburn WD, Jr., Tami JA, et al. A randomized, placebo controlled trial of an antisense oligodeoxynucleotide to intercellular adhesion molecule-1 in the treatment of severe rheumatoid arthritis. J Rheumatol. 2002 Mar;29(3):447-53.

- 1559. Maksymowych WP, Inman RD, Salonen D, et al. Spondyloarthritis Research
 Consortium of Canada magnetic resonance imaging index for assessment of spinal inflammation in ankylosing spondylitis.
 Arthritis Rheum. 2005 Aug 15;53(4):502-9.
- 1560. Maksymowych WP, Inman RD, Salonen D, et al. Spondyloarthritis research Consortium of Canada magnetic resonance imaging index for assessment of sacroiliac joint inflammation in ankylosing spondylitis.

 Arthritis Rheum. 2005 Oct 15;53(5):703-9.
- 1561. Maksymowych WP, Jhangri GS, Lambert RG, et al. Infliximab in ankylosing spondylitis: a prospective observational inception cohort analysis of efficacy and safety. J Rheumatol. 2002 May;29(5):959-65.
- 1562. Maksymowych WP, Poole AR, Hiebert L, et al. Etanercept exerts beneficial effects on articular cartilage biomarkers of degradation and turnover in patients with ankylosing spondylitis. J Rheumatol. 2005
 Oct;32(10):1911-7.
- 1563. Maksymowych WP, Reeve JP, Reveille JD, et al. High-throughput single-nucleotide polymorphism analysis of the IL1RN locus in patients with ankylosing spondylitis by matrix-assisted laser desorption ionization-time-of-flight mass spectrometry. Arthritis Rheum. 2003 Jul;48(7):2011-8.
- 1564. Malaviya AN, Kapoor S, Garg S, et al. A new strategy of drug treatment in NSAID-unresponsive ankylosing spondylitis: combination of pamidronate and methylprednisolone monthly intravenous infusions on the background of a combination of disease modifying drugs sulfasalazine and methotrexate. J Assoc Physicians India. 2007 Mar;55:193-7.
- 1565. Malesci D, Tirri R, Buono R, et al.
 Leflunomide in psoriatic arthritis: a
 retrospective study of discontinuation rate in
 daily clinical practice compared with
 methotrexate. Clin Exp Rheumatol. 2007
 Nov-Dec;25(6):881-4.
- 1566. Malfait AM, Verbruggen G, Almqvist KF, et al. Coculture of human articular chondrocytes with peripheral blood

- mononuclear cells as a model to study cytokine-mediated interactions between inflammatory cells and target cells in the rheumatoid joint. In Vitro Cell Dev Biol Anim. 1994 Nov;30A(11):747-52.
- 1567. Malipeddi AS, Rajendran R, Kallarackal G. Disseminated tuberculosis after anti-TNFalpha treatment. Lancet. 2007 Jan 13;369(9556):162.
- 1568. Malysheva OA, Wahle M, Wagner U, et al. Low-dose prednisolone in rheumatoid arthritis: adverse effects of various disease modifying antirheumatic drugs. J Rheumatol 2008;35(6):979-85.
- 1569. Manadan AM, Block JA, Sequeira W. Mycobacteria tuberculosis peritonitis associated with etanercept therapy. Clin Exp Rheumatol. 2003 Jul-Aug;21(4):526.
- 1570. Mancarella L, Bobbio-Pallavicini F, Ceccarelli F, et al. Good clinical response, remission, and predictors of remission in rheumatoid arthritis patients treated with tumor necrosis factor-alpha blockers: the GISEA study. J Rheumatol. 2007 Aug;34(8):1670-3.
- 1571. Manda G, Neagu M, Constantin C, et al. Patterns of peripheral cellular immune disorders in severe rheumatoid arthritis. Roum Arch Microbiol Immunol. 2005 Jan-Dec;64(1-4):17-26.
- 1572. Mang R, Stege H, Ruzicka T, et al. Response of severe psoriasis to infliximab. Dermatology. 2002;204(2):156-7.
- 1573. Mangat P, Whittle S, Cleland L, et al.
 Digital vasculitis: a late complication of
 anti-tumour necrosis factor alpha therapy.
 Clin Rheumatol. 2008 Dec;27(12):1593-5.
- 1574. Manger B, Rech J, Schett G. Use of methotrexate in adult-onset Still's disease. Clin Exp Rheumatol. 2010 Sep-Oct;28(5 Suppl 61):S168-71.
- 1575. Marchesoni A, Arreghini M, Panni B, et al. Life-threatening reversible bone marrow toxicity in a rheumatoid arthritis patient switched from leflunomide to infliximab.

- Rheumatology (Oxford). 2003 Jan;42(1):193-4.
- 1576. Marchesoni A, Ceravolo GP, Battafarano N, et al. Cyclosporin A in the treatment of adult onset Still's disease. J Rheumatol. 1997 Aug;24(8):1582-7.
- 1577. Marchesoni A, Puttini PS, Gorla R, et al. Cyclosporine in addition to infliximab and methotrexate in refractory rheumatoid arthritis. Clin Exp Rheumatol. 2005 Nov-Dec;23(6):916-7.
- 1578. Marchesoni A, Zaccara E, Gorla R, et al. TNF-alpha antagonist survival rate in a cohort of rheumatoid arthritis patients observed under conditions of standard clinical practice. Ann N Y Acad Sci 2009;1173837-46.
- 1579. Mariette X, Ravaud P, Steinfeld S, et al. Inefficacy of infliximab in primary Sjogren's syndrome: results of the randomized, controlled Trial of Remicade in Primary Sjogren's Syndrome (TRIPSS). Arthritis Rheum. 2004 Apr;50(4):1270-6.
- 1580. Maripuri S, Grande JP, Osborn TG, et al. Renal involvement in primary Sjogren's syndrome: a clinicopathologic study. Clin J Am Soc Nephrol. 2009 Sep;4(9):1423-31.
- 1581. Markatseli TE, Kaltsonoudis ES, Voulgari PV, et al. Induction of psoriatic skin lesions in a patient with rheumatoid arthritis treated with rituximab. Clin Exp Rheumatol. 2009 Nov-Dec;27(6):996-8.
- 1582. Marotte H, Arnaud B, Diasparra J, et al. Association between the level of circulating bioactive tumor necrosis factor alpha and the tumor necrosis factor alpha gene polymorphism at -308 in patients with rheumatoid arthritis treated with a tumor necrosis factor alpha inhibitor. Arthritis Rheum. 2008 May;58(5):1258-63.
- 1583. Marotte H, Gineyts E, Miossec P, et al. Effects of infliximab therapy on biological markers of synovium activity and cartilage breakdown in patients with rheumatoid arthritis. Ann Rheum Dis. 2009 Jul;68(7):1197-200.

- 1584. Marotte H, Maslinski W, Miossec P. Circulating tumour necrosis factor-alpha bioactivity in rheumatoid arthritis patients treated with infliximab: link to clinical response. Arthritis Res Ther. 2005;7(1):R149-55.
- 1585. Marotte H, Pallot-Prades B, Grange L, et al. The shared epitope is a marker of severity associated with selection for, but not with response to, infliximab in a large rheumatoid arthritis population. Ann Rheum Dis. 2006 Mar;65(3):342-7.
- 1586. Marsh P, Pflugfelder SC. Topical nonpreserved methylprednisolone therapy for keratoconjunctivitis sicca in Sjogren syndrome. Ophthalmology. 1999
 Apr;106(4):811-6.
- 1587. Marshall NJ, Wilson G, Lapworth K, et al. Patients' perceptions of treatment with anti-TNF therapy for rheumatoid arthritis: a qualitative study. Rheumatology (Oxford). 2004 Aug;43(8):1034-8.
- 1588. Marti L, Golmia R, Golmia AP, et al. Alterations in cytokine profile and dendritic cells subsets in peripheral blood of rheumatoid arthritis patients before and after biologic therapy. Ann N Y Acad Sci. 2009 Sep;1173:334-42.
- 1589. Martin JA, Jarrett P. Rheumatoid papules treated with dapsone. Clin Exp Dermatol. 2004 Jul;29(4):387-9.
- 1590. Martin JC, Munro R, Campbell MK, et al. Effects of disease and corticosteroids on appendicular bone mass in postmenopausal women with rheumatoid arthritis: comparison with axial measurements. Br J Rheumatol. 1997 Jan;36(1):43-9.
- 1591. Martin JM, Ricart JM, Alcacer J, et al. Adalimumab-induced lupus erythematosus. Lupus. 2008 Jul;17(7):676-8.
- 1592. Martin K, Bentaberry F, Dumoulin C, et al. Peripheral neuropathy associated with leflunomide: is there a risk patient profile? Pharmacoepidemiol Drug Saf. 2007 Jan;16(1):74-8.

- 1593. Martin Martin LS, Migliore A, Todino V, et al. Infliximab therapy in patients with secondary Sjogren's syndrome: functional evaluation. Clin Exp Rheumatol. 2003 May-Jun;21(3):412.
- 1594. Martin N, Innes JA, Lambert CM, et al. Hypersensitivity pneumonitis associated with leflunomide therapy. J Rheumatol. 2007 Sep;34(9):1934-7.
- 1595. Martinez A, Salido M, Bonilla G, et al. Association of the major histocompatibility complex with response to infliximab therapy in rheumatoid arthritis patients. Arthritis Rheum. 2004 Apr;50(4):1077-82.
- 1596. Martinez Lopez JA, Loza E, Carmona L. Systematic review on the safety of methotrexate in rheumatoid arthritis regarding the reproductive system (fertility, pregnancy, and breastfeeding). Clin Exp Rheumatol 2009;27(4):678-84.
- 1597. Maruani A, Wierzbicka E, Machet MC, et al. Reversal of multifocal cutaneous lymphoproliferative disease associated with Epstein-Barr virus after withdrawal of methotrexate therapy for rheumatoid arthritis. J Am Acad Dermatol. 2007 Nov;57(5 Suppl):S69-71.
- 1598. Marzo-Ortega H, McGonagle D, Jarrett S, et al. Infliximab in combination with methotrexate in active ankylosing spondylitis: a clinical and imaging study.

 Ann Rheum Dis. 2005 Nov;64(11):1568-75.
- 1599. Marzo-Ortega H, McGonagle D, O'Connor P, et al. Efficacy of etanercept in the treatment of the entheseal pathology in resistant spondylarthropathy: a clinical and magnetic resonance imaging study. Arthritis Rheum. 2001 Sep;44(9):2112-7.
- 1600. Marzo-Ortega H, McGonagle D, Rhodes LA, et al. Efficacy of infliximab on MRI-determined bone oedema in psoriatic arthritis. Ann Rheum Dis. 2007 Jun;66(6):778-81.
- 1601. Marzo-Ortega H, Misbah S, Emery P. Minocycline induced autoimmune disease in rheumatoid arthritis: a missed diagnosis? J Rheumatol. 2001 Feb;28(2):377-8.

- 1602. Masera RG, Carignola R, Sartori ML, et al. Circadian abnormalities of natural killer cell activity in rheumatoid arthritis. Ann N Y Acad Sci. 1999 Jun 22;876:88-90.
- 1603. Masi AT, Aldag JC, Chatterton RT, et al. Adrenal androgen and glucocorticoid dissociation in premenopausal rheumatoid arthritis: a significant correlate or precursor to onset? Z Rheumatol. 2000;59 Suppl 2:II/54-61.
- 1604. Masi AT, Chatterton RT, Aldag JC, et al. Perspectives on the relationship of adrenal steroids to rheumatoid arthritis. Ann N Y Acad Sci. 2002 Jun;966:1-12.
- 1605. Masiero S, Boniolo A, Wassermann L, et al. Effects of an educational-behavioral joint protection program on people with moderate to severe rheumatoid arthritis: a randomized controlled trial. Clin Rheumatol. 2007 Dec;26(12):2043-50.
- 1606. Massarotti EM. Medical aspects of rheumatoid arthritis. Diagnosis and treatment. Hand Clin. 1996 Aug;12(3):463-75.
- 1607. Mastroianni A, Minutilli E, Mussi A, et al. Cytokine profiles during infliximab monotherapy in psoriatic arthritis. Br J Dermatol. 2005 Sep;153(3):531-6.
- 1608. Masuda K, Mochida Y, Fujii J, et al.
 Primary cervical epidural malignant
 lymphoma with rheumatoid arthritis: a case
 report. Mod Rheumatol. 2007;17(3):239-42.
- 1609. Mateo L, Nolla JM, Bonnin MR, et al. Sex hormone status and bone mineral density in men with rheumatoid arthritis. J Rheumatol. 1995 Aug;22(8):1455-60.
- 1610. Mathias SD, Colwell HH, Miller DP, et al. Health-related quality of life and functional status of patients with rheumatoid arthritis randomly assigned to receive etanercept or placebo. Clin Ther. 2000 Jan;22(1):128-39.
- 1611. Mathieu S, Vellin JF, Poujol D, et al. Cat scratch disease during etanercept therapy. Joint Bone Spine. 2007 Mar;74(2):184-6.

- 1612. Matsuda M, Morita H, Ikeda S. Long-term follow-up of systemic reactive AA amyloidosis secondary to rheumatoid arthritis: successful treatment with intermediate-dose corticosteroid. Intern Med. 2002 May;41(5):403-7.
- 1613. Matsui T, Komiya A, Shimada K, et al. Neutrophil CD64 as a marker of infection in patients treated with tocilizumab. Mod Rheumatol. 2009;19(6):696-7.
- 1614. Matsui T, Kuga Y, Kaneko A, et al. Disease Activity Score 28 (DAS28) using C-reactive protein underestimates disease activity and overestimates EULAR response criteria compared with DAS28 using erythrocyte sedimentation rate in a large observational cohort of rheumatoid arthritis patients in Japan. Ann Rheum Dis. 2007 Sep;66(9):1221-6.
- 1615. Matsui T, Ohsumi K, Ozawa N, et al. CD64 on neutrophils is a sensitive and specific marker for detection of infection in patients with rheumatoid arthritis. J Rheumatol. 2006 Dec;33(12):2416-24.
- 1616. Matsumoto K, Hukuda S, Nishioka J, et al. Rupture of the Achilles tendon in rheumatoid arthritis with histologic evidence of enthesitis. A case report. Clin Orthop Relat Res. 1992 Jul(280):235-40.
- 1617. Matsumoto T, Kaneko T, Seto M, et al. The membrane proteinase 3 expression on neutrophils was downregulated after treatment with infliximab in patients with rheumatoid arthritis. Clin Appl Thromb Hemost. 2008 Apr;14(2):186-92.
- 1618. Matsuo T, Koyama T, Morimoto N, et al. Retinal vasculitis as a complication of rheumatoid arthritis. Ophthalmologica. 1990;201(4):196-200.
- 1619. Matsushita I, Uzuki M, Matsuno H, et al. Rheumatoid nodulosis during methotrexate therapy in a patient with rheumatoid arthritis. Mod Rheumatol. 2006;16(6):401-3.
- 1620. Mattey DL, Brownfield A, Dawes PT.
 Relationship between pack-year history of smoking and response to tumor necrosis factor antagonists in patients with

- rheumatoid arthritis. J Rheumatol 2009;36(6):1180-7.
- 1621. Matthews C, Fitzgerald O. Seropositive erosive rheumatoid arthritis (RA). Rheumatology (Oxford). 2006 Sep;45(9):1100.
- 1622. Maugars Y, Mathis C, Berthelot JM, et al. Assessment of the efficacy of sacroiliac corticosteroid injections in spondylarthropathies: a double-blind study. Br J Rheumatol. 1996 Aug;35(8):767-70.
- 1623. Mavragani CP, La DT, Stohl W, et al. Association of the response to tumor necrosis factor antagonists with plasma type I interferon activity and interferonbeta/alpha ratios in rheumatoid arthritis patients: a post hoc analysis of a predominantly Hispanic cohort. Arthritis Rheum. 2010 Feb;62(2):392-401.
- 1624. Mavropoulos JC, Cuchacovich M, Llanos C, et al. Anti-tumor necrosis factor-alpha therapy augments dipeptidyl peptidase IV activity and decreases autoantibodies to GRP78/BIP and phosphoglucose isomerase in patients with rheumatoid arthritis. J Rheumatol. 2005 Nov;32(11):2116-24.
- 1625. Maxwell JR, Potter C, Hyrich KL, et al. Association of the tumour necrosis factor-308 variant with differential response to anti-TNF agents in the treatment of rheumatoid arthritis. Hum Mol Genet. 2008 Nov 15:17(22):3532-8.
- 1626. Mayer DF, Matteson EL. Testicular involvement in rheumatoid vasculitis. Clin Exp Rheumatol. 2004;22(6 Suppl 36):S62-4.
- 1627. Mayer Y, Balbir-Gurman A, Machtei EE. Anti-tumor necrosis factor-alpha therapy and periodontal parameters in patients with rheumatoid arthritis. J Periodontol. 2009 Sep;80(9):1414-20.
- 1628. Mazokopakis E, Katsogridakis K, Koutsopoulos A, et al. Fatal methotrexateinduced pneumonitis in a psoriatic patient. Mil Med. 2004 Apr;169(4):298-300.
- 1629. Mazzotta A, Esposito M, Costanzo A, et al. Efficacy and safety of etanercept in psoriasis

- after switching from other treatments: an observational study. Am J Clin Dermatol. 2009;10(5):319-24.
- 1630. Mazzotta A, Esposito M, Schipani C, et al. Long-term experience with etanercept in psoriatic arthritis patients: a 3-year observational study. J Dermatolog Treat. 2009;20(6):354-8.
- 1631. McCain ME, Quinet RJ, Davis WE. Etanercept and infliximab associated with cutaneous vasculitis. Rheumatology (Oxford). 2002 Jan;41(1):116-7.
- 1632. McCarthy CJ, Regan M, Coughlan RJ. Treatment of rheumatoid hand synovitis with a regional block technique. Ir J Med Sci. 1993 Apr;162(4):143-4.
- 1633. McCombe PA, Klestov AC, Tannenberg AE, et al. Sensorimotor peripheral neuropathy in rheumatoid arthritis. Clin Exp Neurol. 1991;28:146-53.
- 1634. McDonald JR, Zeringue AL, Caplan L, et al. Herpes zoster risk factors in a national cohort of veterans with rheumatoid arthritis. Clin Infect Dis 2009;48(10):1364-71.
- 1635. McGarry F, Neilly J, Anderson N, et al. A polymorphism within the interleukin 1 receptor antagonist (IL-1Ra) gene is associated with ankylosing spondylitis. Rheumatology (Oxford). 2001 Dec;40(12):1359-64.
- 1636. McGonagle D, Tan AL, Madden J, et al. Rituximab use in everyday clinical practice as a first-line biologic therapy for the treatment of DMARD-resistant rheumatoid arthritis. Rheumatology (Oxford). 2008 Jun;47(6):865-7.
- 1637. McMinn JR, Jr., Cohen S, Moore J, et al. Complete recovery from refractory immune thrombocytopenic purpura in three patients treated with etanercept. Am J Hematol. 2003 Jun;73(2):135-40.
- 1638. Mease PJ, Cohen S, Gaylis NB, et al.
 Efficacy and safety of retreatment in patients
 with rheumatoid arthritis with previous
 inadequate response to tumor necrosis factor

- inhibitors: results from the SUNRISE trial. J Rheumatol 2010;37(5):917-27.
- 1639. Mease PJ, Gladman DD, Ritchlin CT, et al. Adalimumab for the treatment of patients with moderately to severely active psoriatic arthritis: results of a double-blind, randomized, placebo-controlled trial. Arthritis Rheum 2005;52(10):3279-89.
- 1640. Mease PJ, Goffe BS, Metz J, et al. Etanercept in the treatment of psoriatic arthritis and psoriasis: a randomised trial. Lancet. 2000 Jul 29;356(9227):385-90.
- 1641. Mease PJ, Kivitz AJ, Burch FX, et al. Continued inhibition of radiographic progression in patients with psoriatic arthritis following 2 years of treatment with etanercept. J Rheumatol 2006;33(4):712-21.
- 1642. Mease PJ, Kivitz AJ, Burch FX, et al. Etanercept treatment of psoriatic arthritis: safety, efficacy, and effect on disease progression. Arthritis Rheum 2004;50(7):2264-72.
- 1643. Mease PJ, Ory P, Sharp JT, et al.
 Adalimumab for long-term treatment of psoriatic arthritis: 2-year data from the Adalimumab Effectiveness in Psoriatic Arthritis Trial (ADEPT). Ann Rheum Dis. 2009 May;68(5):702-9.
- 1644. Mease PJ, Reich K. Alefacept with methotrexate for treatment of psoriatic arthritis: open-label extension of a randomized, double-blind, placebocontrolled study. J Am Acad Dermatol. 2009 Mar;60(3):402-11.
- 1645. Mease PJ, Revicki DA, Szechinski J, et al. Improved health-related quality of life for patients with active rheumatoid arthritis receiving rituximab: Results of the Dose-Ranging Assessment: International Clinical Evaluation of Rituximab in Rheumatoid Arthritis (DANCER) Trial. J Rheumatol 2008;35(1):20-30.
- 1646. Mease PJ, Ritchlin CT, Martin RW, et al. Pneumococcal vaccine response in psoriatic arthritis patients during treatment with etanercept. J Rheumatol. 2004 Jul;31(7):1356-61.

- 1647. Mease PJ, Woolley JM, Singh A, et al.
 Patient-reported outcomes in a randomized trial of etanercept in psoriatic arthritis. J
 Rheumatol 2010;37(6):1221-7.
- 1648. Mehta BM, Hashkes PJ, Avery R, et al. A 21-year-old man with Still's disease with fever, rash, and pancytopenia. Arthritis Care Res (Hoboken). 2010 Apr;62(4):575-9.
- 1649. Meijer JM, Meiners PM, Vissink A, et al. Effectiveness of rituximab treatment in primary Sjogren's syndrome: a randomized, double-blind, placebo-controlled trial. Arthritis Rheum. 2010 Apr;62(4):960-8.
- 1650. Meirer R, Muller-Gerbl M, Huemer GM, et al. Quantitative assessment of periarticular osteopenia in patients with early rheumatoid arthritis: a preliminary report. Scand J Rheumatol. 2004;33(5):307-11.
- 1651. Melikoglu MA, Melikoglu M, Gurbuz U, et al. Hydroxychloroquine-induced hyperpigmentation: a case report. J Clin Pharm Ther. 2008 Dec;33(6):699-701.
- 1652. Menard O, Petit N, Gillet P, et al. Association of histologically proven rheumatoid arthritis with pulmonary sarcoidosis. Eur Respir J. 1995 Mar;8(3):472-3.
- 1653. Menninger H, Herborn G, Sander O, et al. A 36 month comparative trial of methotrexate and gold sodium thiomalate in the treatment of early active and erosive rheumatoid arthritis. Br J Rheumatol. 1998 Oct;37(10):1060-8.
- 1654. Mertens M, Singh JA. Anakinra for rheumatoid arthritis. Cochrane Database Syst Rev 2009(1):CD005121.
- 1655. Mertz LE, Blair JE. Coccidioidomycosis in rheumatology patients: incidence and potential risk factors. Ann N Y Acad Sci 2007;1111343-57.
- 1656. Messina OD, Barreira JC, Zanchetta JR, et al. Effect of low doses of deflazacort vs prednisone on bone mineral content in premenopausal rheumatoid arthritis. J Rheumatol. 1992 Oct;19(10):1520-6.

- 1657. Meusch U, Rossol M, Baerwald C, et al. Outside-to-inside signaling through transmembrane tumor necrosis factor reverses pathologic interleukin-1beta production and deficient apoptosis of rheumatoid arthritis monocytes. Arthritis Rheum. 2009 Sep;60(9):2612-21.
- 1658. Miceli-Richard C, Comets E, Verstuyft C, et al. A single tumour necrosis factor haplotype influences the response to adalimumab in rheumatoid arthritis. Ann Rheum Dis. 2008 Apr;67(4):478-84.
- 1659. Michaelsson G, Kajermo U, Michaelsson A, et al. Infliximab can precipitate as well as worsen palmoplantar pustulosis: possible linkage to the expression of tumour necrosis factor-alpha in the normal palmar eccrine sweat duct? Br J Dermatol. 2005 Dec;153(6):1243-4.
- 1660. Michaud K, Wolfe F. The association of rheumatoid arthritis and its treatment with sinus disease. J Rheumatol 2006;33(12):2412-5.
- 1661. Michel BA, Bloch DA, Fries JF. Predictors of fractures in early rheumatoid arthritis. J Rheumatol. 1991 Jun;18(6):804-8.
- 1662. Michel BA, Bloch DA, Wolfe F, et al. Fractures in rheumatoid arthritis: an evaluation of associated risk factors. J Rheumatol. 1993 Oct;20(10):1666-9.
- 1663. Michel M, Duvoux C, Hezode C, et al. Fulminant hepatitis after infliximab in a patient with hepatitis B virus treated for an adult onset still's disease. J Rheumatol. 2003 Jul;30(7):1624-5.
- 1664. Michel M, Habibi A, Godeau B, et al. Characteristics and outcome of connective tissue diseases in patients with sickle-cell disease: report of 30 cases. Semin Arthritis Rheum. 2008 Dec;38(3):228-40.
- 1665. Mielants H, Goemaere S, De Vos M, et al. Intestinal mucosal permeability in inflammatory rheumatic diseases. I. Role of antiinflammatory drugs. J Rheumatol. 1991 Mar;18(3):389-93.

- 1666. Mielke F, Schweigert M. Safe adalimumab therapy for rheumatoid arthritis in a patient with pre-existing multiple myeloma. Nat Clin Pract Rheumatol. 2008 Apr;4(4):218-21.
- 1667. Migliore A, Bizzi E, Massafra U, et al. Can Cyclosporine-A associated to methotrexate maintain remission induced by anti-TNF agents in rheumatoid arthritis patients? (Cynar pilot study). Int J Immunopathol Pharmacol. 2010 Jul-Sep;23(3):783-90.
- 1668. Migliore A, Massafra U, Capuano A, et al. Combined use of teriparatide and TNFalpha blockade: safety. Aging Clin Exp Res. 2007 Jun;19(3 Suppl):18-20.
- 1669. Migliore A, Signore A, Capuano A, et al. Relevance of 99mTc-HYNIC-tir-octreotide scintigraphy in a patient affected by sarcoidosis with lung and joints involvement and secondary Sjogren's syndrome treated with infliximab: case report. Eur Rev Med Pharmacol Sci. 2008 Mar-Apr;12(2):127-30.
- 1670. Mikashima Y, Kawamura K, Miyawaki M, et al. Neglected spontaneous rupture of the Achilles tendon in elderly patients with rheumatoid arthritis. J Clin Rheumatol. 2010 Aug;16(5):221-4.
- 1671. Mikhail M, Weinberg JM, Smith BL. Successful treatment with etanercept of von Zumbusch pustular psoriasis in a patient with human immunodeficiency virus. Arch Dermatol. 2008 Apr;144(4):453-6.
- 1672. Miller KL, Sawitzke AD, Doane J.
 Abatacept and serious respiratory infections in patients with previous lung disease. Clin Rheumatol. 2008 Dec;27(12):1569-71.
- 1673. Miller-Blair DJ, Robbins DL. Rheumatoid arthritis: new science, new treatment. Geriatrics. 1993 Jun;48(6):28-31, 5-8.
- 1674. Mima T, Nishimoto N. Clinical value of blocking IL-6 receptor. Curr Opin Rheumatol. 2009 May;21(3):224-30.
- 1675. Min JK, Han NI, Kim JA, et al. A case of cholestatic autoimmune hepatitis and acute liver failure: an unusual hepatic manifestation of mixed connective tissue

- disease and Sjogren's syndrome. J Korean Med Sci. 2001 Aug;16(4):512-5.
- 1676. Mirone L, Altomonte L, D'Agostino P, et al. A study of serum androgen and cortisol levels in female patients with rheumatoid arthritis. Correlation with disease activity. Clin Rheumatol. 1996 Jan;15(1):15-9.
- 1677. Misery L, Perrot JL, Gentil-Perret A, et al. Dermatological complications of etanercept therapy for rheumatoid arthritis. Br J Dermatol. 2002 Feb;146(2):334-5.
- 1678. Mishra KK, Pandey HP. A study on physiological changes in essential hypertension and rheumatoid arthritis with reference to the levels of cortisol, blood glucose, triglycerides and cholesterol. Indian J Physiol Pharmacol. 1995 Jan;39(1):68-70.
- 1679. Mishra KK, Pandey HP. A study on physiological changes in certain psychosomatic disorders with reference to cortisol, blood glucose and lipid profile. Indian J Physiol Pharmacol. 1996 Apr;40(2):151-4.
- 1680. Mitamura M, Tada Y, Koarada S, et al. Cyclosporin A treatment for Japanese patients with severe adult-onset Still's disease. Mod Rheumatol. 2009;19(1):57-63.
- 1681. Mittendorf T, Dietz B, Sterz R, et al.
 Personal and economic burden of late-stage rheumatoid arthritis among patients treated with adalimumab: an evaluation from a patient's perspective. Rheumatology (Oxford). 2008 Feb;47(2):188-93.
- 1682. Mittendorf T, Dietz B, Sterz R, et al. Improvement and longterm maintenance of quality of life during treatment with adalimumab in severe rheumatoid arthritis. J Rheumatol. 2007 Dec;34(12):2343-50.
- 1683. Miyagawa Y, Nagata N, Nakanishi Y, et al. A case of steroid-responsive organizing pneumonia in a patient with rheumatoid arthritis showing migratory infiltration and normal glucose levels in pleural effusions. Br J Rheumatol. 1993 Sep;32(9):829-31.
- 1684. Miyamoto S, Kageyama Y, Ozeki T, et al. Bone mineral density after total joint

- arthroplasty of lower extremities in rheumatoid arthritis patients. Arch Orthop Trauma Surg. 2001;121(3):127-30.
- 1685. Miyanishi K, Hara T, Hamada T, et al. Cooccurrence of subchondral insufficiency fracture of the femoral head and contralateral femoral neck fracture in a rheumatic patient receiving steroid treatment. Mod Rheumatol. 2008;18(6):619-22.
- 1686. Miyasaka N. Clinical investigation in highly disease-affected rheumatoid arthritis patients in Japan with adalimumab applying standard and general evaluation: the CHANGE study. Mod Rheumatol 2008;18(3):252-62.
- 1687. Miyazaki T, Fujimaki K, Shirasugi Y, et al. Remission of lymphoma after withdrawal of methotrexate in rheumatoid arthritis: relationship with type of latent Epstein-Barr virus infection. Am J Hematol. 2007 Dec;82(12):1106-9.
- 1688. Moccia F, Mazzarello GP, Morra L. Effect of corticosteroid treatment on hemopoiesis in vivo and in vitro in a patient with Felty's syndrome. Biomed Pharmacother. 1991;45(9):403-8.
- 1689. Mochizuki T, Momohara S, Ikari K, et al. Spontaneous multiple insufficiency fractures after pelvic abscess and sepsis in a rheumatoid arthritis patient treated with high-load corticosteroid therapy: a case report. Clin Rheumatol. 2007
 Nov;26(11):1925-8.
- 1690. Mochizuki T, Momohara S, Ikari K, et al. The serum concentration of infliximab in cases of autologous blood donation for patients with rheumatoid arthritis. Mod Rheumatol. 2007;17(1):24-7.
- 1691. Mody GM, Meyers OL. Therapeutic requirements in rheumatoid arthritis. S Afr Med J. 1990 May 19;77(10):497-9.
- 1692. Moen K, Kvalvik AG, Hellem S, et al. The long-term effect of anti TNF-alpha treatment on temporomandibular joints, oral mucosa, and salivary flow in patients with active rheumatoid arthritis: a pilot study. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 2005 Oct;100(4):433-40.

- 1693. Mogosan C, Stoica V, Mihai C, et al. Rheumatoid arthritis: travelling biological era a Romanian X-ray population. J Med Life. 2009 Oct-Dec;2(4):414-25.
- 1694. Mohammad A, Kilcoyne A, Bond U, et al. Methotrexate information booklet study 2008. Clin Exp Rheumatol. 2009 Jul-Aug;27(4):649-50.
- 1695. Mohan AK, Cote TR, Block JA, et al. Tuberculosis following the use of etanercept, a tumor necrosis factor inhibitor. Clin Infect Dis. 2004 Aug 1;39(3):295-9.
- 1696. Mohan N, Edwards ET, Cupps TR, et al. Demyelination occurring during anti-tumor necrosis factor alpha therapy for inflammatory arthritides. Arthritis Rheum. 2001 Dec;44(12):2862-9.
- 1697. Mohyuddin T, Elyan M, Kushner I. Pericarditis: a rare complication of methotrexate therapy. Clin Rheumatol. 2007 Dec;26(12):2157-8.
- 1698. Mok CC, Lau CS, Wong RW. Clinical characteristics, treatment, and outcome of adult onset Still's disease in southern Chinese. J Rheumatol. 1998
 Dec;25(12):2345-51.
- 1699. Mok MY, Lo Y, Leung PY, et al. Pregnancy outcome in patients with adult onset Still's disease. J Rheumatol. 2004
 Nov;31(11):2307-9.
- 1700. Mok MY, Wong SY, Chan TM, et al. Necrotizing fasciitis in rheumatic diseases. Lupus. 2006;15(6):380-3.
- 1701. Molenaar ET, Bultink IE, Dijkmans BA, et al. Development of fatal tuberculosis in a patient with rheumatoid arthritis after three years of treatment with infliximab: comment on the article by Wolfe et al. Arthritis Rheum. 2005 Apr;52(4):1334-6.
- 1702. Moller B, Kukoc-Zivojnov N, Koyama N, et al. Prednisolone induces interleukin-18 expression in mononuclear blood and myeloid progenitor cells. Inflamm Res. 2002 Sep;51(9):457-63.

- 1703. Molloy E, Ramakrishnan S, Murphy E, et al. Morbidity and mortality in rheumatoid patients during treatment with adalimumab and infliximab. Rheumatology (Oxford). 2004 Apr;43(4):522-3.
- 1704. Momeni M, Mehta AP, Katz JD. Anti-tumor necrosis factor therapy is tolerated in an individual with homozygous complement C2 deficiency. J Clin Rheumatol. 2005 Jun;11(3):180-2.
- 1705. Montagna GL, Malesci D, Buono R, et al. Asthenoazoospermia in patients receiving anti-tumour necrosis factor {alpha} agents. Ann Rheum Dis. 2005 Nov;64(11):1667.
- 1706. Montecucco C, Caporali R, Caprotti P, et al. Sex hormones and bone metabolism in postmenopausal rheumatoid arthritis treated with two different glucocorticoids. J Rheumatol. 1992 Dec;19(12):1895-900.
- 1707. Montero JA, Ruiz-Moreno JM, Rodriguez AE, et al. Endogenous endophthalmitis by Propionibacterium acnes associated with leflunomide and adalimumab therapy. Eur J Ophthalmol. 2006 Mar-Apr;16(2):343-5.
- 1708. Moore A, Phillips C, Hunsche E, et al. Economic evaluation of etoricoxib versus non-selective NSAIDs in the treatment of osteoarthritis and rheumatoid arthritis patients in the UK. Pharmacoeconomics. 2004;22(10):643-60.
- 1709. Moore J, Ma D, Will R, et al. A phase II study of Rituximab in rheumatoid arthritis patients with recurrent disease following haematopoietic stem cell transplantation. Bone Marrow Transplant. 2004 Aug;34(3):241-7.
- 1710. Mor A, Bingham C, 3rd, Barisoni L, et al. Proliferative lupus nephritis and leukocytoclastic vasculitis during treatment with etanercept. J Rheumatol. 2005 Apr;32(4):740-3.
- 1711. Mor A, Bingham CO, 3rd, Kishimoto M, et al. Methotrexate combined with isoniazid treatment for latent tuberculosis is well tolerated in patients with rheumatoid arthritis: experience from an urban arthritis clinic. Ann Rheum Dis. 2008

 Apr;67(4):462-5.

- 1712. Morand EF, Jefferiss CM, Dixey J, et al. Impaired glucocorticoid induction of mononuclear leukocyte lipocortin-1 in rheumatoid arthritis. Arthritis Rheum. 1994 Feb;37(2):207-11.
- 1713. Moreland LW. Inhibitors of tumor necrosis factor: new treatment options for rheumatoid arthritis. Cleve Clin J Med. 1999
 Jun;66(6):367-74.
- 1714. Moreland LW, Alten R, Van den Bosch F, et al. Costimulatory blockade in patients with rheumatoid arthritis: a pilot, dose-finding, double-blind, placebo-controlled clinical trial evaluating CTLA-4Ig and LEA29Y eighty-five days after the first infusion.

 Arthritis Rheum. 2002 Jun;46(6):1470-9.
- 1715. Moreland LW, Bucy RP, Weinblatt ME, et al. Immune function in patients with rheumatoid arthritis treated with etanercept. Clin Immunol. 2002 Apr;103(1):13-21.
- 1716. Moreland LW, Cohen SB, Baumgartner SW, et al. Long-term safety and efficacy of etanercept in patients with rheumatoid arthritis. J Rheumatol. 2001 Jun;28(6):1238-
- 1717. Moreland LW, Schiff MH, Baumgartner SW, et al. Etanercept therapy in rheumatoid arthritis. A randomized, controlled trial. Ann Intern Med. 1999 Mar 16;130(6):478-86.
- 1718. Morelli S, Sgreccia A, Bernardo ML, et al. Primary aspergillosis of the larynx in a patient with Felty's syndrome. Clin Exp Rheumatol. 2000 Jul-Aug;18(4):523-4.
- 1719. Mori K, Iijima M, Koike H, et al. The wide spectrum of clinical manifestations in Sjogren's syndrome-associated neuropathy. Brain. 2005 Nov;128(Pt 11):2518-34.
- 1720. Mori S. A relationship between pharmacokinetics (PK) and the efficacy of infliximab for patients with rheumatoid arthritis: characterization of infliximabresistant cases and PK-based modified therapy. Mod Rheumatol. 2007;17(2):83-91.
- 1721. Mori S, Cho I, Ichiyasu H, et al.
 Asymptomatic carriage of Pneumocystis
 jiroveci in elderly patients with rheumatoid

- arthritis in Japan: a possible association between colonization and development of Pneumocystis jiroveci pneumonia during low-dose MTX therapy. Mod Rheumatol. 2008;18(3):240-6.
- 1722. Mori S, Cho I, Sugimoto M. A followup study of asymptomatic carriers of Pneumocystis jiroveci during immunosuppressive therapy for rheumatoid arthritis. J Rheumatol. 2009
 Aug;36(8):1600-5.
- 1723. Mori S, Ebihara K. A sudden onset of diabetic ketoacidosis and acute pancreatitis after introduction of mizoribine therapy in a patient with rheumatoid arthritis. Mod Rheumatol. 2008;18(6):634-8.
- 1724. Mori S, Imamura F, Kiyofuji C, et al. Pneumocystis jiroveci pneumonia in a patient with rheumatoid arthritis as a complication of treatment with infliximab, anti-tumor necrosis factor alpha neutralizing antibody. Mod Rheumatol. 2006;16(1):58-62.
- 1725. Mori S, Imamura F, Kiyofuji C, et al. Development of interstitial pneumonia in a rheumatoid arthritis patient treated with infliximab, an anti-tumor necrosis factor alpha-neutralizing antibody. Mod Rheumatol. 2006;16(4):251-5.
- 1726. Mori S, Koga Y, Imamura F, et al. Early rheumatoid arthritis in a patient with Sjogren's syndrome and pulmonary nodular amyloidosis: clinical implication of early limited use of infliximab. Mod Rheumatol. 2007;17(6):500-6.
- 1727. Mori S, Tomita Y, Horikawa T, et al. Delayed spinal infection after laminectomy in a patient with rheumatoid arthritis interruptedly exposed to anti-tumor necrosis factor alpha agents. Clin Rheumatol. 2008 Jul;27(7):937-9.
- 1728. Morita Y, Fukazawa T, Hirashima M, et al. The effect of methotrexate (MTX) on expression of signalling lymphocytic activation molecule (SLAM) in patients with rheumatoid arthritis (RA) and its role in the regulation of cytokine production. Scand J Rheumatol. 2006 Jul-Aug;35(4):268-72.

- 1729. Morita Y, Sasae Y, Sakuta T, et al. Efficacy of low-dose tacrolimus added to methotrexate in patients with rheumatoid arthritis in Japan: a retrospective study. Mod Rheumatol. 2008;18(4):379-84.
- 1730. Morozzi G, Fabbroni M, Bellisai F, et al. Low serum level of COMP, a cartilage turnover marker, predicts rapid and high ACR70 response to adalimumab therapy in rheumatoid arthritis. Clin Rheumatol. 2007 Aug;26(8):1335-8.
- 1731. Morrison E, Crosbie D, Capell HA. Attitude of rheumatoid arthritis patients to treatment with oral corticosteroids. Rheumatology (Oxford). 2003 Oct;42(10):1247-50.
- 1732. Moszyk DJ, Sulit DJ. Rheumatoid arthritis in a military aviator. Aviat Space Environ Med. 2007 Jan;78(1):63-6.
- 1733. Motivala SJ, Khanna D, FitzGerald J, et al. Stress activation of cellular markers of inflammation in rheumatoid arthritis: protective effects of tumor necrosis factor alpha antagonists. Arthritis Rheum. 2008 Feb;58(2):376-83.
- 1734. Mourao AF, Rustin M, Isenberg D. Exacerbation of psoriatic skin lesions in patients with psoriatic arthritis receiving anti-tumour necrosis factor-alpha therapy: description of 3 cases and review of the literature. Clin Exp Rheumatol. 2010 May-Jun;28(3):408-10.
- 1735. Mrabet D, Meddeb N, Ajlani H, et al. Cerebral vasculitis in a patient with rheumatoid arthritis. Joint Bone Spine. 2007 Mar;74(2):201-4.
- 1736. Mufti AH, Toye BW, McKendry RR, et al. Mycobacterium abscessus infection after use of tumor necrosis factor alpha inhibitor therapy: case report and review of infectious complications associated with tumor necrosis factor alpha inhibitor use. Diagn Microbiol Infect Dis. 2005 Nov;53(3):233-8.
- 1737. Mugnier B, Balandraud N, Darque A, et al. Polymorphism at position -308 of the tumor necrosis factor alpha gene influences outcome of infliximab therapy in rheumatoid arthritis. Arthritis Rheum. 2003 Jul;48(7):1849-52.

- 1738. Mulherin D, Sheeran TP. Clinical image: hidden costs of anti-tumor necrosis factor alpha therapy. Arthritis Rheum. 2003 Mar;48(3):868.
- 1739. Mullan RH, Bresnihan B. Disease-modifying anti-rheumatic drug therapy and structural damage in early rheumatoid arthritis. Clin Exp Rheumatol. 2003 Sep-Oct;21(5 Suppl 31):S158-64.
- 1740. Muller K, Zak M, Nielsen S, et al.
 Interleukin-1 receptor antagonist in
 neonates, children and adults, and in patients
 with pauci- and polyarticular onset juvenile
 chronic arthritis. Clin Exp Rheumatol. 1997
 Jul-Aug;15(4):439-44.
- 1741. Muntinghe FL, de Filippi JP, Breedveld RW, et al. A young woman with fever and a pericardial effusion. Neth J Med. 2002 Nov;60(10):414-5.
- 1742. Murata K, Yasuda T, Ito H, et al. Lack of increase in postoperative complications with low-dose methotrexate therapy in patients with rheumatoid arthritis undergoing elective orthopedic surgery. Mod Rheumatol. 2006;16(1):14-9.
- 1743. Murphy FT, Enzenauer RJ, Battafarano DF, et al. Etanercept-associated injection-site reactions. Arch Dermatol. 2000 Apr;136(4):556-7.
- 1744. Murphy NG. Current concepts in the management of rheumatoid arthritis. Del Med J. 1992 Apr;64(4):257-64.
- 1745. Murray RP, Bourne MH, Fitzgerald RH, Jr. Metachronous infections in patients who have had more than one total joint arthroplasty. J Bone Joint Surg Am. 1991 Dec;73(10):1469-74.
- 1746. Musial J, Undas A, Celinska-Lowenhoff M. Polymyositis associated with infliximab treatment for rheumatoid arthritis. Rheumatology (Oxford). 2003

 Dec;42(12):1566-8.
- 1747. Muto S, Asano Y, Okazaki H, et al. Renal potassium wasting in distal renal tubular acidosis: role of aldosterone. Intern Med. 1992 Aug;31(8):1047-51.

- 1748. Mutsukura K, Nakamura H, Iwanaga N, et al. Successful treatment of a patient with primary Sjogren's syndrome complicated with pericarditis during pregnancy. Intern Med. 2007;46(14):1143-7.
- 1749. Muzaffer MA, Dayer JM, Feldman BM, et al. Differences in the profiles of circulating levels of soluble tumor necrosis factor receptors and interleukin 1 receptor antagonist reflect the heterogeneity of the subgroups of juvenile rheumatoid arthritis. J Rheumatol. 2002 May;29(5):1071-8.
- 1750. Myers WA, Najarian D, Gottlieb AB. Newonset, debilitating arthritis in psoriasis patients receiving efalizumab. J Dermatolog Treat. 2006;17(6):353-4.
- 1751. Mylona E, Golfinopoulou S, Samarkos M, et al. Acute hepatitis in adult Still's disease during corticosteroid treatment successfully treated with anakinra. Clin Rheumatol. 2008 May;27(5):659-61.
- 1752. Mylona E, Vadala C, Papadakos V, et al. Cutaneous polyarteritis nodosa in adult onset Still's disease. Eur J Dermatol. 2009 Nov-Dec;19(6):621-2.
- 1753. Nabae M, Inoue K, Ushiyama T, et al. Gene expressions of antiinflammatory mediators in THR retrieved interfacial membranes.

 Acta Orthop Scand. 1999 Apr;70(2):149-54.
- 1754. Nadarajah K, Pritchard C. Listeria monocytogenes septic arthritis in a patient treated with etanercept for rheumatoid arthritis. J Clin Rheumatol. 2005 Apr;11(2):120-2.
- 1755. Nadareishvili Z, Michaud K, Hallenbeck JM, et al. Cardiovascular, rheumatologic, and pharmacologic predictors of stroke in patients with rheumatoid arthritis: a nested, case-control study. Arthritis Rheum 2008;59(8):1090-6.
- 1756. Nagasawa H, Kameda H, Sekiguchi N, et al. Normalisation of physical function by infliximab in patients with RA: factors associated with normal physical function. Clin Exp Rheumatol. 2010 May-Jun;28(3):365-72.

- 1757. Nagashima M, Matsuoka T, Saitoh K, et al. Treatment continuation rate in relation to efficacy and toxicity in long-term therapy with low-dose methotrexate, sulfasalazine, and bucillamine in 1,358 Japanese patients with rheumatoid arthritis. Clin Exp Rheumatol 2006;24(3):260-7.
- 1758. Nair B, Raval G, Mehta P. TNF-alpha inhibitor etanercept and hematologic malignancies: report of a case and review of the literature. Am J Hematol. 2007
 Nov;82(11):1022-4.
- 1759. Nakahara H, Mima T, Yoshio-Hoshino N, et al. A case report of a patient with refractory adult-onset Still's disease who was successfully treated with tocilizumab over 6 years. Mod Rheumatol. 2009;19(1):69-72.
- 1760. Nakajima A, Inoue E, Tanaka E, et al.

 Mortality and cause of death in Japanese
 patients with rheumatoid arthritis based on a
 large observational cohort, IORRA. Scand J
 Rheumatol. 2010;39(5):360-7.
- 1761. Nakamura T, Higashi S, Tomoda K, et al. Efficacy of etanercept in patients with AA amyloidosis secondary to rheumatoid arthritis. Clin Exp Rheumatol. 2007 Jul-Aug;25(4):518-22.
- 1762. Nakashima C, Tanioka M, Takahashi K, et al. Diffuse large B-cell lymphoma in a patient with rheumatoid arthritis treated with infliximab and methotrexate. Clin Exp Dermatol. 2008 Jul;33(4):437-9.
- 1763. Nakashima Y, Kondo M, Harada H, et al. Clinical evaluation of tocilizumab for patients with active rheumatoid arthritis refractory to anti-TNF biologics: tocilizumab in combination with methotrexate. Mod Rheumatol. 2010 Aug;20(4):343-52.
- 1764. Nakelchik M, Mangino JE. Reactivation of histoplasmosis after treatment with infliximab. Am J Med. 2002 Jan;112(1):78.
- 1765. Nakou M, Katsikas G, Sidiropoulos P, et al. Rituximab therapy reduces activated B cells in both the peripheral blood and bone marrow of patients with rheumatoid arthritis: depletion of memory B cells

- correlates with clinical response. Arthritis Res Ther. 2009;11(4):R131.
- 1766. Nampei A, Hashimoto J, Koyanagi J, et al. Characteristics of fracture and related factors in patients with rheumatoid arthritis. Mod Rheumatol. 2008;18(2):170-6.
- 1767. Nanke Y, Kotake S, Yonemoto K, et al. Cricoarytenoid arthritis with rheumatoid arthritis and systemic lupus erythematosus. J Rheumatol. 2001 Mar;28(3):624-6.
- 1768. Naranjo A, Sokka T, Descalzo MA, et al. Cardiovascular disease in patients with rheumatoid arthritis: results from the QUEST-RA study. Arthritis Res Ther 2008;10(2):R30.
- 1769. Naredo E, Moller I, Cruz A, et al. Power Doppler ultrasonographic monitoring of response to anti-tumor necrosis factor therapy in patients with rheumatoid arthritis. Arthritis Rheum. 2008 Aug;58(8):2248-56.
- 1770. Narushima M, Suzuki H, Kasai T, et al. Pulmonary nocardiosis in a patient treated with corticosteroid therapy. Respirology. 2002 Mar;7(1):87-9.
- 1771. Narvaez J, Montala N, Busquets-Perez N, et al. Collagenous colitis and spondylarthropathy. Arthritis Rheum. 2006 Jun 15;55(3):507-12.
- 1772. Nash P, Thaci D, Behrens F, et al.
 Leflunomide improves psoriasis in patients with psoriatic arthritis: an in-depth analysis of data from the TOPAS study.
 Dermatology. 2006;212(3):238-49.
- 1773. Nast A, Reytan N, Rosumeck S, et al. Low prescription rate for systemic treatments in the management of severe psoriasis vulgaris and psoriatic arthritis in dermatological practices in Berlin and Brandenburg, Germany: results from a patient registry. J Eur Acad Dermatol Venereol. 2008

 Nov;22(11):1337-42.
- 1774. Natsuga K, Sawamura D, Homma E, et al. Amicrobial pustulosis associated with IgA nephropathy and Sjogren's syndrome. J Am Acad Dermatol. 2007 Sep;57(3):523-6.

- 1775. Nawata M, Saito K, Nakayamada S, et al. Discontinuation of infliximab in rheumatoid arthritis patients in clinical remission. Mod Rheumatol. 2008;18(5):460-4.
- 1776. Ndongo S, Lekpa FK, Ka MM, et al. Presentation and severity of rheumatoid arthritis at diagnosis in Senegal. Rheumatology (Oxford). 2009 Sep;48(9):1111-3.
- 1777. Neeck G, Federlin K, Graef V, et al. Adrenal secretion of cortisol in patients with rheumatoid arthritis. J Rheumatol. 1990 Jan;17(1):24-9.
- 1778. Neeman N, Aronson MD, Schulze JE, et al. Improving pregnancy counseling for women with rheumatoid arthritis taking methotrexate. Am J Med. 2009
 Nov;122(11):998-1000.
- 1779. Neff K, Stack J, Harney S, et al. The use of abatacept in debilitating cavitating lung disease associated with rheumatoid arthritis, bronchocentric granulomatosis and aspergillosis. Thorax. 2010 Jun;65(6):545-6.
- 1780. Neidel J, Schulze M, Lindschau J.
 Association between degree of bone-erosion and synovial fluid-levels of tumor necrosis factor alpha in the knee-joints of patients with rheumatoid arthritis. Inflamm Res. 1995 May;44(5):217-21.
- 1781. Nemoto Y, Taniguchi A, Kamioka M, et al. Epstein-Barr virus-infected subcutaneous panniculitis-like T-cell lymphoma associated with methotrexate treatment. Int J Hematol. 2010 Sep;92(2):364-8.
- 1782. Nerome Y, Imanaka H, Nonaka Y, et al. A case of planned pregnancy with an interruption in infliximab administration in a 27-year-old female patient with rheumatoid-factor-positive polyarthritis juvenile idiopathic arthritis which improved after restarting infliximab and methotrexate. Mod Rheumatol. 2008;18(2):189-92.
- 1783. Nesheiwat JP, Dillon K, McGlothan K, et al. An elderly man with rheumatoid arthritis and dyspnea. Chest. 2009 Apr;135(4):1090-3.

- 1784. Netea MG, Radstake T, Joosten LA, et al. Salmonella septicemia in rheumatoid arthritis patients receiving anti-tumor necrosis factor therapy: association with decreased interferon-gamma production and Toll-like receptor 4 expression. Arthritis Rheum. 2003 Jul;48(7):1853-7.
- 1785. Neustadt DH. Double blind evaluation of the long-term effects of etodolac versus ibuprofen in patients with rheumatoid arthritis. J Rheumatol Suppl. 1997 Feb:47:17-22.
- 1786. Newman DK, Isaacs JD, Watson PG, et al. Prevention of immune-mediated corneal graft destruction with the anti-lymphocyte monoclonal antibody, CAMPATH-1H. Eye. 1995;9 (Pt 5):564-9.
- 1787. Newton SM, Mackie SL, Martineau AR, et al. Reduction of chemokine secretion in response to mycobacteria in infliximabtreated patients. Clin Vaccine Immunol. 2008 Mar;15(3):506-12.
- 1788. Ng CM, Bruno R, Combs D, et al.
 Population pharmacokinetics of rituximab
 (anti-CD20 monoclonal antibody) in
 rheumatoid arthritis patients during a phase
 II clinical trial. J Clin Pharmacol. 2005
 Jul;45(7):792-801.
- 1789. Niemela RK, Hakala M. Primary Sjogren's syndrome with severe central nervous system disease. Semin Arthritis Rheum. 1999 Aug;29(1):4-13.
- 1790. Niemela RK, Hakala M, Huikuri HV, et al. Comprehensive study of autonomic function in a population with primary Sjogren's syndrome. No evidence of autonomic involvement. J Rheumatol. 2003

 Jan;30(1):74-9.
- 1791. Niewold TB, Gibofsky A. Concomitant interferon-alpha therapy and tumor necrosis factor alpha inhibition for rheumatoid arthritis and hepatitis C. Arthritis Rheum. 2006 Jul;54(7):2335-7.
- 1792. Niitsu N, Okamoto M, Nakamine H, et al. Clinicopathologic correlations of diffuse large B-cell lymphoma in rheumatoid arthritis patients treated with methotrexate. Cancer Sci. 2010 May;101(5):1309-13.

- 1793. Nikas SN, Alamanos Y, Voulgari PV, et al. Infliximab treatment in ankylosing spondylitis: an observational study. Ann Rheum Dis. 2005 Jun;64(6):940-2.
- 1794. Nikas SN, Temekonidis TI, Zikou AK, et al. Treatment of resistant rheumatoid arthritis by intra-articular infliximab injections: a pilot study. Ann Rheum Dis. 2004 Jan;63(1):102-3.
- 1795. Nikas SN, Voulgari PV, Alamanos Y, et al. Efficacy and safety of switching from infliximab to adalimumab: a comparative controlled study. Ann Rheum Dis. 2006 Feb;65(2):257-60.
- 1796. Nikas SN, Voulgari PV, Takalou IP, et al. Healing of psoriatic skin lesions, and improvement of psoriatic arthritis resistant to immunosuppressive drugs, after infliximab treatment. Ann Rheum Dis. 2005 Nov;64(11):1665-7.
- 1797. Nishida K, Okada Y, Nawata M, et al. Induction of hyperadiponectinemia following long-term treatment of patients with rheumatoid arthritis with infliximab (IFX), an anti-TNF-alpha antibody. Endocr J. 2008 Mar;55(1):213-6.
- 1798. Nishie W, Sawamura D, Iitoyo M, et al. Intravascular histiocytosis associated with rheumatoid arthritis. Dermatology. 2008;217(2):144-5.
- 1799. Nishimoto N, Hashimoto J, Miyasaka N, et al. Study of active controlled monotherapy used for rheumatoid arthritis, an IL-6 inhibitor (SAMURAI): evidence of clinical and radiographic benefit from an x ray reader-blinded randomised controlled trial of tocilizumab. Ann Rheum Dis 2007;66(9):1162-7.
- 1800. Nishimoto N, Miyasaka N, Yamamoto K, et al. Study of active controlled tocilizumab monotherapy for rheumatoid arthritis patients with an inadequate response to methotrexate (SATORI): significant reduction in disease activity and serum vascular endothelial growth factor by IL-6 receptor inhibition therapy. Mod Rheumatol 2009;19(1):12-9.

- 1801. Nishimoto N, Terao K, Mima T, et al. Mechanisms and pathologic significances in increase in serum interleukin-6 (IL-6) and soluble IL-6 receptor after administration of an anti-IL-6 receptor antibody, tocilizumab, in patients with rheumatoid arthritis and Castleman disease. Blood. 2008 Nov 15;112(10):3959-64.
- 1802. Nishimura H, Tachibana H, Makiura N, et al. Corticosteroid-responsive parkinsonism associated with primary Sjogren's syndrome. Clin Neurol Neurosurg. 1994
 Nov;96(4):327-31.
- 1803. Nissinen R, Leirisalo-Repo M, Peltomaa R, et al. Cytokine and chemokine receptor profile of peripheral blood mononuclear cells during treatment with infliximab in patients with active rheumatoid arthritis. Ann Rheum Dis. 2004 Jun;63(6):681-7.
- 1804. Niwa Y, Iio A, Niwa G, et al. Serum albumin metabolism in rheumatic diseases: relationship to corticosteroids and peptic ulcer. J Clin Lab Immunol. 1990 Jan;31(1):11-6.
- 1805. Nizam S, Johnstone A, Green M, et al. Necrotising scleritis and connective tissue disease--three cases and a review. Clin Rheumatol. 2009 Mar;28(3):339-41.
- 1806. Noguera-Pons R, Borras-Blasco J, Romero-Crespo I, et al. Optic neuritis with concurrent etanercept and isoniazid therapy. Ann Pharmacother. 2005 Dec;39(12):2131-5.
- 1807. Nonaka T, Nishisaka F, Fukuda K, et al. Relationship between bone mineral density and urine level of NTx in rheumatoid arthritis. J Bone Miner Metab. 2005;23(4):314-7.
- 1808. Novak S, Cikes N. Infliximab-induced lupus or rheumatoid arthritis (RA) overlapping with systemic lupus erythematosus (SLE) unmasked by infliximab. Clin Exp Rheumatol. 2004 Mar-Apr;22(2):268.
- 1809. Nozaki Y, Nagare Y, Hino S, et al.

 Therapeutic strategy and significance of serum rheumatoid factor in patients with rheumatoid arthritis during infliximab

- treatment. Nihon Rinsho Meneki Gakkai Kaishi. 2010;33(3):135-41.
- 1810. Nozaki Y, Nagare Y, Kinoshita K, et al. Successful treatment using tacrolimus plus corticosteroid in a patient with RA associated with MDS. Rheumatol Int. 2008 Mar;28(5):487-90.
- 1811. Nuijten MJ, Engelfriet P, Duijn K, et al. A cost-cost study comparing etanercept with infliximab in rheumatoid arthritis.

 Pharmacoeconomics. 2001;19(10):1051-64.
- 1812. Nuki G, Bresnihan B, Bear MB, et al. Long-term safety and maintenance of clinical improvement following treatment with anakinra (recombinant human interleukin-1 receptor antagonist) in patients with rheumatoid arthritis: extension phase of a randomized, double-blind, placebo-controlled trial. Arthritis Rheum. 2002 Nov;46(11):2838-46.
- 1813. Nunez-Cornejo C, Borras-Blasco J, Gracia-Perez A, et al. Septic shock and community-acquired pneumonia associated with etanercept therapy. Int J Clin Pharmacol Ther. 2008 Apr;46(4):193-7.
- 1814. Nyhall-Wahlin BM, Petersson IF, Nilsson JA, et al. High disease activity disability burden and smoking predict severe extraarticular manifestations in early rheumatoid arthritis. Rheumatology (Oxford). 2009 Apr;48(4):416-20.
- 1815. Oberstein EM, Kromo O, Tozman EC. Type I reaction of Hansen's disease with exposure to adalimumab: a case report. Arthritis Rheum. 2008 Jul 15;59(7):1040-3.
- 1816. Ochi S, Harigai M, Mizoguchi F, et al. Leflunomide-related acute interstitial pneumonia in two patients with rheumatoid arthritis: autopsy findings with a mosaic pattern of acute and organizing diffuse alveolar damage. Mod Rheumatol. 2006;16(5):316-20.
- 1817. Ochi S, Taniguchi K, Nagashima M. Leflunomide-induced polymyositis in a patient with rheumatoid arthritis. Mod Rheumatol. 2009;19(4):443-6.

- 1818. Ochiai T, Washio H, Shiraiwa H, et al. Psoriatic onycho-pachydermo-periostitis successfully treated with low-dose methotrexate. Med Sci Monit. 2006 Apr;12(4):CS27-30.
- 1819. O'Connor PA, Eustace S, O'Byrne J. Spinal cord injury following osteoporotic vertebral fracture: case report. Spine. 2002 Sep 15;27(18):E413-5.
- 1820. Oda S, Fujinaga H, Takahashi K. Infectious myositis involving the piriformis in a patient with rheumatoid arthritis. Mod Rheumatol. 2006;16(4):260-3.
- 1821. O'Dell J. Conventional DMARD options for patients with a suboptimal response to methotrexate. J Rheumatol Suppl. 2001 Jun;62:21-6.
- 1822. O'Dell JR, Petersen K, Leff R, et al. Etanercept in combination with sulfasalazine, hydroxychloroquine, or gold in the treatment of rheumatoid arthritis. J Rheumatol. 2006 Feb;33(2):213-8.
- 1823. Odessey E, Cohn A, Beaman K, et al. Invasive mucormycosis of the maxillary sinus: extensive destruction with an indolent presentation. Surg Infect (Larchmt). 2008 Feb;9(1):91-8.
- 1824. Oei HB, Hooker RS, Cipher DJ, et al. High rates of stopping or switching biological medications in veterans with rheumatoid arthritis. Clin Exp Rheumatol 2009;27(6):926-34.
- 1825. Oelzner P, Schwabe A, Lehmann G, et al. Significance of risk factors for osteoporosis is dependent on gender and menopause in rheumatoid arthritis. Rheumatol Int. 2008 Sep;28(11):1143-50.
- 1826. Ogawa H, Itokazu M, Ito Y, et al. Quality of life evaluated by Short Form-8 in patients with rheumatoid arthritis who were receiving infusion of infliximab. Mod Rheumatol. 2009;19(1):27-32.
- 1827. Ogiwara Y, Mochizuki H, Morioka T, et al. A case with life-threatening interstitial pneumonia associated with bucillamine

- treatment. Mod Rheumatol. 2008;18(5):522-5.
- 1828. Oguz FM, Oguz A, Uzunlulu M. The effect of infliximab treatment on insulin resistance in patients with rheumatoid arthritis. Acta Clin Belg. 2007 Jul-Aug;62(4):218-22.
- 1829. Oh J, Arkfeld DG, Horwitz DA.
 Development of Crohn's disease in a patient taking etanercept. J Rheumatol. 2005
 Apr;32(4):752-3.
- 1830. Oh WM, Hwang IN, Son HH, et al. Rapid periapical bone destruction during endodontic treatment of a patient with rheumatoid arthritis. J Endod. 2008 Oct;34(10):1261-3.
- 1831. Ohshima S, Mima T, Sasai M, et al. Tumour necrosis factor alpha (TNF-alpha) interferes with Fas-mediated apoptotic cell death on rheumatoid arthritis (RA) synovial cells: a possible mechanism of rheumatoid synovial hyperplasia and a clinical benefit of anti-TNF-alpha therapy for RA. Cytokine. 2000 Mar;12(3):281-8.
- 1832. Ohsugi Y, Kishimoto T. The recombinant humanized anti-IL-6 receptor antibody tocilizumab, an innovative drug for the treatment of rheumatoid arthritis. Expert Opin Biol Ther. 2008 May;8(5):669-81.
- 1833. Oili KS, Niinisalo H, Korpilahde T, et al. Treatment of reactive arthritis with infliximab. Scand J Rheumatol. 2003;32(2):122-4.
- 1834. Okamoto H, Koizumi K, Kamitsuji S, et al. Beneficial action of statins in patients with rheumatoid arthritis in a large observational cohort. J Rheumatol. 2007 May;34(5):964-8.
- 1835. Okamoto O, Oishi M, Fujiwara S. Steroidresistant adult-onset Still's disease which showed a quick response to methotrexate. J Dermatol. 2008 Feb;35(2):106-10.
- 1836. Okuda Y, Takasugi K. Successful use of a humanized anti-interleukin-6 receptor antibody, tocilizumab, to treat amyloid A amyloidosis complicating juvenile idiopathic arthritis. Arthritis Rheum. 2006 Sep;54(9):2997-3000.

- 1837. Okuda Y, Takasugi K, Oyama T, et al. Intractable diarrhoea associated with secondary amyloidosis in rheumatoid arthritis. Ann Rheum Dis. 1997 Sep;56(9):535-41.
- 1838. Olewicz-Gawlik A, Korczowska-Lacka I, Lacki JK, et al. Fucosylation of serum alpha1-acid glycoprotein in rheumatoid arthritis patients treated with infliximab. Clin Rheumatol. 2007 Oct;26(10):1679-84.
- 1839. Olive A, del Blanco J, Pons M, et al. The clinical spectrum of remitting seronegative symmetrical synovitis with pitting edema.

 The Catalan Group for the Study of RS3PE.

 J Rheumatol. 1997 Feb;24(2):333-6.
- 1840. Oliveira B, Arkfeld DG, Weitz IC, et al. Successful rituximab therapy of acquired factor VIII inhibitor in a patient with rheumatoid arthritis. J Clin Rheumatol. 2007 Apr;13(2):89-91.
- 1841. Olivieri I, de Portu S, Salvarani C, et al. The psoriatic arthritis cost evaluation study: a cost-of-illness study on tumour necrosis factor inhibitors in psoriatic arthritis patients with inadequate response to conventional therapy. Rheumatology (Oxford). 2008 Nov;47(11):1664-70.
- 1842. Olivieri I, de Stefano G, Padula A, et al. Infliximab in a case of early adult-onset Still's disease. Clin Rheumatol. 2003 Oct;22(4-5):369-70.
- 1843. Olivieri I, Palazzi C, Peruz G, et al. Management issues with elderly-onset rheumatoid arthritis: an update. Drugs Aging. 2005;22(10):809-22.
- 1844. Ollendorf DA, Massarotti E, Birbara C, et al. Frequency, predictors, and economic impact of upward dose adjustment of infliximab in managed care patients with rheumatoid arthritis. J Manag Care Pharm. 2005 Jun;11(5):383-93.
- 1845. Ollendorf DA, Peterson AN, Doyle J, et al. Impact of leflunomide versus biologic agents on the costs of care for rheumatoid arthritis in a managed care population. Am J Manag Care. 2002 May;8(7 Suppl):S203-13.

- 1846. Omdal R, Gunnarsson R. The effect of interleukin-1 blockade on fatigue in rheumatoid arthritis--a pilot study.
 Rheumatol Int. 2005 Aug;25(6):481-4.
- 1847. Ongaro A, De Mattei M, Pellati A, et al. Can tumor necrosis factor receptor II gene 676T>G polymorphism predict the response grading to anti-TNFalpha therapy in rheumatoid arthritis? Rheumatol Int. 2008 Jul;28(9):901-8.
- 1848. Onuma S, Yamaji K, Kempe K, et al. Investigation of the clinical effect of large volume leukocytapheresis on methotrexateresistant rheumatoid arthritis. Ther Apher Dial. 2006 Oct;10(5):404-11.
- 1849. Ooi KG, Wingate R, Adler PA. Necrotising anterior scleritis in a late-onset rheumatoid arthritis (LORA) patient. Ocul Immunol Inflamm. 2007 Jan-Feb;15(1):33-6.
- 1850. Oren S, Mandelboim M, Braun-Moscovici Y, et al. Vaccination against influenza in patients with rheumatoid arthritis: the effect of rituximab on the humoral response. Ann Rheum Dis. 2008 Jul;67(7):937-41.
- 1851. Ornetti P, Solau E, Gaudin P, et al. Increase in methotrexate dose in patients with rheumatoid arthritis who have an inadequate response to infliximab. Ann Rheum Dis. 2005 Sep;64(9):1379-80.
- 1852. Orstavik RE, Haugeberg G, Mowinckel P, et al. Vertebral deformities in rheumatoid arthritis: a comparison with population-based controls. Arch Intern Med. 2004 Feb 23;164(4):420-5.
- 1853. Orstavik RE, Haugeberg G, Uhlig T, et al. Vertebral deformities in 229 female patients with rheumatoid arthritis: associations with clinical variables and bone mineral density. Arthritis Rheum. 2003 Jun 15;49(3):355-60.
- 1854. Orstavik RE, Haugeberg G, Uhlig T, et al. Incidence of vertebral deformities in 255 female rheumatoid arthritis patients measured by morphometric X-ray absorptiometry. Osteoporos Int. 2005 Jan;16(1):35-42.

- 1855. Orstavik RE, Haugeberg G, Uhlig T, et al. Quantitative ultrasound and bone mineral density: discriminatory ability in patients with rheumatoid arthritis and controls with and without vertebral deformities. Ann Rheum Dis. 2004 Aug;63(8):945-51.
- 1856. Ortiz-Santamaria V, Valls-Roc M, Sanmarti M, et al. Anti-TNF treatment in secondary amyloidosis. Rheumatology (Oxford). 2003 Nov;42(11):1425-6.
- 1857. Osawa H, Yamabe H, Seino S, et al. A case of Sjogren's syndrome associated with Sweet's syndrome. Clin Rheumatol. 1997 Jan;16(1):101-5.
- 1858. Ostanek L, Pawlik A, Brzosko I, et al. The urinary excretion of pyridinoline and deoxypyridinoline during rheumatoid arthritis therapy with infliximab. Clin Rheumatol. 2004 Jun;23(3):214-7.
- 1859. Ostensen M, Eigenmann GO. Etanercept in breast milk. J Rheumatol. 2004 May;31(5):1017-8.
- 1860. Ostensen M, Forger F. Management of RA medications in pregnant patients. Nat Rev Rheumatol. 2009 Jul;5(7):382-90.
- 1861. Ostensen M, Raio L. A woman with rheumatoid arthritis whose condition did not improve during pregnancy. Nat Clin Pract Rheumatol. 2005 Dec;1(2):111-4; quiz 1 p following 4.
- 1862. Ostergaard M, Duer A, Nielsen H, et al. Magnetic resonance imaging for accelerated assessment of drug effect and prediction of subsequent radiographic progression in rheumatoid arthritis: a study of patients receiving combined anakinra and methotrexate treatment. Ann Rheum Dis. 2005 Oct;64(10):1503-6.
- 1863. Ostor AJ, Crisp AJ, Somerville MF, et al. Fatal exacerbation of rheumatoid arthritis associated fibrosing alveolitis in patients given infliximab. BMJ. 2004 Nov 27;329(7477):1266.
- 1864. Ostrov BE. Beneficial effect of etanercept on rheumatoid lymphedema. Arthritis Rheum. 2001 Jan;44(1):240-1.

- 1865. Ostuni P, Botsios C, Punzi L, et al. Hepatitis B reactivation in a chronic hepatitis B surface antigen carrier with rheumatoid arthritis treated with infliximab and low dose methotrexate. Ann Rheum Dis. 2003 Jul;62(7):686-7.
- 1866. O'Sullivan MM, Amos N, Bedwell A, et al. Complement-mediated inhibition of immune precipitation in rheumatoid vasculitis. Rheumatol Int. 1990;10(4):159-63.
- 1867. Otabe S, Muto S, Asano Y, et al. Selective hypoaldosteronism in a patient with Sjogren's syndrome: insensitivity to angiotensin II. Nephron. 1991;59(3):466-70.
- 1868. Otsuka T, Koyama T, Ohtani R, et al.
 Leflunomide-induced lung injury that
 developed after its withdrawal, coinciding
 with peripheral blood lymphocyte count
 decrease. Mod Rheumatol. 2008;18(1):96-9.
- 1869. Ott SJ, Baron A, Berghaus T, et al. Liver failure in adult Still's disease during corticosteroid treatment. Eur J Gastroenterol Hepatol. 2003 Jan;15(1):87-90.
- 1870. Ouedraogo DD, Palazzo E, Nlome-Nze M, et al. Predominant cervical involvement in patients with psoriatic arthritis: report of two cases. Joint Bone Spine. 2007

 Mar;74(2):175-8.
- 1871. Owino BO, Oyoo GO, Otieno CF. Sociodemographic and clinical aspects of rheumatoid arthritis. East Afr Med J. 2009 May;86(5):204-11.
- 1872. Ozaki D, Shirai Y, Nakayama Y, et al. A case report of insufficiency fracture of the Fossa acetabuli in a patient with rheumatoid arthritis. J Nippon Med Sch. 2000 Aug;67(4):267-70.
- 1873. Ozgocmen S, Godekmerdan A, Ozkurt-Zengin F. Acute-phase response, clinical measures and disease activity in ankylosing spondylitis. Joint Bone Spine. 2007 May;74(3):249-53.
- 1874. Ozgocmen S, Ozdemir H, Kiris A, et al.
 Clinical evaluation and power Doppler
 sonography in rheumatoid arthritis: evidence
 for ongoing synovial inflammation in

- clinical remission. South Med J. 2008 Mar;101(3):240-5.
- 1875. Pace J, Adami JZ, Mallia C, et al. Toxic epidermal necrolysis in a patient with psoriatic arthritis. Adv Exp Med Biol. 1999;455:557-60.
- 1876. Pachot A, Arnaud B, Marrote H, et al. Increased tumor necrosis factor-alpha mRNA expression in whole blood from patients with rheumatoid arthritis: reduction after infliximab treatment does not predict response. J Rheumatol. 2007
 Nov;34(11):2158-61.
- 1877. Padyukov L, Lampa J, Heimburger M, et al. Genetic markers for the efficacy of tumour necrosis factor blocking therapy in rheumatoid arthritis. Ann Rheum Dis. 2003 Jun;62(6):526-9.
- 1878. Pagliano P, Attanasio V, Fusco U, et al. Does etanercept monotherapy enhance the risk of Listeria monocytogenes meningitis? Ann Rheum Dis. 2004 Apr;63(4):462-3.
- 1879. Paira S, Caliani L, Luraquiz N. Distal extremity swelling with pitting oedema in rheumatoid arthritis. Clin Rheumatol. 2001;20(1):76-9.
- 1880. Palanichamy A, Roll P, Theiss R, et al. Modulation of molecular imprints in the antigen-experienced B cell repertoire by rituximab. Arthritis Rheum. 2008 Dec;58(12):3665-74.
- 1881. Palazzi C, D'Amico E, Pennese E, et al. Purpura and serum mixed cryoglobulinemia in psoriatic arthritis. Rheumatol Int. 2006 Dec;27(2):187-9.
- 1882. Palkonyai E, Kolarz G, Kopp M, et al. Depressive symptoms in early rheumatoid arthritis: a comparative longitudinal study. Clin Rheumatol. 2007 May;26(5):753-8.
- 1883. Pallinti V, Ganesan N, Anbazhagan M, et al. Serum biochemical markers in rheumatoid arthritis. Indian J Biochem Biophys. 2009 Aug;46(4):342-4.
- 1884. Pallotta P, Cianchini G, Ruffelli M, et al. Infliximab-induced lupus-like reaction in a

- patient with psoriatic arthritis. Rheumatology (Oxford). 2006 Jan;45(1):116-7.
- 1885. Palm S, Hinrichsen H, Barth J, et al. Modulation of lymphocyte subsets due to psychological stress in patients with rheumatoid arthritis. Eur J Clin Invest. 1992 Oct;22 Suppl 1:26-9.
- 1886. Pamuk ON, Harmandar F. A case of cervical spine meningioma following etanercept use in a patient with RA. Nat Rev Rheumatol. 2009 Aug;5(8):457-60.
- 1887. Pamuk ON, Harmandar F, Cakir N. The development of trigeminal neuralgia related to auricular chondritis in a patient with rheumatoid arthritis-relapsing polychondritis and its treatment with etanercept.

 Description of the first case. Clin Exp Rheumatol. 2009 Jan-Feb;27(1):128-9.
- 1888. Pan SM, Dehler S, Ciurea A, et al.
 Comparison of drug retention rates and
 causes of drug discontinuation between antitumor necrosis factor agents in rheumatoid
 arthritis. Arthritis Rheum 2009;61(5):560-8.
- 1889. Panfilio CB, Hernandez-Cossio O, Hernandez-Fustes OJ. Orbital myositis and rheumatoid arthritis: case report. Arq Neuropsiquiatr. 2000 Mar;58(1):174-7.
- 1890. Panoulas VF, Douglas KM, Stavropoulos-Kalinoglou A, et al. Long-term exposure to medium-dose glucocorticoid therapy associates with hypertension in patients with rheumatoid arthritis. Rheumatology (Oxford). 2008 Jan;47(1):72-5.
- 1891. Panthakalam S, Bhatnagar D, Klimiuk P. The prevalence and management of hyperglycaemia in patients with rheumatoid arthritis on corticosteroid therapy. Scott Med J. 2004 Nov;49(4):139-41.
- 1892. Papadaki HA, Kritikos HD, Valatas V, et al. Anemia of chronic disease in rheumatoid arthritis is associated with increased apoptosis of bone marrow erythroid cells: improvement following anti-tumor necrosis factor-alpha antibody therapy. Blood. 2002 Jul 15;100(2):474-82.

- 1893. Papadopoulos IA, Katsimbri P, Alamanos Y, et al. Early rheumatoid arthritis patients: relationship of age. Rheumatol Int. 2003 Mar;23(2):70-4.
- 1894. Papageorgiou SG, Kontaxis T, Bonakis A, et al. Orofacial dystonia related to Sjogren's syndrome. Clin Rheumatol. 2007
 Oct;26(10):1779-81.
- 1895. Papagoras CE, Argyropoulou MI, Voulgari PV, et al. A case of Brucella spondylitis in a patient with psoriatic arthritis receiving infliximab. Clin Exp Rheumatol. 2009 Jan-Feb;27(1):124-7.
- 1896. Papanikolaou IC, Sharma OP. A 47-year-old woman with rheumatoid arthritis and dyspnea on exertion. Chest. 2009
 Dec;136(6):1694-7.
- 1897. Papoutsaki M, Chimenti MS, Costanzo A, et al. Adalimumab for severe psoriasis and psoriatic arthritis: an open-label study in 30 patients previously treated with other biologics. J Am Acad Dermatol. 2007 Aug;57(2):269-75.
- 1898. Parambil JG, Myers JL, Lindell RM, et al. Interstitial lung disease in primary Sjogren syndrome. Chest. 2006 Nov;130(5):1489-95.
- 1899. Parambil JG, Yi ES, Ryu JH. Obstructive bronchiolar disease identified by CT in the non-transplant population: analysis of 29 consecutive cases. Respirology. 2009 Apr;14(3):443-8.
- 1900. Park IN, Kim DS, Shim TS, et al. Acute exacerbation of interstitial pneumonia other than idiopathic pulmonary fibrosis. Chest. 2007 Jul;132(1):214-20.
- 1901. Park JH, Seo GY, Lee JS, et al. Positive conversion of tuberculin skin test and performance of interferon release assay to detect hidden tuberculosis infection during anti-tumor necrosis factor agent trial. J Rheumatol. 2009 Oct;36(10):2158-63.
- 1902. Park MC, Chung SJ, Park YB, et al.
 Relationship of serum TWEAK level to
 cytokine level, disease activity, and response
 to anti-TNF treatment in patients with

- rheumatoid arthritis. Scand J Rheumatol. 2008 May-Jun;37(3):173-8.
- 1903. Park SH, Kim CG, Kim JY, et al.
 Spontaneous regression of EBV-associated diffuse lymphoproliferative disease in a patient with rheumatoid arthritis after discontinuation of etanercept treatment.
 Rheumatol Int. 2008 Mar;28(5):475-7.
- 1904. Park YB, Ahn CW, Choi HK, et al. Atherosclerosis in rheumatoid arthritis: morphologic evidence obtained by carotid ultrasound. Arthritis Rheum. 2002
 Jul;46(7):1714-9.
- 1905. Park YB, Choi HK, Kim MY, et al. Effects of antirheumatic therapy on serum lipid levels in patients with rheumatoid arthritis: a prospective study. Am J Med. 2002 Aug 15;113(3):188-93.
- 1906. Park YB, Lee SK, Lee WK, et al. Lipid profiles in untreated patients with rheumatoid arthritis. J Rheumatol. 1999 Aug;26(8):1701-4.
- 1907. Parke FA, Reveille JD. Anti-tumor necrosis factor agents for rheumatoid arthritis in the setting of chronic hepatitis C infection.

 Arthritis Rheum. 2004 Oct 15;51(5):800-4.
- 1908. Parker A, Izmailova ES, Narang J, et al. Peripheral blood expression of nuclear factor-kappab-regulated genes is associated with rheumatoid arthritis disease activity and responds differentially to anti-tumor necrosis factor-alpha versus methotrexate. J Rheumatol. 2007 Sep;34(9):1817-22.
- 1909. Parker SR, Solomon AR, Lane JE. A report of Epstein-Barr virus-positive primary cutaneous natural killer-/T-cell lymphoma. J Am Acad Dermatol. 2008 Jul;59(1):157-61.
- 1910. Paroli MP, Bruscolini A, De Carlo L, et al. Ring keratopathy in a patient with psoriatic arthritis and ulcerative rectocolitis. Ocul Immunol Inflamm. 2007 Jan-Feb;15(1):51-6.
- 1911. Parra Ruiz J, Ortego Centeno N, Raya Alvarez E. Development of tuberculosis in a patient treated with infliximab who had received prophylactic therapy with

- isoniazid. J Rheumatol. 2003 Jul;30(7):1657-8.
- 1912. Pasek M, Duk M, Podbielska M, et al. Galactosylation of IgG from rheumatoid arthritis (RA) patients--changes during therapy. Glycoconj J. 2006 Nov;23(7-8):463-71.
- 1913. Patel A, Kesler B, Wise RA. Persistent pneumomediastinum in interstitial fibrosis associated with rheumatoid arthritis: treatment with high-concentration oxygen. Chest. 2000 Jun;117(6):1809-13.
- 1914. Patel NK, Salathe C, Vu C, et al. Esophagitis dissecans: a rare cause of odynophagia. Endoscopy. 2007 Feb;39 Suppl 1:E127.
- 1915. Paulus HE, Di Primeo D, Sanda M, et al. Progression of radiographic joint erosion during low dose corticosteroid treatment of rheumatoid arthritis. J Rheumatol. 2000 Jul;27(7):1632-7.
- 1916. Paulus HE, Di Primeo D, Sharp JT, et al. Patient retention and hand-wrist radiograph progression of rheumatoid arthritis during a 3-year prospective study that prohibited disease modifying antirheumatic drugs. J Rheumatol. 2004 Mar;31(3):470-81.
- 1917. Pavelka K, Gatterova J, Tegzova D, et al. Radiographic progression of rheumatoid arthritis in patients from the Czech National Registry receiving infliximab treatment. Clin Exp Rheumatol. 2007 Jul-Aug;25(4):540-5.
- 1918. Pavletic SZ, Klassen LW, Pope R, et al. Treatment of relapse after autologous blood stem cell transplantation for severe rheumatoid arthritis. J Rheumatol Suppl. 2001 Oct;64:28-31.
- 1919. Pavlica L, Peric-Hajzler Z, Jovelic A, et al. Psoriatic arthritis: a retrospective study of 162 patients. Vojnosanit Pregl. 2005 Sep;62(9):613-20.
- 1920. Pawlik A, Herczynska M, Kurzawski M, et al. The effect of exon (19C>A) dihydroorotate dehydrogenase gene polymorphism on rheumatoid arthritis

- treatment with leflunomide. Pharmacogenomics. 2009 Feb;10(2):303-9.
- 1921. Pawlik A, Herczynska M, Kurzawski M, et al. IL-1beta, IL-6, and TNF gene polymorphisms do not affect the treatment outcome of rheumatoid arthritis patients with leflunomide. Pharmacol Rep. 2009 Mar-Apr;61(2):281-7.
- 1922. Pawlik A, Ostanek L, Brzosko I, et al. Therapy with infliximab decreases the CD4+CD28- T cell compartment in peripheral blood in patients with rheumatoid arthritis. Rheumatol Int. 2004 Nov;24(6):351-4.
- 1923. Peddle L, Butt C, Snelgrove T, et al. Interleukin (IL) 1alpha, IL1beta, IL receptor antagonist, and IL10 polymorphisms in psoriatic arthritis. Ann Rheum Dis. 2005 Jul;64(7):1093-4.
- 1924. Pelivani N, Hassan AS, Braathen LR, et al. Alopecia areata universalis elicited during treatment with adalimumab. Dermatology. 2008;216(4):320-3.
- 1925. Penn SK, Kao AH, Schott LL, et al. Hydroxychloroquine and glycemia in women with rheumatoid arthritis and systemic lupus erythematosus. J Rheumatol. 2010 Jun;37(6):1136-42.
- 1926. Perdriger A, Mariette X, Kuntz JL, et al. Safety of infliximab used in combination with leflunomide or azathioprine in daily clinical practice. J Rheumatol. 2006 May;33(5):865-9.
- 1927. Perera LC, Tymms KE, Wilson BJ, et al. Etanercept in severe active rheumatoid arthritis: first Australian experience. Intern Med J. 2006 Oct;36(10):625-31.
- 1928. Perez-De-Lis M, Akasbi M, Siso A, et al. Cardiovascular risk factors in primary Sjogren's syndrome: a case-control study in 624 patients. Lupus. 2010;19(8):941-8.
- 1929. Perez-Ezquerra PR, de Barrio Fernandez M, de Castro Martinez FJ, et al. Delayed hypersensitivity to hydroxychloroquine manifested by two different types of cutaneous eruptions in the same patient.

- Allergol Immunopathol (Madr). 2006 Jul-Aug;34(4):174-5.
- 1930. Perez-Garcia C, Maymo J, Lisbona Perez MP, et al. Drug-induced systemic lupus erythematosus in ankylosing spondylitis associated with infliximab. Rheumatology (Oxford). 2006 Jan;45(1):114-6.
- 1931. Perez-Guijo VC, Cravo AR, Castro Mdel C, et al. Increased efficacy of infliximab associated with methotrexate in ankylosing spondylitis. Joint Bone Spine. 2007 May;74(3):254-8.
- 1932. Perhala RS, Wilke WS, Clough JD, et al. Local infectious complications following large joint replacement in rheumatoid arthritis patients treated with methotrexate versus those not treated with methotrexate. Arthritis Rheum. 1991 Feb;34(2):146-52.
- 1933. Peris P, Font J, Grau JM, et al. Calcitriol-mediated hypercalcaemia and increased interleukins in a patient with sarcoid myopathy. Clin Rheumatol. 1999;18(6):488-91.
- 1934. Perkins DJ, St Clair EW, Misukonis MA, et al. Reduction of NOS2 overexpression in rheumatoid arthritis patients treated with anti-tumor necrosis factor alpha monoclonal antibody (cA2). Arthritis Rheum. 1998 Dec;41(12):2205-10.
- 1935. Perlmutter A, Mittal A, Menter A.
 Tuberculosis and tumour necrosis factoralpha inhibitor therapy: a report of three cases in patients with psoriasis.
 Comprehensive screening and therapeutic guidelines for clinicians. Br J Dermatol. 2009 Jan;160(1):8-15.
- 1936. Perotti LA, Peretti L, Lovino C, et al.
 Concentration of cortisol in the synovial
 fluid of patients with untreated rheumatoid
 arthritis. Relation to in vitro IL-8 production
 by synovial mononuclear cells. Ann N Y
 Acad Sci. 1999 Jun 22;876:255-8.
- 1937. Perry MG, Kirwan JR, Jessop DS, et al. Overnight variations in cortisol, interleukin 6, tumour necrosis factor alpha and other cytokines in people with rheumatoid arthritis. Ann Rheum Dis. 2009

 Jan;68(1):63-8.

- 1938. Pers JO, Saraux A, Pierre R, et al. Anti-TNF-alpha immunotherapy is associated with increased gingival inflammation without clinical attachment loss in subjects with rheumatoid arthritis. J Periodontol. 2008 Sep;79(9):1645-51.
- 1939. Peters MJ, Vis M, van Halm VP, et al. Changes in lipid profile during infliximab and corticosteroid treatment in rheumatoid arthritis. Ann Rheum Dis. 2007
 Jul;66(7):958-61.
- 1940. Peterson JR, Hsu FC, Simkin PA, et al. Effect of tumour necrosis factor alpha antagonists on serum transaminases and viraemia in patients with rheumatoid arthritis and chronic hepatitis C infection.

 Ann Rheum Dis. 2003 Nov;62(11):1078-82.
- 1941. Peyrou J, Saxer-Sekulic N, Lerch R, et al. Fast progression of aortic stenosis in rheumatoid arthritis. Arch Cardiovasc Dis. 2009 Mar;102(3):251-2.
- 1942. Pfeil A, Lippold J, Eidner T, et al. Effects of leflunomide and methotrexate in rheumatoid arthritis detected by digital X-ray radiogrammetry and computer-aided joint space analysis. Rheumatol Int. 2009 Jan;29(3):287-95.
- 1943. Pflugfelder SC, Jones D, Ji Z, et al. Altered cytokine balance in the tear fluid and conjunctiva of patients with Sjogren's syndrome keratoconjunctivitis sicca. Curr Eye Res. 1999 Sep;19(3):201-11.
- 1944. Pham TN, Rahman P, Richardson VJ.
 Divergent effects of infliximab and anakinra therapies on macrophage phenotype from patients with refractory rheumatoid arthritis.
 Int J Immunopathol Pharmacol. 2010 Apr-Jun;23(2):491-501.
- 1945. Phillips K, Aliprantis A, Coblyn J. Strategies for the prevention and treatment of osteoporosis in patients with rheumatoid arthritis. Drugs Aging. 2006;23(10):773-9.
- 1946. Phillips K, Weinblatt M. Granulomatous lung disease occurring during etanercept treatment. Arthritis Rheum. 2005 Aug 15;53(4):618-20.

- 1947. Pickartz T, Pickartz H, Lochs H, et al.
 Overlap syndrome of autoimmune
 pancreatitis and cholangitis associated with
 secondary Sjogren's syndrome. Eur J
 Gastroenterol Hepatol. 2004
 Nov;16(12):1295-9.
- 1948. Pijpe J, Meijer JM, Bootsma H, et al. Clinical and histologic evidence of salivary gland restoration supports the efficacy of rituximab treatment in Sjogren's syndrome. Arthritis Rheum. 2009 Nov;60(11):3251-6.
- 1949. Pijpe J, van Imhoff GW, Spijkervet FK, et al. Rituximab treatment in patients with primary Sjogren's syndrome: an open-label phase II study. Arthritis Rheum. 2005 Sep;52(9):2740-50.
- 1950. Pijpe J, van Imhoff GW, Vissink A, et al. Changes in salivary gland immunohistology and function after rituximab monotherapy in a patient with Sjogren's syndrome and associated MALT lymphoma. Ann Rheum Dis. 2005 Jun;64(6):958-60.
- 1951. Pileggi GS, de Souza CB, Ferriani VP. Safety and immunogenicity of varicella vaccine in patients with juvenile rheumatic diseases receiving methotrexate and corticosteroids. Arthritis Care Res (Hoboken). 2010 Jul;62(7):1034-9.
- 1952. Pillemer SR, Brennan MT, Sankar V, et al. Pilot clinical trial of dehydroepiandrosterone (DHEA) versus placebo for Sjogren's syndrome. Arthritis Rheum. 2004 Aug 15;51(4):601-4.
- 1953. Pincus T, Ferraccioli G, Sokka T, et al. Evidence from clinical trials and long-term observational studies that disease-modifying anti-rheumatic drugs slow radiographic progression in rheumatoid arthritis: updating a 1983 review. Rheumatology (Oxford). 2002 Dec;41(12):1346-56.
- 1954. Pincus T, Olsen NJ, Russell IJ, et al. Multicenter study of recombinant human erythropoietin in correction of anemia in rheumatoid arthritis. Am J Med. 1990 Aug;89(2):161-8.
- 1955. Pincus T, Swearingen CJ, Bergman M, et al. RAPID3 (Routine Assessment of Patient Index Data 3), a rheumatoid arthritis index

- without formal joint counts for routine care: proposed severity categories compared to disease activity score and clinical disease activity index categories. J Rheumatol. 2008 Nov;35(11):2136-47.
- 1956. Pisitkun P, Pattarowas C, Siriwongpairat P, et al. Reappraisal of cervical spine subluxation in Thai patients with rheumatoid arthritis. Clin Rheumatol. 2004 Feb;23(1):14-8.
- 1957. Pitsillides AA, Will RK, Bayliss MT, et al. Circulating and synovial fluid hyaluronan levels. Effects of intraarticular corticosteroid on the concentration and the rate of turnover. Arthritis Rheum. 1994 Jul;37(7):1030-8.
- 1958. Pittoni V, Bombardieri M, Spinelli FR, et al. Anti-tumour necrosis factor (TNF) alpha treatment of rheumatoid arthritis (infliximab) selectively down regulates the production of interleukin (IL) 18 but not of IL12 and IL13. Ann Rheum Dis. 2002 Aug;61(8):723-5.
- 1959. Pizzuti P, Liote F, Cerf-Payrastre I, et al. Hypersensitivity to glucocorticoids: does it exist? Rev Rhum Engl Ed. 1996
 Mar;63(3):223-6.
- 1960. Plant MJ, Borg AA, Dziedzic K, et al. Radiographic patterns and response to corticosteroid hip injection. Ann Rheum Dis. 1997 Aug;56(8):476-80.
- 1961. Podgorski MR, Goulding NJ, Hall ND, et al. Autoantibodies to lipocortin-1 are associated with impaired glucocorticoid responsiveness in rheumatoid arthritis. J Rheumatol. 1992 Nov;19(11):1668-71.
- 1962. Pollet SM, Vogt PJ, Leek JC. Serous peritonitis in adult Still's syndrome. J Rheumatol. 1990 Jan;17(1):98-101.
- 1963. Polzer K, Baeten D, Soleiman A, et al. Tumour necrosis factor blockade increases lymphangiogenesis in murine and human arthritic joints. Ann Rheum Dis. 2008 Nov;67(11):1610-6.
- 1964. Pomerantz RG, Mody E, Husni ME, et al. Follow-up of psoriatic arthritis mutilans

- patients treated with anti-TNF-alpha therapy. J Drugs Dermatol. 2009 Apr;8(4):406-12.
- 1965. Pool AJ, Whipp BJ, Skasick AJ, et al. Serum cortisol reduction and abnormal prolactin and CD4+/CD8+ T-cell response as a result of controlled exercise in patients with rheumatoid arthritis and systemic lupus erythematosus despite unaltered muscle energetics. Rheumatology (Oxford). 2004 Jan;43(1):43-8.
- 1966. Poor G, Strand V. Efficacy and safety of leflunomide 10 mg versus 20 mg once daily in patients with active rheumatoid arthritis: multinational double-blind, randomized trial. Rheumatology (Oxford). 2004
 Jun;43(6):744-9.
- 1967. Popa C, Leandro MJ, Cambridge G, et al. Repeated B lymphocyte depletion with rituximab in rheumatoid arthritis over 7 yrs. Rheumatology (Oxford). 2007 Apr;46(4):626-30.
- 1968. Popa C, Netea MG, de Graaf J, et al.
 Circulating leptin and adiponectin
 concentrations during tumor necrosis factor
 blockade in patients with active rheumatoid
 arthritis. J Rheumatol. 2009 Apr;36(4):724-
- 1969. Popa C, Netea MG, Radstake TR, et al. Markers of inflammation are negatively correlated with serum leptin in rheumatoid arthritis. Ann Rheum Dis. 2005
 Aug;64(8):1195-8.
- 1970. Popa C, van den Hoogen FH, Radstake TR, et al. Modulation of lipoprotein plasma concentrations during long-term anti-TNF therapy in patients with active rheumatoid arthritis. Ann Rheum Dis. 2007
 Nov;66(11):1503-7.
- 1971. Popa C, van Tits LJ, Barrera P, et al. Antiinflammatory therapy with tumour necrosis factor alpha inhibitors improves highdensity lipoprotein cholesterol antioxidative capacity in rheumatoid arthritis patients. Ann Rheum Dis. 2009 Jun;68(6):868-72.
- 1972. Pope RM, Kniker WT, Talal N, et al. Delayed type hypersensitivity in patients

- with rheumatoid arthritis. J Rheumatol. 1993 Jan;20(1):17-20.
- 1973. Porola P, Laine M, Virtanen I, et al.
 Androgens and integrins in salivary glands in Sjogren's syndrome. J Rheumatol. 2010
 Jun;37(6):1181-7.
- 1974. Porola P, Virkki L, Przybyla BD, et al. Androgen deficiency and defective intracrine processing of dehydroepiandrosterone in salivary glands in Sjogren's syndrome. J Rheumatol. 2008 Nov;35(11):2229-35.
- 1975. Portales P, Fabre S, Vincent T, et al. Peripheral blood T4 cell surface CCR5 density as a marker of activity in rheumatoid arthritis treated with anti-CD20 monoclonal antibody. Immunology. 2009 Sep;128(1 Suppl):e738-45.
- 1976. Porterfield LM. Why has this patient developed sepsis? Rn. 1999 Aug;62(8):89.
- 1977. Porterfield LM. Rheumatoid arthritis patient's respiratory distress. Rn. 2009 Jan;72(1):21.
- 1978. Posten W, Swan J. Recurrence of alopecia areata in a patient receiving etanercept injections. Arch Dermatol. 2005
 Jun;141(6):759-60.
- 1979. Potter C, Cordell HJ, Barton A, et al. Association between anti-tumour necrosis factor treatment response and genetic variants within the TLR and NF{kappa}B signalling pathways. Ann Rheum Dis. 2010 Jul;69(7):1315-20.
- 1980. Potter C, Hyrich KL, Tracey A, et al.
 Association of rheumatoid factor and anticyclic citrullinated peptide positivity, but not carriage of shared epitope or PTPN22 susceptibility variants, with anti-tumour necrosis factor response in rheumatoid arthritis. Ann Rheum Dis 2009;68(1):69-74.
- 1981. Pou MA, Diaz-Torne C, Vidal S, et al.
 Development of autoimmune diseases after vaccination. J Clin Rheumatol. 2008
 Aug;14(4):243-4.

- 1982. Price-Forbes AN, Callaghan R, Allen ME, et al. A regional audit of the use of COX-2 selective non-steroidal anti-inflammatory drugs (NSAIDs) in rheumatology clinics in the West Midlands, in relation to NICE guidelines. Rheumatology (Oxford). 2005 Jul;44(7):921-4.
- 1983. Priori R, Ceccarelli F, Barone F, et al. Clinical, biological and sonographic response to IL-1 blockade in adult-onset Still's disease. Clin Exp Rheumatol. 2008 Sep-Oct;26(5):933-7.
- 1984. Probst C, Pongratz G, Capellino S, et al. Cryptococcosis mimicking cutaneous cellulitis in a patient suffering from rheumatoid arthritis: a case report. BMC Infect Dis. 2010;10:239.
- 1985. Probst LE, Holland EJ. Intraocular lens implantation in patients with juvenile rheumatoid arthritis. Am J Ophthalmol. 1996 Aug;122(2):161-70.
- 1986. Proudman SM, Keen HI, Stamp LK, et al. Response-driven combination therapy with conventional disease-modifying antirheumatic drugs can achieve high response rates in early rheumatoid arthritis with minimal glucocorticoid and nonsteroidal anti-inflammatory drug use. Semin Arthritis Rheum. 2007 Oct;37(2):99-111.
- 1987. Provenzano G, Termini A, Le Moli C, et al. Efficacy of infliximab in psoriatic arthritis resistant to treatment with disease modifying antirheumatic drugs: an open pilot study. Ann Rheum Dis. 2003 Jul;62(7):680-1.
- 1988. Puechal X, Miceli-Richard C, Mejjad O, et al. Anti-tumour necrosis factor treatment in patients with refractory systemic vasculitis associated with rheumatoid arthritis. Ann Rheum Dis. 2008 Jun;67(6):880-4.
- 1989. Pullerits R, Bokarewa M, Dahlberg L, et al. Synovial fluid expression of autoantibodies specific for RAGE relates to less erosive course of rheumatoid arthritis.

 Rheumatology (Oxford). 2007

 Aug;46(8):1367-71.
- 1990. Pulsatelli L, Dolzani P, Silvestri T, et al. Synovial expression of vasoactive intestinal

- peptide in polymyalgia rheumatica. Clin Exp Rheumatol. 2006 Sep-Oct;24(5):562-6.
- 1991. Pun YL, Barraclough DR, Muirden KD. Leg ulcers in rheumatoid arthritis. Med J Aust. 1990 Nov 19;153(10):585-7.
- 1992. Puri PK, Lountzis NI, Tyler W, et al. Hydroxychloroquine-induced hyperpigmentation: the staining pattern. J Cutan Pathol. 2008 Dec;35(12):1134-7.
- 1993. Pyrpasopoulou A, Douma S, Triantafyllou A, et al. Response to rituximab and timeframe to relapse in rheumatoid arthritis patients: association with B-cell markers.

 Mol Diagn Ther. 2010 Feb 1;14(1):43-8.
- 1994. Quallich LG, Greenson J, Haftel HM, et al. Is it Crohn's disease? A severe systemic granulomatous reaction to sulfasalazine in patient with rheumatoid arthritis. BMC Gastroenterol. 2001;1:8.
- 1995. Quartier P, Taupin P, Bourdeaut F, et al. Efficacy of etanercept for the treatment of juvenile idiopathic arthritis according to the onset type. Arthritis Rheum. 2003 Apr;48(4):1093-101.
- 1996. Quartuccio L, De Re V, Fabris M, et al. Atypical lymphoproliferation progressing into B-cell lymphoma in rheumatoid arthritis treated with different biological agents: clinical course and molecular characterization. Haematologica. 2006 May;91(5):691-4.
- 1997. Quartuccio L, Maset M, De Vita S. Efficacy of abatacept in a refractory case of adultonset Still's disease. Clin Exp Rheumatol. 2010 Mar-Apr;28(2):265-7.
- 1998. Queiro R, Torre JC, Belzunegui J, et al. Clinical features and predictive factors in psoriatic arthritis-related uveitis. Semin Arthritis Rheum. 2002 Feb;31(4):264-70.
- 1999. Quinn MA, Conaghan PG, O'Connor PJ, et al. Very early treatment with infliximab in addition to methotrexate in early, poorprognosis rheumatoid arthritis reduces magnetic resonance imaging evidence of synovitis and damage, with sustained benefit after infliximab withdrawal: results from a

- twelve-month randomized, double-blind, placebo-controlled trial. Arthritis Rheum. 2005 Jan;52(1):27-35.
- 2000. Rachapalli S, O'Daunt S. Septic arthritis due to Listeria monocytogenes in a patient receiving etanercept. Arthritis Rheum. 2005 Mar;52(3):987.
- 2001. Racunica T, Cassidy D, Cicuttini F, et al. Trouble with tumor necrosis factor alpha inhibitors, not just tuberculosis. Arthritis Care Res (Hoboken) 2010;62(6):770-4.
- 2002. Radikova Z, Rovensky J, Vlcek M, et al. Adrenocortical response to low-dose ACTH test in female patients with rheumatoid arthritis. Ann N Y Acad Sci. 2008 Dec;1148:562-6.
- 2003. Radovits BJ, Kievit W, Laan RF. Tumour necrosis factor-alpha antagonists in the management of rheumatoid arthritis in the elderly: a review of their efficacy and safety. Drugs Aging. 2009;26(8):647-64.
- 2004. Radstake TR, Fransen J, Toonen EJ, et al. Macrophage migration inhibitory factor polymorphisms do not predict therapeutic response to glucocorticoids or to tumour necrosis factor alpha-neutralising treatments in rheumatoid arthritis. Ann Rheum Dis. 2007 Nov;66(11):1525-30.
- 2005. Raghavendra S, Nair MD, Chemmanam T, et al. Disseminated necrotizing leukoencephalopathy following low-dose oral methotrexate. Eur J Neurol. 2007 Mar;14(3):309-14.
- 2006. Rahman MU, Strusberg I, Geusens P, et al. Double-blinded infliximab dose escalation in patients with rheumatoid arthritis. Ann Rheum Dis. 2007 Sep;66(9):1233-8.
- 2007. Rahman N, Healy C, Flint SR, et al.
 Cautionary note: a possible association
 between oral squamous cell carcinoma and
 tumor necrosis factor antagonists; need for
 oral screening. J Clin Rheumatol. 2010
 Jun;16(4):197-9.
- 2008. Rahmlow M, Shuster EA, Dominik J, et al. Leflunomide-associated progressive

- multifocal leukoencephalopathy. Arch Neurol. 2008 Nov;65(11):1538-9.
- 2009. Rajagopala S, Singh N, Gupta K, et al. Pulmonary amyloidosis in Sjogren's syndrome: a case report and systematic review of the literature. Respirology. 2010 Jul;15(5):860-6.
- 2010. Rajakulendran S, Deighton C. Delayed multiple injection site reaction in a rheumatoid arthritis patient treated with etanercept. Rheumatology (Oxford). 2004 Dec;43(12):1588-9.
- 2011. Rajakulendran S, Deighton C. Adverse dermatological reactions in rheumatoid arthritis patients treated with etanercept, an anti-TNFalpha drug. Curr Drug Saf. 2006 Aug;1(3):259-64.
- 2012. Rajakulendran S, Gadsby K, Deighton C. Rheumatoid arthritis, alcohol, leflunomide and methotrexate. Can changes to the BSR guidelines for leflunomide and methotrexate on alcohol consumption be justified?

 Musculoskeletal Care. 2008 Dec;6(4):233-45.
- 2013. Rajaraman RT, Kimura Y, Li S, et al. Retrospective case review of pediatric patients with uveitis treated with infliximab. Ophthalmology. 2006 Feb;113(2):308-14.
- 2014. Ramirez-Hernandez M, Marras C, Martinez-Escribano JA. Infliximab-induced vitiligo. Dermatology. 2005;210(1):79-80.
- 2015. Ramos-Casals M, Brito-Zeron P, Siso A, et al. High prevalence of serum metabolic alterations in primary Sjogren's syndrome: influence on clinical and immunological expression. J Rheumatol. 2007
 Apr;34(4):754-61.
- 2016. Ramos-Casals M, Garcia-Hernandez FJ, de Ramon E, et al. Off-label use of rituximab in 196 patients with severe, refractory systemic autoimmune diseases. Clin Exp Rheumatol. 2010 Jul-Aug;28(4):468-76.
- 2017. Ramos-Casals M, Lopez-Guillermo A, Brito-Zeron P, et al. Treatment of B-cell lymphoma with rituximab in two patients with Sjogren's syndrome associated with

- hepatitis C virus infection. Lupus. 2004;13(12):969-71.
- 2018. Ranganathan P. Infliximab-induced scleredema in a patient with rheumatoid arthritis. J Clin Rheumatol. 2005 Dec;11(6):319-22.
- 2019. Rantalaiho V, Korpela M, Hannonen P, et al. The good initial response to therapy with a combination of traditional diseasemodifying antirheumatic drugs is sustained over time: the eleven-year results of the Finnish rheumatoid arthritis combination therapy trial. Arthritis Rheum. 2009 May;60(5):1222-31.
- 2020. Raterman HG, Hoving JL, Nurmohamed MT, et al. Work ability: a new outcome measure in rheumatoid arthritis? Scand J Rheumatol. 2010 Mar;39(2):127-31.
- 2021. Rau R, Sander O, van Riel P, et al. Intravenous human recombinant tumor necrosis factor receptor p55-Fc IgG1 fusion protein Ro 45-2081 (lenercept): a double blind, placebo controlled dose-finding study in rheumatoid arthritis. J Rheumatol. 2003 Apr;30(4):680-90.
- 2022. Rau R, Sander O, Wassenberg S. Erosion healing in rheumatoid arthritis after anakinra treatment. Ann Rheum Dis. 2003
 Jul;62(7):671-3.
- 2023. Rau R, Simianer S, van Riel PL, et al. Rapid alleviation of signs and symptoms of rheumatoid arthritis with intravenous or subcutaneous administration of adalimumab in combination with methotrexate. Scand J Rheumatol. 2004;33(3):145-53.
- 2024. Ravindran J, Shenker N, Bhalla AK, et al. Case report: Response in proteinuria due to AA amyloidosis but not Felty's syndrome in a patient with rheumatoid arthritis treated with TNF-alpha blockade. Rheumatology (Oxford). 2004 May;43(5):669-72.
- 2025. Raza N, Hameed A, Ali MK. Detection of subclinical joint involvement in psoriasis with bone scintigraphy and its response to oral methotrexate. Clin Exp Dermatol. 2008 Jan;33(1):70-3.

- 2026. Reddy AR, Backhouse OC. Does etanercept induce uveitis? Br J Ophthalmol. 2003 Jul;87(7):925.
- 2027. Reed A, Haugen M, Pachman LM, et al. Abnormalities in serum osteocalcin values in children with chronic rheumatic diseases. J Pediatr. 1990 Apr;116(4):574-80.
- 2028. Regula CG, Hennessy J, Clarke LE, et al. Interstitial granulomatous drug reaction to anakinra. J Am Acad Dermatol. 2008 Aug;59(2 Suppl 1):S25-7.
- 2029. Rehnberg M, Amu S, Tarkowski A, et al. Short- and long-term effects of anti-CD20 treatment on B cell ontogeny in bone marrow of patients with rheumatoid arthritis. Arthritis Res Ther. 2009;11(4):R123.
- 2030. Rehnberg M, Brisslert M, Amu S, et al. Vaccination response to protein and carbohydrate antigens in patients with rheumatoid arthritis after rituximab treatment. Arthritis Res Ther. 2010;12(3):R111.
- 2031. Reitman CA, Lidsky MD, Heggeness MH. Neurologic and morphologic features of dural ectasia in ankylosing spondylitis and rheumatoid arthritis: a case report. Am J Orthop. 2006 Nov;35(11):530-1.
- 2032. Rejon E, Gimenez MD, Mayordomo L, et al. Therapeutic efficacy and safety of multiple intravenous infusions of infliximab in refractory ankylosing spondylitis patients with axial involvement. Scand J Rheumatol. 2004;33(5):323-6.
- 2033. Ren H, Wang WM, Chen XN, et al. Renal involvement and followup of 130 patients with primary Sjogren's syndrome. J Rheumatol. 2008 Feb;35(2):278-84.
- 2034. Renato GM. B cell depletion in early rheumatoid arthritis: a new concept in therapeutics. Ann N Y Acad Sci. 2009 Sep;1173:729-35.
- 2035. Resmini E, Farkas C, Murillo B, et al. Body composition after endogenous (Cushing's syndrome) and exogenous (rheumatoid arthritis) exposure to glucocorticoids. Horm Metab Res. 2010 Jul;42(8):613-8.

- 2036. Ribbens C, Andre B, Marcelis S, et al. Rheumatoid hand joint synovitis: gray-scale and power Doppler US quantifications following anti-tumor necrosis factor-alpha treatment: pilot study. Radiology. 2003 Nov;229(2):562-9.
- 2037. Ribbens C, Martin y Porras M, Franchimont N, et al. Increased matrix metalloproteinase-3 serum levels in rheumatic diseases: relationship with synovitis and steroid treatment. Ann Rheum Dis. 2002 Feb;61(2):161-6.
- 2038. Richards BL, Spies J, McGill N, et al. Effect of leflunomide on the peripheral nerves in rheumatoid arthritis. Intern Med J. 2007 Feb;37(2):101-7.
- 2039. Richette P, Dieude P, Damiano J, et al. Sensory neuropathy revealing necrotizing vasculitis during infliximab therapy for rheumatoid arthritis. J Rheumatol. 2004 Oct;31(10):2079-81.
- 2040. Richette P, Francois M, Vicaut E, et al. A high interleukin 1 receptor antagonist/IL-1beta ratio occurs naturally in knee osteoarthritis. J Rheumatol. 2008 Aug;35(8):1650-4.
- 2041. Richez C, Blanco P, Lagueny A, et al. Neuropathy resembling CIDP in patients receiving tumor necrosis factor-alpha blockers. Neurology. 2005 Apr 26;64(8):1468-70.
- 2042. Richez C, Dumoulin C, Schaeverbeke T. Infliximab induced chilblain lupus in a patient with rheumatoid arthritis. J Rheumatol. 2005 Apr;32(4):760-1.
- 2043. Richter C, Wanke L, Steinmetz J, et al. Mononeuritis secondary to rheumatoid arthritis responds to etanercept. Rheumatology (Oxford). 2000 Dec;39(12):1436-7.
- 2044. Richter J, Benson V, Grobarova V, et al. CD161 receptor participates in both impairing NK cell cytotoxicity and the response to glycans and vimentin in patients with rheumatoid arthritis. Clin Immunol. 2010 Jul;136(1):139-47.

- 2045. Riepl B, Grassel S, Wiest R, et al. Tumor necrosis factor and norepinephrine lower the levels of human neutrophil peptides 1-3 secretion by mixed synovial tissue cultures in osteoarthritis and rheumatoid arthritis. Arthritis Res Ther. 2010;12(3):R110.
- 2046. Rihl M, Kruithof E, Barthel C, et al. Involvement of neurotrophins and their receptors in spondyloarthritis synovitis: relation to inflammation and response to treatment. Ann Rheum Dis. 2005
 Nov;64(11):1542-9.
- 2047. Rihl M, Ulbricht K, Schmidt RE, et al. Treatment of sicca symptoms with hydroxychloroquine in patients with Sjogren's syndrome. Rheumatology (Oxford). 2009 Jul;48(7):796-9.
- 2048. Riise T, Jacobsen BK, Gran JT. Changes in therapy of rheumatoid arthritis during the period 1979 to 1996. Scand J Rheumatol. 2001;30(4):199-202.
- 2049. Rijkeboer A, Voskuyl A, Van Agtmael M. Fatal Salmonella enteritidis septicaemia in a rheumatoid arthritis patient treated with a TNF-alpha antagonist. Scand J Infect Dis. 2007;39(1):80-3.
- 2050. Rimar D, Rozenbaum M, Slobodin G, et al. Etanercept related pseudo-empyema in rheumatoid arthritis. Clin Rheumatol 2010;29(5):547-9.
- 2051. Rinaldi F, Provenzano G, Termini A, et al. Long term infliximab treatment for severe psoriatic arthritis: evidence of sustained clinical and radiographic response. Ann Rheum Dis. 2005 Sep;64(9):1375-6.
- 2052. Rindfleisch JA, Muller D. Diagnosis and management of rheumatoid arthritis. Am Fam Physician. 2005 Sep 15;72(6):1037-47.
- 2053. Rivers JK, Podgorski MR, Goulding NJ, et al. The presence of autoantibody to recombinant lipocortin-I in patients with psoriasis and psoriatic arthritis. Br J Dermatol. 1990 Nov;123(5):569-72.
- 2054. Rizzo R, Rubini M, Govoni M, et al. HLA-G 14-bp polymorphism regulates the methotrexate response in rheumatoid

- arthritis. Pharmacogenet Genomics. 2006 Sep;16(9):615-23.
- 2055. Rodrigues K, Neves FS, Stoeterau KB, et al. Pulmonary amyloidosis in Sjogren's syndrome: a rare diagnosis for nodular lung lesions. Int J Rheum Dis. 2009
 Dec;12(4):358-60.
- 2056. Rodriguez-Escalera C, Belzunegui J, Lopez-Dominguez L, et al. Multifocal motor neuropathy with conduction block in a patient with rheumatoid arthritis on infliximab therapy. Rheumatology (Oxford). 2005 Jan;44(1):132-3.
- 2057. Rodriguez-Padilla JA, Hedges TR, 3rd, Monson B, et al. High-speed ultra-high-resolution optical coherence tomography findings in hydroxychloroquine retinopathy. Arch Ophthalmol. 2007 Jun;125(6):775-80.
- 2058. Rokhsar C, Rabhan N, Cohen SR. Etanercept monotherapy for a patient with psoriasis, psoriatic arthritis, and concomitant hepatitis C infection. J Am Acad Dermatol. 2006 Feb;54(2):361-2.
- 2059. Roll P, Dorner T, Tony HP. Anti-CD20 therapy in patients with rheumatoid arthritis: predictors of response and B cell subset regeneration after repeated treatment.

 Arthritis Rheum. 2008 Jun;58(6):1566-75.
- 2060. Roll P, Palanichamy A, Kneitz C, et al. Regeneration of B cell subsets after transient B cell depletion using anti-CD20 antibodies in rheumatoid arthritis. Arthritis Rheum. 2006 Aug;54(8):2377-86.
- 2061. Rooryck C, Barnetche T, Richez C, et al. Influence of FCGR3A-V212F and TNFRSF1B-M196R genotypes in patients with rheumatoid arthritis treated with infliximab therapy. Clin Exp Rheumatol. 2008 Mar-Apr;26(2):340-2.
- 2062. Roos JC, Ostor AJ. Orbital cellulitis in a patient receiving infliximab for Ankylosing spondylitis. Am J Ophthalmol. 2006 Apr;141(4):767-9.
- 2063. Rosenvinge A, Krogh-Madsen R, Baslund B, et al. Insulin resistance in patients with rheumatoid arthritis: effect of anti-TNFalpha

- therapy. Scand J Rheumatol. 2007 Mar-Apr;36(2):91-6.
- 2064. Rosmarin D, Bush M, Scheinman PL. Patch testing a patient with allergic contact hand dermatitis who is taking infliximab. J Am Acad Dermatol. 2008 Jul;59(1):145-7.
- 2065. Roth EB, Stenberg P, Book C, et al. Antibodies against transglutaminases, peptidylarginine deiminase and citrulline in rheumatoid arthritis--new pathways to epitope spreading. Clin Exp Rheumatol. 2006 Jan-Feb;24(1):12-8.
- 2066. Roth S. Effects of Prosorba column apheresis in patients with chronic refractory rheumatoid arthritis. J Rheumatol. 2004 Nov;31(11):2131-5.
- 2067. Roubenoff R, Roubenoff RA, Ward LM, et al. Catabolic effects of high-dose corticosteroids persist despite therapeutic benefit in rheumatoid arthritis. Am J Clin Nutr. 1990 Dec;52(6):1113-7.
- 2068. Roux CH, Brocq O, Albert CBV, et al. Cutaneous vasculitis and glomerulonephritis in a patient taking the anti-TNF alpha agent etanercept for rheumatoid arthritis. Joint Bone Spine. 2004 Sep;71(5):444-5.
- 2069. Roux N, Flipo RM, Cortet B, et al. Pneumocystis carinii pneumonia in rheumatoid arthritis patients treated with methotrexate. A report of two cases. Rev Rhum Engl Ed. 1996 Jun;63(6):453-6.
- 2070. Roux-Lombard P, Eberhardt K, Saxne T, et al. Cytokines, metalloproteinases, their inhibitors and cartilage oligomeric matrix protein: relationship to radiological progression and inflammation in early rheumatoid arthritis. A prospective 5-year study. Rheumatology (Oxford). 2001 May;40(5):544-51.
- 2071. Rovensky J, Bakosova J, Koska J, et al. Somatotropic, lactotropic and adrenocortical responses to insulin-induced hypoglycemia in patients with rheumatoid arthritis. Ann N Y Acad Sci. 2002 Jun:966:263-70.
- 2072. Rovensky J, Bakosova J, Payer J, et al. Increased demand for steroid therapy in

- hyperprolactinemic patients with rheumatoid arthritis. Int J Tissue React. 2001;23(4):145-9.
- 2073. Rovensky J, Imrich R, Koska J, et al. Cortisol elimination from plasma in premenopausal women with rheumatoid arthritis. Ann Rheum Dis. 2003 Jul;62(7):674-6.
- 2074. Rovensky J, Radikova Z, Imrich R, et al. Gonadal and adrenal steroid hormones in plasma and synovial fluid of patients with rheumatoid arthritis. Endocr Regul. 2004 Dec;38(4):143-9.
- 2075. Rovensky J, Simorova E, Radikova Z, et al. Comparison of hormone transfer to pleural and synovial exudates. Endocr Regul. 2006 Jun;40(2):29-36.
- 2076. Rovere Querini P, Vecellio M, Sabbadini MG, et al. Miliary tuberculosis after biological therapy for rheumatoid arthritis. Rheumatology (Oxford). 2002 Feb;41(2):231.
- 2077. Roy A, Mould DR, Wang XF, et al. Modeling and simulation of abatacept exposure and interleukin-6 response in support of recommended doses for rheumatoid arthritis. J Clin Pharmacol. 2007 Nov;47(11):1408-20.
- 2078. Roy DB, Conte ET, Cohen DJ. The treatment of pyoderma gangrenosum using etanercept. J Am Acad Dermatol. 2006 Mar;54(3 Suppl 2):S128-34.
- 2079. Rozenbaum M, Boulman N, Slobodin G, et al. Polyarthritis flare complicating rheumatoid arthritis infliximab therapy: a paradoxic adverse reaction. J Clin Rheumatol. 2006 Dec;12(6):269-71.
- 2080. Rozenbaum M, Rosner I, Portnoy E. Remission of Behcet's syndrome with TNFalpha blocking treatment. Ann Rheum Dis. 2002 Mar;61(3):283-4.
- 2081. Ruderman EM, Pope RM. The evolving clinical profile of abatacept (CTLA4-Ig): a novel co-stimulatory modulator for the treatment of rheumatoid arthritis. Arthritis Res Ther. 2005;7 Suppl 2:S21-5.

- 2082. Rudwaleit M, Baraliakos X, Listing J, et al. Magnetic resonance imaging of the spine and the sacroiliac joints in ankylosing spondylitis and undifferentiated spondyloarthritis during treatment with etanercept. Ann Rheum Dis. 2005 Sep;64(9):1305-10.
- 2083. Rudwaleit M, Listing J, Brandt J, et al. Prediction of a major clinical response (BASDAI 50) to tumour necrosis factor alpha blockers in ankylosing spondylitis. Ann Rheum Dis. 2004 Jun;63(6):665-70.
- 2084. Rudwaleit M, Van den Bosch F, Kron M, et al. Effectiveness and safety of adalimumab in patients with ankylosing spondylitis or psoriatic arthritis and history of anti-tumor necrosis factor therapy. Arthritis Res Ther. 2010;12(3):R117.
- 2085. Ruppert M, De Clerck L, van Offel J, et al. Intestinal necrosis in a patient with rheumatoid arthritis receiving anti-TNF treatment. Acta Chir Belg. 2006 Mar-Apr;106(2):225-7.
- 2086. Russell A, Haraoui B, Keystone E, et al. Current and emerging therapies for rheumatoid arthritis, with a focus on infliximab: clinical impact on joint damage and cost of care in canada. Clin Ther. 2001 Nov;23(11):1824-38; discussion 791.
- 2087. Russell E, Zeihen M, Wergin S, et al. Patients receiving etanercept may develop antibodies that interfere with monoclonal antibody laboratory assays. Arthritis Rheum. 2000 Apr;43(4):944.
- 2088. Ruyssen-Witrand A, Gossec L, Salliot C, et al. Complication rates of 127 surgical procedures performed in rheumatic patients receiving tumor necrosis factor alpha blockers. Clin Exp Rheumatol. 2007 May-Jun;25(3):430-6.
- 2089. Saad AA, Ashcroft DM, Watson KD, et al. Improvements in quality of life and functional status in patients with psoriatic arthritis receiving anti-tumor necrosis factor therapies. Arthritis Care Res (Hoboken) 2010;62(3):345-53.
- 2090. Saad AA, Symmons DP, Noyce PR, et al. Risks and benefits of tumor necrosis factor-

- alpha inhibitors in the management of psoriatic arthritis: systematic review and metaanalysis of randomized controlled trials. J Rheumatol. 2008 May;35(5):883-90.
- 2091. Saadeh C, Saadeh C. Asthma remission in a patient with rheumatoid arthritis while on antiangiogenesis therapy during a rheumatoid arthritis trial demonstrated by forced oscillation and spirometry. J Asthma. 2007 May;44(4):281-3.
- 2092. Saag KG, Koehnke R, Caldwell JR, et al. Low dose long-term corticosteroid therapy in rheumatoid arthritis: an analysis of serious adverse events. Am J Med. 1994 Feb;96(2):115-23.
- 2093. Saario R, Sonninen P, Mottonen T, et al. Bone mineral density of the lumbar spine in patients with advanced rheumatoid arthritis. Influence of functional capacity and corticosteroid use. Scand J Rheumatol. 1999;28(6):363-7.
- 2094. Saba NS, Kosseifi SG, Charaf EA, et al. Adalimumab-induced acute myelogenic leukemia. South Med J. 2008 Dec;101(12):1261-2.
- 2095. Saber TP, Ng CT, Renard G, et al.
 Remission in psoriatic arthritis: is it possible and how can it be predicted? Arthritis Res
 Ther. 2010;12(3):R94.
- 2096. Saeki Y, Ohshima S, Ishida T, et al. Remission of the renal involvement in a patient with primary Sjogren's syndrome (SS) after pulse high-dose corticosteroid infusion therapy. Clin Rheumatol. 2001;20(3):225-8.
- 2097. Saeki Y, Ohshima S, Mima T, et al. Suboptimal clinical response to anti-tumor necrosis factor alpha (TNFalpha) antibody therapy in a patient with severe rheumatoid arthritis and lymphadenopathy. Scand J Rheumatol. 1998;27(4):303-5.
- 2098. Sahin M, Keskin M, Tunc SE, et al. Kaposi's sarcoma complicating rheumatoid arthritis treated with corticosteroid Kaposi's sarcoma and rheumatoid arthritis. Saudi Med J. 2007 Jul;28(7):1133-4.

- 2099. Saiki O, Takao R, Naruse Y, et al. Infliximab but not methotrexate induces extra-high levels of VLDL-triglyceride in patients with rheumatoid arthritis. J Rheumatol. 2007 Oct;34(10):1997-2004.
- 2100. Saint Marcoux B, De Bandt M. Vasculitides induced by TNFalpha antagonists: a study in 39 patients in France. Joint Bone Spine. 2006 Dec;73(6):710-3.
- 2101. Saito S, Momohara S, Taniguchi A, et al. The intra-articular efficacy of hyaluronate injections in the treatment of rheumatoid arthritis. Mod Rheumatol. 2009;19(6):643-51.
- 2102. Sakai K, Hamaguchi T, Yamada M. Multiple cranial nerve enhancement on MRI in primary Sjogren's syndrome. Intern Med. 2010;49(9):857-9.
- 2103. Sakai Y, Sakai S, Otsuka T, et al. Efficacy of high-throughput leukocytapheresis for rheumatoid arthritis with a reduced response to infliximab. Ther Apher Dial. 2009 Jun;13(3):179-85.
- 2104. Sakamoto O, Saita N, Ando M, et al. Two cases of Sjogren's syndrome with multiple bullae. Intern Med. 2002 Feb;41(2):124-8.
- 2105. Sakaura H, Hosono N, Mukai Y, et al. Paraparesis due to exacerbation of preexisting spinal pseudoarthrosis following infliximab therapy for advanced ankylosing spondylitis. Spine J. 2006 May-Jun;6(3):325-9.
- 2106. Sakellariou GT, Vounotrypidis P, Berberidis C. Infliximab treatment in two patients with psoriatic arthritis and secondary IgA nephropathy. Clin Rheumatol. 2007 Jul;26(7):1132-3.
- 2107. Salamon L, Salamon T, Morovic-Vergles J. Thrombotic microangiopathy in adult-onset Still's disease: case report and review of the literature. Wien Klin Wochenschr. 2009;121(17-18):583-8.
- 2108. Saleem B, Brown AK, Keen H, et al.
 Disease remission state in patients treated with the combination of tumor necrosis factor blockade and methotrexate or with

- disease-modifying antirheumatic drugs: A clinical and imaging comparative study. Arthritis Rheum 2009;60(7):1915-22.
- 2109. Saleem B, Mackie S, Quinn M, et al. Does the use of tumour necrosis factor antagonist therapy in poor prognosis, undifferentiated arthritis prevent progression to rheumatoid arthritis? Ann Rheum Dis. 2008
 Aug;67(8):1178-80.
- 2110. Saleem G, Li SC, MacPherson BR, et al. Hepatitis with interface inflammation and IgG, IgM, and IgA anti-double-stranded DNA antibodies following infliximab therapy: comment on the article by Charles et al. Arthritis Rheum. 2001 Aug;44(8):1966-8.
- 2111. Salli A, Sahin N, Paksoy Y, et al. Treatment of periodontoid pannus with infliximab in a patient with rheumatoid arthritis. J Clin Rheumatol. 2009 Aug;15(5):250-1.
- 2112. Salliot C, Dougados M, Gossec L. Risk of serious infections during rituximab, abatacept and anakinra treatments for rheumatoid arthritis: meta-analyses of randomised placebo-controlled trials. Ann Rheum Dis 2009;68(1):25-32.
- 2113. Salliot C, van der Heijde D. Long-term safety of methotrexate monotherapy in patients with rheumatoid arthritis: a systematic literature research. Ann Rheum Dis. 2009 Jul;68(7):1100-4.
- 2114. Salloum E, Cooper DL, Howe G, et al. Spontaneous regression of lymphoproliferative disorders in patients treated with methotrexate for rheumatoid arthritis and other rheumatic diseases. J Clin Oncol. 1996 Jun;14(6):1943-9.
- 2115. Salvarani C, Cantini F, Olivieri I, et al. Efficacy of infliximab in resistant psoriatic arthritis. Arthritis Rheum. 2003 Aug 15;49(4):541-5.
- 2116. Salvarani C, Cantini F, Olivieri I, et al. Distal extremity swelling with pitting edema in psoriatic arthritis: evidence of 2 pathological mechanisms. J Rheumatol. 1999 Aug;26(8):1831-4.

- 2117. Samanta J, Kendall J, Samanta A. Polyarthralgia. BMJ. 2003 Apr 19;326(7394):859.
- 2118. Sambrook P, Birmingham J, Champion D, et al. Postmenopausal bone loss in rheumatoid arthritis: effect of estrogens and androgens. J Rheumatol. 1992 Mar;19(3):357-61.
- 2119. Sanchez A, Maximiano C, Cantos B, et al. Neurological symptoms simulating cord compression in breast cancer patient. J Neurooncol. 2005 Apr;72(2):149-50.
- 2120. Sanchez G, Castro JS, Snih SA, et al.
 Durability of treatment with methotrexate in
 Venezuelan patients with rheumatoid
 arthritis. Rheumatol Int. 2007
 Apr;27(6):531-6.
- 2121. Sandler C, Lindstedt KA, Joutsiniemi S, et al. Selective activation of mast cells in rheumatoid synovial tissue results in production of TNF-alpha, IL-1beta and IL-1Ra. Inflamm Res. 2007 Jun;56(6):230-9.
- 2122. Sankar V, Brennan MT, Kok MR, et al. Etanercept in Sjogren's syndrome: a twelveweek randomized, double-blind, placebocontrolled pilot clinical trial. Arthritis Rheum. 2004 Jul;50(7):2240-5.
- 2123. Sanmarti R, Gomez-Centeno A, Ercilla G, et al. Prognostic factors of radiographic progression in early rheumatoid arthritis: a two year prospective study after a structured therapeutic strategy using DMARDs and very low doses of glucocorticoids. Clin Rheumatol. 2007 Jul;26(7):1111-8.
- 2124. Sano H, Arai K, Murai T, et al. Tight control is important in patients with rheumatoid arthritis treated with an anti-tumor necrosis factor biological agent: prospective study of 91 cases who used a biological agent for more than 1 year. Mod Rheumatol. 2009;19(4):390-4.
- 2125. Santiago-Casas Y, Gonzalez-Rivera TC, Castro-Santana LE, et al. Impact of age on clinical manifestations and outcome in Puerto Ricans with rheumatoid arthritis. Ethn Dis. 2010 Winter;20(1 Suppl 1):S1-191-5.

- 2126. Santos-Ocampo AS, Santos-Ocampo RS. Non-contrast computed tomography-guided intra-articular corticosteroid injections of severe bilateral hip arthritis in a patient with ankylosing spondylitis. Clin Exp Rheumatol. 2003 Mar-Apr;21(2):239-40.
- 2127. Sany J, Bourgeois P, Saraux A, et al.
 Characteristics of patients with rheumatoid
 arthritis in France: a study of 1109 patients
 managed by hospital based rheumatologists.
 Ann Rheum Dis. 2004 Oct;63(10):1235-40.
- 2128. Sany J, Cohen JD, Combescure C, et al. Medico-economic evaluation of infliximab in rheumatoid arthritis--prospective French study of a cohort of 635 patients monitored for two years. Rheumatology (Oxford). 2009 Oct;48(10):1236-41.
- 2129. Sany J, Kaiser MJ, Jorgensen C, et al. Study of the tolerance of infliximab infusions with or without betamethasone premedication in patients with active rheumatoid arthritis.

 Ann Rheum Dis. 2005 Nov;64(11):1647-9.
- 2130. Sanz I, Anolik J. Reconstitution of the adult B cell repertoire after treatment with rituximab. Arthritis Res Ther. 2005;7(5):175-6.
- 2131. Saraux A, Devauchelle-Pensec V, Engerran L, et al. Most rheumatologists are conservative in active rheumatoid arthritis despite methotrexate therapy: results of the PRISME survey. J Rheumatol. 2006 Jul;33(7):1258-65.
- 2132. Sari I, Akar S, Birlik M, et al. Anti-tumor necrosis factor-alpha-induced psoriasis. J Rheumatol. 2006 Jul;33(7):1411-4.
- 2133. Saruhan-Direskeneli G, Inanc M, Fresko I, et al. The role of HLA-DRB1 shared epitope alleles in predicting short-term response to leflunomide in rheumatoid arthritis. Rheumatology (Oxford). 2007
 Dec;46(12):1842-4.
- 2134. Sarzi-Puttini P, Antivalle M, Marchesoni A, et al. Efficacy and safety of anti-TNF agents in the Lombardy rheumatoid arthritis network (LORHEN). Reumatismo. 2008 Oct-Dec;60(4):290-5.

- 2135. Sarzi-Puttini P, Atzeni F, Scholmerich J, et al. Anti-TNF antibody treatment improves glucocorticoid induced insulin-like growth factor 1 (IGF1) resistance without influencing myoglobin and IGF1 binding proteins 1 and 3. Ann Rheum Dis. 2006 Mar;65(3):301-5.
- 2136. Sato H, Kazama JJ, Wada Y, et al.
 Decreased levels of circulating alpha2Heremans-Schmid glycoprotein/Fetuin-A
 (AHSG) in patients with rheumatoid
 arthritis. Intern Med. 2007;46(20):1685-91.
- 2137. Sato H, Sakai T, Sugaya T, et al.

 Tocilizumab dramatically ameliorated lifethreatening diarrhea due to secondary
 amyloidosis associated with rheumatoid
 arthritis. Clin Rheumatol. 2009
 Sep;28(9):1113-6.
- 2138. Sato M, Takeda A, Honzu H, et al. Adult Still's disease with Sjogren's syndrome successfully treated with intravenous pulse methylprednisolone and oral cyclophosphamide. Intern Med. 1993 Sep;32(9):730-2.
- 2139. Sato T, Inokuma S, Sagawa A, et al. Factors associated with fatal outcome of leflunomide-induced lung injury in Japanese patients with rheumatoid arthritis. Rheumatology (Oxford). 2009 Oct;48(10):1265-8.
- 2140. Satoh K, Yoshida N, Imaizumi K, et al. Reversible methotrexate-associated lymphoproliferative disorder resembling advanced gastric cancer in a patient with rheumatoid arthritis. Am J Med Sci. 2009 Oct;338(4):334-5.
- 2141. Saunders SA, Capell HA, Stirling A, et al. Triple therapy in early active rheumatoid arthritis: a randomized, single-blind, controlled trial comparing step-up and parallel treatment strategies. Arthritis Rheum 2008;58(5):1310-7.
- 2142. Saviola G, Abdi Ali L, Shams Eddin S, et al. Compared clinical efficacy and bone metabolic effects of low-dose deflazacort and methyl prednisolone in male inflammatory arthropathies: a 12-month open randomized pilot study. Rheumatology (Oxford). 2007 Jun;46(6):994-8.

- 2143. Saxne T, Larsson L, Geborek P. Results of anakinra treatment in rheumatoid arthritis patients previously treated with tumor necrosis factor alpha blockade: comment on the article by Buch et al. Arthritis Rheum. 2004 Sep;50(9):3049-50; author reply 50-1.
- 2144. Scali JJ, Visentini S, Salomon J, et al. Rapid and deep control of inflammation in rheumatoid arthritis with infliximab and its correlation with acute-phase reactants. Ann N Y Acad Sci. 2007 Sep;1110:389-401.
- 2145. Scarpa R, Peluso R, Atteno M, et al. The effectiveness of a traditional therapeutical approach in early psoriatic arthritis: results of a pilot randomised 6-month trial with methotrexate. Clin Rheumatol. 2008 Jul;27(7):823-6.
- 2146. Scarsi M, Ziglioli T, Airo P. Decreased circulating CD28-negative T cells in patients with rheumatoid arthritis treated with abatacept are correlated with clinical response. J Rheumatol. 2010 May;37(5):911-6.
- 2147. Schafer JA, Kjesbo NK, Gleason PP. Formulary review of 2 new biologic agents: tocilizumab for rheumatoid arthritis and ustekinumab for plaque psoriasis. J Manag Care Pharm. 2010 Jul-Aug;16(6):402-16.
- 2148. Schalk E, Krogel C, Scheinpflug K, et al. Lymphomatoid granulomatosis in a patient with rheumatoid arthritis receiving methotrexate: successful treatment with the anti-CD20 antibody mabthera. Onkologie. 2009 Jul;32(7):440-1.
- 2149. Schapira D, Militeanu D, Israel O, et al. Insufficiency fractures of the pubic ramus. Semin Arthritis Rheum. 1996 Jun;25(6):373-82.
- 2150. Scharf SL, Christophidis N. Second-line agents for rheumatoid arthritis. Med J Aust. 1995 Aug 21;163(4):215-8.
- 2151. Schatteman L, Gyselbrecht L, De Clercq L, et al. Treatment of refractory inflammatory monoarthritis in ankylosing spondylitis by intraarticular injection of infliximab. J Rheumatol. 2006 Jan;33(1):82-5.

- 2152. Scheinberg M, Guedes-Barbosa LS, Mangueira C, et al. Yellow fever revaccination during infliximab therapy. Arthritis Care Res (Hoboken) 2010;62(6):896-8.
- 2153. Scheinberg M, Hamerschlak N, Kutner JM, et al. Rituximab in refractory autoimmune diseases: Brazilian experience with 29 patients (2002-2004). Clin Exp Rheumatol. 2006 Jan-Feb;24(1):65-9.
- 2154. Scheinfeld N. Menorrhagia and severe menstrual pain related to the use of adalimumab in a psoriatic. J Dermatolog Treat. 2008;19(3):188-9.
- 2155. Scherak O, Popp W, Kolarz G, et al. Bronchoalveolar lavage and lung biopsy in rheumatoid arthritis. In vivo effects of disease modifying antirheumatic drugs. J Rheumatol. 1993 Jun;20(6):944-9.
- 2156. Schett G, Herak P, Graninger W, et al. Listeria-associated arthritis in a patient undergoing etanercept therapy: case report and review of the literature. J Clin Microbiol. 2005 May;43(5):2537-41.
- 2157. Schiff M, Keiserman M, Codding C, et al. Efficacy and safety of abatacept or infliximab vs placebo in ATTEST: a phase III, multi-centre, randomised, double-blind, placebo-controlled study in patients with rheumatoid arthritis and an inadequate response to methotrexate. Ann Rheum Dis 2008;67(8):1096-103.
- 2158. Schiff MH, DiVittorio G, Tesser J, et al. The safety of anakinra in high-risk patients with active rheumatoid arthritis: six-month observations of patients with comorbid conditions. Arthritis Rheum. 2004 Jun;50(6):1752-60.
- 2159. Schipper LG, Fransen J, Barrera P, et al. Methotrexate therapy in rheumatoid arthritis after failure to sulphasalazine: to switch or to add? Rheumatology (Oxford) 2009;48(10):1247-53.
- 2160. Schipper LG, Fransen J, Barrera P, et al.
 Methotrexate in combination with
 sulfasalazine is more effective in rheumatoid
 arthritis patients who failed sulfasalazine

- than in patients naive to both drugs. Rheumatology (Oxford) 2009;48(7):828-33.
- 2161. Schirren CA, Zachoval R, Schirren CG, et al. A role for chronic hepatitis C virus infection in a patient with cutaneous vasculitis, cryoglobulinemia, and chronic liver disease. Effective therapy with interferon-alpha. Dig Dis Sci. 1995
 Jun;40(6):1221-5.
- 2162. Schlaghecke R, Beuscher D, Kornely E, et al. Effects of glucocorticoids in rheumatoid arthritis. Diminished glucocorticoid receptors do not result in glucocorticoid resistance. Arthritis Rheum. 1994
 Aug;37(8):1127-31.
- 2163. Schlaghecke R, Kornely E, Wollenhaupt J, et al. Glucocorticoid receptors in rheumatoid arthritis. Arthritis Rheum. 1992 Jul;35(7):740-4.
- 2164. Schmeling H, Horneff G. Infliximab in two patients with juvenile ankylosing spondylitis. Rheumatol Int. 2004 May;24(3):173-6.
- 2165. Schmeling H, Horneff G. Etanercept and uveitis in patients with juvenile idiopathic arthritis. Rheumatology (Oxford). 2005 Aug;44(8):1008-11.
- 2166. Schmid L, Muller M, Treumann T, et al. Induction of complete and sustained remission of rheumatoid pachymeningitis by rituximab. Arthritis Rheum. 2009

 Jun;60(6):1632-4.
- 2167. Schmidt M, Hartung R, Capellino S, et al. Estrone/17beta-estradiol conversion to, and tumor necrosis factor inhibition by, estrogen metabolites in synovial cells of patients with rheumatoid arthritis and patients with osteoarthritis. Arthritis Rheum. 2009 Oct;60(10):2913-22.
- 2168. Schmidt M, Weidler C, Naumann H, et al. Reduced capacity for the reactivation of glucocorticoids in rheumatoid arthritis synovial cells: possible role of the sympathetic nervous system? Arthritis Rheum. 2005 Jun;52(6):1711-20.

- 2169. Schneeweiss S, Setoguchi S, Weinblatt ME, et al. Anti-tumor necrosis factor alpha therapy and the risk of serious bacterial infections in elderly patients with rheumatoid arthritis. Arthritis Rheum 2007;56(6):1754-64.
- 2170. Schneider SW, Staender S, Schluter B, et al. Infliximab-induced lupus erythematosus tumidus in a patient with rheumatoid arthritis. Arch Dermatol. 2006

 Jan;142(1):115-6.
- 2171. Schoels M, Aletaha D, Funovits J, et al. Application of the DAREA/DAPSA score for assessment of disease activity in psoriatic arthritis. Ann Rheum Dis. 2010 Aug;69(8):1441-7.
- 2172. Schoels M, Kapral T, Stamm T, et al. Stepup combination versus switching of nonbiological disease-modifying antirheumatic drugs in rheumatoid arthritis: results from a retrospective observational study. Ann Rheum Dis 2007;66(8):1059-65.
- 2173. Schotte H, Schluter B, Drynda S, et al. Interleukin 10 promoter microsatellite polymorphisms are associated with response to long term treatment with etanercept in patients with rheumatoid arthritis. Ann Rheum Dis. 2005 Apr;64(4):575-81.
- 2174. Schotte H, Schluter B, Willeke P, et al. Long-term treatment with etanercept significantly reduces the number of proinflammatory cytokine-secreting peripheral blood mononuclear cells in patients with rheumatoid arthritis. Rheumatology (Oxford). 2004 Aug;43(8):960-4.
- 2175. Schramm C, Schneider A, Marx A, et al. Adalimumab could suppress the activity of non alcoholic steatohepatitis (NASH). Z Gastroenterol. 2008 Dec;46(12):1369-71.
- 2176. Schuh A, Zeiler G, Holzwarth U, et al. Malignant fibrous histiocytoma at the site of a total hip arthroplasty. Clin Orthop Relat Res. 2004 Aug(425):218-22.
- 2177. Schumacher HR, Chen LX. Injectable corticosteroids in treatment of arthritis of the knee. Am J Med. 2005 Nov;118(11):1208-14.

- 2178. Schwartz JI, Agrawal NG, Wong PH, et al. Examination of the effect of increasing doses of etoricoxib on oral methotrexate pharmacokinetics in patients with rheumatoid arthritis. J Clin Pharmacol. 2009 Oct;49(10):1202-9.
- 2179. Schwetz BA. From the Food and Drug Administration. JAMA. 2002 Mar 6;287(9):1103.
- 2180. Scott DL, Kingsley GH. Tumor necrosis factor inhibitors for rheumatoid arthritis. N Engl J Med. 2006 Aug 17;355(7):704-12.
- 2181. Scrivo R, Conti F, Spinelli FR, et al. Switching between TNFalpha antagonists in rheumatoid arthritis: personal experience and review of the literature. Reumatismo. 2009 Apr-Jun;61(2):107-17.
- 2182. Scuderi F, Convertino R, Molino N, et al. Effect of pro-inflammatory/anti-inflammatory agents on cytokine secretion by peripheral blood mononuclear cells in rheumatoid arthritis and systemic lupus erythematosus. Autoimmunity. 2003 Mar;36(2):71-7.
- 2183. Seidl C, Donner H, Fischer B, et al. CTLA4 codon 17 dimorphism in patients with rheumatoid arthritis. Tissue Antigens. 1998 Jan;51(1):62-6.
- 2184. Seitz CS, Berens N, Brocker EB, et al. Leg ulceration in rheumatoid arthritis--an underreported multicausal complication with considerable morbidity: analysis of thirty-six patients and review of the literature.

 Dermatology. 2010;220(3):268-73.
- 2185. Seitz M, Loetscher P, Dewald B, et al. Production of interleukin-1 receptor antagonist, inflammatory chemotactic proteins, and prostaglandin E by rheumatoid and osteoarthritic synoviocytes--regulation by IFN-gamma and IL-4. J Immunol. 1994 Feb 15;152(4):2060-5.
- 2186. Seitz M, Zwicker M, Villiger PM.
 Pretreatment cytokine profiles of peripheral blood mononuclear cells and serum from patients with rheumatoid arthritis in different american college of rheumatology response groups to methotrexate. J
 Rheumatol. 2003 Jan;30(1):28-35.

- 2187. Sekigawa I, Yanagida M, Iwabuchi K, et al. Protein biomarker analysis by mass spectrometry in patients with rheumatoid arthritis receiving anti-tumor necrosis factoralpha antibody therapy. Clin Exp Rheumatol. 2008 Mar-Apr;26(2):261-7.
- 2188. Sekiguchi N, Kawauchi S, Furuya T, et al. Messenger ribonucleic acid expression profile in peripheral blood cells from RA patients following treatment with an anti-TNF-alpha monoclonal antibody, infliximab. Rheumatology (Oxford). 2008 Jun;47(6):780-8.
- 2189. Sekiya H, Horii T, Kariya Y, et al. Arthroscopic-assisted tibiotalocalcaneal arthrodesis using an intramedullary nail with fins: a case report. J Foot Ankle Surg. 2006 Jul-Aug;45(4):266-70.
- 2190. Sellam J, Bouvard B, Masson C, et al. Use of infliximab to treat psoriatic arthritis in HIV-positive patients. Joint Bone Spine. 2007 Mar;74(2):197-200.
- 2191. Semmler M, Seeck U, Neustadt B, et al. No effects of adalimumab therapy on the activation of NF-kappaB in lymphocytes from patients with severe rheumatoid arthritis. Clin Rheumatol. 2007 Sep;26(9):1499-504.
- 2192. Sennels H, Sorensen S, Ostergaard M, et al. Circulating levels of osteopontin, osteoprotegerin, total soluble receptor activator of nuclear factor-kappa B ligand, and high-sensitivity C-reactive protein in patients with active rheumatoid arthritis randomized to etanercept alone or in combination with methotrexate. Scand J Rheumatol. 2008 Jul-Aug;37(4):241-7.
- 2193. Seong SS, Choi CB, Woo JH, et al. Incidence of tuberculosis in Korean patients with rheumatoid arthritis (RA): effects of RA itself and of tumor necrosis factor blockers. J Rheumatol. 2007 Apr;34(4):706-11.
- 2194. Serelis J, Kontogianni MD, Katsiougiannis S, et al. Effect of anti-TNF treatment on body composition and serum adiponectin levels of women with rheumatoid arthritis. Clin Rheumatol. 2008 Jun;27(6):795-7.

- 2195. Seriolo B, Ferretti V, Sulli A, et al. Serum prolactin concentrations in male patients with rheumatoid arthritis. Ann N Y Acad Sci. 2002 Jun;966:258-62.
- 2196. Seriolo B, Paolino S, Sulli A, et al. Effects of anti-TNF-alpha treatment on lipid profile in patients with active rheumatoid arthritis.

 Ann N Y Acad Sci. 2006 Jun;1069:414-9.
- 2197. Seriolo B, Paolino S, Sulli A, et al. Bone metabolism changes during anti-TNF-alpha therapy in patients with active rheumatoid arthritis. Ann N Y Acad Sci. 2006 Jun;1069:420-7.
- 2198. Seror P, Pluvinage P, d'Andre FL, et al. Frequency of sepsis after local corticosteroid injection (an inquiry on 1160000 injections in rheumatological private practice in France). Rheumatology (Oxford). 1999 Dec;38(12):1272-4.
- 2199. Seror R, Sordet C, Guillevin L, et al. Tolerance and efficacy of rituximab and changes in serum B cell biomarkers in patients with systemic complications of primary Sjogren's syndrome. Ann Rheum Dis. 2007 Mar;66(3):351-7.
- 2200. Serratrice J, Granel B, Disdier P, et al. Resolution with etanercept of nephrotic syndrome due to renal AA amyloidosis in adult Still's disease. Am J Med. 2003 Nov;115(7):589-90.
- 2201. Setoguchi S, Schneeweiss S, Avorn J, et al. Tumor necrosis factor-alpha antagonist use and heart failure in elderly patients with rheumatoid arthritis. Am Heart J 2008;156(2):336-41.
- 2202. Seton M. Giant cell arteritis in a patient taking etanercept and methotrexate. J Rheumatol. 2004 Jul;31(7):1467.
- 2203. Settas LD, Tsimirikas G, Vosvotekas G, et al. Reactivation of pulmonary tuberculosis in a patient with rheumatoid arthritis during treatment with IL-1 receptor antagonists (anakinra). J Clin Rheumatol. 2007 Aug;13(4):219-20.

- 2204. Settergren M, Tornvall P. Does TNF-alpha blockade cause plaque rupture? Atherosclerosis. 2004 Mar;173(1):149.
- 2205. Sfikakis PP. The first decade of biologic TNF antagonists in clinical practice: lessons learned, unresolved issues and future directions. Curr Dir Autoimmun. 2010;11:180-210.
- 2206. Sfikakis PP, Iliopoulos A, Elezoglou A, et al. Psoriasis induced by anti-tumor necrosis factor therapy: a paradoxical adverse reaction. Arthritis Rheum. 2005
 Aug;52(8):2513-8.
- 2207. Shadick NA, Fanta CH, Weinblatt ME, et al. Bronchiectasis. A late feature of severe rheumatoid arthritis. Medicine (Baltimore). 1994 May;73(3):161-70.
- 2208. Shakiba K, Falcone T. Tumour necrosis factor-alpha blockers: potential limitations in the management of advanced endometriosis? A case report. Hum Reprod. 2006 Sep;21(9):2417-20.
- 2209. Shakoor N, Michalska M, Harris CA, et al. Drug-induced systemic lupus erythematosus associated with etanercept therapy. Lancet. 2002 Feb 16;359(9306):579-80.
- 2210. Shan SJ, Wu EI, Akpek EK. Sterile corneal melt after descemet stripping endothelial keratoplasty in patients with previously undiagnosed Sjogren syndrome. Arch Ophthalmol. 2009 Feb;127(2):219-20.
- 2211. Sharma A, Baethge BA, Acebes JC, et al. Arthroscopic lavage treatment in rheumatoid arthritis of the knee. J Rheumatol. 1996 Nov;23(11):1872-4.
- 2212. Sharma S, Das M, Kumar A, et al.
 Interaction of genes from influxmetabolism-efflux pathway and their
 influence on methotrexate efficacy in
 rheumatoid arthritis patients among Indians.
 Pharmacogenet Genomics. 2008
 Dec;18(12):1041-9.
- 2213. Sharma S, Das M, Kumar A, et al. Purine biosynthetic pathway genes and methotrexate response in rheumatoid arthritis patients among north Indians.

- Pharmacogenet Genomics. 2009 Oct;19(10):823-8.
- 2214. Shastri V, Betkerur J, Kushalappa PA, et al. Severe cutaneous adverse drug reaction to leflunomide: a report of five cases. Indian J Dermatol Venereol Leprol. 2006 Jul-Aug;72(4):286-9.
- 2215. Shawe D, Hesp R, Gumpel JM, et al. Physical activity as a determinant of bone conservation in the radial diaphysis in rheumatoid arthritis. Ann Rheum Dis. 1993 Aug;52(8):579-81.
- 2216. Shbeeb M, Uramoto KM, Gibson LE, et al. The epidemiology of psoriatic arthritis in Olmsted County, Minnesota, USA, 1982-1991. J Rheumatol. 2000 May;27(5):1247-50.
- 2217. Shedd AD, Reddy SG, Meffert JJ, et al. Acute onset of rash and oligoarthritis. J Fam Pract. 2007 Oct;56(10):811-4.
- 2218. Shehan JM, Sarma DP. Mycobacterium mucogenicum: report of a skin infection associated with etanercept. Dermatol Online J. 2008;14(1):5.
- 2219. Shergy WJ, Isern RA, Cooley DA, et al. Open label study to assess infliximab safety and timing of onset of clinical benefit among patients with rheumatoid arthritis. J Rheumatol. 2002 Apr;29(4):667-77.
- 2220. Sherrer Y. Abatacept in biologic-naive patients and TNF inadequate responders: clinical data in focus. Curr Med Res Opin. 2008 Aug;24(8):2283-94.
- 2221. Shibata S, Ubara Y, Sawa N, et al. Severe interstitial cystitis associated with Sjogren's syndrome. Intern Med. 2004 Mar;43(3):248-52.
- 2222. Shih WJ, Ghesani N, Hongming Z, et al. F-18 FDG positron emission tomography demonstrates resolution of non-Hodgkin's lymphoma of the parotid gland in a patient with Sjogren's syndrome: before and after anti-CD20 antibody rituximab therapy. Clin Nucl Med. 2002 Feb;27(2):142-3.

- 2223. Shimada K, Matsui T, Kawakami M, et al. Methotrexate-related lymphomatoid granulomatosis: a case report of spontaneous regression of large tumours in multiple organs after cessation of methotrexate therapy in rheumatoid arthritis. Scand J Rheumatol. 2007 Jan-Feb;36(1):64-7.
- 2224. Shimizu H, Miyashita N, Obase Y, et al. An asymptomatic case of pulmonary cryptococcosis with endobronchial polypoid lesions and bilateral infiltrative shadow. J Infect Chemother. 2008 Aug;14(4):315-8.
- 2225. Shimojima Y, Ishii W, Matsuda M, et al. Cytomegalovirus-induced infectious mononucleosis-like syndrome in a rheumatoid arthritis patient treated with methotrexate and infliximab. Intern Med. 2010;49(10):937-40.
- 2226. Shimoyama M, Ohtahara A, Fukui H, et al. Acute secondary gastrointestinal amyloidosis in a patient with rheumatoid arthritis. Am J Med Sci. 2003 Sep;326(3):145-7.
- 2227. Shimura C, Satoh T, Takayama K, et al. Methotrexate-related lymphoproliferative disorder with extensive vascular involvement in a patient with rheumatoid arthritis. J Am Acad Dermatol. 2009 Jul;61(1):126-9.
- 2228. Shin IS, Baer AN, Kwon HJ, et al. Guillain-Barre and Miller Fisher syndromes occurring with tumor necrosis factor alpha antagonist therapy. Arthritis Rheum. 2006 May;54(5):1429-34.
- 2229. Shin K, Lee JC, Choi HJ, et al. Radiation synovectomy using 188Re-tin colloid improves knee synovitis as shown by MRI in refractory rheumatoid arthritis. Nucl Med Commun. 2007 Apr;28(4):239-44.
- 2230. Shin SJ, Na KS, Jung SS, et al. Acute acalculous cholecystitis associated with systemic lupus erythematosus with Sjogren's syndrome. Korean J Intern Med. 2002 Mar;17(1):61-4.
- 2231. Shingu M, Fujikawa Y, Wada T, et al.
 Increased IL-1 receptor antagonist (IL-1ra)
 production and decreased IL-1 beta/IL-1ra
 ratio in mononuclear cells from rheumatoid

- arthritis patients. Br J Rheumatol. 1995 Jan;34(1):24-30.
- 2232. Shinoda K, Taki H, Hounoki H, et al. Severe autoimmune hemolytic anemia associated with IgM warm auto-antibodies in primary Sjogren's syndrome. Int J Rheum Dis. 2010 Feb 1;13(1):94-6.
- 2233. Shinozaki M, Inoue E, Nakajima A, et al. Elevation of serum matrix metalloproteinase-3 as a predictive marker for the long-term disability of rheumatoid arthritis patients in a prospective observational cohort IORRA. Mod Rheumatol. 2007;17(5):403-8.
- 2234. Shio K, Homma F, Kanno Y, et al. Doppler sonographic comparative study on usefulness of synovial vascularity between knee and metacarpophalangeal joints for evaluation of articular inflammation in patients with rheumatoid arthritis treated by infliximab. Mod Rheumatol. 2006;16(4):220-5.
- 2235. Shoda H, Inokuma S, Yajima N, et al. Higher maximal serum concentration of methotrexate predicts the incidence of adverse reactions in Japanese rheumatoid arthritis patients. Mod Rheumatol. 2007;17(4):311-6.
- 2236. Sholsberg J, Jackson R. Best evidence topic report. Intra-articular corticosteroid injections in acute rheumatoid monoarthritides. Emerg Med J. 2004 Mar;21(2):204.
- 2237. Shovman O, Anouk M, Vinnitsky N, et al. QuantiFERON-TB Gold in the identification of latent tuberculosis infection in rheumatoid arthritis: a pilot study. Int J Tuberc Lung Dis. 2009 Nov;13(11):1427-32.
- 2238. Shrestha RK, Stoller JK, Honari G, et al. Pneumonia due to Cryptococcus neoformans in a patient receiving infliximab: possible zoonotic transmission from a pet cockatiel. Respir Care. 2004 Jun;49(6):606-8.
- 2239. Shrim A, Koren G. Tumour necrosis factor alpha and use of infliximab. Safety during pregnancy. Can Fam Physician. 2005
 May;51:667-8.

- 2240. Sibbitt WL, Jr., Peisajovich A, Michael AA, et al. Does sonographic needle guidance affect the clinical outcome of intraarticular injections? J Rheumatol. 2009 Sep;36(9):1892-902.
- 2241. Sibilia J, Javier RM, Albert A, et al. Pancytopenia secondary to hemophagocytic syndrome in rheumatoid arthritis treated with methotrexate and sulfasalazine. J Rheumatol. 1998 Jun;25(6):1218-20.
- 2242. Sichletidis L, Settas L, Spyratos D, et al. Tuberculosis in patients receiving anti-TNF agents despite chemoprophylaxis. Int J Tuberc Lung Dis. 2006 Oct;10(10):1127-32.
- 2243. Sicotte NL, Voskuhl RR. Onset of multiple sclerosis associated with anti-TNF therapy. Neurology. 2001 Nov 27;57(10):1885-8.
- 2244. Sidiropoulos P, Bertsias G, Kritikos HD, et al. Infliximab treatment for rheumatoid arthritis, with dose titration based on the Disease Activity Score: dose adjustments are common but not always sufficient to assure sustained benefit. Ann Rheum Dis. 2004 Feb;63(2):144-8.
- 2245. Sidiropoulos P, Kritikos HD, Siakka P, et al. Low dose of infliximab is inadequate in most patients with spondylarthropathies. Clin Exp Rheumatol. 2005 Jul-Aug;23(4):513-6.
- 2246. Sidiropoulos PI, Siakka P, Pagonidis K, et al. Sustained improvement of vascular endothelial function during anti-TNFalpha treatment in rheumatoid arthritis patients. Scand J Rheumatol. 2009 Jan-Feb;38(1):6-10.
- 2247. Sidiropoulos PI, Siakka P, Raptopoulou A, et al. An open label, single dose study to evaluate the safety, efficacy, and effects on CD25 expression of ciclosporin in patients with active rheumatoid arthritis despite treatment with methotrexate and infliximab. Ann Rheum Dis. 2006 Apr;65(4):538-41.
- 2248. Sieper J, Baraliakos X, Listing J, et al.
 Persistent reduction of spinal inflammation
 as assessed by magnetic resonance imaging
 in patients with ankylosing spondylitis after
 2 yrs of treatment with the anti-tumour
 necrosis factor agent infliximab.

- Rheumatology (Oxford). 2005 Dec;44(12):1525-30.
- 2249. Sills ES, Perloe M, Tucker MJ, et al. Successful ovulation induction, conception, and normal delivery after chronic therapy with etanercept: a recombinant fusion anticytokine treatment for rheumatoid arthritis. Am J Reprod Immunol. 2001

 Nov;46(5):366-8.
- 2250. Simms R, Kipgen D, Dahill S, et al. ANCA-associated renal vasculitis following anti-tumor necrosis factor alpha therapy. Am J Kidney Dis. 2008 Mar;51(3):e11-4.
- 2251. Simsek I, Erdem H, Pay S, et al. Optic neuritis occurring with anti-tumour necrosis factor alpha therapy. Ann Rheum Dis. 2007 Sep;66(9):1255-8.
- 2252. Singh JA, Mahowald ML. Intra-articular botulinum toxin A as an adjunctive therapy for refractory joint pain in patients with rheumatoid arthritis receiving biologics: a report of two cases. Joint Bone Spine. 2009 Mar;76(2):190-4.
- 2253. Singh JA, Noorbaloochi S, Singh G. Golimumab for rheumatoid arthritis. Cochrane Database Syst Rev 2010(1):CD008341.
- 2254. Singh JA, Pando JA, Tomaszewski J, et al. Quantitative analysis of immunohistologic features of very early rheumatoid synovitis in disease modifying antirheumatic drugand corticosteroid-naive patients. J Rheumatol. 2004 Jul;31(7):1281-5.
- 2255. Singh P, Taylor SF, Murali R, et al.
 Disseminated mucormycosis and orbital
 ischaemia in combination
 immunosuppression with a tumour necrosis
 factor alpha inhibitor. Clin Experiment
 Ophthalmol. 2007 Apr;35(3):275-80.
- 2256. Singh R, Cuchacovich R, Huang W, et al. Infliximab treatment in a patient with rheumatoid arthritis on hemodialysis. J Rheumatol. 2002 Mar;29(3):636-7.
- 2257. Singh S, Samant R, Joshi VR. Adult onset Still's disease: a study of 14 cases. Clin Rheumatol. 2008 Jan;27(1):35-9.

- 2258. Sinha A, Patient C. Rheumatoid arthritis in pregnancy: successful outcome with anti-TNF agent (Etanercept). J Obstet Gynaecol. 2006 Oct;26(7):689-91.
- 2259. Sinigaglia L, Nervetti A, Mela Q, et al. A multicenter cross sectional study on bone mineral density in rheumatoid arthritis. Italian Study Group on Bone Mass in Rheumatoid Arthritis. J Rheumatol. 2000 Nov;27(11):2582-9.
- 2260. Sinsawaiwong S, Tiyapun N, Hirunpat C, et al. Simultaneous bilateral painful ophthalmoplegia and exudative retinal detachment in rheumatoid arthritis. J Med Assoc Thai. 1999 Nov;82(11):1170-3.
- 2261. Slifman NR, Gershon SK, Lee JH, et al. Listeria monocytogenes infection as a complication of treatment with tumor necrosis factor alpha-neutralizing agents. Arthritis Rheum. 2003 Feb;48(2):319-24.
- 2262. Sliwinska-Stanczyk P, Pazdur J, Ziolkowska M, et al. The effect of methylprednisolone on proliferation of PBMCs obtained from steroid-sensitive and steroid-resistant rheumatoid arthritis patients. Scand J Rheumatol. 2007 May-Jun;36(3):167-71.
- 2263. Slovis BS, Eyler AE. A 33-year-old man with pharyngitis, transient rash, and multiorgan system failure. Chest. 2007 Sep;132(3):1080-3.
- 2264. Smedby KE, Hjalgrim H, Askling J, et al. Autoimmune and chronic inflammatory disorders and risk of non-Hodgkin lymphoma by subtype. J Natl Cancer Inst. 2006 Jan 4;98(1):51-60.
- 2265. Smeets TJ, Kraan MC, van Loon ME, et al. Tumor necrosis factor alpha blockade reduces the synovial cell infiltrate early after initiation of treatment, but apparently not by induction of apoptosis in synovial tissue. Arthritis Rheum. 2003 Aug;48(8):2155-62.
- 2266. Smith AP, Musacchio MJ, O'Toole JE. Spinal epidural abscess associated with infliximab treatment for psoriatic arthritis. Case report. J Neurosurg Spine. 2008 Sep;9(3):261-4.

- 2267. Smith D, Letendre S. Viral pneumonia as a serious complication of etanercept therapy. Ann Intern Med. 2002 Jan 15;136(2):174.
- 2268. Smith GR, Tymms KE, Falk M. Etanercept treatment of renal amyloidosis complicating rheumatoid arthritis. Intern Med J. 2004 Sep-Oct;34(9-10):570-2.
- 2269. Smith KJ, Skelton HG. Rapid onset of cutaneous squamous cell carcinoma in patients with rheumatoid arthritis after starting tumor necrosis factor alpha receptor IgG1-Fc fusion complex therapy. J Am Acad Dermatol. 2001 Dec;45(6):953-6.
- 2270. Smith MD, Slavotinek J, Au V, et al. Successful treatment of rheumatoid arthritis is associated with a reduction in synovial membrane cytokines and cell adhesion molecule expression. Rheumatology (Oxford). 2001 Sep;40(9):965-77.
- 2271. Smith N, Ding T, Butt S, et al. The importance of the baseline Disease Activity Score 28 in determining responders and non-responders to anti-TNF in UK clinical practice. Rheumatology (Oxford). 2008 Sep;47(9):1389-91.
- 2272. Smitten AL, Choi HK, Hochberg MC, et al. The risk of herpes zoster in patients with rheumatoid arthritis in the United States and the United Kingdom. Arthritis Rheum 2007;57(8):1431-8.
- 2273. Smitten AL, Choi HK, Hochberg MC, et al. The risk of hospitalized infection in patients with rheumatoid arthritis. J Rheumatol 2008;35(3):387-93.
- 2274. Smolen J, Landewe RB, Mease P, et al. Efficacy and safety of certolizumab pegol plus methotrexate in active rheumatoid arthritis: the RAPID 2 study. A randomised controlled trial. Ann Rheum Dis 2009;68(6):797-804.
- 2275. Smolen JS, Beaulieu A, Rubbert-Roth A, et al. Effect of interleukin-6 receptor inhibition with tocilizumab in patients with rheumatoid arthritis (OPTION study): a double-blind, placebo-controlled, randomised trial. Lancet 2008;371(9617):987-97.

- 2276. Smolen JS, Han C, Bala M, et al. Evidence of radiographic benefit of treatment with infliximab plus methotrexate in rheumatoid arthritis patients who had no clinical improvement: a detailed subanalysis of data from the anti-tumor necrosis factor trial in rheumatoid arthritis with concomitant therapy study. Arthritis Rheum 2005;52(4):1020-30.
- 2277. Smolen JS, Han C, van der Heijde D, et al. Infliximab treatment maintains employability in patients with early rheumatoid arthritis. Arthritis Rheum. 2006 Mar;54(3):716-22.
- 2278. Smolen JS, Han C, van der Heijde DM, et al. Radiographic changes in rheumatoid arthritis patients attaining different disease activity states with methotrexate monotherapy and infliximab plus methotrexate: the impacts of remission and tumour necrosis factor blockade. Ann Rheum Dis 2009:68(6):823-7.
- 2279. Smolen JS, Kay J, Doyle MK, et al. Golimumab in patients with active rheumatoid arthritis after treatment with tumour necrosis factor alpha inhibitors (GO-AFTER study): a multicentre, randomised, double-blind, placebo-controlled, phase III trial. Lancet 2009;374(9685):210-21.
- 2280. Snowden JA, Biggs JC, Milliken ST, et al. A phase I/II dose escalation study of intensified cyclophosphamide and autologous blood stem cell rescue in severe, active rheumatoid arthritis. Arthritis Rheum. 1999 Nov;42(11):2286-92.
- 2281. Sobhani I, Brousse N, Vissuzaine C, et al. A diffuse T lymphocytic gastrointestinal mucosal infiltration associated with Sjogren's syndrome resulting in a watery diarrhea syndrome and responsive to immunosuppressive therapy. Am J Gastroenterol. 1998 Dec;93(12):2584-6.
- 2282. Soderlin MK, Lindroth Y, Jacobsson LT. Trends in medication and health-related quality of life in a population-based rheumatoid arthritis register in Malmo, Sweden. Rheumatology (Oxford) 2007;46(8):1355-8.

- 2283. Soh MC, Hart HH, Corkill M. Pericardial effusions with tamponade and visceral constriction in patients with rheumatoid arthritis on tumour necrosis factor (TNF)-inhibitor therapy. Int J Rheum Dis. 2009 Apr;12(1):74-7.
- 2284. Sokka T, Kautiainen H, Toloza S, et al. QUEST-RA: quantitative clinical assessment of patients with rheumatoid arthritis seen in standard rheumatology care in 15 countries. Ann Rheum Dis. 2007 Nov;66(11):1491-6.
- 2285. Sokka T, Mottonen T, Hannonen P.

 Mortality in early "sawtooth" treated rheumatoid arthritis patients during the first 8-14 years. Scand J Rheumatol. 1999;28(5):282-7.
- 2286. Sokka T, Pincus T. Contemporary disease modifying antirheumatic drugs (DMARD) in patients with recent onset rheumatoid arthritis in a US private practice: methotrexate as the anchor drug in 90% and new DMARD in 30% of patients. J Rheumatol. 2002 Dec;29(12):2521-4.
- 2287. Sokka T, Pincus T. Eligibility of patients in routine care for major clinical trials of antitumor necrosis factor alpha agents in rheumatoid arthritis. Arthritis Rheum. 2003 Feb;48(2):313-8.
- 2288. Sokka T, Pincus T. Ascendancy of weekly low-dose methotrexate in usual care of rheumatoid arthritis from 1980 to 2004 at two sites in Finland and the United States. Rheumatology (Oxford). 2008 Oct;47(10):1543-7.
- 2289. Sokolove J, Strand V, Greenberg JD, et al. Risk of elevated liver enzymes associated with TNF inhibitor utilisation in patients with rheumatoid arthritis. Ann Rheum Dis 2010;69(9):1612-7.
- 2290. Sokolovic S, Kasumagic S, Mackic-Durovic M, et al. The impact of Rituximab therapy on the chromosomes of patients with Rheumatoid arthritis. Bosn J Basic Med Sci. 2010 May;10(2):121-4.
- 2291. Solau-Gervais E, Legrand JL, Cortet B, et al. Magnetic resonance imaging of the hand for the diagnosis of rheumatoid arthritis in

- the absence of anti-cyclic citrullinated peptide antibodies: a prospective study. J Rheumatol. 2006 Sep;33(9):1760-5.
- 2292. Soliotis F, Glover M, Jawad AS. Severe skin reaction after leflunomide and etanercept in a patient with rheumatoid arthritis. Ann Rheum Dis. 2002 Sep;61(9):850-1.
- 2293. Solomon DH, Katz JN, Cabral D, et al. Osteoporosis management in patients with rheumatoid arthritis: Evidence for improvement. Arthritis Rheum. 2006 Dec 15;55(6):873-7.
- 2294. Solomon DH, Kuntz KM. Should postmenopausal women with rheumatoid arthritis who are starting corticosteroid treatment be screened for osteoporosis? A cost-effectiveness analysis. Arthritis Rheum. 2000 Sep;43(9):1967-75.
- 2295. Solomon DH, Stedman M, Licari A, et al. Agreement between patient report and medical record review for medications used for rheumatoid arthritis: the accuracy of self-reported medication information in patient registries. Arthritis Rheum. 2007 Mar 15;57(2):234-9.
- 2296. Somer BG, Tsai DE, Downs L, et al. Improvement in Sjogren's syndrome following therapy with rituximab for marginal zone lymphoma. Arthritis Rheum. 2003 Jun 15;49(3):394-8.
- 2297. Sommer WH, Ganiere V, Gachoud D, et al. Neurological and pulmonary adverse effects of subcutaneous methotrexate therapy. Scand J Rheumatol. 2008 Jul-Aug;37(4):306-9.
- 2298. Sorajja P, Poirier MK, Bundrick JB, et al. Autonomic failure and proximal skeletal myopathy in a patient with primary Sjogren syndrome. Mayo Clin Proc. 1999 Jul;74(7):695-7.
- 2299. Sordet C, Gottenberg JE, Hellmich B, et al. Lack of efficacy of rituximab in Felty's syndrome. Ann Rheum Dis. 2005 Feb;64(2):332-3.
- 2300. Sorensen LK, Havemose-Poulsen A, Bendtzen K, et al. Aggressive periodontitis

- and chronic arthritis: blood mononuclear cell gene expression and plasma protein levels of cytokines and cytokine inhibitors. J Periodontol. 2009 Feb;80(2):282-9.
- 2301. Soubrier M, Haik S, Hauw JJ, et al.
 Creutzfeldt-Jakob disease in a patient treated
 by etanercept for rheumatoid arthritis (RA):
 just a coincidence? Joint Bone Spine. 2010
 Mar;77(2):174-5.
- 2302. Soubrier M, Jeannin G, Kemeny JL, et al. Organizing pneumonia after rituximab therapy: Two cases. Joint Bone Spine. 2008 May;75(3):362-5.
- 2303. Soubrier M, Jouanel P, Mathieu S, et al. Effects of anti-tumor necrosis factor therapy on lipid profile in patients with rheumatoid arthritis. Joint Bone Spine. 2008

 Jan;75(1):22-4.
- 2304. Soubrier M, Mathieu S, Payet S, et al. Elderly-onset rheumatoid arthritis. Joint Bone Spine. 2010 Jul;77(4):290-6.
- 2305. Soubrier M, Puechal X, Sibilia J, et al. Evaluation of two strategies (initial methotrexate monotherapy vs its combination with adalimumab) in management of early active rheumatoid arthritis: data from the GUEPARD trial. Rheumatology (Oxford). 2009
 Nov;48(11):1429-34.
- 2306. Sowter MC, Burgess NA, Woodsford PV, et al. Delayed presentation of an extradural abscess complicating thoracic extradural analgesia. Br J Anaesth. 1992
 Jan;68(1):103-5.
- 2307. Spadaro A, Scrivo R, Riccieri V, et al. Effect of tumor necrosis factor alpha antagonists in a patient with rheumatoid arthritis and primary biliary cirrhosis. Joint Bone Spine. 2008 Jan;75(1):87-9.
- 2308. Spalding JR, Hay J. Cost effectiveness of tumour necrosis factor-alpha inhibitors as first-line agents in rheumatoid arthritis. Pharmacoeconomics. 2006;24(12):1221-32.
- 2309. Spanakis E, Sidiropoulos P, Papadakis J, et al. Modest but sustained increase of serum high density lipoprotein cholesterol levels in

- patients with inflammatory arthritides treated with infliximab. J Rheumatol. 2006 Dec;33(12):2440-6.
- 2310. Sperling RI, Coblyn JS, Larkin JK, et al. Inhibition of leukotriene B4 synthesis in neutrophils from patients with rheumatoid arthritis by a single oral dose of methotrexate. Arthritis Rheum. 1990 Aug;33(8):1149-55.
- 2311. Sprekeler R, Lemmel EM, Obert HJ.
 Correlation of clinical and serological
 findings in patients with rheumatoid arthritis
 treated for one year with interferon-gamma.
 Z Rheumatol. 1990 Jan-Feb;49(1):1-7.
- 2312. Squirrell DM, Winfield J, Amos RS.
 Peripheral ulcerative keratitis 'corneal melt'
 and rheumatoid arthritis: a case series.
 Rheumatology (Oxford). 1999
 Dec;38(12):1245-8.
- 2313. Sri JC, Tsai CL, Deng A, et al.
 Osteomyelitis occurring during infliximab treatment of severe psoriasis. J Drugs
 Dermatol. 2007 Feb;6(2):207-10.
- 2314. Srivastava KC, Mustafa T. Ginger (Zingiber officinale) in rheumatism and musculoskeletal disorders. Med Hypotheses. 1992 Dec;39(4):342-8.
- 2315. St Clair EW, van der Heijde DM, Smolen JS, et al. Combination of infliximab and methotrexate therapy for early rheumatoid arthritis: a randomized, controlled trial. Arthritis Rheum. 2004 Nov;50(11):3432-43.
- 2316. Stafford L, Bleasel J, Giles A, et al.
 Androgen deficiency and bone mineral
 density in men with rheumatoid arthritis. J
 Rheumatol. 2000 Dec;27(12):2786-90.
- 2317. Stalenheim G, Gudbjornsson B. Antiinflammatory drugs do not alleviate bronchial hyperreactivity in Sjogren's syndrome. Allergy. 1997 Apr;52(4):423-7.
- 2318. Stamp LK, O'Donnell JL, Chapman PT, et al. Determinants of red blood cell methotrexate polyglutamate concentrations in rheumatoid arthritis patients receiving long-term methotrexate treatment. Arthritis Rheum. 2009 Aug;60(8):2248-56.

- 2319. Stamp LK, O'Donnell JL, Chapman PT, et al. Methotrexate polyglutamate concentrations are not associated with disease control in rheumatoid arthritis patients receiving long-term methotrexate therapy. Arthritis Rheum. 2010 Feb;62(2):359-68.
- 2320. Stanescu D, Bodaghi B, Huong du LT, et al. Pseudotumor cerebri associated with Sjogren's syndrome. Graefes Arch Clin Exp Ophthalmol. 2003 Apr;241(4):339-42.
- 2321. Starmans-Kool MJ, Peeters HR, Houben HH. Pustular skin lesions in patients treated with infliximab: report of two cases.

 Rheumatol Int. 2005 Sep;25(7):550-2.
- 2322. Starosta MA, Brandwein SR. Clinical manifestations and treatment of rheumatoid pachymeningitis. Neurology. 2007 Mar 27;68(13):1079-80.
- 2323. Steens SC, Steup-Beekman GM, Bosma GP, et al. The effect of corticosteroid medication on quantitative MR parameters of the brain. AJNR Am J Neuroradiol. 2005 Nov-Dec;26(10):2475-80.
- 2324. Steinfeld SD, Demols P, Salmon I, et al. Infliximab in patients with primary Sjogren's syndrome: a pilot study. Arthritis Rheum. 2001 Oct;44(10):2371-5.
- 2325. Stepien KE, Han DP, Schell J, et al. Spectral-domain optical coherence tomography and adaptive optics may detect hydroxychloroquine retinal toxicity before symptomatic vision loss. Trans Am Ophthalmol Soc. 2009 Dec;107:28-33.
- 2326. Sterling LP. Rheumatoid arthritis: current concepts and management, Part 2. Am Pharm. 1990 Sep;NS30(9):49-54.
- 2327. Stern R, Wolfe F. Infliximab dose and clinical status: results of 2 studies in 1642 patients with rheumatoid arthritis. J Rheumatol. 2004 Aug;31(8):1538-45.
- 2328. Sterry W, Ortonne JP, Kirkham B, et al.
 Comparison of two etanercept regimens for
 treatment of psoriasis and psoriatic arthritis:
 PRESTA randomised double blind
 multicentre trial. Bmj. 2010;340:c147.

- 2329. Stewart M, Malkovska V, Krishnan J, et al. Lymphoma in a patient with rheumatoid arthritis receiving methotrexate treatment: successful treatment with rituximab. Ann Rheum Dis. 2001 Sep;60(9):892-3.
- 2330. Stewart MW, Palmer DG, Knight RG. A self-report articular index measure of arthritic activity: investigations of reliability, validity and sensitivity. J Rheumatol. 1990 Aug;17(8):1011-5.
- 2331. Stock CJ, Ogilvie EM, Samuel JM, et al. Comprehensive association study of genetic variants in the IL-1 gene family in systemic juvenile idiopathic arthritis. Genes Immun. 2008 Jun;9(4):349-57.
- 2332. Stokes MB, Foster K, Markowitz GS, et al. Development of glomerulonephritis during anti-TNF-alpha therapy for rheumatoid arthritis. Nephrol Dial Transplant. 2005 Jul;20(7):1400-6.
- 2333. Stoll ML, Solomon DH, Batra KL, et al. TNFalpha inhibitors may improve asthma symptoms: a case series of 12 patients with rheumatoid arthritis and asthma. J Clin Rheumatol. 2009 Jun;15(4):198-200.
- 2334. Stone M, Salonen D, Lax M, et al. Clinical and imaging correlates of response to treatment with infliximab in patients with ankylosing spondylitis. J Rheumatol. 2001 Jul;28(7):1605-14.
- 2335. Stone MA, Inman RD, Wright JG, et al. Validation exercise of the Ankylosing Spondylitis Assessment Study (ASAS) group response criteria in ankylosing spondylitis patients treated with biologics. Arthritis Rheum. 2004 Jun 15;51(3):316-20.
- 2336. Stone MA, Payne U, Pacheco-Tena C, et al. Cytokine correlates of clinical response patterns to infliximab treatment of ankylosing spondylitis. Ann Rheum Dis. 2004 Jan;63(1):84-7.
- 2337. Strangfeld A, Hierse F, Rau R, et al. Risk of incident or recurrent malignancies among patients with rheumatoid arthritis exposed to biologic therapy in the German biologics register RABBIT. Arthritis Res Ther 2010;12(1):R5.

- 2338. Strangfeld A, Listing J, Herzer P, et al. Risk of herpes zoster in patients with rheumatoid arthritis treated with anti-TNF-alpha agents. Jama 2009;301(7):737-44.
- 2339. Stranzl T, Wolf J, Leeb BF, et al. Expression of folylpolyglutamyl synthetase predicts poor response to methotrexate therapy in patients with rheumatoid arthritis. Clin Exp Rheumatol. 2003 Jan-Feb;21(1):27-32.
- 2340. Stratigos AJ, Antoniou C, Stamathioudaki S, et al. Discoid lupus erythematosus-like eruption induced by infliximab. Clin Exp Dermatol. 2004 Mar;29(2):150-3.
- 2341. Straub RH, Gunzler C, Miller LE, et al. Anti-inflammatory cooperativity of corticosteroids and norepinephrine in rheumatoid arthritis synovial tissue in vivo and in vitro. Faseb J. 2002 Jul;16(9):993-1000.
- 2342. Straub RH, Harle P, Atzeni F, et al. Sex hormone concentrations in patients with rheumatoid arthritis are not normalized during 12 weeks of anti-tumor necrosis factor therapy. J Rheumatol. 2005 Jul;32(7):1253-8.
- 2343. Straub RH, Harle P, Yamana S, et al. Antiinterleukin-6 receptor antibody therapy favors adrenal androgen secretion in patients with rheumatoid arthritis: a randomized, double-blind, placebo-controlled study. Arthritis Rheum. 2006 Jun;54(6):1778-85.
- 2344. Straub RH, Kittner JM, Heijnen C, et al. Infusion of epinephrine decreases serum levels of cortisol and 17-hydroxyprogesterone in patients with rheumatoid arthritis. J Rheumatol. 2002 Aug;29(8):1659-64.
- 2345. Straub RH, Paimela L, Peltomaa R, et al. Inadequately low serum levels of steroid hormones in relation to interleukin-6 and tumor necrosis factor in untreated patients with early rheumatoid arthritis and reactive arthritis. Arthritis Rheum. 2002

 Mar;46(3):654-62.
- 2346. Straub RH, Pongratz G, Cutolo M, et al. Increased cortisol relative to adrenocorticotropic hormone predicts improvement during anti-tumor necrosis

- factor therapy in rheumatoid arthritis. Arthritis Rheum. 2008 Apr;58(4):976-84.
- 2347. Straub RH, Pongratz G, Hirvonen H, et al. Acute cold stress in rheumatoid arthritis inadequately activates stress responses and induces an increase of interleukin 6. Ann Rheum Dis. 2009 Apr;68(4):572-8.
- 2348. Straub RH, Pongratz G, Scholmerich J, et al. Long-term anti-tumor necrosis factor antibody therapy in rheumatoid arthritis patients sensitizes the pituitary gland and favors adrenal androgen secretion. Arthritis Rheum. 2003 Jun;48(6):1504-12.
- 2349. Straub RH, Sarzi-Puttini P, Atzeni F, et al. Anti-tumour necrosis factor antibody treatment does not change serum levels of cortisol binding globulin in patients with rheumatoid arthritis but it increases androstenedione relative to cortisol. Ann Rheum Dis. 2005 Sep;64(9):1353-6.
- 2350. Straub RH, Weidler C, Demmel B, et al. Renal clearance and daily excretion of cortisol and adrenal androgens in patients with rheumatoid arthritis and systemic lupus erythematosus. Ann Rheum Dis. 2004 Aug;63(8):961-8.
- 2351. Strober B, Teller C, Yamauchi P, et al. Effects of etanercept on C-reactive protein levels in psoriasis and psoriatic arthritis. Br J Dermatol. 2008 Aug;159(2):322-30.
- 2352. Strober BE. Successful treatment of psoriasis and psoriatic arthritis with etanercept and methotrexate in a patient newly unresponsive to infliximab. Arch Dermatol. 2004 Mar;140(3):366.
- 2353. Strober BE, Clarke S. Etanercept for the treatment of psoriasis: combination therapy with other modalities. J Drugs Dermatol. 2004 May-Jun;3(3):270-2.
- 2354. Stucki G, Bruhlmann P, Stoll T, et al. Low serum creatine kinase activity is associated with muscle weakness in patients with rheumatoid arthritis. J Rheumatol. 1996 Apr;23(4):603-8.

- 2355. Studenski SA. Rheumatology, geriatrics, and a way forward. J Am Geriatr Soc. 2002 Oct;50(10):1737-8.
- 2356. Suarez-Almazor ME, Soskolne CL, Saunders LD, et al. Use of second line drugs for the treatment of rheumatoid arthritis in Edmonton, Alberta. Patterns of prescription and longterm effectiveness. J Rheumatol. 1995 May;22(5):836-43.
- 2357. Sugihara M, Tsutsumi A, Suzuki E, et al. Effects of infliximab therapy on gene expression levels of tumor necrosis factor alpha, tristetraprolin, T cell intracellular antigen 1, and Hu antigen R in patients with rheumatoid arthritis. Arthritis Rheum. 2007 Jul;56(7):2160-9.
- 2358. Sugimori S, Watanabe T, Tabuchi M, et al. Evaluation of small bowel injury in patients with rheumatoid arthritis by capsule endoscopy: effects of anti-rheumatoid arthritis drugs. Digestion. 2008;78(4):208-13.
- 2359. Sugimoto T, Yasuda M, Sakaguchi M, et al. Acute interstitial nephritis associated with etanercept. Rheumatol Int. 2008
 Oct;28(12):1283-4.
- 2360. Sugioka Y, Inui K, Koike T. Use of etanercept in a patient with rheumatoid arthritis on hemodialysis. Mod Rheumatol. 2008;18(3):293-5.
- 2361. Suissa S, Bernatsky S, Hudson M.
 Antirheumatic drug use and the risk of acute myocardial infarction. Arthritis Rheum 2006;55(4):531-6.
- 2362. Suissa S, Ernst P, Hudson M. TNF-alpha antagonists and the prevention of hospitalisation for chronic obstructive pulmonary disease. Pulm Pharmacol Ther. 2008;21(1):234-8.
- 2363. Suissa S, Hudson M, Ernst P. Leflunomide use and the risk of interstitial lung disease in rheumatoid arthritis. Arthritis Rheum. 2006 May;54(5):1435-9.
- 2364. Sulit DJ, Clarke JE. Psoriatic arthritis in a military aviator. Aviat Space Environ Med. 2005 Jul;76(7):684-8.

- 2365. Sulli A, Maestroni GJ, Villaggio B, et al. Melatonin serum levels in rheumatoid arthritis. Ann N Y Acad Sci. 2002 Jun;966:276-83.
- 2366. Sulli A, Montecucco CM, Caporali R, et al. Glucocorticoid effects on adrenal steroids and cytokine responsiveness in polymyalgia rheumatica and elderly onset rheumatoid arthritis. Ann N Y Acad Sci. 2006
 Jun;1069:307-14.
- 2367. Sundberg E, Grundtman C, Af Klint E, et al. Systemic TNF blockade does not modulate synovial expression of the pro-inflammatory mediator HMGB1 in rheumatoid arthritis patients--a prospective clinical study. Arthritis Res Ther. 2008;10(2):R33.
- 2368. Suresh R, Gupta S, Sathananthan R. Sulphasalazine induced three-week syndrome. J Clin Rheumatol. 2009 Sep;15(6):311-2.
- 2369. Suwannalai P, Auethavekiat P, Udomsubpayakul U, et al. The infectious profiles of anti-tumor necrosis factor agents in a Thai population: a retrospective study a the university-based hospital. Int J Rheum Dis 2009;12(2):118-24.
- 2370. Suzuki K, Kimura Y, Aoki M, et al. Persistent plaques and linear pigmentation in adult-onset Still's disease. Dermatology. 2001;202(4):333-5.
- 2371. Suzuki K, Saito K, Tsujimura S, et al.
 Tacrolimus, a calcineurin inhibitor,
 overcomes treatment unresponsiveness
 mediated by P-glycoprotein on lymphocytes
 in refractory rheumatoid arthritis. J
 Rheumatol. 2010 Mar;37(3):512-20.
- 2372. Suzuki T, Tsutsumi A, Suzuki H, et al. Tristetraprolin (TTP) gene polymorphisms in patients with rheumatoid arthritis and healthy individuals. Mod Rheumatol. 2008;18(5):472-9.
- 2373. Suzuki Y, Inoue K, Chiba J, et al. Histological analysis of synovium by treatment of etanercept for rheumatoid arthritis. Int J Rheum Dis. 2009 Apr;12(1):7-13.

- 2374. Suzuki Y, Mizushima Y. Osteoporosis in rheumatoid arthritis. Osteoporos Int. 1997;7 Suppl 3:S217-22.
- 2375. Suzuki Y, Uehara R, Tajima C, et al. Elevation of serum hepatic aminotransferases during treatment of rheumatoid arthritis with low-dose methotrexate. Risk factors and response to folic acid. Scand J Rheumatol. 1999;28(5):273-81.
- 2376. Svenson M, Geborek P, Saxne T, et al. Monitoring patients treated with anti-TNF-alpha biopharmaceuticals: assessing serum infliximab and anti-infliximab antibodies. Rheumatology (Oxford). 2007 Dec;46(12):1828-34.
- 2377. Svensson B, Ahlmen M, Forslind K.
 Treatment of early RA in clinical practice: a comparative study of two different
 DMARD/corticosteroid options. Clin Exp
 Rheumatol. 2003 May-Jun;21(3):327-32.
- 2378. Svensson B, Hafstrom I, Forslind K, et al. Increased expression of proto-oncogene survivin predicts Joint destruction and persistent disease activity in early rheumatoid arthritis. Ann Med. 2010;42(1):45-54.
- 2379. Svensson B, Schaufelberger C, Teleman A, et al. Remission and response to early treatment of RA assessed by the Disease Activity Score. BARFOT study group. Better Anti-rheumatic Farmacotherapy. Rheumatology (Oxford). 2000 Sep;39(9):1031-6.
- 2380. Swale VJ, Perrett CM, Denton CP, et al. Etanercept-induced systemic lupus erythematosus. Clin Exp Dermatol. 2003 Nov:28(6):604-7.
- 2381. Swaneveld FH, van Vugt RM, de Boer JP, et al. A 57-year-old man who developed arthritis during R-CHOP chemotherapy for non-Hodgkin lymphoma. Clin Rheumatol. 2008 Feb;27(2):249-51.
- 2382. Swanson DL, Barnes SA, Mengden Koon SJ, et al. Caffeine consumption and methotrexate dosing requirement in psoriasis and psoriatic arthritis. Int J Dermatol. 2007 Feb;46(2):157-9.

- 2383. Sweet DD, Isac G, Morrison B, et al. Purulent pericarditis in a patient with rheumatoid arthritis treated with etanercept and methotrexate. Cjem. 2007 Jan;9(1):40-2.
- 2384. Szeto T, Peterson J, Silva F. A case of tuberculous peritonitis in the United States in a patient with rheumatoid arthritis treated with adalimumab. J Clin Rheumatol. 2010 Apr;16(3):135-7.
- 2385. Szturmowicz M, Wilinska E, Paczek A, et al. Primary Sjogren's Syndrome with two extraglandular sites involvement case report. Pneumonol Alergol Pol. 2010;78(6):445-50.
- 2386. Taban M, Dupps WJ, Mandell B, et al. Etanercept (enbrel)-associated inflammatory eye disease: case report and review of the literature. Ocul Immunol Inflamm. 2006 Jun;14(3):145-50.
- 2387. Tack CJ, Kleijwegt FS, Van Riel PL, et al. Development of type 1 diabetes in a patient treated with anti-TNF-alpha therapy for active rheumatoid arthritis. Diabetologia. 2009 Jul;52(7):1442-4.
- 2388. Tada Y, Fukuoka M, Mitamura M, et al. Nocardiosis in adult-onset Still's disease and vasculitis syndrome. Am J Med Sci. 2008 Jul;336(1):77-80.
- 2389. Tai TL, O'Rourke KP, McWeeney M, et al. Pneumocystis carinii pneumonia following a second infusion of infliximab.
 Rheumatology (Oxford). 2002
 Aug;41(8):951-2.
- 2390. Taira T, Matsuyama W, Mitsuyama H, et al. Increased serum high mobility group box-1 level in Churg-Strauss syndrome. Clin Exp Immunol. 2007 May;148(2):241-7.
- 2391. Taiwo B, Lee C, Venkat D, et al. Can tumor necrosis factor alpha blockade predispose to severe babesiosis? Arthritis Rheum. 2007 Feb 15;57(1):179-81.
- 2392. Takahashi A, Takeda I, Kanno T, et al. CD8-positive T cell-induced liver damage was found in a patient with polymyositis. Intern Med. 2006;45(18):1059-63.

- 2393. Takahashi H, Shigehara K, Yamamoto M, et al. Interferon gamma assay for detecting latent tuberculosis infection in rheumatoid arthritis patients during infliximab administration. Rheumatol Int. 2007 Oct;27(12):1143-8.
- 2394. Takahashi H, Tezuka F, Fujita S, et al. Vascular changes in major and lingual minor salivary glands in primary Sjogren's syndrome. Anal Cell Pathol. 1995
 Dec;9(4):243-56.
- 2395. Takahashi M, Mizutani H, Nakamura Y, et al. A case of multicentric reticulohistiocytosis, systemic sclerosis and Sjogren syndrome. J Dermatol. 1997 Aug;24(8):530-4.
- 2396. Takahashi T, Satoh M, Satoh H. Unilateral acute exacerbation of pulmonary fibrosis in association with Sjogren's syndrome. Intern Med. 1996 Oct;35(10):811-4.
- 2397. Takami A, Nakao S, Miyamori H, et al. Adult-onset Still's disease with submassive hepatic necrosis. Intern Med. 1995 Feb;34(2):89-91.
- 2398. Takasugi JE, Godwin JD. Lung abscess caused by Rhodococcus equi. J Thorac Imaging. 1991 Apr;6(2):72-4.
- 2399. Takatori R, Takahashi KA, Tokunaga D, et al. ABCB1 C3435T polymorphism influences methotrexate sensitivity in rheumatoid arthritis patients. Clin Exp Rheumatol. 2006 Sep-Oct;24(5):546-54.
- 2400. Takeuchi T, Miyasaka N, Inoue K, et al. Impact of trough serum level on radiographic and clinical response to infliximab plus methotrexate in patients with rheumatoid arthritis: results from the RISING study. Mod Rheumatol 2009;19(5):478-87.
- 2401. Takeuchi T, Tatsuki Y, Nogami Y, et al. Postmarketing surveillance of the safety profile of infliximab in 5000 Japanese patients with rheumatoid arthritis. Ann Rheum Dis. 2008 Feb;67(2):189-94.
- 2402. Takeuchi T, Yamanaka H, Inoue E, et al. Retrospective clinical study on the notable

- efficacy and related factors of infliximab therapy in a rheumatoid arthritis management group in Japan: one-year outcome of joint destruction (RECONFIRM-2J). Mod Rheumatol. 2008;18(5):447-54.
- 2403. Talip F, Walker N, Khan W, et al. Treatment of Felty's syndrome with leflunomide. J Rheumatol. 2001 Apr;28(4):868-70.
- 2404. Tam LS, Griffith JF, Yu AB, et al. Rapid improvement in rheumatoid arthritis patients on combination of methotrexate and infliximab: clinical and magnetic resonance imaging evaluation. Clin Rheumatol. 2007 Jun;26(6):941-6.
- 2405. Tam LS, Tomlinson B, Chu TT, et al. Impact of TNF inhibition on insulin resistance and lipids levels in patients with rheumatoid arthritis. Clin Rheumatol. 2007 Sep;26(9):1495-8.
- 2406. Tam MM, Meehan CJ. Subcutaneous granuloma annulare in a patient with rheumatoid arthritis and diabetes mellitus.

 Australas J Dermatol. 1996 Nov;37(4):199-201
- 2407. Tambo Y, Fujimura M, Yasui M, et al. Eosinophilic pneumonia (EP) associated with rheumatoid arthritis in which druginduced eosinophilic pneumonia could be ruled out. Intern Med. 2008;47(6):527-31.
- 2408. Tamura S, Koreeda T, Nakano T, et al. A case of rheumatoid arthritis which developed after recovery from adult respiratory distress syndrome. Jpn J Med. 1990 Nov-Dec;29(6):611-5.
- 2409. Tan AL, Marzo-Ortega H, O'Connor P, et al. Efficacy of anakinra in active ankylosing spondylitis: a clinical and magnetic resonance imaging study. Ann Rheum Dis. 2004 Sep;63(9):1041-5.
- 2410. Tan RJ, Gibbons LJ, Potter C, et al.
 Investigation of rheumatoid arthritis
 susceptibility genes identifies association of
 AFF3 and CD226 variants with response to
 anti-tumour necrosis factor treatment. Ann
 Rheum Dis 2010;69(6):1029-35.

- 2411. Tanaka A, Shigematsu H, Kojima M, et al. Methotrexate-associated lymphoproliferative disorder arising in a patient with adult Still's disease. J Oral Maxillofac Surg. 2008 Jul;66(7):1492-5.
- 2412. Tanaka E, Inoue E, Kawaguchi Y, et al. Acceptability and usefulness of mizoribine in the management of rheumatoid arthritis in methotrexate-refractory patients and elderly patients, based on analysis of data from a large-scale observational cohort study. Mod Rheumatol. 2006;16(4):214-9.
- 2413. Tanaka N, Sakahashi H, Hirose K, et al. Volume of a wash and the other conditions for maximum therapeutic effect of arthroscopic lavage in rheumatoid knees. Clin Rheumatol. 2006 Feb;25(1):65-9.
- 2414. Tanaka Y, Takeuchi T, Inoue E, et al. Retrospective clinical study on the notable efficacy and related factors of infliximab therapy in a rheumatoid arthritis management group in Japan: one-year clinical outcomes (RECONFIRM-2). Mod Rheumatol. 2008;18(2):146-52.
- 2415. Tanaka Y, Takeuchi T, Mimori T, et al.
 Discontinuation of infliximab after attaining
 low disease activity in patients with
 rheumatoid arthritis: RRR (remission
 induction by Remicade in RA) study. Ann
 Rheum Dis. 2010 Jul;69(7):1286-91.
- 2416. Tang B, Rahman M, Waters HC, et al.
 Treatment persistence with adalimumab,
 etanercept, or infliximab in combination
 with methotrexate and the effects on health
 care costs in patients with rheumatoid
 arthritis. Clin Ther. 2008 Jul;30(7):1375-84.
- 2417. Taniguchi A, Urano W, Tanaka E, et al. Validation of the associations between single nucleotide polymorphisms or haplotypes and responses to disease-modifying antirheumatic drugs in patients with rheumatoid arthritis: a proposal for prospective pharmacogenomic study in clinical practice. Pharmacogenet Genomics. 2007 Jun;17(6):383-90.
- 2418. Tanno M, Nakajima A, Ishiwata T, et al. Effect of general anesthesia on the abnormal immune response in patients with

- rheumatoid arthritis. Clin Exp Rheumatol. 2004 Nov-Dec;22(6):727-32.
- 2419. Taraborelli M, Andreoli L, Archetti S, et al. Methylenetetrahydrofolate reductase polymorphisms and methotrexate: no association with response to therapy nor with drug-related adverse events in an Italian population of rheumatic patients. Clin Exp Rheumatol 2009;27(3):499-502.
- 2420. Targonska-Stepniak B, Majdan M, Dryglewska M. Leptin serum levels in rheumatoid arthritis patients: relation to disease duration and activity. Rheumatol Int. 2008 Apr;28(6):585-91.
- 2421. Tascioglu F, Oner C, Armagan O. The effect of low-dose methotrexate on bone mineral density in patients with early rheumatoid arthritis. Rheumatol Int. 2003
 Sep;23(5):231-5.
- 2422. Tassiopoulos S, Benopoulou O, Mytilineou E, et al. Late onset of long-lasting fever as a sole complication of treatment with anti-TNFalpha. Clin Exp Rheumatol. 2005 Jan-Feb;23(1):122-3.
- 2423. Tateiwa T, Shinmura K, Ko M, et al. Iliopectineal bursitis associated with rapid destruction of a rheumatoid hip joint. J Orthop Sci. 2009 Jul;14(4):455-8.
- 2424. Tauber T, Turetz J, Barash J, et al. Optic neuritis associated with etanercept therapy for juvenile arthritis. J Aapos. 2006 Feb;10(1):26-9.
- 2425. Taylor JC, Orkin R, Lanham J. Tuberculosis following therapy with infliximab may be refractory to antibiotic therapy.
 Rheumatology (Oxford). 2003
 Jul;42(7):901-2.
- 2426. Taylor WJ, Rajapakse CN, Harris KA, et al. Inpatient treatment of rheumatoid arthritis with synacthen depot: a double blind placebo controlled trial with 6 month followup. J Rheumatol. 1999

 Dec;26(12):2544-50.
- 2427. Tchetverikov I, Kraan MC, van El B, et al. Leflunomide and methotrexate reduce levels of activated matrix metalloproteinases in

- complexes with alpha2 macroglobulin in serum of rheumatoid arthritis patients. Ann Rheum Dis. 2008 Jan;67(1):128-30.
- 2428. Teh J, Stevens K, Williamson L, et al. Power Doppler ultrasound of rheumatoid synovitis: quantification of therapeutic response. Br J Radiol. 2003

 Dec;76(912):875-9.
- 2429. Tektonidou MG, Skopouli FN. Visceral leishmaniasis in a patient with psoriatic arthritis treated with infliximab: reactivation of a latent infection? Clin Rheumatol. 2008 Apr;27(4):541-2.
- 2430. Temekonidis TI, Alamanos Y, Nikas SN, et al. Infliximab therapy in patients with ankylosing spondylitis: an open label 12 month study. Ann Rheum Dis. 2003 Dec;62(12):1218-20.
- 2431. Temekonidis TI, Georgiadis AN, Alamanos Y, et al. Infliximab treatment in combination with cyclosporin A in patients with severe refractory rheumatoid arthritis. Ann Rheum Dis. 2002 Sep;61(9):822-5.
- 2432. ten Tusscher MP, Jacobs PJ, Busch MJ, et al. Bilateral anterior toxic optic neuropathy and the use of infliximab. BMJ. 2003 Mar 15;326(7389):579.
- 2433. Teng YK, Levarht EW, Hashemi M, et al. Immunohistochemical analysis as a means to predict responsiveness to rituximab treatment. Arthritis Rheum. 2007 Dec;56(12):3909-18.
- 2434. Teng YK, Levarht EW, Toes RE, et al. Residual inflammation after rituximab treatment is associated with sustained synovial plasma cell infiltration and enhanced B cell repopulation. Ann Rheum Dis. 2009 Jun;68(6):1011-6.
- 2435. Tengstrand B, Carlstrom K, Fellander-Tsai L, et al. Abnormal levels of serum dehydroepiandrosterone, estrone, and estradiol in men with rheumatoid arthritis: high correlation between serum estradiol and current degree of inflammation. J Rheumatol. 2003 Nov;30(11):2338-43.

- 2436. Tengstrand B, Hafstrom I. Bone mineral density in men with rheumatoid arthritis is associated with erosive disease and sulfasalazine treatment but not with sex hormones. J Rheumatol. 2002
 Nov;29(11):2299-305.
- 2437. Tengstrand B, Larsson E, Klareskog L, et al. Randomized withdrawal of long-term prednisolone treatment in rheumatoid arthritis: effects on inflammation and bone mineral density. Scand J Rheumatol. 2007 Sep-Oct;36(5):351-8.
- 2438. Terrier B, Lacroix C, Guillevin L, et al. Diagnostic and prognostic relevance of neuromuscular biopsy in primary Sjogren's syndrome-related neuropathy. Arthritis Rheum. 2007 Dec 15;57(8):1520-9.
- 2439. Terslev L, Torp-Pedersen S, Qvistgaard E, et al. Spectral Doppler and resistive index. A promising tool in ultrasonographic evaluation of inflammation in rheumatoid arthritis. Acta Radiol. 2003 Nov;44(6):645-52
- 2440. Terslev L, Torp-Pedersen S, Qvistgaard E, et al. Effects of treatment with etanercept (Enbrel, TNRF:Fc) on rheumatoid arthritis evaluated by Doppler ultrasonography. Ann Rheum Dis. 2003 Feb;62(2):178-81.
- 2441. Theodoridou A, Kartsios C, Yiannaki E, et al. Reversible T-large granular lymphocyte expansion and neutropenia associated with adalimumab therapy. Rheumatol Int. 2006 Dec;27(2):201-2.
- 2442. Thomaidis T, Schorn C, Flaig W, et al. Immunoadsorption with tryptophan columns: a therapeutic option for the treatment of rheumatoid arthritis with septic complications. J Clin Apher. 2009;24(1):37-41.
- 2443. Thomas JE, Taoka CR, Gibbs BT, et al. Fatal pulmonary Mycobacterium abscessus infection in a patient using etanercept. Hawaii Med J. 2006 Jan;65(1):12-5.
- 2444. Thomas JW, Pflugfelder SC. Therapy of progressive rheumatoid arthritis-associated corneal ulceration with infliximab. Cornea. 2005 Aug;24(6):742-4.

- 2445. Thomason RW, Craig FE, Banks PM, et al. Epstein-Barr virus and lymphoproliferation in methotrexate-treated rheumatoid arthritis. Mod Pathol. 1996 Mar;9(3):261-6.
- 2446. Thompson AE, Bashook PG.
 Rheumatologists' recommended patient information when prescribing methotrexate for rheumatoid arthritis. Clin Exp
 Rheumatol. 2010 Jul-Aug;28(4):539-45.
- 2447. Thonhofer R, Gaugg M, Kriessmayr M, et al. Spontaneous remission of marginal zone B cell lymphoma in a patient with seropositive rheumatoid arthritis after discontinuation of infliximab-methotrexate treatment. Ann Rheum Dis. 2005 Jul;64(7):1098-9.
- 2448. Thonhofer R, Soleiman A, Kriessmayr M, et al. Decrease of proteinuria in a patient with adult-onset Still's disease and glomerulonephritis after anti-TNFalpha therapy. Scand J Rheumatol. 2006 Nov-Dec;35(6):485-8.
- 2449. Thorne JE, Volpe NJ, Liu GT. Magnetic resonance imaging of acquired Brown syndrome in a patient with psoriasis. Am J Ophthalmol. 1999 Feb;127(2):233-5.
- 2450. Thorne JE, Woreta FA, Dunn JP, et al. Risk of cataract development among children with juvenile idiopathic arthritis-related uveitis treated with topical corticosteroids. Ophthalmology. 2010 Jul;117(7):1436-41.
- 2451. Thumboo J, Uramoto K, Shbeeb MI, et al. Risk factors for the development of psoriatic arthritis: a population based nested case control study. J Rheumatol. 2002

 Apr;29(4):757-62.
- 2452. Thurlings RM, Vos K, Gerlag DM, et al. Disease activity-guided rituximab therapy in rheumatoid arthritis: the effects of retreatment in initial nonresponders versus initial responders. Arthritis Rheum. 2008 Dec;58(12):3657-64.
- 2453. Thurlings RM, Vos K, Wijbrandts CA, et al. Synovial tissue response to rituximab: mechanism of action and identification of biomarkers of response. Ann Rheum Dis. 2008 Jul;67(7):917-25.

- 2454. Tiderius CJ, Sandin J, Svensson J, et al. Knee cartilage quality assessed with dGEMRIC in rheumatoid arthritis patients before and after treatment with a TNF inhibitor. Acta Radiol. 2010 Nov;51(9):1034-7.
- 2455. Tikiz H, Arslan O, Pirildar T, et al. The effect of anti-tumor necrosis factor (TNF)-alpha therapy with etanercept on endothelial functions in patients with rheumatoid arthritis. Anadolu Kardiyol Derg. 2010 Apr;10(2):98-103.
- 2456. Tikly M, Zannettou N, Hopley M. A longitudinal study of rheumatoid arthritis in South Africans. MedGenMed. 2003 Feb 5;5(1):2.
- 2457. Tiliakos AN, Tiliakos NA. Ocular inflammatory disease in patients with RA taking etanercept: is discontinuation of etanercept necessary? J Rheumatol. 2003 Dec;30(12):2727.
- 2458. Tilling L, Townsend S, David J.

 Methotrexate and hepatic toxicity in rheumatoid arthritis and psoriatic arthritis.

 Clin Drug Investig. 2006;26(2):55-62.
- 2459. Todoerti M, Scire CA, Boffini N, et al. Early disease control by low-dose prednisone comedication may affect the quality of remission in patients with early rheumatoid arthritis. Ann N Y Acad Sci 2010;1193(1):139-45.
- 2460. Toh ML, Marotte H, Blond JL, et al. Overexpression of synoviolin in peripheral blood and synoviocytes from rheumatoid arthritis patients and continued elevation in nonresponders to infliximab treatment. Arthritis Rheum. 2006 Jul;54(7):2109-18.
- 2461. Tokayer A, Carsons SE, Chokshi B, et al. High levels of interleukin 13 in rheumatoid arthritis sera are modulated by tumor necrosis factor antagonist therapy: association with dendritic cell growth activity. J Rheumatol. 2002 Mar;29(3):454-61.
- 2462. Tokuda H, Sakai F, Yamada H, et al. Clinical and radiological features of Pneumocystis pneumonia in patients with rheumatoid arthritis, in comparison with

- methotrexate pneumonitis and Pneumocystis pneumonia in acquired immunodeficiency syndrome: a multicenter study. Intern Med. 2008;47(10):915-23.
- 2463. Tolusso B, Pietrapertosa D, Morelli A, et al. IL-1B and IL-1RN gene polymorphisms in rheumatoid arthritis: relationship with protein plasma levels and response to therapy. Pharmacogenomics. 2006 Jul;7(5):683-95.
- 2464. Toms TE, Panoulas VF, John H, et al. Methotrexate therapy associates with reduced prevalence of the metabolic syndrome in rheumatoid arthritis patients over the age of 60- more than just an anti-inflammatory effect? A cross sectional study. Arthritis Res Ther. 2009;11(4):R110.
- 2465. Tong D, Eather S, Manolios N. Psoriatic arthritis and chronic lymphoedema: treatment efficacy by adalimumab. Clin Rheumatol. 2009 Nov;28(11):1349-50.
- 2466. Toonen EJ, Coenen MJ, Kievit W, et al. The tumour necrosis factor receptor superfamily member 1b 676T>G polymorphism in relation to response to infliximab and adalimumab treatment and disease severity in rheumatoid arthritis. Ann Rheum Dis. 2008 Aug;67(8):1174-7.
- 2467. Torii H, Nakagawa H. Infliximab monotherapy in Japanese patients with moderate-to-severe plaque psoriasis and psoriatic arthritis. A randomized, double-blind, placebo-controlled multicenter trial. J Dermatol Sci. 2010 Jul;59(1):40-9.
- 2468. Torikai E, Kageyama Y, Suzuki M, et al. The effect of infliximab on chemokines in patients with rheumatoid arthritis. Clin Rheumatol. 2007 Jul;26(7):1088-93.
- 2469. Torikai E, Kageyama Y, Takahashi M, et al. The effect of methotrexate on bone metabolism markers in patients with rheumatoid arthritis. Mod Rheumatol. 2006;16(6):350-4.
- 2470. Toritsuka Y, Nakamura N, Lee SB, et al.
 Osteoclastogenesis in iliac bone marrow of patients with rheumatoid arthritis. J
 Rheumatol. 1997 Sep;24(9):1690-6.

- 2471. Torrance GW, Tugwell P, Amorosi S, et al. Improvement in health utility among patients with rheumatoid arthritis treated with adalimumab (a human anti-TNF monoclonal antibody) plus methotrexate. Rheumatology (Oxford). 2004
 Jun;43(6):712-8.
- 2472. Torre-Cisneros J, Del Castillo M, Caston JJ, et al. Infliximab does not activate replication of lymphotropic herpesviruses in patients with refractory rheumatoid arthritis. Rheumatology (Oxford). 2005 Sep;44(9):1132-5.
- 2473. Torsteinsdottir I, Arvidson NG, Hallgren R, et al. Monocyte activation in rheumatoid arthritis (RA): increased integrin, Fc gamma and complement receptor expression and the effect of glucocorticoids. Clin Exp Immunol. 1999 Mar;115(3):554-60.
- 2474. Toubi E, Kessel A, Slobodin G, et al. Changes in macrophage function after rituximab treatment in patients with rheumatoid arthritis. Ann Rheum Dis. 2007 Jun;66(6):818-20.
- 2475. Tourinho TF, Capp E, Brenol JC, et al. Physical activity prevents bone loss in premenopausal women with rheumatoid arthritis: a cohort study. Rheumatol Int. 2008 Aug;28(10):1001-7.
- 2476. Tournadre A, Ledoux-Eberst J, Poujol D, et al. Exacerbation of interstitial lung disease during etanercept therapy: Two cases. Joint Bone Spine. 2008 Mar;75(2):215-8.
- 2477. Toussirot E, Berthelot JM, Pertuiset E, et al. Pulmonary nodulosis and aseptic granulomatous lung disease occurring in patients with rheumatoid arthritis receiving tumor necrosis factor-alpha-blocking agent: a case series. J Rheumatol. 2009
 Nov;36(11):2421-7.
- 2478. Toussirot E, Nguyen NU, Dumoulin G, et al. Relationship between growth hormone-IGF-I-IGFBP-3 axis and serum leptin levels with bone mass and body composition in patients with rheumatoid arthritis. Rheumatology (Oxford). 2005 Jan;44(1):120-5.
- 2479. Toussirot E, Pertuiset E, Sordet C, et al. Safety of rituximab in rheumatoid arthritis

- patients with a history of severe or recurrent bacterial infection: observational study of 30 cases in everyday practice. Joint Bone Spine. 2010 Mar;77(2):142-5.
- 2480. Toussirot E, Wendling D. Bacillus calmetteguerin vaccination in a patient treated with infliximab. J Rheumatol. 2005 Dec;32(12):2500-1.
- 2481. Toy WC, Jasin HE. An unusual case of hypokalemic paralysis associated with primary Sjogren's syndrome. J Ark Med Soc. 2008 Jun;104(12):286-7.
- Toyoda T, Inokuchi S, Saito S, et al. Bone loss of the radius in rheumatoid arthritis.
 Comparison between 34 patients and 40 controls. Acta Orthop Scand. 1996
 Jun;67(3):269-73.
- 2483. Toyokawa Y, Kingetsu I, Yasuda C, et al. Pancytopenia, including macrocytic anemia, associated with leflunomide in a rheumatoid arthritis patient. Mod Rheumatol. 2007;17(5):436-40.
- 2484. Toyozawa S, Yamamoto Y, Nishide T, et al. Case report: a case of pyoderma gangrenosum with intractable leg ulcers treated by allogeneic cultured dermal substitutes. Dermatol Online J. 2008;14(11):17.
- 2485. Traer EA, Williams MR, Keenan JN. Erysipelothrix rhusiopathiae infection of a total knee arthroplasty an occupational hazard. J Arthroplasty. 2008 Jun;23(4):609-11.
- 2486. Tresch S, Trueb RM, Kamarachev J, et al. Disseminated herpes zoster mimicking rheumatoid vasculitis in a rheumatoid arthritis patient on etanercept. Dermatology. 2009;219(4):347-9.
- 2487. Trethewey P. The role of tumor necrosis factor inhibitors in patients with RA. Jaapa. 2002 Sep;15(9):23-4, 7, 30 passim.
- 2488. True DG, Penmetcha M, Peckham SJ.
 Disseminated cryptococcal infection in rheumatoid arthritis treated with methotrexate and infliximab. J Rheumatol. 2002 Jul;29(7):1561-3.

- 2489. Tsai TC, Chen CY, Lin WT, et al. Sjogren's syndrome complicated with IgA nephropathy and leukocytoclastic vasculitis. Ren Fail. 2008;30(7):755-8.
- 2490. Tsakonas E, Fitzgerald AA, Fitzcharles MA, et al. Consequences of delayed therapy with second-line agents in rheumatoid arthritis: a 3 year followup on the hydroxychloroquine in early rheumatoid arthritis (HERA) study. J Rheumatol. 2000 Mar;27(3):623-9.
- 2491. Tsubota K, Fujita H, Tadano K, et al. Abnormal expression and function of Fas ligand of lacrimal glands and peripheral blood in Sjogren's syndrome patients with enlarged exocrine glands. Clin Exp Immunol. 2002 Jul;129(1):177-82.
- 2492. Tsujimura S, Saito K, Nawata M, et al. Overcoming drug resistance induced by P-glycoprotein on lymphocytes in patients with refractory rheumatoid arthritis. Ann Rheum Dis. 2008 Mar;67(3):380-8.
- 2493. Tsukahara S, Momohara S, Ikari K, et al. Disturbances of the symphysis pubis in rheumatoid arthritis: report of two cases. Mod Rheumatol. 2007;17(4):344-7.
- 2494. Tsuzaka K, Itami Y, Takeuchi T, et al. ADAMTS5 is a biomarker for prediction of response to infliximab in patients with rheumatoid arthritis. J Rheumatol. 2010 Jul;37(7):1454-60.
- 2495. Tubach F, Salmon D, Ravaud P, et al. Risk of tuberculosis is higher with anti-tumor necrosis factor monoclonal antibody therapy than with soluble tumor necrosis factor receptor therapy: The three-year prospective French Research Axed on Tolerance of Biotherapies registry. Arthritis Rheum. 2009 Jul;60(7):1884-94.
- 2496. Tudhope SJ, von Delwig A, Falconer J, et al. Profound invariant natural killer T-cell deficiency in inflammatory arthritis. Ann Rheum Dis. 2010 Oct;69(10):1873-9.
- 2497. Turesson C, Riesbeck K. Septicemia with Staphylococcus aureus, beta-hemolytic streptococci group B and G, and Escherichia coli in a patient with rheumatoid arthritis treated with a recombinant human

- interleukin 1 receptor antagonist (Anakinra). J Rheumatol. 2004 Sep;31(9):1876.
- 2498. Ueki Y, Sagawa A, Tanimura K, et al. A multicenter study of leukocytapheresis in rheumatoid arthritis. Clin Exp Rheumatol. 2007 Nov-Dec;25(6):810-6.
- 2499. Umeda N, Ito S, Hayashi T, et al. A patient with rheumatoid arthritis who had a normal delivery under etanercept treatment. Intern Med. 2010;49(2):187-9.
- 2500. Uneda S, Sonoki T, Nakamura Y, et al. Rapid vanishing of tumors by withdrawal of methotrexate in Epstein-Barr virus-related B cell lymphoproliferative disorder. Intern Med. 2008;47(15):1445-6.
- 2501. Unger L, Kayser M, Nusslein HG. Successful treatment of severe rheumatoid vasculitis by infliximab. Ann Rheum Dis. 2003 Jun;62(6):587-8.
- 2502. Unlu E, Pamuk ON, Cakir N. Color and duplex Doppler sonography to detect sacroiliitis and spinal inflammation in ankylosing spondylitis. Can this method reveal response to anti-tumor necrosis factor therapy? J Rheumatol. 2007 Jan;34(1):110-6.
- 2503. Usui Y, Kimula Y, Miura H, et al. A case of bronchiolitis obliterans organizing pneumonia associated with primary Sjogren's syndrome who died of superimposed diffuse alveolar damage. Respiration. 1992;59(2):122-4.
- 2504. Uthman I, Bizri AR, Hajj Ali R, et al. Miliary tuberculosis presenting as tenosynovitis in a case of rheumatoid arthritis. J Infect. 1998 Sep;37(2):196-8.
- 2505. Uthman I, Husari A, Touma Z, et al. Fatal streptococcal toxic shock syndrome in a patient with rheumatoid arthritis treated with etanercept. Rheumatology (Oxford). 2005 Sep;44(9):1200-1.
- 2506. Uthman I, Vazquez-Abad D, Senecal JL. Distinctive features of idiopathic inflammatory myopathies in French Canadians. Semin Arthritis Rheum. 1996 Aug;26(1):447-58.

- 2507. Vaglio A, Palmisano A, Ferretti S, et al. Peripheral inflammatory arthritis in patients with chronic periaortitis: report of five cases and review of the literature. Rheumatology (Oxford). 2008 Mar;47(3):315-8.
- 2508. Vaidya B, Pearce SH, Charlton S, et al. An association between the CTLA4 exon 1 polymorphism and early rheumatoid arthritis with autoimmune endocrinopathies. Rheumatology (Oxford). 2002 Feb;41(2):180-3.
- 2509. Valentino R, Savastano S, Tommaselli AP, et al. Hormonal pattern in women affected by rheumatoid arthritis. J Endocrinol Invest. 1993 Sep;16(8):619-24.
- 2510. Valenzuela-Castano A, Garcia-Lopez A, Perez-Vilches D, et al. The predictive value of the HLA shared epitope for severity of radiological joint damage in patients with rheumatoid arthritis. A 10 year observational prospective study. J Rheumatol. 2000 Mar;27(3):571-4.
- 2511. Valleala H, Mandelin J, Laasonen L, et al. Effect of cyclical intermittent etidronate therapy on circulating osteoprotegerin levels in patients with rheumatoid arthritis. Eur J Endocrinol. 2003 May;148(5):527-30.
- 2512. Vallerskog T, Heimburger M, Gunnarsson I, et al. Differential effects on BAFF and APRIL levels in rituximab-treated patients with systemic lupus erythematosus and rheumatoid arthritis. Arthritis Res Ther. 2006;8(6):R167.
- 2513. Valtysdottir ST, Wide L, Hallgren R. Low serum dehydroepiandrosterone sulfate in women with primary Sjogren's syndrome as an isolated sign of impaired HPA axis function. J Rheumatol. 2001
 Jun;28(6):1259-65.
- 2514. Valtysdottir ST, Wide L, Hallgren R. Mental wellbeing and quality of sexual life in women with primary Sjogren's syndrome are related to circulating dehydroepiandrosterone sulphate. Ann Rheum Dis. 2003 Sep;62(9):875-9.
- 2515. van Baarsen LG, Wijbrandts CA, Rustenburg F, et al. Regulation of IFN response gene activity during infliximab

- treatment in rheumatoid arthritis is associated with clinical response to treatment. Arthritis Res Ther. 2010;12(1):R11.
- 2516. van de Putte LB, Atkins C, Malaise M, et al. Efficacy and safety of adalimumab as monotherapy in patients with rheumatoid arthritis for whom previous disease modifying antirheumatic drug treatment has failed. Ann Rheum Dis. 2004 May;63(5):508-16.
- 2517. van de Putte LB, Rau R, Breedveld FC, et al. Efficacy and safety of the fully human anti-tumour necrosis factor alpha monoclonal antibody adalimumab (D2E7) in DMARD refractory patients with rheumatoid arthritis: a 12 week, phase II study. Ann Rheum Dis. 2003 Dec;62(12):1168-77.
- 2518. van den Bemt BJ, den Broeder AA, Snijders GF, et al. Sustained effect after lowering high-dose infliximab in patients with rheumatoid arthritis: a prospective dose titration study. Ann Rheum Dis. 2008 Dec;67(12):1697-701.
- 2519. Van den Bosch F, Kruithof E, Baeten D, et al. Effects of a loading dose regimen of three infusions of chimeric monoclonal antibody to tumour necrosis factor alpha (infliximab) in spondyloarthropathy: an open pilot study. Ann Rheum Dis. 2000 Jun;59(6):428-33.
- 2520. Van den Bosch F, Kruithof E, De Vos M, et al. Crohn's disease associated with spondyloarthropathy: effect of TNF-alpha blockade with infliximab on articular symptoms. Lancet. 2000 Nov 25;356(9244):1821-2.
- 2521. Van den Bosch F, Manger B, Goupille P, et al. Effectiveness of adalimumab in treating patients with active psoriatic arthritis and predictors of good clinical responses for arthritis, skin and nail lesions. Ann Rheum Dis. 2010 Feb;69(2):394-9.
- 2522. van den Brink HR, van Wijk MJ, Bijlsma JW. Influence of steroid hormones on proliferation of peripheral blood mononuclear cells in patients with

- rheumatoid arthritis. Br J Rheumatol. 1992 Oct;31(10):663-7.
- 2523. van den Brink HR, van Wijk MJ, Geertzen RG, et al. Influence of corticosteroid pulse therapy on the serum levels of soluble interleukin 2 receptor, interleukin 6 and interleukin 8 in patients with rheumatoid arthritis. J Rheumatol. 1994 Mar;21(3):430-4
- 2524. van den Hout WB, Goekoop-Ruiterman YP, Allaart CF, et al. Cost-utility analysis of treatment strategies in patients with recentonset rheumatoid arthritis. Arthritis Rheum. 2009 Mar 15;61(3):291-9.
- 2525. van der Bijl AE, Breedveld FC, Antoni CE, et al. An open-label pilot study of the effectiveness of adalimumab in patients with rheumatoid arthritis and previous infliximab treatment: relationship to reasons for failure and anti-infliximab antibody status. Clin Rheumatol. 2008 Aug;27(8):1021-8.
- 2526. van der Bijl AE, Emmer BJ, Breedveld FC, et al. Advanced magnetic resonance imaging of the brain in patients treated with TNF-alpha blocking agents. Clin Exp Rheumatol. 2007 Mar-Apr;25(2):301-4.
- 2527. van der Bijl AE, Goekoop-Ruiterman YP, de Vries-Bouwstra JK, et al. Infliximab and methotrexate as induction therapy in patients with early rheumatoid arthritis. Arthritis Rheum. 2007 Jul;56(7):2129-34.
- 2528. van der Heide A, Jacobs JW, Bijlsma JW, et al. The effectiveness of early treatment with "second-line" antirheumatic drugs. A randomized, controlled trial. Ann Intern Med. 1996 Apr 15;124(8):699-707.
- 2529. van der Heijde D, Burmester G, Melo-Gomes J, et al. The safety and efficacy of adding etanercept to methotrexate or methotrexate to etanercept in moderately active rheumatoid arthritis patients previously treated with monotherapy. Ann Rheum Dis. 2008 Feb;67(2):182-8.
- 2530. van der Heijde D, Dijkmans B, Geusens P, et al. Efficacy and safety of infliximab in patients with ankylosing spondylitis: results of a randomized, placebo-controlled trial

- (ASSERT). Arthritis Rheum. 2005 Feb;52(2):582-91.
- 2531. van der Heijde D, Klareskog L, Boers M, et al. Comparison of different definitions to classify remission and sustained remission: 1 year TEMPO results. Ann Rheum Dis. 2005 Nov;64(11):1582-7.
- 2532. van der Heijde D, Klareskog L, Rodriguez-Valverde V, et al. Comparison of etanercept and methotrexate, alone and combined, in the treatment of rheumatoid arthritis: two-year clinical and radiographic results from the TEMPO study, a double-blind, randomized trial. Arthritis Rheum. 2006 Apr;54(4):1063-74.
- 2533. van der Heijde D, Klareskog L, Singh A, et al. Patient reported outcomes in a trial of combination therapy with etanercept and methotrexate for rheumatoid arthritis: the TEMPO trial. Ann Rheum Dis. 2006 Mar;65(3):328-34.
- 2534. van der Heijde D, Landewe R, Klareskog L, et al. Presentation and analysis of data on radiographic outcome in clinical trials: experience from the TEMPO study. Arthritis Rheum. 2005 Jan;52(1):49-60.
- 2535. van der Helm-van Mil AH, le Cessie S, van Dongen H, et al. A prediction rule for disease outcome in patients with recentonset undifferentiated arthritis: how to guide individual treatment decisions. Arthritis Rheum. 2007 Feb;56(2):433-40.
- 2536. van der Klooster JM, Bosman RJ, Oudemans-van Straaten HM, et al. Disseminated tuberculosis, pulmonary aspergillosis and cutaneous herpes simplex infection in a patient with infliximab and methotrexate. Intensive Care Med. 2003 Dec;29(12):2327-9.
- 2537. van der Kooij SM, de Vries-Bouwstra JK, Goekoop-Ruiterman YP, et al. Patientreported outcomes in a randomized trial comparing four different treatment strategies in recent-onset rheumatoid arthritis. Arthritis Rheum. 2009 Jan 15;61(1):4-12.
- 2538. van der Kooij SM, de Vries-Bouwstra JK, Goekoop-Ruiterman YP, et al. Limited efficacy of conventional DMARDs after

- initial methotrexate failure in patients with recent onset rheumatoid arthritis treated according to the disease activity score. Ann Rheum Dis. 2007 Oct;66(10):1356-62.
- 2539. van der Kooij SM, Goekoop-Ruiterman YP, de Vries-Bouwstra JK, et al. Drug-free remission, functioning and radiographic damage after 4 years of response-driven treatment in patients with recent-onset rheumatoid arthritis. Ann Rheum Dis 2009:68(6):914-21.
- 2540. van der Kooij SM, le Cessie S, Goekoop-Ruiterman YP, et al. Clinical and radiological efficacy of initial vs delayed treatment with infliximab plus methotrexate in patients with early rheumatoid arthritis. Ann Rheum Dis. 2009 Jul;68(7):1153-8.
- 2541. van der Laken CJ, Lems WF, van Soesbergen RM, et al. Paraplegia in a patient receiving anti-tumor necrosis factor therapy for rheumatoid arthritis: comment on the article by Mohan et al. Arthritis Rheum. 2003 Jan;48(1):269-70.
- 2542. van der Laken CJ, Voskuyl AE, Roos JC, et al. Imaging and serum analysis of immune complex formation of radiolabelled infliximab and anti-infliximab in responders and non-responders to therapy for rheumatoid arthritis. Ann Rheum Dis. 2007 Feb:66(2):253-6.
- 2543. van der Pouw Kraan TC, Wijbrandts CA, van Baarsen LG, et al. Responsiveness to anti-tumour necrosis factor alpha therapy is related to pre-treatment tissue inflammation levels in rheumatoid arthritis patients. Ann Rheum Dis. 2008 Apr;67(4):563-6.
- 2544. van der Veen MJ, Bijlsma JW. Effects of different regimes of corticosteroid treatment on calcium and bone metabolism in rheumatoid arthritis. Clin Rheumatol. 1992 Sep;11(3):388-92.
- 2545. van der Veen MJ, Bijlsma JW. The effect of methylprednisolone pulse therapy on methotrexate treatment of rheumatoid arthritis. Clin Rheumatol. 1993

 Dec;12(4):500-5.
- 2546. van der Veen MJ, Dekker JJ, Dinant HJ, et al. Fatal pulmonary fibrosis complicating

- low dose methotrexate therapy for rheumatoid arthritis. J Rheumatol. 1995 Sep;22(9):1766-8.
- 2547. Van Doornum S, McColl G, Wicks IP.
 Tumour necrosis factor antagonists improve disease activity but not arterial stiffness in rheumatoid arthritis. Rheumatology (Oxford). 2005 Nov;44(11):1428-32.
- 2548. van Ede A, den Broeder A, Wagenaar M, et al. Etanercept-related extensive pulmonary nodulosis in a patient with rheumatoid arthritis. J Rheumatol. 2007 Jul;34(7):1590-2.
- 2549. van Eijk IC, Peters MJ, Nurmohamed MT, et al. Decrease of fructosamine levels during treatment with adalimumab in patients with both diabetes and rheumatoid arthritis. Eur J Endocrinol. 2007 Mar;156(3):291-3.
- 2550. van Everdingen AA, Huisman AM, Wenting MJ, et al. Down regulation of glucocorticoid receptors in early-diagnosed rheumatoid arthritis. Clin Exp Rheumatol. 2002 Jul-Aug;20(4):463-8.
- 2551. van Halm VP, Nurmohamed MT, Twisk JW, et al. Disease-modifying antirheumatic drugs are associated with a reduced risk for cardiovascular disease in patients with rheumatoid arthritis: a case control study. Arthritis Res Ther 2006;8(5):R151.
- 2552. van Ingen J, Boeree M, Janssen M, et al. Pulmonary Mycobacterium szulgai infection and treatment in a patient receiving antitumor necrosis factor therapy. Nat Clin Pract Rheumatol. 2007 Jul;3(7):414-9.
- 2553. van Leeuwen MA, van der Heijde DM, van Rijswijk MH, et al. Interrelationship of outcome measures and process variables in early rheumatoid arthritis. A comparison of radiologic damage, physical disability, joint counts, and acute phase reactants. J Rheumatol. 1994 Mar;21(3):425-9.
- 2554. van Leeuwen MA, van Rijswijk MH, van der Heijde DM, et al. The acute-phase response in relation to radiographic progression in early rheumatoid arthritis: a prospective study during the first three years of the disease. Br J Rheumatol. 1993 Jun;32 Suppl 3:9-13.

- 2555. van Lieshout AW, Fransen J, Flendrie M, et al. Circulating levels of the chemokine CCL18 but not CXCL16 are elevated and correlate with disease activity in rheumatoid arthritis. Ann Rheum Dis. 2007 Oct;66(10):1334-8.
- 2556. van Middendorp H, Geenen R, Sorbi MJ, et al. Neuroendocrine-immune relationships between emotion regulation and health in patients with rheumatoid arthritis.

 Rheumatology (Oxford). 2005

 Jul;44(7):907-11.
- 2557. van Oosterhout M, Levarht EW, Sont JK, et al. Clinical efficacy of infliximab plus methotrexate in DMARD naive and DMARD refractory rheumatoid arthritis is associated with decreased synovial expression of TNF alpha and IL18 but not CXCL12. Ann Rheum Dis. 2005 Apr;64(4):537-43.
- 2558. van Roon EN, Hoekstra M, Tobi H, et al. Leflunomide in the treatment of rheumatoid arthritis. An analysis of predictors for treatment continuation. Br J Clin Pharmacol. 2005 Sep;60(3):319-25.
- 2559. van Roon EN, van den Bemt PM, Jansen TL, et al. An evidence-based assessment of the clinical significance of drug-drug interactions between disease-modifying antirheumatic drugs and non-antirheumatic drugs according to rheumatologists and pharmacists. Clin Ther. 2009
 Aug;31(8):1737-46.
- 2560. van Roon JA, Hartgring SA, Wenting-van Wijk M, et al. Persistence of interleukin 7 activity and levels on tumour necrosis factor alpha blockade in patients with rheumatoid arthritis. Ann Rheum Dis. 2007 May;66(5):664-9.
- 2561. van Staa TP, Geusens P, Bijlsma JW, et al. Clinical assessment of the long-term risk of fracture in patients with rheumatoid arthritis. Arthritis Rheum. 2006 Oct;54(10):3104-12.
- 2562. van Thiel RJ, van der Burg S, Groote AD, et al. Bronchiolitis obliterans organizing pneumonia and rheumatoid arthritis. Eur Respir J. 1991 Jul;4(7):905-11.

- 2563. Van Tilt I, Lories RJ, Westhovens R, et al. Unusual cervical spine involvement in psoriatic arthritis: a case series. Clin Rheumatol. 2009 Nov;28(11):1343-6.
- 2564. van Tuyl LH, Lems WF, Voskuyl AE, et al. Tight control and intensified COBRA combination treatment in early rheumatoid arthritis: 90% remission in a pilot trial. Ann Rheum Dis. 2008 Nov;67(11):1574-7.
- 2565. van Tuyl LH, Plass AM, Lems WF, et al. Facilitating the use of COBRA combination therapy in early rheumatoid arthritis: a pilot implementation study. J Rheumatol. 2009 Jul:36(7):1380-6.
- 2566. van Vollenhoven R, Harju A, Brannemark S, et al. Treatment with infliximab (Remicade) when etanercept (Enbrel) has failed or vice versa: data from the STURE registry showing that switching tumour necrosis factor alpha blockers can make sense. Ann Rheum Dis. 2003

 Dec;62(12):1195-8.
- 2567. van Vollenhoven RF, Cifaldi MA, Ray S, et al. Improvement in work place and household productivity for patients with early rheumatoid arthritis treated with adalimumab plus methotrexate: work outcomes and their correlations with clinical and radiographic measures from a randomized controlled trial companion study. Arthritis Care Res (Hoboken) 2010;62(2):226-34.
- 2568. van Vollenhoven RF, Emery P, Bingham CO, 3rd, et al. Longterm safety of patients receiving rituximab in rheumatoid arthritis clinical trials. J Rheumatol 2010;37(3):558-67.
- 2569. van Vollenhoven RF, Ernestam S, Geborek P, et al. Addition of infliximab compared with addition of sulfasalazine and hydroxychloroquine to methotrexate in patients with early rheumatoid arthritis (Swefot trial): 1-year results of a randomised trial. Lancet 2009;374(9688):459-66.
- 2570. van Vollenhoven RF, Ernestam S, Harju A, et al. Etanercept versus etanercept plus methotrexate: a registry-based study suggesting that the combination is clinically

- more efficacious. Arthritis Res Ther. 2003;5(6):R347-51.
- 2571. van Vollenhoven RF, Houbiers JG,
 Buttgereit F, et al. The selective estrogen
 receptor alpha agonist Org 37663 induces
 estrogenic effects but lacks antirheumatic
 activity: a phase IIa trial investigating
 efficacy and safety of Org 37663 in
 postmenopausal female rheumatoid arthritis
 patients receiving stable background
 methotrexate or sulfasalazine. Arthritis
 Rheum. 2010 Feb;62(2):351-8.
- 2572. van Vollenhoven RF, Klareskog L. Infliximab dosage and infusion frequency in clinical practice: experiences in the Stockholm biologics registry STURE. Scand J Rheumatol. 2007 Nov-Dec;36(6):418-23.
- 2573. van Woerkom JM, Kruize AA, Geenen R, et al. Safety and efficacy of leflunomide in primary Sjogren's syndrome: a phase II pilot study. Ann Rheum Dis. 2007
 Aug;66(8):1026-32.
- 2574. Vander Cruyssen B, Durez P, Westhovens R, et al. Seven-year follow-up of infliximab therapy in rheumatoid arthritis patients with severe long-standing refractory disease: attrition rate and evolution of disease activity. Arthritis Res Ther. 2010;12(3):R77.
- 2575. Vandergheynst F, Gosset J, van de Borne P, et al. Myopericarditis revealing adult-onset Still's disease. Acta Clin Belg. 2005 Sep-Oct;60(4):205-8.
- 2576. Vandooren B, Kruithof E, Yu DT, et al. Involvement of matrix metalloproteinases and their inhibitors in peripheral synovitis and down-regulation by tumor necrosis factor alpha blockade in spondylarthropathy. Arthritis Rheum. 2004 Sep;50(9):2942-53.
- 2577. Varani K, Massara A, Vincenzi F, et al. Normalization of A2A and A3 adenosine receptor up-regulation in rheumatoid arthritis patients by treatment with antitumor necrosis factor alpha but not methotrexate. Arthritis Rheum. 2009 Oct;60(10):2880-91.
- 2578. Varatharajan N, Lim IG, Anandacoomarasamy A, et al. Methotrexate: long-term safety and efficacy in an

- Australian consultant rheumatology practice. Intern Med J. 2009 Apr;39(4):228-36.
- 2579. Vasques Godinho FM, Parreira Santos MJ, Canas da Silva J. Refractory adult onset Still's disease successfully treated with anakinra. Ann Rheum Dis. 2005 Apr;64(4):647-8.
- 2580. Vassallo R, Matteson E, Thomas CF, Jr. Clinical response of rheumatoid arthritis-associated pulmonary fibrosis to tumor necrosis factor-alpha inhibition. Chest. 2002 Sep;122(3):1093-6.
- 2581. Vassilopoulos D, Apostolopoulou A, Hadziyannis E, et al. Long-term safety of anti-TNF treatment in patients with rheumatic diseases and chronic or resolved hepatitis B virus infection. Ann Rheum Dis. 2010 Jul;69(7):1352-5.
- 2582. Vassilopoulos D, Sialevris K, Malahtari S, et al. Subacute thyroiditis presenting as fever of unknown origin in a patient with rheumatoid arthritis under etanercept treatment. J Clin Rheumatol. 2010 Mar;16(2):88-9.
- 2583. Vastesaeger N, Xu S, Aletaha D, et al. A pilot risk model for the prediction of rapid radiographic progression in rheumatoid arthritis. Rheumatology (Oxford). 2009 Sep;48(9):1114-21.
- 2584. Vavricka SR, Wettstein T, Speich R, et al. Pulmonary granulomas after tumour necrosis factor alpha antagonist therapy. Thorax. 2003 Mar;58(3):278-9.
- 2585. Vazquez I, Graell E, Gratacos J, et al. Prognostic markers of clinical remission in early rheumatoid arthritis after two years of DMARDs in a clinical setting. Clin Exp Rheumatol. 2007 Mar-Apr;25(2):231-8.
- 2586. Vazquez-Del Mercado M, Delgado-Rizo V, Munoz-Valle JF, et al. Expression of interleukin-1 beta, tumor necrosis factor alpha, interleukins-6, -10 and -4, and metalloproteases by freshly isolated mononuclear cells from early never-treated and non-acute treated rheumatoid arthritis patients. Clin Exp Rheumatol. 1999 Sep-Oct;17(5):575-83.

- 2587. Vena GA, Altomare G, Ayala F, et al. Incidence of psoriasis and association with comorbidities in Italy: a 5-year observational study from a national primary care database. Eur J Dermatol. 2010 Sep-Oct;20(5):593-8.
- 2588. Venarucci D, Catalini P, Scendoni P, et al. Evaluation of certain immunity parameters in rheumatoid arthritis, treated with cortisone. Panminerva Med. 1994 Dec;36(4):188-91.
- 2589. Vera-Llonch M, Massarotti E, Wolfe F, et al. Cost-effectiveness of abatacept in patients with moderately to severely active rheumatoid arthritis and inadequate response to tumor necrosis factor-alpha antagonists. J Rheumatol. 2008 Sep;35(9):1745-53.
- 2590. Vera-Llonch M, Massarotti E, Wolfe F, et al. Cost-effectiveness of abatacept in patients with moderately to severely active rheumatoid arthritis and inadequate response to methotrexate. Rheumatology (Oxford). 2008 Apr;47(4):535-41.
- 2591. Verbruggen LA, Versaen H, Rebmann V, et al. Soluble HLA-DR levels in serum are associated with therapy and genetic factors in rheumatoid arthritis. Hum Immunol. 2002 Sep;63(9):758-64.
- 2592. Vergara G, Silvestre JF, Betlloch I, et al. Cutaneous drug eruption to infliximab: report of 4 cases with an interface dermatitis pattern. Arch Dermatol. 2002 Sep;138(9):1258-9.
- 2593. Vergunst CE, Gerlag DM, von Moltke L, et al. MLN3897 plus methotrexate in patients with rheumatoid arthritis: safety, efficacy, pharmacokinetics, and pharmacodynamics of an oral CCR1 antagonist in a phase IIa, double-blind, placebo-controlled, randomized, proof-of-concept study. Arthritis Rheum. 2009 Dec;60(12):3572-81.
- 2594. Verhave JC, van Altena R, Wijnands MJ, et al. Tuberculous peritonitis during infliximab therapy. Neth J Med. 2008 Feb;66(2):77-80.
- 2595. Verhelst X, Orlent H, Colle I, et al.
 Subfulminant hepatitis B during treatment
 with adalimumab in a patient with
 rheumatoid arthritis and chronic hepatitis B.

- Eur J Gastroenterol Hepatol. 2010 Apr;22(4):494-9.
- 2596. Verhoef CM, van Roon JA, Vianen ME, et al. The immune suppressive effect of dexamethasone in rheumatoid arthritis is accompanied by upregulation of interleukin 10 and by differential changes in interferon gamma and interleukin 4 production. Ann Rheum Dis. 1999 Jan;58(1):49-54.
- 2597. Verhoeven AC, Boers M, te Koppele JM, et al. Bone turnover, joint damage and bone mineral density in early rheumatoid arthritis treated with combination therapy including high-dose prednisolone. Rheumatology (Oxford). 2001 Nov;40(11):1231-7.
- 2598. Verschueren K, Van Essche E, Verschueren P, et al. Development of sarcoidosis in etanercept-treated rheumatoid arthritis patients. Clin Rheumatol. 2007
 Nov;26(11):1969-71.
- 2599. Verschueren P, Esselens G, Westhovens R. Daily practice effectiveness of a step-down treatment in comparison with a tight step-up for early rheumatoid arthritis. Rheumatology (Oxford). 2008 Jan;47(1):59-64.
- 2600. Verstappen SM, Jacobs JW, van der Veen MJ, et al. Intensive treatment with methotrexate in early rheumatoid arthritis: aiming for remission. Computer Assisted Management in Early Rheumatoid Arthritis (CAMERA, an open-label strategy trial). Ann Rheum Dis. 2007 Nov;66(11):1443-9.
- 2601. Verwilghen J, Lovis R, De Boer M, et al. Expression of functional B7 and CTLA4 on rheumatoid synovial T cells. J Immunol. 1994 Aug 1;153(3):1378-85.
- 2602. Vidal F, Fontova R, Richart C. Severe neutropenia and thrombocytopenia associated with infliximab. Ann Intern Med. 2003 Aug 5;139(3):W-W63.
- 2603. Vieira Serrao V, Martins A, Lopes MJ. Infliximab in recalcitrant generalized pustular arthropatic psoriasis. Eur J Dermatol. 2008 Jan-Feb;18(1):71-3.
- 2604. Vigna-Perez M, Abud-Mendoza C, Portillo-Salazar H, et al. Immune effects of therapy

- with Adalimumab in patients with rheumatoid arthritis. Clin Exp Immunol. 2005 Aug:141(2):372-80.
- 2605. Vignes S, Le Moing V, Meekel P, et al. Acquired hemophilia: a rare complication of Sjogren's syndrome. Clin Exp Rheumatol. 1996 Sep-Oct;14(5):559-60.
- 2606. Viguier M, Richette P, Aubin F, et al. Onset of psoriatic arthritis in patients treated with efalizumab for moderate to severe psoriasis. Arthritis Rheum. 2008 Jun;58(6):1796-802.
- 2607. Vila AT, Puig L, Fernandez-Figueras MT, et al. Adverse cutaneous reactions to anakinra in patients with rheumatoid arthritis: clinicopathological study of five patients. Br J Dermatol. 2005 Aug;153(2):417-23.
- 2608. Vila LM, Molina MJ. Chronic anemia and thrombocytosis as the initial presentation of Still's disease in an elderly patient. Gerontology. 2007;53(5):289-92.
- 2609. Vine JE, Hymes SR, Warner NB, et al. Pustular psoriasis induced by hydroxychloroquine: a case report and review of the literature. J Dermatol. 1996 May;23(5):357-61.
- 2610. Vintimilla M, Joseph A, Ranganathan P. Acquired factor VIII inhibitor in Sjogren's syndrome. Arthritis Care Res (Hoboken). 2010 Jul;62(7):1047-50.
- 2611. Virkki LM, Konttinen YT, Peltomaa R, et al. Cost-effectiveness of infliximab in the treatment of rheumatoid arthritis in clinical practice. Clin Exp Rheumatol. 2008 Nov-Dec;26(6):1059-66.
- 2612. Virkki LM, Porola P, Forsblad-d'Elia H, et al. Dehydroepiandrosterone (DHEA) substitution treatment for severe fatigue in DHEA-deficient patients with primary Sjogren's syndrome. Arthritis Care Res (Hoboken). 2010 Jan 15;62(1):118-24.
- 2613. Vis M, Bos WH, Wolbink G, et al. IgM-rheumatoid factor, anti-cyclic citrullinated peptide, and anti-citrullinated human fibrinogen antibodies decrease during treatment with the tumor necrosis factor blocker infliximab in patients with

- rheumatoid arthritis. J Rheumatol. 2008 Mar;35(3):425-8.
- 2614. Vis M, Nurmohamed MT, Wolbink G, et al. Short term effects of infliximab on the lipid profile in patients with rheumatoid arthritis. J Rheumatol. 2005 Feb;32(2):252-5.
- 2615. Vis M, Voskuyl AE, Wolbink GJ, et al. Bone mineral density in patients with rheumatoid arthritis treated with infliximab. Ann Rheum Dis. 2005 Feb;64(2):336-7.
- 2616. Vis M, Wolbink GJ, Lodder MC, et al. Early changes in bone metabolism in rheumatoid arthritis patients treated with infliximab.

 Arthritis Rheum. 2003 Oct;48(10):2996-7.
- 2617. Visser K, Goekoop-Ruiterman YP, de Vries-Bouwstra JK, et al. A matrix risk model for the prediction of rapid radiographic progression in patients with rheumatoid arthritis receiving different dynamic treatment strategies: post hoc analyses from the BeSt study. Ann Rheum Dis. 2010 Jul;69(7):1333-7.
- 2618. Visvanathan S, Wagner C, Rojas J, et al. Eselectin, interleukin 18, serum amyloid a, and matrix metalloproteinase 9 are associated with clinical response to golimumab plus methotrexate in patients with active rheumatoid arthritis despite methotrexate therapy. J Rheumatol. 2009 Jul;36(7):1371-9.
- 2619. Visvanathan S, Wagner C, Smolen J, et al. IgG and IgM anticardiolipin antibodies following treatment with infliximab plus methotrexate in patients with early rheumatoid arthritis. Arthritis Rheum. 2006 Sep;54(9):2840-4.
- 2620. Vital EM, Dass S, Rawstron AC, et al. Management of nonresponse to rituximab in rheumatoid arthritis: predictors and outcome of re-treatment. Arthritis Rheum. 2010 May;62(5):1273-9.
- 2621. Vivarelli M, D'Urbano LE, Insalaco A, et al. Macrophage migration inhibitory factor (MIF) and oligoarticular juvenile idiopathic arthritis (o-JIA): association of MIF promoter polymorphisms with response to intra-articular glucocorticoids. Clin Exp Rheumatol. 2007 Sep-Oct;25(5):775-81.

- 2622. Vlachaki E, Psathakis K, Tsintiris K, et al. Delayed response to anti-tuberculosis treatment in a patient on infliximab. Respir Med. 2005 May;99(5):648-52.
- 2623. Vlachoyiannopoulos PG, Kanellopoulos PG, Ioannidis JP, et al. Atherosclerosis in premenopausal women with antiphospholipid syndrome and systemic lupus erythematosus: a controlled study. Rheumatology (Oxford). 2003 May;42(5):645-51.
- 2624. Vogl D, Falk W, Dorner M, et al. Serum levels of pregnenolone and 17-hydroxypregnenolone in patients with rheumatoid arthritis and systemic lupus erythematosus: relation to other adrenal hormones. J Rheumatol. 2003 Feb;30(2):269-75.
- 2625. Volpe A, Caramaschi P, Carletto A, et al. Psoriasis onset during infliximab treatment: description of two cases. Rheumatol Int. 2006 Oct;26(12):1158-60.
- 2626. Vonkeman H, ten Napel C, Rasker H, et al. Disseminated primary varicella infection during infliximab treatment. J Rheumatol. 2004 Dec;31(12):2517-8.
- 2627. Voog U, Alstergren P, Eliasson S, et al. Progression of radiographic changes in the temporomandibular joints of patients with rheumatoid arthritis in relation to inflammatory markers and mediators in the blood. Acta Odontol Scand. 2004 Feb;62(1):7-13.
- 2628. Vordenbaumen S, Neuen-Jacob E, Richter J, et al. Inclusion body myositis in a patient with long standing rheumatoid arthritis treated with anti-TNFalpha and rituximab. Clin Rheumatol. 2010 May;29(5):555-8.
- 2629. Vos K, Thurlings RM, Wijbrandts CA, et al. Early effects of rituximab on the synovial cell infiltrate in patients with rheumatoid arthritis. Arthritis Rheum. 2007 Mar;56(3):772-8.
- 2630. Voskuyl AE, Van de Laar MA, Moens HJ, et al. Extra-articular manifestations of rheumatoid arthritis: risk factors for serious gastrointestinal events. Ann Rheum Dis. 1993 Nov;52(11):771-5.

- 2631. Voskuyl AE, Zwinderman AH, Westedt ML, et al. Factors associated with the development of vasculitis in rheumatoid arthritis: results of a case-control study. Ann Rheum Dis. 1996 Mar;55(3):190-2.
- 2632. Voulgarelis M, Giannouli S, Anagnostou D, et al. Combined therapy with rituximab plus cyclophosphamide/doxorubicin/vincristine/p rednisone (CHOP) for Sjogren's syndrome-associated B-cell aggressive non-Hodgkin's lymphomas. Rheumatology (Oxford). 2004 Aug;43(8):1050-3.
- 2633. Voulgari PV, Alamanos Y, Nikas SN, et al. Infliximab therapy in established rheumatoid arthritis: an observational study. Am J Med. 2005 May;118(5):515-20.
- 2634. Voulgari PV, Markatseli TE, Exarchou SA, et al. Granuloma annulare induced by antitumour necrosis factor therapy. Ann Rheum Dis. 2008 Apr;67(4):567-70.
- 2635. Voulgari PV, Venetsanopoulou AI, Exarchou SA, et al. Sustained clinical response and high infliximab survival in psoriatic arthritis patients: a 3-year long-term study. Semin Arthritis Rheum. 2008 Apr;37(5):293-8.
- 2636. Voutilainen M, Sokka T, Juhola M, et al. Nonsteroidal anti-inflammatory drugassociated upper gastrointestinal lesions in rheumatoid arthritis patients. Relationships to gastric histology, Helicobacter pylori infection, and other risk factors for peptic ulcer. Scand J Gastroenterol. 1998 Aug;33(8):811-6.
- 2637. Vrzogic P, Pasic A, Podobnik-Takac T. Psoriasis vulgaris and arthritis psoriatica gravis mutilans. Acta Dermatovenerol Croat. 2003;11(1):22-8.
- 2638. Vytasek R, Sedova L, Vilim V. Increased concentration of two different advanced glycation end-products detected by enzyme immunoassays with new monoclonal antibodies in sera of patients with rheumatoid arthritis. BMC Musculoskelet Disord. 2010;11:83.
- 2639. Wachi K, Prasertsuntarasai T, Kishimoto M, et al. T-cell lymphopenia associated with

- infliximab and cyclophosphamide. Am J Med Sci. 2005 Jul;330(1):48-51.
- 2640. Wagner U, Pierer M, Wahle M, et al. Ex vivo homeostatic proliferation of CD4+ T cells in rheumatoid arthritis is dysregulated and driven by membrane-anchored TNFalpha. J Immunol. 2004 Aug 15;173(4):2825-33.
- 2641. Waguri-Nagaya Y, Kobayashi M, Goto H, et al. Septic arthritis of the right ankle caused by Staphylococcus aureus infection in a rheumatoid arthritis patient treated with etanercept. Mod Rheumatol. 2007;17(4):338-40.
- 2642. Wakabayashi H, Sudo A, Hasegawa M, et al. Retrospective clinical study of the efficacy of lower-dose methotrexate and infliximab therapy in patients with rheumatoid arthritis. Clin Rheumatol 2010;29(6):671-5.
- 2643. Wakefield RJ, Freeston JE, Hensor EM, et al. Delay in imaging versus clinical response: a rationale for prolonged treatment with anti-tumor necrosis factor medication in early rheumatoid arthritis. Arthritis Rheum. 2007 Dec 15;57(8):1564-7.
- 2644. Wall E, Walker-Bone K. Use of bisphosphonates and dual-energy X-ray absorptiometry scans in the prevention and treatment of glucocorticoid-induced osteoporosis in rheumatology. Qjm. 2008 Apr;101(4):317-23.
- 2645. Wallace DJ, Metzger AL, Stecher VJ, et al. Cholesterol-lowering effect of hydroxychloroquine in patients with rheumatic disease: reversal of deleterious effects of steroids on lipids. Am J Med. 1990 Sep;89(3):322-6.
- 2646. Wallberg-Jonsson S, Johansson H, Ohman ML, et al. Extent of inflammation predicts cardiovascular disease and overall mortality in seropositive rheumatoid arthritis. A retrospective cohort study from disease onset. J Rheumatol. 1999 Dec;26(12):2562-71
- 2647. Wallberg-Jonsson S, Ohman M, Rantapaa-Dahlqvist S. Which factors are related to the presence of atherosclerosis in rheumatoid

- arthritis? Scand J Rheumatol. 2004;33(6):373-9.
- 2648. Wallberg-Jonsson S, Ohman ML, Dahlqvist SR. Cardiovascular morbidity and mortality in patients with seropositive rheumatoid arthritis in Northern Sweden. J Rheumatol. 1997 Mar;24(3):445-51.
- 2649. Walsh CA, Fearon U, FitzGerald O, et al. Decreased CD20 expression in rheumatoid arthritis synovium following 8 weeks of rituximab therapy. Clin Exp Rheumatol. 2008 Jul-Aug;26(4):656-8.
- 2650. Walsh CA, Minnock P, Slattery C, et al. Quality of life and economic impact of switching from established infliximab therapy to adalimumab in patients with rheumatoid arthritis. Rheumatology (Oxford). 2007 Jul;46(7):1148-52.
- 2651. Walsh LJ, Wong CA, Pringle M, et al. Use of oral corticosteroids in the community and the prevention of secondary osteoporosis: a cross sectional study. BMJ. 1996 Aug 10;313(7053):344-6.
- 2652. Wang M, Tsai RT, Ou WC, et al. Treatment with cytotoxic immunosuppression agents increases urinary excretion of JCV in patients with autoimmune disease. J Med Virol. 2000 Dec;62(4):505-10.
- 2653. Wang SJ, Yang YH, Lin YT, et al. Attained adult height in juvenile rheumatoid arthritis with or without corticosteroid treatment. Clin Rheumatol. 2002 Sep;21(5):363-8.
- 2654. Ward MM, Fries JF. Trends in antirheumatic medication use among patients with rheumatoid arthritis, 1981-1996. J Rheumatol. 1998 Mar;25(3):408-16.
- 2655. Wardwell NR, Jr., Miller R, Ware LB. Pulmonary alveolar proteinosis associated with a disease-modifying antirheumatoid arthritis drug. Respirology. 2006 Sep;11(5):663-5.
- 2656. Wasko MC, Hubert HB, Lingala VB, et al. Hydroxychloroquine and risk of diabetes in patients with rheumatoid arthritis. Jama. 2007 Jul 11;298(2):187-93.

- 2657. Wasserman MJ, Weber DA, Guthrie JA, et al. Infusion-related reactions to infliximab in patients with rheumatoid arthritis in a clinical practice setting: relationship to dose, antihistamine pretreatment, and infusion number. J Rheumatol. 2004 Oct;31(10):1912-7.
- 2658. Wasserteil V, Bruce S, Sessoms SL, et al. Pyoderma gangrenosum treated with hyperbaric oxygen therapy. Int J Dermatol. 1992 Aug;31(8):594-6.
- 2659. Watanabe H, Suzuki R, Asano T, et al. A case of emphysematous pyelonephritis in a patient with rheumatoid arthritis taking corticosteroid and low-dose methotrexate. Int J Rheum Dis. 2010 May;13(2):180-3.
- 2660. Watanabe T, Tsuchida T, Furue M, et al. Annular erythema, dermatomyositis, and Sjogren's syndrome. Int J Dermatol. 1996 Apr;35(4):285-7.
- 2661. Watson DJ, Rhodes T, Cai B, et al. Lower risk of thromboembolic cardiovascular events with naproxen among patients with rheumatoid arthritis. Arch Intern Med. 2002 May 27;162(10):1105-10.
- 2662. Weaver AL, Lautzenheiser RL, Schiff MH, et al. Real-world effectiveness of select biologic and DMARD monotherapy and combination therapy in the treatment of rheumatoid arthritis: results from the RADIUS observational registry. Curr Med Res Opin. 2006 Jan;22(1):185-98.
- 2663. Weidler C, Struharova S, Schmidt M, et al. Tumor necrosis factor inhibits conversion of dehydroepiandrosterone sulfate (DHEAS) to DHEA in rheumatoid arthritis synovial cells: a prerequisite for local androgen deficiency. Arthritis Rheum. 2005 Jun;52(6):1721-9.
- 2664. Weinblatt ME, Abbott GF, Koreishi AF. Case records of the Massachusetts General Hospital. Case 13-2009. A 54-year-old woman with respiratory failure and a cavitary lesion in the lung. N Engl J Med. 2009 Apr 23;360(17):1770-9.
- 2665. Weinblatt ME, Kavanaugh A, Burgos-Vargas R, et al. Treatment of rheumatoid arthritis with a Syk kinase inhibitor: a twelve-week, randomized, placebo-

- controlled trial. Arthritis Rheum. 2008 Nov;58(11):3309-18.
- 2666. Weinblatt ME, Kavanaugh A, Genovese MC, et al. An oral spleen tyrosine kinase (Syk) inhibitor for rheumatoid arthritis. N Engl J Med. 2010 Sep 30;363(14):1303-12.
- 2667. Weinblatt ME, Keystone EC, Furst DE, et al. Adalimumab, a fully human anti-tumor necrosis factor alpha monoclonal antibody, for the treatment of rheumatoid arthritis in patients taking concomitant methotrexate: the ARMADA trial. Arthritis Rheum. 2003 Jan;48(1):35-45.
- 2668. Weinblatt ME, Kremer JM, Bankhurst AD, et al. A trial of etanercept, a recombinant tumor necrosis factor receptor:Fc fusion protein, in patients with rheumatoid arthritis receiving methotrexate. N Engl J Med. 1999 Jan 28;340(4):253-9.
- 2669. Weinblatt ME, Schiff MH, Ruderman EM, et al. Efficacy and safety of etanercept 50 mg twice a week in patients with rheumatoid arthritis who had a suboptimal response to etanercept 50 mg once a week: results of a multicenter, randomized, double-blind, active drug-controlled study. Arthritis Rheum. 2008 Jul;58(7):1921-30.
- 2670. Weisman MH, Moreland LW, Furst DE, et al. Efficacy, pharmacokinetic, and safety assessment of adalimumab, a fully human anti-tumor necrosis factor-alpha monoclonal antibody, in adults with rheumatoid arthritis receiving concomitant methotrexate: a pilot study. Clin Ther. 2003 Jun;25(6):1700-21.
- 2671. Weisman MH, Paulus HE, Burch FX, et al. A placebo-controlled, randomized, double-blinded study evaluating the safety of etanercept in patients with rheumatoid arthritis and concomitant comorbid diseases. Rheumatology (Oxford) 2007;46(7):1122-5.
- 2672. Weiss AH, Wallace CA, Sherry DD. Methotrexate for resistant chronic uveitis in children with juvenile rheumatoid arthritis. J Pediatr. 1998 Aug;133(2):266-8.
- 2673. Weitoft T, Forsberg C. Importance of immobilization after intraarticular glucocorticoid treatment for elbow synovitis: a randomized controlled study.

- Arthritis Care Res (Hoboken). 2010 May;62(5):735-7.
- 2674. Weitoft T, Larsson A, Ronnblom L. Serum levels of sex steroid hormones and matrix metalloproteinases after intra-articular glucocorticoid treatment in female patients with rheumatoid arthritis. Ann Rheum Dis. 2008 Mar;67(3):422-4.
- 2675. Weitoft T, Ronnblom L. Glucocorticoid resorption and influence on the hypothalamic-pituitary-adrenal axis after intra-articular treatment of the knee in resting and mobile patients. Ann Rheum Dis. 2006 Jul;65(7):955-7.
- 2676. Weitoft T, Uddenfeldt P. Importance of synovial fluid aspiration when injecting intra-articular corticosteroids. Ann Rheum Dis. 2000 Mar;59(3):233-5.
- 2677. Wells G, Becker JC, Teng J, et al.
 Validation of the 28-joint Disease Activity
 Score (DAS28) and European League
 Against Rheumatism response criteria based
 on C-reactive protein against disease
 progression in patients with rheumatoid
 arthritis, and comparison with the DAS28
 based on erythrocyte sedimentation rate.
 Ann Rheum Dis. 2009 Jun;68(6):954-60.
- 2678. Wells G, Li T, Maxwell L, et al.
 Responsiveness of patient reported outcomes including fatigue, sleep quality, activity limitation, and quality of life following treatment with abatacept for rheumatoid arthritis. Ann Rheum Dis 2008;67(2):260-5.
- 2679. Wells G, Li T, Tugwell P. Investigation into the impact of abatacept on sleep quality in patients with rheumatoid arthritis, and the validity of the MOS-Sleep questionnaire Sleep Disturbance Scale. Ann Rheum Dis. 2010 Oct;69(10):1768-73.
- 2680. Wells GA, Boers M, Li T, et al.
 Investigating the validity of the minimal disease activity state for patients with rheumatoid arthritis treated with abatacept. J Rheumatol. 2009 Feb;36(2):260-5.
- 2681. Wendling D, Materne GE, Michel F, et al. Infliximab continuation rates in patients with rheumatoid arthritis in everyday

- practice. Joint Bone Spine. 2005 Jul;72(4):309-12.
- 2682. Wendling D, Streit G, Toussirot E, et al. Herpes zoster in patients taking TNFalpha antagonists for chronic inflammatory joint disease. Joint Bone Spine. 2008 Oct;75(5):540-3.
- 2683. Wessels JA, de Vries-Bouwstra JK,
 Heijmans BT, et al. Efficacy and toxicity of
 methotrexate in early rheumatoid arthritis
 are associated with single-nucleotide
 polymorphisms in genes coding for folate
 pathway enzymes. Arthritis Rheum. 2006
 Apr;54(4):1087-95.
- 2684. Wessels JA, Kooloos WM, De Jonge R, et al. Relationship between genetic variants in the adenosine pathway and outcome of methotrexate treatment in patients with recent-onset rheumatoid arthritis. Arthritis Rheum. 2006 Sep;54(9):2830-9.
- 2685. Wessels JA, van der Kooij SM, le Cessie S, et al. A clinical pharmacogenetic model to predict the efficacy of methotrexate monotherapy in recent-onset rheumatoid arthritis. Arthritis Rheum. 2007 Jun;56(6):1765-75.
- 2686. West SG, Troutner JL, Baker MR, et al. Sacral insufficiency fractures in rheumatoid arthritis. Spine. 1994 Sep 15;19(18):2117-21.
- 2687. Westhovens R, Houssiau F, Joly J, et al. A phase I study assessing the safety, clinical response, and pharmacokinetics of an experimental infliximab formulation for subcutaneous or intramuscular administration in patients with rheumatoid arthritis. J Rheumatol. 2006 May;33(5):847-53.
- 2688. Westhovens R, Nijs J, Taelman V, et al. Body composition in rheumatoid arthritis. Br J Rheumatol. 1997 Apr;36(4):444-8.
- 2689. Weusten BL, Jacobs JW, Bijlsma JW. Corticosteroid pulse therapy in active rheumatoid arthritis. Semin Arthritis Rheum. 1993 Dec;23(3):183-92.

- 2690. Weycker D, Yu EB, Woolley JM, et al. Retrospective study of the costs of care during the first year of therapy with etanercept or infliximab among patients aged > or =65 years with rheumatoid arthritis. Clin Ther. 2005 May;27(5):646-56.
- 2691. White D, Fayez S, Doube A. Atherogenic lipid profiles in rheumatoid arthritis. N Z Med J. 2006;119(1240):U2125.
- 2692. White KL. Psoriasis and psoriatic arthritis, axial type. Dermatol Online J. 2001 Dec;7(2):12.
- 2693. Wiatrowski M, Furfaro N. Patient profiles in psoriatic disease: a case-based approach. Dermatol Nurs. 2007 Oct;Suppl:5-19; quiz 20-1.
- 2694. Wick MC, Ernestam S, Lindblad S, et al. Adalimumab (Humira) restores clinical response in patients with secondary loss of efficacy from infliximab (Remicade) or etanercept (Enbrel): results from the STURE registry at Karolinska University Hospital. Scand J Rheumatol. 2005 Sep-Oct;34(5):353-8.
- 2695. Wiens A, Correr CJ, Pontarolo R, et al. A systematic review and meta-analysis of the efficacy and safety of etanercept for treating rheumatoid arthritis. Scand J Immunol 2009;70(4):337-44.
- 2696. Wiens A, Venson R, Correr CJ, et al. Metaanalysis of the efficacy and safety of adalimumab, etanercept, and infliximab for the treatment of rheumatoid arthritis. Pharmacotherapy 2010;30(4):339-53.
- 2697. Wijbrandts CA, Dijkgraaf MG, Kraan MC, et al. The clinical response to infliximab in rheumatoid arthritis is in part dependent on pretreatment tumour necrosis factor alpha expression in the synovium. Ann Rheum Dis. 2008 Aug;67(8):1139-44.
- 2698. Wijbrandts CA, Klaasen R, Dijkgraaf MG, et al. Bone mineral density in rheumatoid arthritis patients 1 year after adalimumab therapy: arrest of bone loss. Ann Rheum Dis. 2009 Mar;68(3):373-6.

- 2699. Wijbrandts CA, Remans PH, Klarenbeek PL, et al. Analysis of apoptosis in peripheral blood and synovial tissue very early after initiation of infliximab treatment in rheumatoid arthritis patients. Arthritis Rheum. 2008 Nov;58(11):3330-9.
- 2700. Wijngaarden S, van de Winkel JG, Bijlsma JW, et al. Treatment of rheumatoid arthritis patients with anti-TNF-alpha monoclonal antibody is accompanied by down-regulation of the activating Fcgamma receptor I on monocytes. Clin Exp Rheumatol. 2008 Jan-Feb;26(1):89-95.
- 2701. Wikaningrum R, Highton J, Parker A, et al. Pathogenic mechanisms in the rheumatoid nodule: comparison of proinflammatory cytokine production and cell adhesion molecule expression in rheumatoid nodules and synovial membranes from the same patient. Arthritis Rheum. 1998
 Oct;41(10):1783-97.
- 2702. Wiland P, Wiela-Hojenska A, Glowska A, et al. Renal function in rheumatoid arthritis patients treated with methotrexate and infliximab. Clin Exp Rheumatol. 2004 Jul-Aug;22(4):469-72.
- 2703. Wilder RL. Adrenal and gonadal steroid hormone deficiency in the pathogenesis of rheumatoid arthritis. J Rheumatol Suppl. 1996 Mar;44:10-2.
- 2704. Williams CS, Butler E, Roman GC.
 Treatment of myelopathy in Sjogren
 syndrome with a combination of prednisone
 and cyclophosphamide. Arch Neurol. 2001
 May;58(5):815-9.
- 2705. Wilson ML, Sewell LD, Mowad CM. Primary cutaneous Cryptococcosis during therapy with methotrexate and adalimumab. J Drugs Dermatol. 2008 Jan;7(1):53-4.
- 2706. Winfield H, Lain E, Horn T, et al. Eosinophilic cellulitislike reaction to subcutaneous etanercept injection. Arch Dermatol. 2006 Feb;142(2):218-20.
- 2707. Wirnsberger RM, de Vries J, Wouters EF, et al. Clinical presentation of sarcoidosis in The Netherlands an epidemiological study. Neth J Med. 1998 Aug;53(2):53-60.

- 2708. Wislowska M, Jakubicz D. Preliminary evaluation in rheumatoid arthritis activity in patients treated with TNF-alpha blocker plus methotrexate versus methotrexate or leflunomide alone. Rheumatol Int. 2007 May;27(7):641-7.
- 2709. Wittkowski H, Foell D, af Klint E, et al. Effects of intra-articular corticosteroids and anti-TNF therapy on neutrophil activation in rheumatoid arthritis. Ann Rheum Dis. 2007 Aug;66(8):1020-5.
- 2710. Wolbink GJ, Voskuyl AE, Lems WF, et al. Relationship between serum trough infliximab levels, pretreatment C reactive protein levels, and clinical response to infliximab treatment in patients with rheumatoid arthritis. Ann Rheum Dis. 2005 May;64(5):704-7.
- 2711. Wolf J, Kapral T, Grisar J, et al. Glucocorticoid treatment in rheumatoid arthritis: low-dose therapy does not reduce responsiveness to higher doses. Clin Exp Rheumatol. 2008 Jan-Feb;26(1):113-6.
- 2712. Wolfe F, Caplan L, Michaud K. Treatment for rheumatoid arthritis and the risk of hospitalization for pneumonia: associations with prednisone, disease-modifying antirheumatic drugs, and anti-tumor necrosis factor therapy. Arthritis Rheum. 2006 Feb;54(2):628-34.
- 2713. Wolfe F, Caplan L, Michaud K. Rheumatoid arthritis treatment and the risk of severe interstitial lung disease. Scand J Rheumatol 2007;36(3):172-8.
- 2714. Wolfe F, Hawley DJ. The comparative risk and predictors of adverse gastrointestinal events in rheumatoid arthritis and osteoarthritis: a prospective 13 year study of 2131 patients. J Rheumatol. 2000 Jul;27(7):1668-73.
- 2715. Wolfe F, Marmor MF. Rates and predictors of hydroxychloroquine retinal toxicity in patients with rheumatoid arthritis and systemic lupus erythematosus. Arthritis Care Res (Hoboken). 2010 Jun;62(6):775-84.
- 2716. Wolfe F, Michaud K. Lymphoma in rheumatoid arthritis: the effect of methotrexate and anti-tumor necrosis factor

- therapy in 18,572 patients. Arthritis Rheum. 2004 Jun;50(6):1740-51.
- 2717. Wolfe F, Michaud K. Heart failure in rheumatoid arthritis: rates, predictors, and the effect of anti-tumor necrosis factor therapy. Am J Med. 2004 Mar 1;116(5):305-
- 2718. Wolfe F, Michaud K. Assessment of pain in rheumatoid arthritis: minimal clinically significant difference, predictors, and the effect of anti-tumor necrosis factor therapy. J Rheumatol. 2007 Aug;34(8):1674-83.
- 2719. Wolfe F, Michaud K. The effect of methotrexate and anti-tumor necrosis factor therapy on the risk of lymphoma in rheumatoid arthritis in 19,562 patients during 89,710 person-years of observation. Arthritis Rheum 2007;56(5):1433-9.
- 2720. Wolfe F, Michaud K, Anderson J, et al. Tuberculosis infection in patients with rheumatoid arthritis and the effect of infliximab therapy. Arthritis Rheum. 2004 Feb;50(2):372-9.
- 2721. Wolfe F, Michaud K, Li T. Sleep disturbance in patients with rheumatoid arthritis: evaluation by medical outcomes study and visual analog sleep scales. J Rheumatol. 2006 Oct;33(10):1942-51.
- 2722. Wollina U, Hansel G, Koch A, et al. Tumor necrosis factor-alpha inhibitor-induced psoriasis or psoriasiform exanthemata: first 120 cases from the literature including a series of six new patients. Am J Clin Dermatol. 2008;9(1):1-14.
- 2723. Wollina U, Konrad H. Treatment of recalcitrant psoriatic arthritis with antitumor necrosis factor-alpha antibody. J Eur Acad Dermatol Venereol. 2002

 Mar;16(2):127-9.
- 2724. Wondergem MJ, Voskuyl AE, van Agtmael MA. A case of legionellosis during treatment with a TNFalpha antagonist. Scand J Infect Dis. 2004;36(4):310-1.
- 2725. Wong JB, Singh G, Kavanaugh A. Estimating the cost-effectiveness of 54

- weeks of infliximab for rheumatoid arthritis. Am J Med. 2002 Oct 1;113(5):400-8.
- 2726. Wong T, Majchrzak B, Bogoch E, et al. Therapeutic implications for interferonalpha in arthritis: a pilot study. J Rheumatol. 2003 May;30(5):934-40.
- 2727. Wood KL, Hage CA, Knox KS, et al. Histoplasmosis after treatment with anti-tumor necrosis factor-alpha therapy. Am J Respir Crit Care Med. 2003 May 1;167(9):1279-82.
- 2728. Wooten MD, Reddy GV, Johnson RD. Atrial fibrillation occurring in a patient taking etanercept plus methotrexate for rheumatoid arthritis. Del Med J. 2000 Dec;72(12):517-9.
- 2729. Wright T, Cron RQ. Pediatric rheumatology for the adult rheumatologist II: uveitis in juvenile idiopathic arthritis. J Clin Rheumatol. 2007 Aug;13(4):205-10.
- 2730. Wu E, Chen L, Birnbaum H, et al. Cost of care for patients with rheumatoid arthritis receiving TNF-antagonist therapy using claims data. Curr Med Res Opin. 2007 Aug;23(8):1749-59.
- 2731. Wulffraat NM, Sanders LA, Kuis W. Autologous hemopoietic stem-cell transplantation for children with refractory autoimmune disease. Curr Rheumatol Rep. 2000 Aug;2(4):316-23.
- 2732. Wung PK, Pipeling MR, Wigley FM. "Still" ill? Am J Med. 2008 Jun;121(6):491-3.
- 2733. Xiao H, Xu J, Zhou X, et al. Associations between the genetic polymorphisms of MTHFR and outcomes of methotrexate treatment in rheumatoid arthritis. Clin Exp Rheumatol. 2010 Sep-Oct;28(5):728-33.
- 2734. Xu JX, Hoshida Y, Hongyo T, et al. Analysis of p53 and Bak gene mutations in lymphoproliferative disorders developing in rheumatoid arthritis. J Cancer Res Clin Oncol. 2007 Feb;133(2):125-33.
- 2735. Xu Z, Vu T, Lee H, et al. Population pharmacokinetics of golimumab, an antitumor necrosis factor-alpha human

- monoclonal antibody, in patients with psoriatic arthritis. J Clin Pharmacol. 2009 Sep;49(9):1056-70.
- 2736. Yakushiji F, Kita M, Hiroi N, et al. Exacerbation of rheumatoid arthritis after removal of adrenal adenoma in Cushing's syndrome. Endocr J. 1995 Apr;42(2):219-23
- 2737. Yam LY, Wong R. Bronchiolitis obliterans and rheumatoid arthritis. Report of a case in a Chinese patient on d-penicillamine and review of the literature. Ann Acad Med Singapore. 1993 May;22(3):365-8.
- 2738. Yamada H, Kato EH, Ebina Y, et al. Fetal treatment of congenital heart block ascribed to anti-SSA antibody: case reports with observation of cardiohemodynamics and review of the literature. Am J Reprod Immunol. 1999 Oct;42(4):226-32.
- 2739. Yamada S, Takagi H, Tsuchiya H, et al.
 Comparative studies on effect of risedronate
 and alfacalcidol against glucocorticoidinduced osteoporosis in rheumatoid arthritic
 patients. Yakugaku Zasshi. 2007
 Sep;127(9):1491-6.
- 2740. Yamada T, Okuda Y, Takasugi K, et al. Relative serum amyloid A (SAA) values: the influence of SAA1 genotypes and corticosteroid treatment in Japanese patients with rheumatoid arthritis. Ann Rheum Dis. 2001 Feb;60(2):124-7.
- 2741. Yamamoto M, Takahashi H, Wakasugi H, et al. Leukoencephalopathy during administration of etanercept for refractory rheumatoid arthritis. Mod Rheumatol. 2007;17(1):72-4.
- 2742. Yamanaka H, Inoue E, Singh G, et al. Improvement of disease activity of rheumatoid arthritis patients from 2000 to 2006 in a large observational cohort study IORRA in Japan. Mod Rheumatol. 2007;17(4):283-9.
- 2743. Yamanaka H, Tanaka Y, Sekiguchi N, et al. Retrospective clinical study on the notable efficacy and related factors of infliximab therapy in a rheumatoid arthritis management group in Japan

- (RECONFIRM). Mod Rheumatol. 2007;17(1):28-32.
- 2744. Yamauchi PS, Gindi V, Lowe NJ. The treatment of psoriasis and psoriatic arthritis with etanercept: practical considerations on monotherapy, combination therapy, and safety. Dermatol Clin. 2004 Oct;22(4):449-59, ix.
- 2745. Yamauchi PS, Turner L, Lowe NJ, et al. Treatment of recurrent Sweet's syndrome with coexisting rheumatoid arthritis with the tumor necrosis factor antagonist etanercept. J Am Acad Dermatol. 2006 Mar;54(3 Suppl 2):S122-6.
- 2746. Yamazawa K, Matsui H, Sekiya S. Gastric perforation induced by combination chemotherapy in a patient with long-term use of corticosteroids. Int J Gynaecol Obstet. 2002 Aug;78(2):165-6.
- 2747. Yamout B, El-Hajj T, Barada W, et al. Successful treatment of refractory neuroSjogren with Rituximab. Lupus. 2007;16(7):521-3.
- 2748. Yang C, Gu J, Rihl M, et al. Serum levels of matrix metalloproteinase 3 and macrophage colony-stimulating factor 1 correlate with disease activity in ankylosing spondylitis. Arthritis Rheum. 2004 Oct 15;51(5):691-9.
- 2749. Yang DH, Chang DM, Lai JH, et al. Etanercept as a rescue agent in patient with adult onset Still's disease complicated with congestive heart failure. Rheumatol Int. 2008 Nov;29(1):95-8.
- 2750. Yasuda M, Yasuda D, Tomooka K, et al. Plasma concentration of human atrial natriuretic hormone in patients with connective tissue diseases. Clin Rheumatol. 1993 Jun;12(2):231-5.
- 2751. Yasunori K, Masaaki T, Tetsuyuki N, et al. Reduction of urinary levels of pyridinoline and deoxypyridinoline and serum levels of soluble receptor activator of NF-kappaB ligand by etanercept in patients with rheumatoid arthritis. Clin Rheumatol. 2008 Sep;27(9):1093-101.

- 2752. Yazdani C, McLaughlin T, Cummins G, et al. Comparison of rheumatoid arthritis care costs in patients starting therapy with leflunomide versus etanercept. Am J Manag Care. 2001 Sep;7(13 Suppl):S419-26.
- 2753. Yazdani-Biuki B, Stadlmaier E, Mulabecirovic A, et al. Blockade of tumour necrosis factor {alpha} significantly alters the serum level of IgG- and IgA-rheumatoid factor in patients with rheumatoid arthritis. Ann Rheum Dis. 2005 Aug;64(8):1224-6.
- 2754. Yazdani-Biuki B, Wohlfahrt K, Mulabecirovic A, et al. Long term treatment of psoriatic arthritis with infliximab. Ann Rheum Dis. 2004 Nov;63(11):1531-2; author reply 2.
- 2755. Yazici S, Yazici M, Erer B, et al. The platelet indices in patients with rheumatoid arthritis: mean platelet volume reflects disease activity. Platelets. 2010;21(2):122-5.
- 2756. Yazici Y, Erkan D. Do etanercept-naive patients with rheumatoid arthritis respond better to infliximab than patients for whom etanercept has failed? Ann Rheum Dis. 2004 May;63(5):607-8; author reply 8.
- 2757. Yazici Y, Erkan D, Kulman I, et al.
 Decreased flares of rheumatoid arthritis
 during the first year of etanercept treatment:
 further evidence of clinical effectiveness in
 the "real world". Ann Rheum Dis. 2002
 Jul;61(7):638-40.
- 2758. Yazici Y, Erkan D, Lockshin MD. A preliminary study of etanercept in the treatment of severe, resistant psoriatic arthritis. Clin Exp Rheumatol. 2000 Nov-Dec;18(6):732-4.
- 2759. Yazici Y, Erkan D, Lockshin MD. Etanercept in the treatment of severe, resistant psoriatic arthritis: continued efficacy and changing patterns of use after two years. Clin Exp Rheumatol. 2002 Jan-Feb;20(1):115.
- 2760. Yazici Y, Krasnokutsky S, Barnes JP, et al. Changing patterns of tumor necrosis factor inhibitor use in 9074 patients with rheumatoid arthritis. J Rheumatol. 2009 May;36(5):907-13.

- 2761. Yazici Y, McMorris BJ, Darkow T, et al. Patient and physician perception of the infusion process of the biologic agents abatacept, infliximab, and rituximab for the treatment of rheumatoid arthritis. Clin Exp Rheumatol. 2009 Nov-Dec;27(6):907-13.
- 2762. Yee CS, Filer A, Pace A, et al. The prevalence of patients with rheumatoid arthritis in the West Midlands fulfilling the BSR criteria for anti-tumour necrosis factor therapy: an out-patient study. Rheumatology (Oxford). 2003 Jul;42(7):856-9.
- 2763. Yeh HM, Liu MF, Chang KK, et al. Adultonset Still's disease complicated with hemophagocytic syndrome. J Formos Med Assoc. 2010 Jan;109(1):85-8.
- 2764. Yelin E, Trupin L, Katz P, et al. Association between etanercept use and employment outcomes among patients with rheumatoid arthritis. Arthritis Rheum. 2003
 Nov;48(11):3046-54.
- 2765. Yelin EH, Trupin LS, Katz PP. Impact of managed care on the use of biologic agents for rheumatoid arthritis. Arthritis Rheum. 2005 Jun 15;53(3):423-30.
- 2766. Yeo SW, Park SN. Immune-mediated sensorineural hearing loss in a patient with ankylosing spondylitis: a case report.

 Otolaryngol Head Neck Surg. 2001
 Jul;125(1):113-4.
- 2767. Yigla M, Simsolo C, Goralnik L, et al. The problem of empyematous pleural effusion in rheumatoid arthritis: report of two cases and review of the literature. Clin Rheumatol. 2002 May;21(2):180-3.
- 2768. Yilmaz L, Ozoran K, Gunduz OH, et al. Alendronate in rheumatoid arthritis patients treated with methotrexate and glucocorticoids. Rheumatol Int. 2001 Feb;20(2):65-9.
- 2769. Yim K, Nazeer SH, Kiska D, et al. Recurrent Mycobacterium xenopi infection in a patient with rheumatoid arthritis receiving etanercept. Scand J Infect Dis. 2004;36(2):150-4.

- 2770. Yocum DE, Furst DE, Bensen WG, et al. Safety of tacrolimus in patients with rheumatoid arthritis: long-term experience. Rheumatology (Oxford). 2004 Aug;43(8):992-9.
- 2771. Yokoo H, Nakazato Y, Harigaya Y, et al. Massive myelinolytic leukoencephalopathy in a patient medicated with low-dose oral methotrexate for rheumatoid arthritis: an autopsy report. Acta Neuropathol. 2007 Oct;114(4):425-30.
- 2772. Yokota S, Imagawa T, Mori M, et al. Efficacy and safety of tocilizumab in patients with systemic-onset juvenile idiopathic arthritis: a randomised, double-blind, placebo-controlled, withdrawal phase III trial. Lancet. 2008 Mar 22;371(9617):998-1006.
- 2773. Yokoyama E, Muto M. Adult variant of self-healing papular mucinosis in a patient with rheumatoid arthritis: predominant proliferation of dermal dendritic cells expressing CD34 or factor XIIIa in association with dermal deposition of mucin. J Dermatol. 2006 Jan;33(1):30-5.
- 2774. Yonezawa T, Tsuji H, Matsui H, et al. Subaxial lesions in rheumatoid arthritis. Radiographic factors suggestive of lower cervical myelopathy. Spine. 1995 Jan 15;20(2):208-15.
- 2775. Yoshida A, Morozumi K, Suganuma T, et al. Clinicopathological findings of bucillamine-induced nephrotic syndrome in patients with rheumatoid arthritis. Am J Nephrol. 1991;11(4):284-8.
- 2776. Yoshida K, Bandoh S, Fujita J, et al. Pyothorax caused by Nocardia otitidiscaviarum in a patient with rheumatoid vasculitis. Intern Med. 2004 Jul;43(7):615-9.
- 2777. Yoshida K, Yokoyama T, Toyokawa Y, et al. Cryofibrinogenemia associated with Sjogren's syndrome: a case of successful treatment with high-dose corticosteroid. Intern Med. 2007;46(13):1039-42.
- 2778. Yoshioka T, Tachihara A, Koyama T, et al. Rapid destruction of the hip joint associated with enlarged iliopsoas bursa in a patient

- with refractory rheumatoid arthritis. J Nippon Med Sch. 2008 Aug;75(4):233-8.
- 2779. Yosipovitch G, Tang MB. Practical management of psoriasis in the elderly: epidemiology, clinical aspects, quality of life, patient education and treatment options. Drugs Aging. 2002;19(11):847-63.
- 2780. You CG, Yin YS, Xie XD, et al. Sex influences on the penetrance of IL-1beta and IL-1RN genotypes for rheumatoid arthritis in the Chinese population. J Int Med Res. 2007 May-Jun;35(3):323-8.
- 2781. You CR, Kim HR, Yoon CH, et al.

 Macrophage activation syndrome in juvenile rheumatoid arthritis successfully treated with cyclosporine A: a case report. J Korean Med Sci. 2006 Dec;21(6):1124-7.
- 2782. Youm JY, Woo JH, Kim TH, et al. Interleukin-1beta and interleukin-1 receptor antagonist gene polymorphisms in Korean patients with adult-onset Still's disease. Scand J Rheumatol. 2007 Sep-Oct;36(5):390-3.
- 2783. Young MG, Rijhsinghani S. Leflunomide and acute hypocalcemia. Endocr Pract. 2007 Nov-Dec;13(7):805-7.
- 2784. Young PJ, Weeden S, Kirwan JR. The analysis of a bivariate multi-state Markov transition model for rheumatoid arthritis with an incomplete disease history. Stat Med. 1999 Jul 15;18(13):1677-90.
- 2785. Yount S, Sorensen MV, Cella D, et al. Adalimumab plus methotrexate or standard therapy is more effective than methotrexate or standard therapies alone in the treatment of fatigue in patients with active, inadequately treated rheumatoid arthritis. Clin Exp Rheumatol. 2007 Nov-Dec;25(6):838-46.
- 2786. Yousem SA, Dacic S. Pulmonary lymphohistiocytic reactions temporally related to etanercept therapy. Mod Pathol. 2005 May;18(5):651-5.
- 2787. Yu EN, Meniconi ME, Tufail F, et al.
 Outcomes of treatment with
 immunomodulatory therapy in patients with

- corticosteroid-resistant juvenile idiopathic arthritis-associated chronic iridocyclitis. Ocul Immunol Inflamm. 2005 Sep-Oct;13(5):353-60.
- 2788. Yu EN, Paredes I, Foster CS. Surgery for hypotony in patients with juvenile idiopathic arthritis-associated uveitis. Ocul Immunol Inflamm. 2007 Jan-Feb;15(1):11-7.
- 2789. Yu X, Ma J, Tian J, et al. A controlled study of double filtration plasmapheresis in the treatment of active rheumatoid arthritis. J Clin Rheumatol. 2007 Aug;13(4):193-8.
- 2790. Yukawa E, Mori S, Ueda K, et al. Population pharmacokinetic investigation of low-dose methotrexate in rheumatoid arthritics Japanese patients. J Clin Pharm Ther. 2007 Dec;32(6):573-8.
- 2791. Yukawa S, Yamaoka K, Sawamukai N, et al. Involvement of mast cells in systemic sclerosis. Nihon Rinsho Meneki Gakkai Kaishi. 2010;33(2):81-6.
- 2792. Yukioka M, Komatsubara Y, Yukioka K, et al. Adrenocorticotropic hormone and dehydroepiandrosterone sulfate levels of rheumatoid arthritis patients treated with glucocorticoids. Mod Rheumatol. 2006;16(1):30-5.
- 2793. Yum HK, Kim ES, Ok KS, et al.
 Lymphocytic interstitial pneumonitis
 associated with Epstein-Barr virus in
 Systemic Lupus Erythematosus and
 Sjogren's Syndrome. Complete remission
 with corticosteriod and cyclophosphamide.
 Korean J Intern Med. 2002 Sep;17(3):198203.
- 2794. Yun JE, Lee SW, Kim TH, et al. The incidence and clinical characteristics of Mycobacterium tuberculosis infection among systemic lupus erythematosus and rheumatoid arthritis patients in Korea. Clin Exp Rheumatol. 2002 Mar-Apr;20(2):127-32.
- 2795. Zabinski SJ, Sculco TP, Dicarlo EF, et al. Osteonecrosis in the rheumatoid femoral head. J Rheumatol. 1998 Sep;25(9):1674-80.

- 2796. Zamarron C, Maceiras F, Gonzalez J, et al. Worsening of obstructive sleep apnoeas in a patient with rheumatoid arthritis treated with anti-tumor necrosis factor. Respir Med. 2004 Feb;98(2):123-5.
- 2797. Zamarron C, Maceiras F, Mera A, et al. Effect of the first infliximab infusion on sleep and alertness in patients with active rheumatoid arthritis. Ann Rheum Dis. 2004 Jan;63(1):88-90.
- 2798. Zandbelt MM, de Wilde P, van Damme P, et al. Etanercept in the treatment of patients with primary Sjogren's syndrome: a pilot study. J Rheumatol. 2004 Jan;31(1):96-101.
- 2799. Zandbelt MM, van den Hoogen FH, de Wilde PC, et al. Reversibility of histological and immunohistological abnormalities in sublabial salivary gland biopsy specimens following treatment with corticosteroids in Sjogren's syndrome. Ann Rheum Dis. 2001 May;60(5):511-3.
- 2800. Zangrilli A, Papoutsaki M, Talamonti M, et al. Long-term efficacy of adalimumab in generalized pustular psoriasis. J Dermatolog Treat. 2008;19(3):185-7.
- 2801. Zautra AJ, Burleson MH, Matt KS, et al. Interpersonal stress, depression, and disease activity in rheumatoid arthritis and osteoarthritis patients. Health Psychol. 1994 Mar;13(2):139-48.
- 2802. Zeidler HK, Kvien TK, Hannonen P, et al. Progression of joint damage in early active severe rheumatoid arthritis during 18 months of treatment: comparison of low-dose cyclosporin and parenteral gold. Br J Rheumatol. 1998 Aug;37(8):874-82.
- 2803. Zhang LL, Wei W, Xiao F, et al. A randomized, double-blind, multicenter, controlled clinical trial of chicken type II collagen in patients with rheumatoid arthritis. Arthritis Rheum. 2008 Jul 15;59(7):905-10.
- 2804. Zhang W, Bansback N, Guh D, et al. Short-term influence of adalimumab on work productivity outcomes in patients with rheumatoid arthritis. J Rheumatol. 2008 Sep;35(9):1729-36.

- 2805. Zhao B, Takami M, Miyamoto Y, et al. Characterization of synovial cell clones isolated from rheumatoid arthritis patients: possible involvement of TNF-alpha in reduction of osteoprotegerin in synovium. Cytokine. 2008 Jan;41(1):61-70.
- 2806. Zhou H. Clinical pharmacokinetics of etanercept: a fully humanized soluble recombinant tumor necrosis factor receptor fusion protein. J Clin Pharmacol. 2005 May;45(5):490-7.
- 2807. Zhou H, Buckwalter M, Boni J, et al. Population-based pharmacokinetics of the soluble TNFr etanercept: a clinical study in 43 patients with ankylosing spondylitis compared with post hoc data from patients with rheumatoid arthritis. Int J Clin Pharmacol Ther. 2004 May;42(5):267-76.
- 2808. Zhou H, Mayer PR, Wajdula J, et al. Unaltered etanercept pharmacokinetics with concurrent methotrexate in patients with rheumatoid arthritis. J Clin Pharmacol. 2004 Nov;44(11):1235-43.
- 2809. Zhu G, Liu G, Liu Y, et al. Liver abnormalities in adult onset Still's disease: a retrospective study of 77 Chinese patients. J Clin Rheumatol. 2009 Sep;15(6):284-8.
- 2810. Ziakas PD, Giannouli S, Tzioufas AG, et al. Lymphoma development in a patient receiving anti-TNF therapy. Haematologica. 2003 Jul;88(7):ECR25.
- 2811. Zikou AK, Argyropoulou MI, Voulgari PV, et al. Magnetic resonance imaging quantification of hand synovitis in patients with rheumatoid arthritis treated with adalimumab. J Rheumatol. 2006 Feb;33(2):219-23.
- 2812. Zink A, Listing J, Kary S, et al. Treatment continuation in patients receiving biological agents or conventional DMARD therapy. Ann Rheum Dis. 2005 Sep;64(9):1274-9.
- 2813. Zink A, Listing J, Ziemer S, et al. Practice variation in the treatment of rheumatoid arthritis among German rheumatologists. J Rheumatol. 2001 Oct;28(10):2201-8.

- 2814. Zintzaras E, Dahabreh IJ, Giannouli S, et al. Infliximab and methotrexate in the treatment of rheumatoid arthritis: a systematic review and meta-analysis of dosage regimens. Clin Ther. 2008 Nov;30(11):1939-55.
- 2815. Ziolkowska M, Kurowska M, Radzikowska A, et al. High levels of osteoprotegerin and soluble receptor activator of nuclear factor kappa B ligand in serum of rheumatoid arthritis patients and their normalization after anti-tumor necrosis factor alpha treatment. Arthritis Rheum. 2002

 Jul;46(7):1744-53.
- 2816. Ziswiler HR, Aeberli D, Villiger PM, et al. High-resolution ultrasound confirms reduced synovial hyperplasia following rituximab treatment in rheumatoid arthritis. Rheumatology (Oxford). 2009 Aug;48(8):939-43.
- 2817. Zoli A, Ferlisi EM, Lizzio M, et al. Prolactin/cortisol ratio in rheumatoid arthritis. Ann N Y Acad Sci. 2002 Jun;966:508-12.
- 2818. Zoli A, Lizzio MM, Ferlisi EM, et al. ACTH, cortisol and prolactin in active rheumatoid arthritis. Clin Rheumatol. 2002 Aug;21(4):289-93.
- 2819. Zoukos Y, Leonard JP, Thomaides T, et al. beta-Adrenergic receptor density and function of peripheral blood mononuclear cells are increased in multiple sclerosis: a regulatory role for cortisol and interleukin-1. Ann Neurol. 1992 Jun;31(6):657-62

Reference Source: International Pharmaceutical Abstracts

- 1. First Latin American position paper on the pharmacological treatment of rheumatoid arthritis. Rheumatology. 2006 01/01/;45(JUN):7-2.
- Aggarwal R, Manadan AM, Poliyedath A, et al. Safety of Etanercept in Patients at High Risk for Mycobacterial Tuberculosis Infections. Journal of Rheumatology. 2009;36:914.
- 3. Alcorn N, Saunders S, Madhok R, et al. Benefit-Risk Assessment of Leflunomide An Appraisal of Leflunomide in Rheumatoid Arthritis 10 Years After Licensing. Drug Safety (New Zealand). 2009;32:1123.
- Aletaha D, Funovits J, Breedveld FC, et al. Rheumatoid Arthritis Joint Progression in Sustained Remission Is Determined by Disease Activity Levels Preceding the Period of Radiographic Assessment. Arthritis and Rheumatism (USA) 2009:601242.
- 5. Anonymous. Atlizumab Anti-IL-6 receptor antibody Chugai, anti-interleukin-6 receptor antibody Chugai, MRA Chugai. BioDrugs. 2003;17:369-72.
- 6. Anonymous. Tocilizumab for rheumatoid arthritis. Drug and Therapeutics Bulletin (England). 2010;48:9.
- 7. Antoniu SA, Apr. Cytokine Antagonists for the Treatment of Asthma Progress to Date. BioDrugs (New Zealand) 2009;23241.
- 8. Asahina A, Ohshima N, Nakayama H, et al. Henoch-Schonlein purpura in a patient with rheumatoid arthritis receiving etanercept. European Journal of Dermatology (France). 2010;20:521-2.
- 9. Baggott JE, Morgan SL, Aug. Methotrexate Catabolism to 7-Hydroxymethotrexate in Rheumatoid Arthritis Alters Drug Efficacy and Retention and Is Reduced by Folic Acid Supplementation. Arthritis and Rheumatism (USA) 2009;602257.

- 10. Bansard C, Lequerre T, Daveau M, et al. Can rheumatoid arthritis responsiveness to methotrexate and biologics be predicted? Rheumatology 2009;481021.
- 11. Bansback NJ, Ara R, Barkham N, et al. Estimating the cost and health status consequences of treatment with TNF antagonists in patients with psoriatic arthritis. Rheumatology. 2006 08/01/;45(Aug):1029-38.
- 12. Bathon JM, Fleischmann RM, van der Heijde DM, et al. Safety and efficacy of etanercept treatment in elderly subjects with rheumatoid arthritis. Journal of Rheumatology. 2006 02/01/;33(Feb):234-43.
- 13. Bell S. Payers have biologic alternative for patients with moderate to severe rheumatoid arthritis who do not respond to other DMARD therapies. Biotechnology Healthcare. 2006 06/01/;3(Jun):24-8.
- 14. Benhamou M, Rincheval N, Roy C, et al.
 The Gap Between Practice and Guidelines in
 the Choice of First-line Disease Modifying
 Antirheumatic Drug in Early Rheumatoid
 Arthritis: Results from the ESPOIR Cohort.
 Journal of Rheumatology 2009;36934.
- Bernatsky S, Habel Y, Rahme E.
 Observational Studies of Infections in Rheumatoid Arthritis: A Metaanalysis of Tumor Necrosis Factor Antagonists. Journal of Rheumatology 2010;37928-31.
- 16. Bingham CO, Ince A, Haraoui B, et al. Effectiveness and safety of etanercept in subjects with RA who have failed infliximab therapy: 16-week, open-label, observational study. Current Medical Research and Opinion (England) 2009;251131.
- 17. Borah BJ, Huang XY, Zarotsky V, et al. Trends in RA patients' adherence to subcutaneous anti-TNF therapies and costs. Current Medical Research and Opinion (England) 2009;251365.
- 18. Bours MJ, Peeters RH, Landewe RB, et al. Adenosine 5'-triphosphate infusions reduced disease activity and inflammation in a

- patient with active rheumatoid arthritis. Rheumatology (Oxford). 2010;49:2223-5.
- 19. Boyce EG, Halilovic J, Stan-Ugbene O. Golimumab: Review of the Efficacy and Tolerability of a Recently Approved Tumor Necrosis Factor-alpha Inhibitor. Clinical Therapeutics (USA). 2010;32:1681-703.
- 20. Bruce SP. Recent Developments in the Treatment of Rheumatoid Arthritis. Journal of Pharmacy Practice. 2009;22:65-74.
- 21. Bullano MF, McNeeley BJ, Yu YF, et al. Comparison of costs associated with the use of etanercept, infliximab, and adamlimumab for the treatment of rheumatoid arthritis.

 Managed Care Interface (USA). 2006
 09/01/;19(Sep):47-53.
- 22. Butterly SJ, Pillans P, Horn B, et al. Offlabel use of rituximab in a tertiary Queensland hospital. Internal Medicine Journal. 2010;40:443-52.
- 23. Cambridge G, Stohl W, Leandro MJ, et al. Circulating levels of B lymphocyte stimulator in patients with rheumatoid arthritis following rituximab treatment Relationships with B cell depletion, circulating antibodies, and clinical relapse. Arthritis and Rheumatism (USA). 2006 03/01/;54(Mar):723-32.
- 24. Campas-Moya C. Golimumab: A novel anti-INF-alpha human monoclonal antibody for rheumatoid arthritis, psoriatic arthritis and ankylosing spondylitis. Drugs of Today (Spain). 2010;46:13-22.
- 25. Cannon CP, Curtis SP, Bolognese JA, et al. Clinical trial design and patient demographics of the multinational etoricoxib and diclofenac arthritis long-term (MEDAL) study program: Cardiovascular outcomes with etoricoxib versus diclofenac in patients with osteoarthritis and rheumatoid arthritis. American Heart Journal. 2006 02/01/;152(Feb):237-45.
- 26. Cannon CP, Curtis SP, FitzGerald GA, et al. Cardiovascular outcomes with etoricoxib and diclofenac in patients with osteoarthritis and rheumatoid arthritis in the Multinational Etoricoxib and Diclofenac Arthritis Longterm (MEDAL) programme: a randomised

- comparison. Lancet, The (USA). 2006 01/01/;368(Jan):1771-81.
- 27. Cantaert T, van Baarsen LG, Wijbrandts CA, et al. Type I interferons have no major influence on humoral autoimmunity in rheumatoid arthritis. Rheumatology (Oxford). 2010;49:156.
- 28. Carazo JL, Santos LM, Martinez VO. Safety of etanercept in psoriasis A critical review. Drug Safety (New Zealand). 2006 08/01/;29(Aug):675-85.
- 29. Cavill I, Auerbach M, Bailie GR, et al. Iron and the anaemia of chronic disease: a review and strategic recommendations. Current Medical Research and Opinion (England). 2006 04/01/;22(Apr):731-7.
- 30. Chung SJ, Kim JK, Park MC, et al.
 Reactivation of Hepatitis B Viral Infection
 in Inactive HBsAg Carriers Following AntiTumor Necrosis Factor-alpha Therapy.
 Journal of Rheumatology 2009;362416.
- 31. Coates LC, Helliwell PS. Validation of Minimal Disease Activity Criteria for Psoriatic Arthritis Using Interventional Trial Data. Arthritis Care and Research. 2010;62:965.
- Cohen PR, May. Neutrophilic Dermatoses A Review of Current Treatment Options.
 American Journal of Clinical Dermatology (New Zealand) 2009;10301.
- 33. Cohen SB. Updates from B cell trials: Efficacy. Journal of Rheumatology. 2006 01/01/;33(MAY):12-7.
- 34. Cui J, Saevarsdottir S, Thomson B, et al. Rheumatoid Arthritis Risk Allele <it>PTPRC</it> Is Also Associated With Response to Anti-Tumor Necrosis Factor alpha Therapy. Arthritis and Rheumatism (USA). 2010;62:1849.
- 35. Curtis JR, Chen L, Harrold LR, et al. Physician Preference Motivates the Use of Anti-Tumor Necrosis Factor Therapy Independent of Clinical Disease Activity. Arthritis Care and Research. 2010;62:101-7.

- 36. Curtis SP, Ko AT, Bolognese JA, et al. Pooled analysis of thrombotic cardiovascular events in clinical trials of the COX-2 selective inhibitor etoricoxib. Current Medical Research and Opinion (England). 2006 12/01/;22(Dec):2365-74.
- 37. DaSilva V, Roux CH, Bernard E, et al.
 Neuromeningeal Tuberculosis in a Patient
 with Rheumatoid Arthritis Previously
 Exposed to Ineffective Etanercept Therapy
 and Revealed by Infliximab. Journal of
 Rheumatology. 2010;37:471-2.
- 38. De Rycke L, Baeten D, Kruithof E, et al. Infliximab, but not etanercept, induces IgM anti-double-stranded DNA autoantibodies as main antinuclear reactivity Biologic and clinical implications in autoimmune arthritis. Arthritis and Rheumatism (USA). 2005 07/01/;52(Jul):2192-201.
- 39. de Vlam K, Lories RJ. Efficacy, effectiveness and safety of etanercept in monotherapy for refractory psoriatic arthritis: a 26-week observational study. Rheumatology. 2006 03/01/;45(Mar):321-4.
- 40. de Vries-Bouwstra J, Le Cessie S, Allaart C, et al. Using predicted disease outcome to provide differentiated treatment of early rheumatoid arthritis. Journal of Rheumatology. 2006 09/01/;33(Sep):1747-53.
- 41. Deighton C, Hyrich K, Ding T, et al. BSR and BHPR rheumatoid arthritis guidelines on eligibility criteria for the first biological therapy. Rheumatology (Oxford). 2010;49:1197-9.
- 42. Dewan P, Jawad A, Goldsmith P, et al. Melanoma in patients with rheumatoid arthritis treated with antitumour necrosis factor: cause or coincidence? Report of two cases. British Journal of Dermatology (England) 2009;1611412.
- 43. Doan QV, Chiou CF, Dubois RW. Review of eight pharmacoeconomic studies of the value of biologic DMARDs (adalimumab, etanercept, and infliximab) in the management of rheumatoid arthritis. Journal of Managed Care Pharmacy (USA). 2006 07/01/;12(Jul):555-69.

- 44. Driessen RJ, de Jong EM, Salemink GW, et al. Analysis of 4-year Dutch reimbursement application data of biological therapies for psoriatic arthritis. Rheumatology (Oxford). 2010;49:588-91.
- 45. Duggan ST, Keam SJ, Jun. Certolizumab Pegol In Rheumatoid Arthritis. BioDrugs (New Zealand). 2009;23:407.
- Eder L, Chandran V, Ueng J, et al.
 Predictors of response to intra-articular steroid injection in psoriatic arthritis.
 Rheumatology (Oxford). 2010;49:1367-73.
- 47. El Miedany Y, Youssef SS, El Gaafary M. Short-term outcome after anti-tumor necrosis factor-alpha therapy in rheumatoid arthritis: Do we need to revise our assessment criteria? Journal of Rheumatology. 2006;33(3):490-6.
- 48. Emery P, Fleischmann R, Filipowicz-Sosnowska A, et al. The efficacy and safety of rituximab in patients with active rheumatoid arthritis despite methotrexate treatment Results of a phase IIb randomized, double-blind, placebocontrolled, dose-ranging trial. Arthritis and Rheumatism (USA) 2006;54(May):1390-400.
- 49. Emery P, Genovese MC, van Vollenhoven R, et al. Less Radiographic Progression with Adalimumab Plus Methotrexate Versus Methotrexate Monotherapy Across the Spectrum of Clinical Response in Early Rheumatoid Arthritis. Journal of Rheumatology 2009;361429.
- 50. Emery P, Kosinski M, Li T, et al. Treatment of rheumatoid arthritis patients with abatacept and methotrexate significantly improved health-related quality of life. Journal of Rheumatology 2006;33(Apr):681-9.
- 51. Esposito M, Mazzotta A, de Felice C, et al. Treatment of erythrodermic psoriasis with etanercept. British Journal of Dermatology (England). 2006 01/01/;155(Jan):156-9.
- 52. Finckh A, Bansback N, Marra CA, et al.
 Treatment of Very Early Rheumatoid
 Arthritis With Symptomatic Therapy,
 Disease-Modifying Antirheumatic Drugs, or

- Biologic Agents A Cost-Effectiveness Analysis. Annals of Internal Medicine (USA). 2009;151:612.
- 53. Fleurence R, Spackman E. Costeffectiveness of biologic agents for treatment of autoimmune disorders:
 Structured review of the literature. Journal of Rheumatology. 2006
 11/01/;33(Nov):2124-31.
- 54. Fouache D, Goeb V, Massy-Guillemant N, et al. Paradoxical adverse events of anti-tumour necrosis factor therapy for spondyloarthropathies: a retrospective study. Rheumatology 2009;48761.
- 55. Frey N, Grange S, Woodworth T. Population Pharmacokinetic Analysis of Tocilizumab in Patients With Rheumatoid Arthritis. Journal of Clinical Pharmacology (USA). 2010;50:754-66.
- 56. Furlan AD, Sandoval JA, Mailis-Gagnon A, et al. Opioids for chronic noncancer pain: a meta-analysis of effectiveness and side effects. Canadian Medical Association Journal (Canada). 2006 11/01/;174(Nov):1589-94.
- 57. Gaffo A, Saag KG, Curtis JR. Treatment of rheumatoid arthritis. American Journal of Health-System Pharmacy (USA). 2006 01/01/;63(Jan):2451-65.
- Garcia JJ, Lobato JP, Garrido SL, et al. Biological therapies in rheumatoid arthritis. Atencion Farmaceutica: European Journal of Clinical Pharmacy. 2008;10(98):100-11.
- 59. Garnero P, Thompson E, Woodworth T, et al. Rapid and Sustained Improvement in Bone and Cartilage Turnover Markers With the Anti-Interleukin-6 Receptor Inhibitor Tocilizumab Plus Methotrexate in Rheumatoid Arthritis Patients With an Inadequate Response to Methotrexate Results From a Substudy of the Multicenter Double-Blind, Placebo-Controlled Trial of Tocilizumab in Inadequate Responders to Methotrexate Alone. Arthritis and Rheumatism (USA). 2010;62:33.
- 60. Gladman DD, Sampalis JS, Illouz O, et al. Responses to Adalimumab in Patients with Active Psoriatic Arthritis Who Have Not

- Adequately Responded to Prior Therapy: Effectiveness and Safety Results From an Open-label Study. Journal of Rheumatology. 2010:37:1898.
- 61. Gladman DD, Tom BD, Mease PJ, et al. Informing Response Criteria for Psoriatic Arthritis. I: Discrimination Models Based on Data from 3 Anti-Tumor Necrosis Factor Randomized Studies. Journal of Rheumatology. 2010;37:1892-7.
- 62. Gompels LL, Smith A, Charles PJ, et al. Single-blind randomized trial of combination antibiotic therapy in rheumatoid arthritis. Journal of Rheumatology. 2006 02/01/;33(Feb):224-7.
- 63. Gonzalez-Juanatey C, Llorca J, Garcia-Porrua C, et al. Effect of anti-tumor necrosis factor alpha therapy on the progression of subclinical atherosclerosis in severe rheumatoid arthritis. Arthritis and Rheumatism-Arthritis Care and Research. 2006 01/01/;55(Jan):150-3.
- 64. Graudal N, Juergens G. Similar Effects of Disease-Modifying Antirheumatic Drugs, Glucocorticoids, and Biologic Agents on Radiographic Progression in Rheumatoid Arthritis Meta-Analysis of 70 Randomized Placebo-Controlled or Drug-Controlled Studies, Including 112 Comparisons. Arthritis and Rheumatism (USA). 2010;62:2852.
- 65. Grijalva CG, Kaltenbach L, Arbogast PG, et al. Initiation of rheumatoid arthritis treatments and the risk of serious infections. Rheumatology (Oxford) 2010;4982-90.
- 66. Hallinen TA, Soini EJ, Eklund K, et al. Cost-utility of different treatment strategies after the failure of tumour necrosis factor inhibitor in rheumatoid arthritis in the Finnish setting. Rheumatology (Oxford). 2010;49:767-77.
- 67. Haringman JJ, Gerlag DM, Smeets TJ, et al. A randomized controlled trial with an anti-CCL2 (anti-monocyte chemotactic protein 1) monoclonal antibody in patients with rheumatoid arthritis. Arthritis and Rheumatism (USA). 2006 08/01/;54(Aug):2387-92.

- 68. Harris CL, Raisch DW, Abhyankar U, et al. GI risk factors and use of GI protective agents among patients receiving nonsteroidal antiinflammatory drugs. Annals of Pharmacotherapy (USA). 2006 11/01/;40(Nov):1924-31.
- 69. Hassan B, Maxwell JR, Hyrich KL, et al. Genotype at the sIL-6R A358C polymorphism does not influence response to anti-TNF therapy in patients with rheumatoid arthritis. Rheumatology (Oxford). 2010;49:43-7.
- 70. Hetland ML, Christensen IJ, Tarp U, et al.
 Direct Comparison of Treatment Responses,
 Remission Rates, and Drug Adherence in
 Patients With Rheumatoid Arthritis Treated
 With Adalimumab, Etanercept, or
 Infliximab Results From Eight Years of
 Surveillance of Clinical Practice in the
 Nationwide Danish DANBIO Registry.
 Arthritis and Rheumatism (USA)
 2010:6222-32.
- 71. Hetland ML, Stengaard-Pedersen K, Junker P, et al. Combination treatment with methotrexate, cyclosporine, and intraarticular betamethasone compared with methotrexate and intraarticular betamethasone in early active rheumatoid arthritis An investigator-initiated, multicenter, randomized, double-blind, parallel-group, placebo-controlled study. Arthritis and Rheumatism (USA). 2006 05/01/;54(May):1401-9.
- 72. Hu CP, Xu ZH, Rahman MU, et al. A latent variable approach for modeling categorical endpoints among patients with rheumatoid arthritis treated with golimumab plus methotrexate. Journal of Pharmacokinetics and Pharmacodynamics (USA). 2010;37:309-21.
- 73. Hudson M, Suissa S. Avoiding Common Pitfalls in the Analysis of Observational Studies of New Treatments for Rheumatoid Arthritis. Arthritis Care and Research. 2010;62:805-10.
- 74. Hyrich KL, Watson KD, Silman AJ, et al. Predictors of response to anti-TNF-alpha therapy among patients with rheumatoid arthritis: results from the British Society for

- Rheumatology Biologics Register. Rheumatology 2006;45(Dec):1558-65.
- 75. Isenberg DA. B cell targeted therapies in autoimmune diseases. Journal of Rheumatology. 2006 01/01/;33(MAY):24-8.
- 76. Jacobs JW, van Everdingen AA, Verstappen SM, et al. Followup radiographic data on patients with rheumatoid arthritis who participated in a two-year trial of prednisone therapy or placebo. Arthritis and Rheumatism (USA). 2006 05/01/;54(May):1422-8.
- 77. Jarand J, Zochodne DW, Martin LO, et al. Neurological complications of infliximab. Journal of Rheumatology. 2006 05/01/;33(May):1018-20.
- 78. Jazayeri JA, Carroll GJ, Vernallis AB.
 Interleukin-6 subfamily cytokines and rheumatoid arthritis: Role of antagonists.
 International Immunopharmacology (USA). 2010;10:1-8.
- 79. Kavanaugh A. Anakinra (interleukin-1 receptor antagonist) has positive effects on function and quality of life in patients with rheumatoid arthritis. Advances in Therapy (USA). 2006 02/01/;23(Feb):208-17.
- 80. Kavanaugh AF. B cell targeted therapies: Safety considerations. Journal of Rheumatology. 2006 01/01/;33(MAY):18-23.
- 81. Kawai S, Hashimoto H, Kondo H, et al. Comparison of tacrolimus and mizoribine in a randomized, double-blind controlled study in patients with rheumatoid arthritis. Journal of Rheumatology. 2006 11/01/;33(Nov):2153-61.
- 82. Kawai S, Yamamoto K. Safety of tacrolimus, an immunosuppressive agent, in the treatment of rheumatoid arthritis in elderly patients. Rheumatology. 2006 04/01/;45(Apr):441-4.
- 83. Kawakami K, Ikari K, Kawamura K, et al.
 Complications and features after joint
 surgery in rheumatoid arthritis patients
 treated with tumour necrosis factor-alpha
 blockers: perioperative interruption of

- tumour necrosis factor-alpha blockers decreases complications? Rheumatology (Oxford) 2010;49341-7.
- 84. Kawashiri SY, Kawakami A, Iwamoto N, et al. Proinflammatory Cytokines Synergistically Enhance the Production of Chemokine Ligand 20 (CCL20) from Rheumatoid Fibroblast-like Synovial Cells <it>in vitro</it> and Serum CCL20 Is Reduced <it>in vivo</it> by Biologic Disease-modifying Antirheumatic Drugs. Journal of Rheumatology 2009;362397.
- 85. Kay LJ, Griffiths ID, Management BSRBR. UK consultant rheumatologists' access to biological agents and views on the BSR Biologics Register. Rheumatology. 2006 11/01/;45(Nov):1376-9.
- 86. Kivitz A, Cohen S, Dowd JE, et al. Clinical assessment of pain, tolerability, and preference of an autoinjection pen versus a prefilled syringe for patient self-administration of the fully human, monoclonal antibody adalimumab: The TOUCH trial. Clinical Therapeutics (USA). 2006 10/01/;28(Oct):1619-29.
- 87. Kling MC, Larian AA, Scordi-Bello I, et al. Fatal Influenza A(H1N1) Respiratory Tract Infection in a Patient Having Psoriasis Treated With Infliximab. Archives of Dermatology (USA). 2010;146:651-4.
- 88. Koeller MD, Aletaha D, Funovits J, et al. Response of elderly patients with rheumatoid arthritis to methotrexate or TNF inhibitors compared with younger patients. Rheumatology 2009;481575.
- 89. Korkina L, Trakhtman P, De Luca C, et al. EFFICACY AND SAFETY OF BIOLOGICALS AGAINST IMMUNE-MEDIATED DISEASES: DO BENEFITS OUTWEIGH RISKS? Drugs of Today (Spain). 2010;46:119-36.
- 90. Krathen MS, Gottlieb AB, Mease PJ.
 Pharmacologic Immunomodulation and
 Cutaneous Malignancy in Rheumatoid
 Arthritis, Psoriasis, and Psoriatic Arthritis.
 Journal of Rheumatology. 2010;37:2205-15.
- 91. Kremer JM, Genant HK, Moreland LW, et al. Effects of abatacept in patients with

- methotrexate-resistant active rheumatoid arthritis A randomized trial. Annals of Internal Medicine (USA) 2006;144(Dec):865-76.
- 92. Kuan WP, Tam LS, Wong CK, et al. CXCL 9 and CXCL 10 as Sensitive Markers of Disease Activity in Patients with Rheumatoid Arthritis. Journal of Rheumatology. 2010;37:257-64.
- 93. Landewe R, van der Heijde D, Klareskog L, et al. Disconnect between inflammation and joint destruction after treatment with etanercept plus methotrexate Results from the trial of etanercept and methotrexate with radiographic and patient outcomes. Arthritis and Rheumatism (USA). 2006 10/01/;54(Oct):3119-25.
- 94. Lee YH, Ji JD, Bae SC, et al. Associations Between Tumor Necrosis Factor-alpha (TNF-alpha) -308 and -238 G/A Polymorphisms and Shared Epitope Status and Responsiveness to TNF-alpha Blockers in Rheumatoid Arthritis: A Metaanalysis Update. Journal of Rheumatology. 2010;37:740-6.
- 95. Lee YH, Song GG. Associations between the C677T and A1298C Polymorphisms of <it>MTHFR</it> and the Efficacy and Toxicity of Methotrexate in Rheumatoid Arthritis A Meta-Analysis. Clinical Drug Investigation (New Zealand). 2010;30:101-8.
- 96. Lester SE, Proudman SM, Lee AT, et al. Treatment-induced stable, moderate reduction in blood cell counts correlate to disease control in early rheumatoid arthritis. Internal Medicine Journal. 2009;39:296.
- 97. Looney RJ. B cell-targeted therapy for rheumatoid arthritis An update on the evidence. Drugs (New Zealand). 2006 05/01/;66(May):625-39.
- 98. Luman KL, Amireh H, Gonzalez ER. A medication utilization evaluation of abatacept: a retrospective study. ASHP Midyear Clinical Meeting. 2010;2009:119.
- 99. Luman KL, Amireh H, Gonzalez ER. A medication utilization evaluation of

- infliximab: a retrospective study. ASHP Midyear Clinical Meeting. 2010;2009:120.
- 100. Luqmani R, Hennell S, Estrach C, et al. British society for rheumatology and british health professionals in rheumatology guideline for the management of rheumatoid arthritis (the first two years). Rheumatology. 2006 09/01/;45(Sep):1167-9.
- 101. Ma MH, Kingsley GH, Scott DL. A systematic comparison of combination DMARD therapy and tumour necrosis inhibitor therapy with methotrexate in patients with early rheumatoid arthritis. Rheumatology (Oxford). 2010;49:91-8.
- 102. Madland TM, Bjoerkkjaer T, Brunborg LA, et al. Subjective improvement in patients with psoriatic arthritis after short-term oral treatment with seal oil. A pilot study with double blind comparison to soy oil. Journal of Rheumatology. 2006 02/01/;33(Feb):307-10.
- 103. Magnusson M, Brisslert M, Zendjanchi K, et al. Epstein-Barr virus in bone marrow of rheumatoid arthritis patients predicts response to rituximab treatment.

 Rheumatology (Oxford). 2010;49:1911-9.
- 104. Maignen F, Hauben M, Tsintis P. Modelling the Time to Onset of Adverse Reactions with Parametric Survival Distributions A Potential Approach to Signal Detection and Evaluation. Drug Safety (New Zealand). 2010;33:417-34.
- 105. Marra C. Rheumatoid arthritis: A primer for pharmacists. American Journal of Health-System Pharmacy (USA). 2006 01/01/;63(Feb):S4-10.
- 106. McCluggage LK, Scholtz JM. Golimumab: A Tumor Necrosis Factor Alpha Inhibitor for the Treatment of Rheumatoid Arthritis. Annals of Pharmacotherapy (USA). 2010;44:135-44.
- 107. McDermott MF, Jun. RILONACEPT IN THE TREATMENT OF CHRONIC INFLAMMATORY DISORDERS. Drugs of Today (Spain) 2009;45423.

- 108. McLean-Tooke A, Aldridge C, Waugh S, et al. Methotrexate, rheumatoid arthritis and infection riskwhat is the evidence. Rheumatology. 2009;48:867.
- 109. Mease PJ, Gladman DD, Keystone EC, et al. Alefacept in combination with methotrexate for the treatment of psoriatic arthritis Results of a randomized, double-blind, placebo-controlled study. Arthritis and Rheumatism (USA). 2006 05/01/;54(May):1638-45.
- 110. Michot C, Costes V, Gerard-Dran D, et al. Subcutaneous panniculitis-like T-cell lymphoma in a patient receiving etanercept for rheumatoid arthritis. British Journal of Dermatology (England) 2009;160889.
- 111. Montecucco C. Remission, a therapeutic goal in inflammatory arthropathies? Clinical data from adalimumab studies. Drugs (New Zealand). 2006 01/01/;66(Mar):1783-95.
- 112. Muhammad K, Roll P, Einsele H, et al.
 Delayed Acquisition of Somatic
 Hypermutations in Repopulated
 IgD+CD27+ Memory B Cell Receptors
 After Rituximab Treatment. Arthritis and
 Rheumatism (USA) 2009;602284.
- 113. Mulleman D, Lin DC, Ducourau E, et al.
 Trough Infliximab Concentrations Predict
 Efficacy and Sustained Control of Disease
 Activity in Rheumatoid Arthritis.
 Therapeutic Drug Monitoring (USA).
 2010;32:232.
- 114. Nagashima T, Minota S. Subcutaneous calcification following injection of triamcinolone hexacetonide for plantar fasciitis. Rheumatology, Dec. 2008;47:1838-40.
- 115. Nakamura T, Higashi S, Tomoda K, et al. Significance of SAA1.3 allele genotype in Japanese patients with amyloidosis secondary to rheumatoid arthritis. Rheumatology. 2006 01/01/;45(Jan):43-9.
- 116. Nannini C, Cantini F, Niccoli L, et al. Single-Center Series and Systematic Review of Randomized Controlled Trials of Malignancies in Patients With Rheumatoid Arthritis, Psoriatic Arthritis, and Ankylosing Spondylitis Receiving Anti-Tumor Necrosis

- Factor alpha Therapy: Is There a Need for More Comprehensive Screening Procedures? Arthritis and Rheumatism-Arthritis Care and Research 2009:61801.
- 117. Navarro-Sarabia F, Ariza-Ariza R, Hernandez-Cruz B, et al. Adalimumab for treating rheumatoid arthritis. Journal of Rheumatology 2006;33(Jun):1075-81.
- 118. Odai T, Matsunawa M, Takahashi R, et al.
 Correlation of CX3CL1 and CX3CR1
 Levels with Response to Infliximab Therapy
 in Patients with Rheumatoid Arthritis.
 Journal of Rheumatology 2009;361158.
- 119. Oldfield V, Dhillon S, Plosker GL.
 Tocilizumab A Review of its Use in the
 Management of Rheumatoid Arthritis.
 Drugs. 2009;69:609-32.
- 120. Paul-Pletzer K. Tocilizumab: Blockade of interleukin-6 signaling pathway as a therapeutic strategy for inflammatory disorders. Drugs of Today (Spain). 2006 09/01/;42(Sep):559-76.
- 121. Phung OJ, Coleman CI, Sep. Golimumab: A human anti-TNF-alpha monoclonal antibody for the treatment of autoimmune joint diseases. Formulary (USA) 2009;44264.
- 122. Pincus T, Chung C, Segurado OG, et al. An index of patient reported outcomes (PRO-Index) discriminates effectively between active and control treatment in 4 clinical trials of adalimumab in rheumatoid arthritis. Journal of Rheumatology. 2006 11/01/;33(Nov):2146-52.
- 123. Plushner SL. Tocilizumab: An Interleukin-6 Receptor Inhibitor for the Treatment of Rheumatoid Arthritis. Annals of Pharmacotherapy. 2008;42:1660-8.
- 124. Polinski JM, Mohr PE, Johnson L, et al. Impact of Medicare Part D on Access to and Cost Sharing for Specialty Biologic Medications for Beneficiaries With Rheumatoid Arthritis. Arthritis and Rheumatism-Arthritis Care and Research. 2009;61:745.
- 125. Prodanovich S, Ricotti C, Glick BP, et al. Etanercept: An Evolving Role in Psoriasis

- and Psoriatic Arthritis. American Journal of Clinical Dermatology (New Zealand). 2010;11:3-9.
- 126. Pucino F, Harbus PT, Goldbach-Mansky R. Use of biologics in rheumatoid arthritis: Where are we going? American Journal of Health-System Pharmacy (USA). 2006 01/01/;63(Feb):S19-S41.
- 127. Quartuccio L, Fabris M, Salvin S, et al. Rheumatoid factor positivity rather than anti-CCP positivity, a lower disability and a lower number of anti-TNF agents failed are associated with response to rituximab in rheumatoid arthritis. Rheumatology 2009;481557.
- 128. Rachapalli SM, Williams R, Walsh DA, et al. First-line DMARD choice in early rheumatoid arthritis-do prognostic factors play a role? Rheumatology (Oxford). 2010;49:1267-71.
- 129. Raghavendran RR, Peart F, Grindulis KA. Long-term tocilizumab therapy in a patient with rheumatoid arthritis and chronic hepatitis B. Rheumatology, Dec. 2008;47.
- 130. Ranganathan P, McLeod HL. Methotrexate pharmacogenetics The first step toward individualized therapy in rheumatoid arthritis. Arthritis and Rheumatism (USA). 2006 05/01/:54(May):1366-77.
- 131. Raterman HG, Simsek S, Lems WF, et al. Rituximab and Thyroid Function. Archives of Internal Medicine (USA) 2009;1691073.
- 132. Reiff A, Lovell DJ, van Adelsberg J, et al. Evaluation of the comparative efficacy and tolerability of rofecoxib and naproxen in children and adolescents with juvenile rheumatoid arthritis: A 12-week randomized controlled clinical trial with a 52-week open-label extension. Journal of Rheumatology. 2006 05/01/;33(May):985-95.
- 133. Resman-Targoff BH. Medical therapy: Where are we now? American Journal of Health-System Pharmacy (USA). 2006 01/01/;63(Feb):S11-S8.

- 134. Ristic GG, Lepic T, Gilsic B, et al.
 Rheumatoid arthritis is an independent risk factor for increased carotid intima-media thickness: impact of anti-inflammatory treatment. Rheumatology (Oxford).
 2010;49:1076.
- 135. Ritchlin CT. Therapies for psoriatic enthesopathy. A systematic review. Journal of Rheumatology. 2006 07/01/;33(Jul):1435-8.
- 136. Robinson V, Boers M, Brooks P, et al. Patient-reported pain is central to OMERACT rheumatology core measurement sets. Drug Information Journal (USA). 2006 01/01/;40(Jan):111-6.
- 137. Roman-Blas JA, Castaneda S, Cutolo M, et al. Efficacy and Safety of a Selective Estrogen Receptor beta Agonist, ERB-041, in Patients With Rheumatoid Arthritis: A 12-Week, Randomized, Placebo-Controlled, Phase II Study. Arthritis Care and Research. 2010;62:1588-93.
- 138. Rongioletti F, Burlando M, Parodi A. Adverse Effects of Biological Agents in the Treatment of Psoriasis. American Journal of Clinical Dermatology (New Zealand). 2010;11:35-7.
- 139. Rottem M, Mader R. Successful Use of Etanercept in Acquired Angioedema in a Patient with Psoriatic Arthritis. Journal of Rheumatology. 2010;37:209.
- 140. Roux CH, Brocq O, Breuil V, et al. Safety of anti-TNF-alpha therapy in rheumatoid arthritis and spondylarthropathies with concurrent B or C chronic hepatitis.

 Rheumatology. 2006 10/01/;45(Oct):1294-7.
- 141. Saad AA, Ashcroft DM, Watson KD, et al. Efficacy and safety of anti-TNF therapies in psoriatic arthritis: an observational study from the British Society for Rheumatology Biologics Register. Rheumatology (Oxford) 2010;49697-705.
- 142. Saraux A, Gossec L, Goupille P, et al. Costeffectiveness modelling of biological treatment sequences in moderate to severe rheumatoid arthritis in France.

 Rheumatology (Oxford). 2010;49:733-40.

- 143. Schiff MH, Yu EB, Weinblatt ME, et al. Long-term experience with etanercept in the treatment of rheumatoid arthritis in elderly and younger patients Patient-reported outcomes from multiple controlled and open-label extension studies. Drugs and Aging (New Zealand). 2006 02/01/;23(Feb):167-78.
- 144. Schlesselman LS, Hussey AP. Tocilizumab A humanized anti-IL-6 receptor monoclonal antibody for the treatment of rheumatoid arthritis. Formulary. 2008;43:272-9.
- 145. Scott DL. Pursuit of optimal outcomes in rheumatoid arthritis. PharmacoEconomics (New Zealand). 2004 02/01/;22(Feb):13-26.
- 146. Sebba A. Tocilizumab: The first interleukin-6-receptor inhibitor. American Journal of Health System Pharmacy. 2008;65:1413-8.
- 147. Shadick NA, Cook NR, Karlson EW, et al. C-reactive protein in the prediction of rheumatoid arthritis in women. Archives of Internal Medicine (USA). 2006 01/01/;166(Jan):2490-4.
- 148. Sheth NU, Hilas O, Charneski L. Abatacept: A novel agent for rheumatoid arthritis.

 Journal of Pharmacy Technology (USA).
 2006 06/01/;22(Jun):336-41.
- 149. Siddigui MA, Scott LJ. Spotlight on infliximab in Crohn disease and rheumatoid arthritis. BioDrugs (New Zealand). 2006 01/01/;20(Jan):67-70.
- 150. Siegel JN, Zhen BG. Use of the American College of Rheumatology N (ACR-N) Index of improvement in rheumatoid arthritis Argument in favor. Arthritis and Rheumatism (USA). 2005 06/01/;52(Jun):1637-41.
- 151. Signorovitch JE, Wu EQ, Yu AP, et al.
 Comparative Effectiveness Without Headto-Head Trials A Method for MatchingAdjusted Indirect Comparisons Applied to
 Psoriasis Treatment with Adalimumab or
 Etanercept. PharmacoEconomics (New
 Zealand). 2010;28:935-45.
- 152. Sihvonen S, Korpela M, Mustonen J, et al. Mortality in patients with rheumatoid

- arthritis treated with low-dose oral glucocorticoids. A population-based cohort study. Journal of Rheumatology. 2006 09/01/;33(Sep):1740-6.
- 153. Silverman GJ. Therapeutic B cell depletion and regeneration in rheumatoid arthritis Emerging patterns and paradigms. Arthritis and Rheumatism (USA). 2006 08/01/;54(Aug):2356-67.
- 154. Singh JA, Christensen R, Wells GA, et al. A network meta-analysis of randomized controlled trials of biologics for rheumatoid arthritis: a Cochrane overview. Canadian Medical Association Journal (Canada) 2009;181787.
- 155. Smolen JS, Han C, Bala M, et al. Evidence of radiographic benefit of treatment with infliximab plus methotrexate in rheumatoid arthritis patients who had no clinical improvement A detailed subanalysis of data from the anti-tumor necrosis factor trial in rheumatoid arthritis with concomitant therapy study. Arthritis and Rheumatism (USA). 2005 04/01/;52(Apr):1020-30.
- 156. Smolen JS, van der Heijde DM, St Clair EW, et al. Predictors of joint damage in patients with early rheumatoid arthritis treated with high-dose methotrexate with or without concomitant infliximab Results from the ASPIRE trial. Arthritis and Rheumatism (USA). 2006 03/01/;54(Mar):702-10.
- 157. Snyder RA. Psoriatic Arthritis: A
 Dermatologist's Perspective. American
 Journal of Clinical Dermatology (New
 Zealand). 2010;11:19-22.
- 158. Sobanko JF, Freeman AF, Palmore TN, et al. A Sri Lankan woman with rheumatoid arthritis and anesthetic plaques. Journal of the American Academy of Dermatology (USA) 2009;601018.
- 159. Solomon DH, Avorn J, Katz JN, et al. Immunosuppressive medications and hospitalization for cardiovascular events in patients with rheumatoid arthritis. Arthritis and Rheumatism (USA) 2006;54(Dec):3790-8.

- 160. Soubrier M, Puechal X, Sibilia J, et al. Evaluation of two strategies (initial methotrexate monotherapy <it>vs</it> its combination with adalimumab) in management of early active rheumatoid arthritis: data from the GUEPARD trial. Rheumatology. 2009;48:1429.
- 161. Stockl KM, Shin JS, Lew HC, et al. Outcomes of a Rheumatoid Arthritis Disease Therapy Management Program Focusing on Medication Adherence. Journal of Managed Care Pharmacy (USA). 2010;16:593-604.
- 162. Strand V, Cohen S, Crawford B, et al. Patient-reported outcomes better discriminate active treatment from placebo in randomized controlled trials in rheumatoid arthritis. Rheumatology. 2004 05/01/;43(May):640-7.
- 163. Strand V, Singh JA. Newer Biological Agents in Rheumatoid Arthritis Impact on Health-Related Quality of Life and Productivity. Drugs (New Zealand). 2010;70:121-45.
- 164. Straub RH, Haerle P, Yamana S, et al. Antiinterleukin-6 receptor antibody therapy favors adrenal androgen secretion in patients with rheumatoid arthritis - A randomized, double-blind, placebo-controlled study. Arthritis and Rheumatism (USA). 2006 06/01/;54(Jun):1778-85.
- 165. Stuhlmueller B, Haeupl T, Hernandez MM, et al. CD11c as a Transcriptional Biomarker to Predict Response to Anti-TNF Monotherapy With Adalimumab in Patients With Rheumatoid Arthritis. Clinical Pharmacology and Therapeutics (USA). 2010;87:311-21.
- 166. Sweet BV. Abatacept. American Journal of Health-System Pharmacy (USA). 2006 01/01/;63(Jan):2065-77.
- 167. Takatori S, Kamata Y, Murosaki T, et al. Abrupt Development of Sarcoidosis with a Prodromal Increase in Plasma Osteopontin in a Patient with Rheumatoid Arthritis During Treatment with Etanercept. Journal of Rheumatology. 2010;37:210-2.
- 168. Taylor PC, Steuer A, Gruber J, et al. Ultrasonographic and radiographic results

- from a two-year controlled trial of immediate or one-year-delayed addition of infliximab to ongoing methotrexate therapy in patients with erosive early rheumatoid arthritis. Arthritis and Rheumatism (USA). 2006 01/01/;54(Jan):47-53.
- 169. Thayer S, Watson C, Song R, et al.
 Etanercept treatment patterns in managedcare patients with psoriasis or psoriatic
 arthritis. Journal of Medical Economics
 (England). 2010;13:228-35.
- 170. Tielemans MM, Eikendal T, Jansen JB, et al. Identification of NSAID Users at Risk for Gastrointestinal Complications A Systematic Review of Current Guidelines and Consensus Agreements. Drug Safety (New Zealand). 2010;33:443-53.
- 171. Torikai E, Kageyama Y, Takahashi M, et al. The effect of infliximab on bone metabolism markers in patients with rheumatoid arthritis. Rheumatology. 2006 06/01/;45(Jun):761-4.
- 172. Tran S, Hooker RS, Cipher DJ, et al. Patterns of Biologic Agent Use in Older Males with Inflammatory Diseases An Institution-Focused, Observational Post-Marketing Study. Drugs and Aging (New Zealand). 2009;26:607.
- 173. Tubach F, Ravaud P, Salmon-Ceron D, et al. Emergence of <it>Legionella pneumophila</it> pneumonia in patients receiving tumor necrosis factor-alpha antagonist. Clinical Infectious Diseases. 2006 10/01/;43(Oct):E95-100.
- 174. van Assen S, Holvast A, Benne CA, et al. Humoral Responses After Influenza Vaccination Are Severely Reduced in Patients With Rheumatoid Arthritis Treated With Rituximab. Arthritis and Rheumatism (USA). 2010;62:75-81.
- 175. van der Linden MP, van der Woude D, Ioan-Facsinay A, et al. Value of Anti-Modified Citrullinated Vimentin and Third-Generation Anti-Cyclic Citrullinated Peptide Compared With Second-Generation Anti-Cyclic Citrullinated Peptide and Rheumatoid Factor in Predicting Disease Outcome in Undifferentiated Arthritis and Rheumatoid

- Arthritis. Arthritis and Rheumatism (USA) 2009;602232.
- 176. Van Rijthoven AW, Bijlsma JW, Canninga-Van Dijk M, et al. Onset of systemic lupus erythematosus after conversion of infliximab to adalimumab treatment in rheumatoid arthritis with a pre-existing anti-dsDNA antibody level. Rheumatology. 2006 10/01/;45(Oct):1317-9.
- 177. Vanags D, Williams B, Johnson B, et al. Therapeutic efficacy and safety of chaperonin 10 in patients with rheumatoid arthritis: a double-blind randomised trial. Lancet, The (USA). 2006 01/01/;368(Apr):855-63.
- 178. Varani K, Massara A, Vincenzi F, et al. Normalization of A<INF>2A</INF> and A<INF>3</INF> Adenosine Receptor Up-Regulation in Rheumatoid Arthritis Patients by Treatment With Anti-Tumor Necrosis Factor alpha but Not Methotrexate. Arthritis and Rheumatism (USA) 2009;602880.
- 179. Vergles JM, Radic M, Kovacic J, et al. Successful Use of Adalimumab for Treating Rheumatoid Arthritis with Autoimmune Sensorineural Hearing Loss: Two Birds with One Stone. Journal of Rheumatology. 2010;37:1080.
- 180. Villa-Blanco JI, Calvo-Alen J, Sep. Elderly Onset Rheumatoid Arthritis Differential Diagnosis and Choice of First-Line and Subsequent Therapy. Drugs and Aging (New Zealand) 2009;26739.
- 181. Virkki LM, Sumathikutty BC, Aarnio M, et al. Biological Therapy for Psoriatic Arthritis in Clinical Practice: Outcomes Up to 2 Years. Journal of Rheumatology 2010;372362-8.
- 182. Watson DJ, Bolognese JA, Yu C, et al. Use of gastroprotective agents and discontinuations due to dyspepsia with the selective cyclooxygenase-2 inhibitor etoricoxib compared with non-selective NSAIDs. Current Medical Research and Opinion (England). 2004 12/01/;20(Dec):1899-908.
- 183. Weisman MH, Durez P, Hallegua D, et al. Reduction of inflammatory biomarker

- response by abatacept in treatment of rheumatoid arthritis. Journal of Rheumatology. 2006 11/01/;33(Nov):2162-6.
- 184. Welsing PM, Severens JL, Hartman M, et al. The initial validation of a Markov model for the economic evaluation of (New) treatments for rheumatoid arthritis. PharmacoEconomics (New Zealand). 2006 10/01/;24(Oct):1011-20.
- 185. Weng HH, Ranganath VK, Khanna D, et al. Equivalent Responses to Disease-modifying Antirheumatic Drugs Initiated at Any Time During the First 15 Months After Symptom Onset in Patients with Seropositive Rheumatoid Arthritis. Journal of Rheumatology. 2010;37:550-7.
- 186. Westhovens R, Cole JC, Li T, et al.
 Improved health-related quality of life for rheumatoid arthritis patients treated with abatacept who have inadequate response to anti-TNF therapy in a double-blind, placebocontrolled, multicentre randomized clinical trial. Rheumatology 2006;45(Oct):1238-46.
- 187. Westlake SL, Colebatch AN, Baird J, et al.
 The effect of methotrexate on cardiovascular disease in patients with rheumatoid arthritis: a systematic literature review.
 Rheumatology (Oxford). 2010;49:295.
- 188. White DH, Chapman PT, O'Donnell JL, et al. Lack of association between elevated mean red cell volume and haematological toxicity in patients receiving long-term methotrexate for rheumatoid arthritis.

 Internal Medicine Journal. 2010;40:561-5.
- 189. Williams GW, Kivitz AJ, Brown MT, et al. A comparison of valdecoxib and naproxen in the treatment of rheumatoid arthritis symptoms. Clinical Therapeutics (USA). 2006 02/01/;28(Feb):204-21.
- 190. Wolbink GJ, Vis M, Lems W, et al.
 Development of antiinfliximab antibodies and relationship to clinical response in patients with rheumatoid arthritis. Arthritis and Rheumatism (USA). 2006 03/01/;54(Mar):711-5.
- 191. Yuan Y, Trivedi D, Maclean R, et al. Indirect cost-effectiveness analyses of

- abatacept and rituximab in patients with moderate-to-severe rheumatoid arthritis in the United States. Journal of Medical Economics (England) 2010;13(1):33-41.
- 192. Zaiac M. The Role of Biological Agents in the Treatment of Nail Psoriasis. American Journal of Clinical Dermatology (New Zealand). 2010;11:27.
- 193. Zandbelt MM, Houbiers JG, van den Hoogen FH, et al. Intranasal administration of recombinant human cartilage glycoprotein-39. A phase I escalating cohort study in patients with rheumatoid arthritis. Journal of Rheumatology. 2006 09/01/;33(Sep):1726-33.
- 194. Zhang XP, Huang Y, Navarro MT, et al. A Proof-of-Concept and Drug-Drug Interaction Study of Pamapimod, a Novel p38 MAP Kinase Inhibitor, With Methotrexate in Patients With Rheumatoid Arthritis. Journal of Clinical Pharmacology (USA). 2010;50:1031-8.
- 195. Zink A, Strangfeld A, Schneider M, et al. Effectiveness of tumor necrosis factor inhibitors in rheumatoid arthritis in an observational cohort study Comparison of patients according to their eligibility for major randomized clinical trials. Arthritis and Rheumatism (USA). 2006 11/01/:54(Nov):3399-407.

Reference Source: Handsearches (e.g., Scopus)

- 1. Cochrane Collaboration guidelines.
- 2. The BUGS Project. Stevens A, Hosted by the MRC Biostatistics Unit, Cambridge, UK. Accessed on May 2, 2011. www.mrc-bsu.cam.ac.uk/bugs/welcome.shtml
- 3. Sulfasalazine in early rheumatoid arthritis.
 The Australian Multicentre Clinical Trial
 Group. J Rheumatol. 1992
 Nov;19(11):1672-7.
- 4. Screening for hydroxychloroquine retinopathy. 2006.
- 5. National and state medical expenditures and lost earnings attributable to arthritis and other rheumatic conditions--United States, 2003. MMWR Morb Mortal Wkly Rep 2007;56(1):4-7.
- 6. Chapter 9: Analysing data and undertaking meta-analyses. Cochrane Handbook of Systematic Reviews of Intervention Version 500 (Updated February 2008). 2008.
- 7. Rituxan (Rituximab) [Package Insert]. 2008.
- 8. Ã stensen M, Motta M. Therapy Insight: The use of antirheumatic drugs during nursing. Nature Clinical Practice Rheumatology. 2007;3(7):400-6.
- 9. Ã'tensen M, Khamashta M, Lockshin M, et al. Anti-inflammatory and immunosuppressive drugs and reproduction. Arthritis Research and Therapy. 2006;8(3).
- 10. Abeles AM, Pillinger MH. The role of the synovial fibroblast in rheumatoid arthritis: Cartilage destruction and the regulation of matrix metalloproteinases. Bulletin of the NYU Hospital for Joint Diseases. 2006;64(1-2):20-4.
- 11. Ackermann C, Kavanaugh A. Economic burden of psoriatic arthritis. PharmacoEconomics 2008;26(2):121-9.
- 12. ACR. Guidelines for the management of rheumatoid arthritis: 2002 Update. Arthritis Rheum. 2002 Feb;46(2):328-46.

- 13. ACR. ACR Hotline: Update on safety issues concerning TNF inhibitors; available at http://www.rheumatology.org/publications/hotline/0506JAMATNF.asp. 2006.
- 14. Agency for Healthcare Research and Quality. Methods reference guide for effectiveness and comparative effectiveness reviews, version 1.0. [Draft posted Oct. 2007]. Rockville, MD. Available at: http://effectivehealthcare.ahrq.gov/repFiles/2007_10DraftMethodsGuide.pdf 2007.
- 15. Agrawal S, Misra R, Aggarwal A. Autoantibodies in rheumatoid arthritis: Association with severity of disease in established RA. Clinical rheumatology. 2007;26(2):201-4.
- 16. Alamanos Y, Voulgari PV, Drosos AA. Incidence and prevalence of psoriatic arthritis: A systematic review. Journal of Rheumatology. 2008;35(7):1354-8.
- 17. Aletaha D, Machold KP, Nell VPK, et al. The perception of rheumatoid arthritis core set measures by rheumatologists. Results of a survey. Rheumatology. 2006;45(9):1133-9
- 18. Aletaha D, Nell VP, Stamm T, et al. Acute phase reactants add little to composite disease activity indices for rheumatoid arthritis: validation of a clinical activity score. Arthritis Res Ther. 2005;7(4):R796-806.
- 19. Aletaha D, Neogi T, Silman AJ, et al. 2010 Rheumatoid arthritis classification criteria: an American College of Rheumatology/European League Against Rheumatism collaborative initiative. Ann Rheum Dis 2010;69(9):1580-8.
- Aletaha D, Smolen JS. The definition and measurement of disease modification in inflammatory rheumatic diseases. Rheumatic Disease Clinics of North America. 2006;32(1):9-44.
- 21. Allaart CF, Goekoop-Ruiterman YP, de Vries-Bouwstra JK, et al. Aiming at low disease activity in rheumatoid arthritis with

- initial combination therapy or initial monotherapy strategies: the BeSt study. Clin Exp Rheumatol. 2006 Nov-Dec;24(6 Suppl 43):S-77-82.
- 22. Alonso-Ruiz A, Pijoan JI, Ansuategui E, et al. Tumor necrosis factor alpha drugs in rheumatoid arthritis: Systematic review and metaanalysis of efficacy and safety. BMC Musculoskeletal Disorders 2008;9.
- 23. American College of Rheumatology Ad Hoc Committee on Clinical Guidelines.
 Guidelines for monitoring drug therapy in rheumatoid arthritis. . Arthritis Rheum. 1996 May;39(5):723-31.
- 24. Anandarajah AP, Ritchlin CT. Pathogenesis of psoriatic arthritis. Curr Opin Rheumatol. 2004 Jul;16(4):338-43.
- 25. Ang DC, Paulus HE, Louie JS. Patient's ethnicity does not influence utilization of effective therapies in rheumatoid arthritis. J Rheumatol. 2006 May;33(5):870-8.
- 26. Angst F, Aeschlimann A, Stucki G. Smallest detectable and minimal clinically important differences of rehabilitation intervention with their implications for required sample sizes using WOMAC and SF-36 quality of life measurement instruments in patients with osteoarthritis of the lower extremities. Arthritis Rheum 2001;45(4):384-91.
- 27. Anonymous. Undertaking systematic reviews of research on effectiveness: CRD's guidance for those carrying out or commissioning reviews. CRD Report Number 4 (2nd edition). 2001 2001.
- Anonymous. Cortisone Acetate package insert. Pharmacia & Upjohn Co. Kalamazoo, MI. 2002.
- 29. Anonymous. Cortef (hydrocortisone) package insert. Pharmacia & Upjohn Co. Kalamazoo, MI. 2002.
- Anonymous. Dexamethasone package insert. Roxane Laboratories, Inc. Columbus, OH. 2003.

- 31. Anonymous. PredniSONE package insert. Roxane Laboratories, Inc. Columbus, OH. 2003.
- 32. Anonymous. Kineret (anakinra) package insert. Amgen, Inc. Thousand Oaks, CA. 2004.
- Anonymous. Hydroxychloroquine package insert. Sandoz, Inc. Broomfield, CO. 2004.
- 34. Anonymous. Orencia (abatacept) package insert. Bristol-Myers Squibb. Princeton, NJ. 2005.
- Anonymous. Methotrexate package insert.
 Mayne Pharma (USA) Inc. Paramus, NJ.
 2005.
- 36. Anonymous. Arava (leflunomide) package insert. Aventis Pharmaceuticals Inc. Kansas City, MO. 2005.
- 37. Anonymous. Remicade (infliximab) package insert. Centocor, Inc. Malvern, PA. 2006.
- Anonymous. Humira (adalimumab) package insert. Abbott Labs. North Chicago, IL. 2006.
- 39. Anonymous. Enbrel (etanercept) package insert. Immunex Corporation. Thousand Oaks, CA. 2006.
- 40. Anonymous. MethylPREDNIsolone package insert. Sandoz, Inc. Princeton, NJ. 2006.
- 41. Anonymous. Azulfidine (sulfasalazine) package insert. Pharmacia & Upjohn Co. NY, NY. 2006.
- 42. Anonymous. Rituxan (rituximab) package insert. Genetech, Inc. South San Francisco, CA. 2007.
- 43. Arkfeld DG. The potential utility of B cell-directed biologic therapy in autoimmune diseases. Rheumatology international. 2008;28(3):205-15.
- 44. Arnett FC, Edworthy SM, Bloch DA, et al.
 The American Rheumatism Association
 1987 revised criteria for the classification of

- rheumatoid arthritis. Arthritis Rheum. 1988 Mar;31(3):315-24.
- 45. Askling J, Fored CM, Brandt L, et al. Risks of solid cancers in patients with rheumatoid arthritis and after treatment with tumour necrosis factor antagonists. Ann Rheum Dis. 2005 Oct;64(10):1421-6.
- 46. AteÅŸ A, Kinikli G, Turgay M, et al. Effects of rheumatoid factor isotypes on disease activity and severity in patients with rheumatoid arthritis: A comparative study. Clinical rheumatology. 2007;26(4):538-45.
- 47. Atkins D, Eccles M, Flottorp S, et al. Systems for grading the quality of evidence and the strength of recommendations I: critical appraisal of existing approaches The GRADE Working Group. BMC Health Serv Res. 2004 Dec 22;4(1):38.
- 48. Baecklund E, Ekbom A, Sparen P, et al. Disease activity and risk of lymphoma in patients with rheumatoid arthritis: nested case-control study. Bmj. 1998 Jul 18;317(7152):180-1.
- 49. Balk EM, Lau J, Bonis PA. Reading and critically appraising systematic reviews and meta-analyses: a short primer with a focus on hepatology. J Hepatol. 2005;43(4):729-36.
- 50. Bansback NJ, Ara R, Barkham N, et al. Estimating the cost and health status consequences of treatment with TNF antagonists in patients with psoriatic arthritis. Rheumatology (Oxford). 2006 Aug;45(8):1029-38.
- 51. Bendtzen K, Geborek P, Svenson M, et al. Individualized monitoring of drug bioavailability and immunogenicity in rheumatoid arthritis patients treated with the tumor necrosis factor alpha inhibitor infliximab. Arthritis Rheum. 2006 Dec;54(12):3782-9.
- 52. Berends MAM, Snoek J, De Jong EMGJ, et al. Liver injury in long-term methotrexate treatment in psoriasis is relatively infrequent. Alimentary Pharmacology and Therapeutics. 2006;24(5):805-11.

- 53. Berglin E, Johansson T, Sundin U, et al. Radiological outcome in rheumatoid arthritis is predicted by presence of antibodies against cyclic citrullinated peptide before and at disease onset, and by IgA-RF at disease onset. Annals of the rheumatic diseases. 2006;65(4):453-8.
- 54. Bergman GJ, Hochberg MC, Boers M, et al. Indirect comparison of tocilizumab and other biologic agents in patients with rheumatoid arthritis and inadequate response to disease-modifying antirheumatic drugs. Semin Arthritis Rheum 2010;39(6):425-41.
- 55. Berliner AR, Haas M, Choi MJ. Sarcoidosis: the nephrologist's perspective. Am J Kidney Dis. 2006 Nov;48(5):856-70.
- 56. Bermas BL. Use of immunosuppressive drugs in pregnancy and lactation. 2007.
- 57. Bliddal H, Terslev L, Qvistgaard E, et al. A randomized, controlled study of a single intra-articular injection of etanercept or glucocorticosteroids in patients with rheumatoid arthritis. Scand J Rheumatol. 2006 Sep-Oct;35(5):341-5.
- 58. BlueCross BlueShield Technology Evaluation Center (TEC). Special report: evidence on sequencing of conventional and biological disease-modifying anti-rheumatic drugs. 2003 2003;18(11).
- 59. Boers M. Add-on or step-up trials for new drug development in rheumatoid arthritis: a new standard? Arthritis Rheum. 2003 Jun;48(6):1481-3.
- 60. Boers M. Abatacept in rheumatoid arthritis: a new branch on the "biologics" tree. Ann Intern Med. 2006 Jun 20;144(12):933-5.
- 61. Boetticher NC, Peine CJ, Kwo P, et al. A randomized, double-blinded, placebocontrolled multicenter trial of etanercept in the treatment of alcoholic hepatitis.

 Gastroenterology. 2008 Dec;135(6):1953-60.
- 62. Boini S, Fuillemin F. Review. Radiographic scoring methods as outcome measures in rheumatoid arthritis: properties and

- advantages. Ann Rheum Dis. 2001;60:817-27.
- 63. Boini S, Guillemin F. Radiographic scoring methods as outcome measures in rheumatoid arthritis: properties and advantages. Ann Rheum Dis. 2001 Sep;60(9):817-27.
- 64. Bolen J, Helmick CG, Sacks JJ, et al. Prevalence of self-reported arthritis or chronic joint symptoms among adults--United States, 2001. MMWR Morb Mortal Wkly Rep. 2002 Oct 25;51(42):948-50.
- 65. Bologna C, Viu P, Picot MC, et al. Longterm follow-up of 453 rheumatoid arthritis patients treated with methotrexate: an open, retrospective, observational study. Br J Rheumatol. 1997 May;36(5):535-40.
- 66. Bond SJ, Farewell VT, Schentag CT, et al. Predictors for radiological damage in psoriatic arthritis: Results from a single centre. Ann Rheum Dis. 2006 Aug 17.
- 67. Bongartz T, Sutton AJ, Sweeting MJ, et al. Anti-TNF antibody therapy in rheumatoid arthritis and the risk of serious infections and malignancies: systematic review and meta-analysis of rare harmful effects in randomized controlled trials. JAMA. 2006 May 17;295(19):2275-85.
- 68. Bongartz T, Warren FC, Mines D, et al. Etanercept therapy in rheumatoid arthritis and the risk of malignancies: a systematic review and individual patient data metanalysis of randomised controlled trials. Ann Rheum Dis 2009;68(7):1177-83.
- 69. Borman P, Toy GG, Babaoglu S, et al. A comparative evaluation of quality of life and life satisfaction in patients with psoriatic and rheumatoid arthritis. Clin Rheumatol. 2006 Apr 19.
- 70. Bradburn MJ, Deeks JJ, Berlin JA, et al. Much ado about nothing: A comparison of the performance of meta-analytical methods with rare events. Statistics in Medicine. 2007;26(1):53-77.
- 71. Braun J, McHugh N, Singh A, et al.
 Improvement in patient-reported outcomes
 for patients with ankylosing spondylitis

- treated with etanercept 50 mg once-weekly and 25 mg twice-weekly. Rheumatology (Oxford). 2007 Jun;46(6):999-1004.
- 72. Braun J, Sieper J. Biological therapies in the spondyloarthritides--the current state. Rheumatology (Oxford). 2004 Sep;43(9):1072-84.
- 73. Bren L. The importance of patient-reported outcomes... it's all about the patients. FDA Consumer. 2006;40(6).
- 74. Brennan FM, McInnes IB. Evidence that cytokines play a role in rheumatoid arthritis. Journal of Clinical Investigation. 2008;118(11):3537-45.
- 75. Bruce SP, Boyce EG. Update on abatacept: A selective costimulation modulator for rheumatoid arthritis. Annals of Pharmacotherapy. 2007;41(7-8):1153-62.
- 76. Bruce TO. Comorbid depression in rheumatoid arthritis: pathophysiology and clinical implications. Curr Psychiatry Rep 2008;10(3):258-64.
- 77. Bruynesteyn K, van der Heijde D, Boers M, et al. Determination of the minimal clinically important difference in rheumatoid arthritis joint damage of the Sharp/van der Heijde and Larsen/Scott scoring methods by clinical experts and comparison with the smallest detectable difference. Arthritis Rheum. 2002 Apr;46(4):913-20.
- 78. Buch MH, Bingham SJ, Bejarano V, et al. Therapy of patients with rheumatoid arthritis: outcome of infliximab failures switched to etanercept. Arthritis Rheum. 2007 Apr 15;57(3):448-53.
- 79. Bucher HC, Guyatt GH, Griffith LE, et al. The results of direct and indirect treatment comparisons in meta-analysis of randomized controlled trials. J Clin Epidemiol. 1997 Jun;50(6):683-91.
- 80. Bucher HC, Guyatt GH, Griffith LE, et al. The results of direct and indirect treatment comparisons in meta-analysis of randomized controlled trials. J Clin Epidemiol. 1997 Jun;50(6):683-91.

- 81. Bukhari MA, Wiles NJ, Lunt M, et al. Influence of disease-modifying therapy on radiographic outcome in inflammatory polyarthritis at five years: results from a large observational inception study. Arthritis Rheum. 2003 Jan;48(1):46-53.
- 82. Burmester GR, Mease P, Dijkmans BA, et al. Adalimumab safety and mortality rates from global clinical trials of six immunemediated inflammatory diseases. Ann Rheum Dis. 2009 Dec;68(12):1863-9.
- 83. Canadian Agency for Drugs and Technologies in Health. CADTH Therapeutic Review: Clinical and Economic Overview: Biological Response Modifier Agents for Adults with Rheumatoid Arthritis. 2010.
- 84. Cannella AC, O'Dell JR. Early rheumatoid arthritis: pitfalls in diagnosis and review of recent clinical trials. Drugs. 2006;66(10):1319-37.
- 85. Capell H, Madhok R, Porter D, et al.
 Combination therapy with sulphasalazine and methotrexate is more effective than either drug alone in rheumatoid arthritis (ra) patients with a suboptimal response to sulphasalazine: Results from the double blind placebo controlled mascot study. Ann Rheum Dis. 2006 August 22, 2006:ard.2006.057133.
- 86. Carlin CS, Feldman SR, Krueger JG, et al. A 50% reduction in the Psoriasis Area and Severity Index (PASI 50) is a clinically significant endpoint in the assessment of psoriasis. J Am Acad Dermatol. 2004 Jun;50(6):859-66.
- 87. Carmona L, Descalzo MÃ, Perez-Pampin E, et al. All-cause and cause-specific mortality in rheumatoid arthritis are not greater than expected when treated with tumour necrosis factor antagonists. Annals of the rheumatic diseases. 2007;66(7):880-5.
- 88. Carmona L, Hernandez-Garcia C, Vadillo C, et al. Increased risk of tuberculosis in patients with rheumatoid arthritis. J Rheumatol. 2003 Jul;30(7):1436-9.

- 89. Cassell S, Kavanaugh AF. Therapies for psoriatic nail disease. A systematic review. J Rheumatol. 2006 Jul;33(7):1452-6.
- 90. Cassell S, Tutuncu Z, Kremer J, et al. Psoriatic arthritis patients have different rates of adverse events than rheumatoid arthritis patients when treated with TNF inhihitors: analysis from CORRONA Database [Abstract 491]. Arthritis Rheum. 2005;52(Suppl 9):S211-S2.
- 91. Chakravarty EF, Michaud K, Wolfe F. Skin cancer, rheumatoid arthritis, and tumor necrosis factor inhibitors. J Rheumatol. 2005 Nov;32(11):2130-5.
- 92. Cheifetz A, Smedley M, Martin S, et al. The incidence and management of infusion reactions to infliximab: a large center experience. Am J Gastroenterol. 2003 Jun;98(6):1315-24.
- 93. Chen Y, Jobanputra P, Barton P, et al. A systematic review of the effectiveness of adalimumab, etanercept and infliximab for the treatment of rheumatoid arthritis in adults and an economic evaluation of their cost-effectiveness. Heath Technology Assessment. 2006;10(42).
- 94. Chernoff MC, Wang M, Anderson JJ, et al. Problems and suggested solutions in creating an archive of clinical trials data to permit later meta-analysis: an example of methotrexate trials in rheumatoid arthritis. Control Clin Trials. 1995 Oct;16(5):342-55.
- 95. Choy EH, Panayi GS. Cytokine pathways and joint inflammation in rheumatoid arthritis. N Engl J Med. 2001 Mar 22;344(12):907-16.
- 96. Chung CP, Thompson JL, Koch GG, et al. Are American College of Rheumatology 50% response criteria superior to 20% criteria in distinguishing active aggressive treatment in rheumatoid arthritis clinical trials reported since 1997? A meta-analysis of discriminant capacities. Annals of the rheumatic diseases. 2006;65(12):1602-7.
- 97. Chung ES, Packer M, Lo KH, et al. Randomized, double-blind, placebocontrolled, pilot trial of infliximab, a chimeric monoclonal antibody to tumor

- necrosis factor-alpha, in patients with moderate-to-severe heart failure: results of the anti-TNF Therapy Against Congestive Heart Failure (ATTACH) trial. Circulation. 2003 Jul 1;107(25):3133-40.
- 98. Coburn LA, Wise PE, Schwartz DA. The successful use of adalimumab to treat active Crohn's disease of an ileoanal pouch during pregnancy. Digestive Diseases and Sciences. 2006;51(11):2045-7.
- 99. Cohen JD, Dougados M, Goupille P, et al. Health assessment questionnaire score is the best predictor of 5-year quality of life in early rheumatoid arthritis. Journal of Rheumatology. 2006;33(10):1936-41.
- 100. Coletta AP, Clark AL, Banarjee P, et al. Clinical trials update: RENEWAL (RENAISSANCE and RECOVER) and ATTACH. Eur J Heart Fail. 2002 Aug;4(4):559-61.
- 101. Combe B, Codreanu C, Fiocco U, et al. Etanercept and sulfasalazine, alone and combined, in patients with active rheumatoid arthritis despite receiving sulfasalazine: A double-blind comparison. Annals of the rheumatic diseases. 2006;65(10):1357-62.
- 102. Combe B, Landewe R, Lukas C, et al. EULAR recommendations for the management of early arthritis: Report of a task force of the European Standing Committee for International Clinical Studies Including Therapeutics (ESCISIT). Annals of the rheumatic diseases. 2007;66(1):34-45.
- 103. Connell L, McInnes IB. New cytokine targets in inflammatory rheumatic diseases. Best Practice and Research: Clinical Rheumatology. 2006;20(5):865-78.
- 104. Cope AP. T cells in rheumatoid arthritis. Arthritis Research and Therapy. 2008;10(SUPPL. 1).
- 105. Corbo M, Tay LK, Leon F, et al. A single dose of abatacept does not prevent the development of a positive immune response to tetanus and pneumococcal vacciness. Ann Rheum Dis. 2006;65(SUPPL. II):184.

- 106. Cvetkovic RS, Scott LJ. Adalimumab: a review of its use in adult patients with rheumatoid arthritis. BioDrugs. 2006;20(5):293-311.
- 107. Davis MJ, Dawes PT, Fowler PD, et al. Should disease-modifying agents be used in mild rheumatoid arthritis? Br J Rheumatol. 1991 Dec;30(6):451-4.
- 108. De Filippis L, Caliri A, Anghelone S, et al. Improving outcomes in tumour necrosis factor a treatment: comparison of the efficacy of the tumour necrosis factor a blocking agents etanercept and infliximab in patients with active rheumatoid arthritis. Panminerva Med 2006;48(2):129-35.
- 109. Deeks JJ, Dinnes J, D'Amico R, et al. Evaluating non-randomised intervention studies. Health Technol Assess. 2003;7(27):iii-x, 1-173.
- 110. Devine EB, Alfonso-Cristancho R, Sullivan SD. Effectiveness of biologic therapies for rheumatoid arthritis: an indirect comparisons approach. Pharmacotherapy 2011;31(1):39-51.
- 111. Dixon WG, Hyrich KL, Watson KD, et al. Drug-specific risk of tuberculosis in patients with rheumatoid arthritis treated with anti-TNF therapy: results from the British Society for Rheumatology Biologics Register (BSRBR). Ann Rheum Dis 2010;69(3):522-8.
- 112. Dixon WG, Symmons DP, Lunt M, et al. Serious infection following anti-tumor necrosis factor alpha therapy in patients with rheumatoid arthritis: lessons from interpreting data from observational studies. Arthritis Rheum 2007;56(9):2896-904.
- 113. Dixon WG, Watson K, Lunt M, et al. Rates of serious infection, including site-specific and bacterial intracellular infection, in rheumatoid arthritis patients receiving antitumor necrosis factor therapy: Results from the British Society for Rheumatology Biologics Register. Arthritis Rheum. 2006 Jul 25;54(8):2368-76.
- 114. Donahue KE, Gartlehner G, Jonas DE, et al. Comparative effectiveness of drug therapy for rheumatoid arthritis and psoriatic

- arthritis in adults. Comparative Effectiveness Review No. 11. (Prepared by RTI-University of North Carolina Evidence-based Practice Center under Contract No. 290-02-0016.) Rockville, MD: Agency for Healthcare Research and Quality; 2007.
- 115. Edmonds J, Saudan A, Lassere M, et al. Introduction to reading radiographs by the Scott modification of the Larsen method. J Rheumatol. 1999;26:740-2.
- 116. Efthimiou P, Kontzias A, Ward CM, et al. Adult-onset Still's disease: can recent advances in our understanding of its pathogenesis lead to targeted therapy? Nat Clin Pract Rheumatol. 2007 Jun;3(6):328-35.
- 117. Egger M, Smith GD, Altman DG. Systematic Reviews in Health Care (2nd edition). 2001 2001.
- 118. Emery P, Breedveld FC, Jubb RW, et al. Efficacy and safety of leflunomide vs. methotrexate in rheumatoid arthritis (RA): results of a double-blind, randomized, 2-year trial. Arthritis and Rheumatism. 1999;42(9 (Suppl)):S271.
- 119. Emery P, Fleischmann R, Filipowicz-Sosnowska A, et al. The efficacy and safety of rituximab in patients with active rheumatoid arthritis despite methotrexate treatment: results of a phase IIB randomized, double-blind, placebocontrolled, dose-ranging trial. Arthritis Rheum 2006;54(5):1390-400.
- 120. Feagan BG, Yan S, Bala M, et al. The effects of infliximab maintenance therapy on health-related quality of life. Am J Gastroenterol. 2003 Oct;98(10):2232-8.
- 121. Felson DT, Anderson JJ, Boers M, et al. The American College of Rheumatology preliminary core set of disease activity measures for rheumatoid arthritis clinical trials. The Committee on Outcome Measures in Rheumatoid Arthritis Clinical Trials. Arthritis Rheum. 1993 Jun;36(6):729-40.
- 122. Felson DT, Anderson JJ, Boers M, et al. ACR preliminary definition of improvement in rheumatoid arthritis. Arthritis Rheum. 1995;38(6):727-35.

- 123. Felson DT, Anderson JJ, Boers M, et al. American College of Rheumatology. Preliminary definition of improvement in rheumatoid arthritis. Arthritis Rheum 1995;38(6):727-35.
- 124. Felson DT, Anderson JJ, Meenan RF. The comparative efficacy and toxicity of second-line drugs in rheumatoid arthritis. Results of two metaanalyses. Arthritis Rheum. 1990 Oct;33(10):1449-61.
- 125. Felson DT, Anderson JJ, Meenan RF. The efficacy and toxicity of combination therapy in rheumatoid arthritis. A meta-analysis.

 Arthritis Rheum. 1994 Oct;37(10):1487-91.
- 126. Fernandez-Espartero MC, Perez-Zafrilla B, Naranjo A, et al. Demyelinating Disease in Patients Treated with TNF Antagonists in Rheumatology: Data from BIOBADASER, a Pharmacovigilance Database, and a Systematic Review. Semin Arthritis Rheum 2010;40(4):330-7.
- 127. Finckh A, Liang MH, Van Herckenrode CM, et al. Long-term impact of early treatment on radiographic progression in rheumatoid arthritis: Ameta-analysis.

 Arthritis and rheumatism. 2006;55(6):86-172.
- 128. Finckh A, Simard JF, Gabay C, et al. Evidence for differential acquired drug resistance to anti-tumour necrosis factor agents in rheumatoid arthritis. Ann Rheum Dis. 2006 Jun;65(6):746-52.
- 129. Firestein GS. Etiology and pathogenesis of rheumatoid arthritis. Kelley's Testbook of Rheumatology 2005;7.
- 130. Fleischmann R, Iqbal I. Risk: benefit profile of etanercept in elderly patients with rheumatoid arthritis, ankylosing spondylitis or psoriatic arthritis. Drugs Aging. 2007;24(3):239-54.
- 131. Fleischmann R, Iqbal I, Nandeshwar P, et al. Safety and efficacy of disease-modifying anti-rheumatic agents: focus on the benefits and risks of etanercept. Drug Saf. 2002;25(3):173-97.

- 132. Fleischmann RM, Baumgartner SW, Tindall EA, et al. Response to etanercept (Enbrel) in elderly patients with rheumatoid arthritis: a retrospective analysis of clinical trial results. J Rheumatol. 2003 Apr;30(4):691-6.
- 133. Flendrie M, Vissers WH, Creemers MC, et al. Dermatological conditions during TNF-alpha-blocking therapy in patients with rheumatoid arthritis: a prospective study. Arthritis Res Ther. 2005;7(3):R666-76.
- 134. Food and Drug Administration. FDA alert on rituximab, available at: http://www.fda.gov/cder/drug/infopage/rituximab/default.htm. 2006.
- 135. Frankel EH, Strober BE, Crowley JJ, et al. Etanercept improves psoriatic arthritis patient-reported outcomes: results from EDUCATE. Cutis. 2007 Apr;79(4):322-6.
- 136. Fransen J, van Riel PL. The Disease Activity Score and the EULAR response criteria. Rheum Dis Clin North Am 2009;35(4):745-57, vii-viii.
- 137. Fredriksson T, Pettersson U. Severe psoriasis--oral therapy with a new retinoid. Dermatologica. 1978;157(4):238-44.
- 138. Friedrich-Rust M, Ong M, Martens S, et al. Performance of Transient Elastography for the Staging of Liver Fibrosis: A Meta-Analysis. Gastroenterology. 2008;134(4).
- 139. Fries JF, Spitz P, Kraines RG, et al.

 Measurement of patient outcome in arthritis.

 Arthritis Rheum. 1980 Feb;23(2):137-45.
- 140. Fries JF, Williams CA, Morfeld D, et al. Reduction in long-term disability in patients with rheumatoid arthritis by disease-modifying antirheumatic drug-based treatment strategies. Arthritis Rheum. 1996 Apr;39(4):616-22.
- 141. Furst D, Luggen M, Thompson A, et al. Adding leflunomide to patients with active rheumatoid arthritis patients while receiving methotrexate improves physical function and health related quality of life. Arthritis and Rheumatism. 2000;43(Suppl):S344.

- 142. Furst DE, Breedveld FC, Kalden JR, et al. Updated consensus statement on biological agents for the treatment of rheumatic diseases, 2007. Annals of the rheumatic diseases. 2007;66(SUPPL. 3).
- 143. Furst DE, Keystone EC, Kirkham B, et al. Updated consensus statement on biological agents for the treatment of rheumatic diseases, 2008. Annals of the rheumatic diseases. 2008;67(SUPPL. 3).
- 144. Galloway JB, Hyrich KL, Mercer LK, et al. Anti-TNF therapy is associated with an increased risk of serious infections in patients with rheumatoid arthritis especially in the first 6 months of treatment: updated results from the British Society for Rheumatology Biologics Register with special emphasis on risks in the elderly. Rheumatology (Oxford, England) 2011;50(1):124-31.
- 145. Galvañ VG, Oltra MR, Rueda D, et al. Severe acute hepatitis related to hydroxychloroquine in a woman with mixed connective tissue disease. Clinical rheumatology. 2007;26(6):971-2.
- 146. Gartlehner G, Hansen R, Thieda P, et al. Drug Class Review on Targeted Immune Modulators, Final AHRQ-approved report December 2006, available at http://www.ohsu.edu/drugeffectiveness/reports/draft.cfm. 2006.
- 147. Gartlehner G, Hansen RA, Jonas BL, et al. The comparative efficacy and safety of biologics for the treatment of rheumatoid arthritis: a systematic review and metaanalysis. J Rheumatol. 2006.
- 148. Gelfand JM, Gladman DD, Mease PJ, et al. Epidemiology of psoriatic arthritis in the population of the United States. J Am Acad Dermatol 2005;53(4):573.
- 149. Genant HK, Peterfy C, Westhovens R.
 Abatacept sustains inhibition of radiographic progression over 2 years in rheumatoid arthritis patients with an inadequate response to methotrexate: Results from the long-term extension of the AIM trial. Ann Rheum Dis. 2006;65(SUPPL. II):57-8.

- 150. Genovese M, Kaine J, Lowenstein M.
 Ocrelizumab, a novel humanized anti-CD20
 antibody: Week 72 results from a phase I/II
 clinical trial in patients with rheumatoid
 arthritis [abstract]. American College of
 Rheumatology Annual Meeting. 2007.
- 151. Genovese MC, Mease PJ, Thomson GT, et al. Safety and efficacy of adalimumab in treatment of patients with psoriatic arthritis who had failed disease modifying antirheumatic drug therapy. J Rheumatol 2007;34(5):1040-50.
- 152. Gilaberte Y, Coscojuela C, Vazquez C, et al. Perforating folliculitis associated with tumour necrosis factor-alpha inhibitors administered for rheumatoid arthritis. Br J Dermatol. 2007 Feb;156(2):368-71.
- 153. Gladman DD. Effectiveness of psoriatic arthritis therapies. Semin Arthritis Rheum. 2003 Aug;33(1):29-37.
- 154. Gladman DD, Antoni C, Mease P, et al. Psoriatic arthritis: epidemiology, clinical features, course, and outcome. Ann Rheum Dis 2005;64 Suppl 2ii14-7.
- 155. Glenny AM, Altman DG, Song F, et al. Indirect comparisons of competing interventions. Health Technol Assess. 2005 Jul;9(26):1-134, iii-iv.
- 156. Glenny AM, Altman DG, Song F, et al. Indirect comparisons of competing interventions. Health Technol Assess 2005;9(26):1-134, iii-iv.
- 157. Golding A, Haque UJ, Giles JT. Rheumatoid arthritis and reproduction. Rheum Dis Clin North Am. 2007 May;33(2):319-43, vi-vii.
- 158. Goldman JA, Xia HA, White B, et al. Evaluation of a modified ACR20 scoring system in patients with rheumatoid arthritis receiving treatment with etanercept. Ann Rheum Dis. 2006 Dec;65(12):1649-52.
- 159. Gonzalez-Lopez MA, Blanco R, Gonzalez-Vela MC, et al. Development of sarcoidosis during etanercept therapy. Arthritis Rheum. 2006 Oct 15;55(5):817-20.

- 160. Goodman SN. Toward evidence-based medical statistics. 2: The Bayes factor. Ann Intern Med. 1999 Jun 15;130(12):1005-13.
- 161. Gottlieb AB, Boehncke WH, Darif M. Safety and efficacy of alefacept in elderly patients and other special populations. J Drugs Dermatol. 2005 Nov-Dec;4(6):718-24.
- 162. Greenberg JD, Reed G, Kremer JM, et al. Association of methotrexate and tumour necrosis factor antagonists with risk of infectious outcomes including opportunistic infections in the CORRONA registry. Ann Rheum Dis 2010;69(2):380-6.
- 163. Greiner A, Plischke H, Kellner H, et al. Association of Anti-Cyclic Citrullinated Peptide Antibodies, Anti-Citrullin Antibodies, and IgM and IgA Rheumatoid Factors with Serological Parameters of Disease Activity in Rheumatoid Arthritis. Ann N Y Acad Sci. 2005 Jun;1050:295-303.
- 164. Grismer LE, Gill SA, Harris MD. Liver biopsy in psoriatic arthritis to detect methotrexate hepatotoxicity. J Clin Rheumatol. 2001 Aug;7(4):224-7.
- 165. Guyatt G, Gutterman D, Baumann MH, et al. Grading strength of recommendations and quality of evidence in clinical guidelines: report from an american college of chest physicians task force. Chest. 2006 Jan;129(1):174-81.
- 166. Häkkinen A, Kautiainen H, Hannonen P, et al. Muscle strength, pain, and disease activity explain individual subdimensions of the Health Assessment Questionnaire disability index, especially in women with rheumatoid arthritis. Annals of the rheumatic diseases. 2006;65(1):30-4.
- 167. Hallert E, Husberg M, Skogh T. Costs and course of disease and function in early rheumatoid arthritis: a 3-year follow-up (the Swedish TIRA project). Rheumatology (Oxford). 2006 Mar;45(3):325-31.
- 168. Han C, Robinson DW, Jr., Hackett MV, et al. Cardiovascular disease and risk factors in patients with rheumatoid arthritis, psoriatic arthritis, and ankylosing spondylitis. J Rheumatol. 2006 Nov;33(11):2167-72.

- 169. Hara M, Abe T, Sugawara S, et al. Efficacy and safety of iguratimod compared with placebo and salazosulfapyridine in active rheumatoid arthritis: a controlled, multicenter, double-blind, parallel-group study. Mod Rheumatol. 2007;17(1):1-9.
- 170. Harris RP, Helfand M, Woolf SH, et al. Current methods of the US Preventive Services Task Force: a review of the process. Am J Prev Med. 2001 Apr;20(3 Suppl):21-35.
- 171. Hasan U. Tumour necrosis factor inhibitors--what we need to know. N Z Med J. 2006;119(1246):U2336.
- 172. Hays RD, Morales LS. The RAND-36 measure of health-related quality of life. Ann Med 2001;33(5):350-7.
- 173. Heiberg MS, Kaufmann C, Rodevand E, et al. The comparative effectiveness of anti-TNF therapy and methotrexate in patients with psoriatic arthritis: 6 month results from a longitudinal, observational, multicentre study. Ann Rheum Dis. 2007 Aug;66(8):1038-42.
- 174. Heiberg MS, Rødevand E, Mikkelsen K, et al. Adalimumab and methotrexate is more effective than adalimumab alone in patients with established rheumatoid arthritis: Results from a 6-month longitudinal, observational, multicentre study. Annals of the rheumatic diseases 2006;65(10):1379-83
- 175. Helliwell PS. Therapies for dactylitis in psoriatic arthritis. A systematic review. J Rheumatol. 2006 Jul;33(7):1439-41.
- 176. Helliwell PS, Ibrahim G. Ethnic differences in responses to disease modifying drugs. Rheumatology (Oxford). 2003
 Oct;42(10):1197-201.
- 177. Helliwell PS, Taylor WJ. Classification and diagnostic criteria for psoriatic arthritis. Ann Rheum Dis. 2005 Mar;64 Suppl 2:ii3-8.
- 178. Helmick CG, Felson DT, Lawrence RC, et al. Estimates of the prevalence of arthritis and other rheumatic conditions in the United

- States. Part I. Arthritis Rheum 2008;58(1):15-25.
- 179. Hewlett S, Hehir M, Kirwan JR. Measuring fatigue in rheumatoid arthritis: A systematic review of scales in use. Arthritis Care and Research. 2007;57(3):429-39.
- 180. Higgins JP, Whitehead A. Borrowing strength from external trials in a meta-analysis. Stat Med 1996;15(24):2733-49.
- 181. Hochberg MC, Tracy JK, Flores RH.
 "Stepping-up" from methotrexate: a
 systematic review of randomised placebo
 controlled trials in patients with rheumatoid
 arthritis with an incomplete response to
 methotrexate. Ann Rheum Dis. 2001 Nov;60
 Suppl 3:iii51-4.
- 182. Hochberg MC, Tracy JK, Hawkins-Holt M, et al. Comparison of the efficacy of the tumour necrosis factor alpha blocking agents adalimumab, etanercept, and infliximab when added to methotrexate in patients with active rheumatoid arthritis. Ann Rheum Dis. 2003 2003;62 Suppl 2:ii13-6.
- 183. Huedo-Medina TB, Sánchez-Meca J, MarÃ-n-MartÃ-nez F, et al. Assessing heterogeneity in meta-analysis: Q statistic or I² Index? Psychological Methods. 2006;11(2):193-206.
- 184. Hurst NP, Kind P, Ruta D, et al. Measuring health-related quality of life in rheumatoid arthritis: validity, responsiveness and reliability of EuroQol (EQ-5D). Br J Rheumatol. 1997 May;36(5):551-9.
- 185. Huscher D, Merkesdal S, Thiele K, et al. Cost of illness in rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis and systemic lupus erythematosus in Germany. Ann Rheum Dis. 2006 Sep;65(9):1175-83.
- 186. Husted JA, Gladman DD, Farewell VT, et al. Health-related quality of life of patients with psoriatic arthritis: a comparison with patients with rheumatoid arthritis. Arthritis Rheum. 2001 Apr;45(2):151-8.
- 187. Hyrich KL, Symmons DP, Watson KD, et al. Comparison of the response to infliximab

- or etanercept monotherapy with the response to cotherapy with methotrexate or another disease-modifying antirheumatic drug in patients with rheumatoid arthritis: Results from the British Society for Rheumatology Biologics Register. Arthritis Rheum. 2006 May 30;54(6):1786-94.
- 188. ICH. International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use ICH Harmonised Tripartite Guideline Clinical Safety Data Management: Definitions and Standards for Expedited Reporting E2A; available at http://www.ich.org/LOB/media/MEDIA436. pdf. 1994.
- 189. Jansen JP, Crawford B, Bergman G, et al. Bayesian meta-analysis of multiple treatment comparisons: an introduction to mixed treatment comparisons. Value Health. 2008 Sep-Oct;11(5):956-64.
- 190. Javitz HS, Ward MM, Farber E, et al. The direct cost of care for psoriasis and psoriatic arthritis in the United States. J Am Acad Dermatol. 2002 Jun;46(6):850-60.
- 191. Jobanputra P, Barton P, Bryan S, et al. The effectiveness of infliximab and etanercept for the treatment of rheumatoid arthritis: a systematic review and economic evaluation. Health Technol Assess. 2002;6(21):1-110.
- 192. Kaine J, Kivitz A, Birbara C, et al. Effect of adalimumab (Humira®) on response to pneumococcal and influenza virus vaccines in patients with rheumatoid arthritis (RA). Ann Rheum Dis. 2006;65(SUPPL. II):304.
- 193. Kaine JL, Kivitz AJ, Birbara C, et al. Immune responses following administration of influenza and pneumococcal vaccines to patients with rheumatoid arthritis receiving adalimumab. J Rheumatol. 2007 Feb;34(2):272-9.
- 194. Kapetanovic M, Saxne T, Nilsson J.
 Influenza vaccination as model for testing immune modulation of anti-TNF and methotrexate therapy in rheumatoid arthritis patients. Ann Rheum Dis. 2006;65(SUPPL. II):184.

- 195. Katchamart W, Ortiz Z, Shea B, et al. Folic acid and folinic acid for reducing side effects in patients receiving methotrexate for rheumatoid arthritis (an update systematic review and metaanalysis). Arthritis Rheum. 2008;58(SUPPL.).
- 196. Kavanaugh A, Antoni C, Mease P, et al. Effect of infliximab therapy on employment, time lost from work, and productivity in patients with psoriatic arthritis. J Rheumatol 2006;33(11):2254-9.
- 197. Kavanaugh A, Krueger GG, Beutler A, et al. Infliximab maintains a high degree of clinical response in patients with active psoriatic arthritis through 1 year of treatment: results from the IMPACT 2 trial. Ann Rheum Dis. 2007 Apr;66(4):498-505.
- 198. Kavanaugh AF, Ritchlin CT. Systematic review of treatments for psoriatic arthritis: an evidence based approach and basis for treatment guidelines. J Rheumatol. 2006 Jul;33(7):1417-21.
- 199. Kievit W, Fransen J, Kupper HH, et al. The drug survival of adalimumab compared to etanercept and infliximab in the treatment of patients with rheumatoid arthritis in daily clinical practice. Ann Rheum Dis. 2006 June 1, 2006;65(Suppl 2):325-.
- 200. Kim HY, Lee SK, Song YW, et al. A randomized, double-blind, placebocontrolled, phase III study of the human anti-tumor necrosis factor antibody adalimumab administered as subcutaneous injections in Korean rheumatoid arthritis patients treated with methotrexate. APLAR Journal of Rheumatology 2007;10(1):9-16.
- 201. Kind P. The EuroQol instrument: An index of health-related quality of life. Quality of life and PharmacoEconomics in Clinical Trials. 2nd ed. Philadelphia: Lippincott-Raven Publishers; 1996.
- 202. Kirwan JR, Bijlsma JW, Boers M, et al. Effects of glucocorticoids on radiological progression in rheumatoid arthritis. Cochrane Database Syst Rev 2007(1):CD006356.
- 203. Kosinski M, Zhao SZ, Dedhiya S, et al. Determining minimally important changes

- in generic and disease-specific health-related quality of life questionnaires in clinical trials of rheumatoid arthritis. Arthritis Rheum 2000;43(7):1478-87.
- 204. Kremer J, Westhovens R, Luggen M. Longterm efficacy and safety of abatacept through 3 years of treatment in rheumatoid arthritis patients in the AIM and ATTAIN trials [abstract]. American College of Rheumatology Meeting.
- 205. Kremer JL, Blanco R, Brzosko M, et al. Tocilizumab inhibits structural joint damage in rheumatoid arthritis patients with inadequate responses to methotrexate at 1 year: The LITHE study. Arthritis Rheum 2010.
- 206. Kremer JM. Safety, efficacy, and mortality in a long-term cohort of patients with rheumatoid arthritis taking methotrexate: followup after a mean of 13.3 years.

 Arthritis Rheum. 1997 May;40(5):984-5.
- 207. Kremer JM, Caldwell JR, Cannon GW, et al. The combination of leflunomide and methotrexate in patients with active rheumatoid arthritis who are failing on methotrexate treatment alone: a double-blind placebo-controlled study. Arthritis Rheum. 2000;43(Suppl 9):S224.
- 208. Kremer JM, Dougados M, Emery P, et al. Treatment of rheumatoid arthritis with the selective costimulation modulator abatacept: twelve-month results of a phase iib, double-blind, randomized, placebo-controlled trial. Arthritis Rheum. 2005 Aug;52(8):2263-71.
- 209. Kristensen LE, Christensen R, Bliddal H, et al. The number needed to treat for adalimumab, etanercept, and infliximab based on ACR50 response in three randomized controlled trials on established rheumatoid arthritis: A systematic literature review. Scandinavian Journal of Rheumatology 2007;36(6):411-7.
- 210. Laivoranta-Nyman S, Mottonen T,
 Hannonen P, et al. Association of tumour
 necrosis factor a, b and c microsatellite
 polymorphisms with clinical disease activity
 and induction of remission in early
 rheumatoid arthritis. Clin Exp Rheumatol.
 2006 Nov-Dec;24(6):636-42.

- 211. Landewe R, van der Heijde D, van der Linden S, et al. Twenty-eight-joint counts invalidate the DAS28 remission definition owing to the omission of the lower extremity joints: a comparison with the original DAS remission. Ann Rheum Dis. 2006 May;65(5):637-41.
- 212. Lard LR, Visser H, Speyer I, et al. Early versus delayed treatment in patients with recent-onset rheumatoid arthritis: comparison of two cohorts who received different treatment strategies. Am J Med. 2001 Oct 15;111(6):446-51.
- 213. Larsen A. Radiological grading of rheumatoid arthritis. An interobserver study. Scand J Rheumatol. 1973;2(3):136-8.
- 214. Larsen A. How to apply Larsen score in evaluating radiographs of rheumatoid arthritis in long-term studies. J Rheumatol. 1995;22:1974-5.
- 215. Larsen A, Dale K, Eek M. Radiographic evaluation of rheumatoid arthritis and related conditions by standard reference films. Acta Radiol Diagn (Stockh). 1977 Jul;18(4):481-91.
- 216. Lau J, Ioannidis JPA, Terrin N, et al. The case of the misleading funnel plot. British Medical Journal. 2006;333(7568):597-600.
- 217. Lawrence RC, Felson DT, Helmick CG, et al. Estimates of the prevalence of arthritis and other rheumatic conditions in the United States. Part II. Arthritis Rheum 2008;58(1):26-35.
- 218. Lee YH, Woo JH, Rho YH, et al. Metaanalysis of the combination of TNF inhibitors plus MTX compared to MTX monotherapy, and the adjusted indirect comparison of TNF inhibitors in patients suffering from active rheumatoid arthritis. Rheumatology international 2008;28(6):553-9.
- 219. Leombruno JP, Einarson TR, Keystone EC. The safety of anti-tumour necrosis factor treatments in rheumatoid arthritis: meta and exposure-adjusted pooled analyses of serious adverse events. Ann Rheum Dis 2009;68(7):1136-45.

- 220. Lequerre T, Vittecoq O, Klemmer N, et al. Management of infusion reactions to infliximab in patients with rheumatoid arthritis or spondyloarthritis: experience from an immunotherapy unit of rheumatology. J Rheumatol. 2006
 Jul;33(7):1307-14.
- 221. Li X, Gignac MA, Anis AH. The indirect costs of arthritis resulting from unemployment, reduced performance, and occupational changes while at work. Med Care 2006;44(4):304-10.
- 222. Liao KP, Batra KL, Chibnik L, et al. Anticyclic citrullinated peptide revised criteria for the classification of rheumatoid arthritis. Ann Rheum Dis 2008;67(11):1557-61.
- 223. Lim LL, Fraunfelder FW, Rosenbaum JT. Do tumor necrosis factor inhibitors cause uveitis? A registry-based study. Arthritis Rheum. 2007 Oct;56(10):3248-52.
- 224. Lindqvist E, Saxne T, Geborek P, et al. Ten year outcome in a cohort of patients with early rheumatoid arthritis: health status, disease process, and damage. Ann Rheum Dis. 2002 Dec;61(12):1055-9.
- 225. Lindsay K, Gough A. Psoriatic arthritis, methotrexate and the liver Are rheumatologists putting their patients at risk? Rheumatology. 2008;47(7):939-41.
- 226. Listing J, Strangfeld A, Rau R, et al. Clinical and functional remission: even though biologics are superior to conventional DMARDs overall success rates remain low-results from RABBIT, the German biologics register. Arthritis Res Ther. 2006;8(3):R66.
- 227. Lu G, Ades AE. Combination of direct and indirect evidence in mixed treatment comparisons. Stat Med. 2004 Oct 30;23(20):3105-24.
- 228. Lumley T. Network meta-analysis for indirect treatment comparisons. Stat Med. 2002 Aug 30;21(16):2313-24.
- 229. Mäki-Petäjä KM, Booth AD, Hall FC, et al. Ezetimibe and Simvastatin Reduce Inflammation, Disease Activity, and Aortic Stiffness and Improve Endothelial Function

- in Rheumatoid Arthritis. Journal of the American College of Cardiology. 2007;50(9):852-8.
- 230. Mader R, Keystone E. Optimizing treatment with biologics. Journal of Rheumatology. 2007;34(SUPPL. 80):16-24.
- 231. Maetzel A, Wong A, Strand V, et al. Metaanalysis of treatment termination rates among rheumatoid arthritis patients receiving disease-modifying anti-rheumatic drugs. Rheumatology (Oxford). 2000 Sep;39(9):975-81.
- 232. Manadan AM, Mohan AK. Tuberculosis and etanercept treatment. Arthritis Rheum. 2002;46:S166.
- 233. Marcora SM, Chester KR, Mittal G, et al. Randomized phase 2 trial of anti-tumor necrosis factor therapy for cachexia in patients with early rheumatoid arthritis. Am J Clin Nutr. 2006 Dec;84(6):1463-72.
- 234. Markham T, Mathews C, Rogers S, et al. Downregulation of the inhibitor of apoptosis protein survivin in keratinocytes and endothelial cells in psoriasis skin following infliximab therapy. British Journal of Dermatology. 2006;155(6):1191-6.
- 235. Martin M, Kosinski M, Bjorner JB, et al. Item response theory methods can improve the measurement of physical function by combining the modified health assessment questionnaire and the SF-36 physical function scale. Qual Life Res. 2007 May;16(4):647-60.
- 236. Mau W, Listing J, Huscher D, et al.
 Employment across chronic inflammatory
 rheumatic diseases and comparison with the
 general population. J Rheumatol. 2005
 Apr;32(4):721-8.
- 237. McHorney CA, Ware JE, Jr., Lu JF, et al. The MOS 36-item Short-Form Health Survey (SF-36): III. Tests of data quality, scaling assumptions, and reliability across diverse patient groups. Med Care. 1994 Jan;32(1):40-66.
- 238. McHorney CA, Ware JE, Jr., Raczek AE. The MOS 36-Item Short-Form Health

- Survey (SF-36): II. Psychometric and clinical tests of validity in measuring physical and mental health constructs. Med Care. 1993 Mar;31(3):247-63.
- 239. McHorney CA, Ware JE, Jr., Rogers W, et al. The validity and relative precision of MOS short- and long-form health status scales and Dartmouth COOP charts. Results from the Medical Outcomes Study. Med Care. 1992 May;30(5 Suppl):MS253-65.
- 240. McInnes IB, Schett G. Cytokines in the pathogenesis of rheumatoid arthritis. Nature Reviews Immunology. 2007;7(6):429-42.
- 241. Mease P. Psoriatic arthritis update. Bulletin of the NYU Hospital for Joint Diseases. 2006;64(1-2):25-31.
- 242. Mease PJ, Antoni CE, Gladman DD, et al. Psoriatic arthritis assessment tools in clinical trials. Ann Rheum Dis. 2005 Mar;64 Suppl 2:ii49-54.
- 243. Mease PJ, Gladman DD, Keystone EC. Alefacept in combination with methotrexate for the treatment of psoriatic arthritis: results of a randomized, double-blind, placebocontrolled study. Arthritis Rheum. 2006 May;54(5):1638-45.
- 244. Michaud K, Messer J, Choi HK, et al. Direct medical costs and their predictors in patients with rheumatoid arthritis: a three-year study of 7,527 patients. Arthritis Rheum. 2003 Oct;48(10):2750-62.
- 245. Miller LG, Hays RD. Adherence to combination antiretroviral therapy: synthesis of the literature and clinical implications. AIDS Read. 2000 Mar;10(3):177-85.
- 246. Moher D, Cook DJ, Eastwood S, et al. Improving the quality of reports of meta-analyses of randomised controlled trials: the QUOROM statement. Quality of Reporting of Meta-analyses. Lancet. 1999 Nov 27;354(9193):1896-900.
- 247. Moher D, Liberati A, Tetzlaff J, et al. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. Int J Surg 2010;8(5):336-41.

- 248. Moreland LW, Baumgartner SW, Schiff MH, et al. Treatment of rheumatoid arthritis with a recombinant human tumor necrosis factor receptor (p75)-Fc fusion protein. N Engl J Med. 1997 Jul 17;337(3):141-7.
- 249. Moreland LW, Cohen SB, Baumgartner S, et al. Long-term use of etanercept in patients with DMARD-refractory arthritis. Arthritis Rheum. 1992;42(Suppl 9):S401.
- 250. Moreland LW, Genovese MC, Sato R, et al. Effect of etanercept on fatigue in patients with recent or established rheumatoid arthritis. Arthritis Rheum. 2006 Apr 15;55(2):287-93.
- 251. Moreland LW, Weinblatt ME, Keystone EC, et al. Etanercept treatment in adults with established rheumatoid arthritis: 7 years of clinical experience. J Rheumatol. 2006 May;33(5):854-61.
- 252. Moss ML, Sklair-Tavron L, Nudelman R. Drug Insight: Tumor necrosis factor-converting enzyme as a pharmaceutical target for rheumatoid arthritis. Nature Clinical Practice Rheumatology. 2008;4(6):300-9.
- 253. Mroczkowski PJ, Weinblatt ME, Kremer JM. Methotrexate and leflunomide combination therapy for patients with active rheumatoid arthritis. Clin Exp Rheumatol. 1999 Nov-Dec;17(6 Suppl 18):S66-8.
- 254. Muller-Ladner U, Pap T, Gay RE, et al. Mechanisms of disease: the molecular and cellular basis of joint destruction in rheumatoid arthritis. Nat Clin Pract Rheumatol. 2005 Dec;1(2):102-10.
- 255. Multi-Parameter Evidence Synthesis (MPES) Research Group. Available at: https://www.bris.ac.uk/cobm/research/mpes/mtc.html.
- 256. Munafo A, Priestley A, Nestorov I, et al. Safety, pharmacokinetics and pharmacodynamics of atacicept in healthy volunteers. European Journal of Clinical Pharmacology. 2007;63(7):647-56.
- 257. Munoz P, Giannella M, Valerio M, et al. Cryptococcal meningitis in a patient treated

- with infliximab. Diagn Microbiol Infect Dis. 2007 Apr;57(4):443-6.
- 258. Nam JL, Winthrop KL, van Vollenhoven RF, et al. Current evidence for the management of rheumatoid arthritis with biological disease-modifying antirheumatic drugs: a systematic literature review informing the EULAR recommendations for the management of RA. Ann Rheum Dis 2010;69(6):976-86.
- 259. Nash P. Therapies for axial disease in psoriatic arthritis. A systematic review. J Rheumatol. 2006 Jul;33(7):1431-4.
- 260. Nathan DM, Angus PW, Gibson PR. Hepatitis B and C virus infections and antitumor necrosis factor-α therapy: Guidelines for clinical approach. Journal of Gastroenterology and Hepatology. 2006;21(9):1366-71.
- 261. Nishimoto N, Kishimoto T. Humanized antihuman IL-6 receptor antibody, tocilizumab. Handbook of experimental pharmacology. 2008(181):151-60.
- 262. Nixon RM, Bansback N, Brennan A. Using mixed treatment comparisons and meta-regression to perform indirect comparisons to estimate the efficacy of biologic treatments in rheumatoid arthritis. Statistics in Medicine. 2007;26(6):1237-54.
- 263. Norris SL, Atkins D. Challenges in using nonrandomized studies in systematic reviews of treatment interventions. Ann Intern Med. 2005 Jun 21;142(12 Pt 2):1112-9.
- 264. O'Dell J, Leff R, Paulsen G, et al. Methotrexate (M)-Hydroxychloroquine (H)-Sulfasalazine (S) versus M-H or M-S for rheumatoid arthritis (RA): results of a double-blind study. Arthritis Rheum. 1999;42(Suppl 9):S117.
- 265. O'Dell JR, Haire CE, Erikson N, et al. Treatment of rheumatoid arthritis with methotrexate alone, sulfasalazine and hydroxychloroquine, or a combination of all three medications. N Engl J Med. 1996 May 16;334(20):1287-91.

- 266. Ogrendik M. Levofloxacin treatment in patients with rheumatoid arthritis receiving methotrexate. South Med J. 2007 Feb;100(2):135-9.
- 267. Ohsugi Y. Recent advances in immunopathophysiology of interleukin-6: An innovative therapeutic drug, tocilizumab (recombinant humanized anti-human interleukin-6 receptor antibody), unveils the mysterious etiology of immune-mediated inflammatory diseases. Biological and Pharmaceutical Bulletin. 2007;30(11):2001-6.
- 268. Ojeda-Uribe M, Gilliot C, Jung G, et al. Administration of rituximab during the first trimester of pregnancy without consequences for the newborn. Journal of Perinatology. 2006;26(4):252-5.
- 269. Okada SK, Siegel JN. Risk of serious infections and malignancies with anti-TNF antibody therapy in rheumatoid arthritis. Jama. 2006 Nov 8;296(18):2201-2; author reply 3-4.
- 270. Olivieri I, Mantovani LG, D'Angelo S, et al. Psoriatic arthritis: pharmacoeconomic considerations. Curr Rheumatol Rep 2009;11(4):263-9.
- 271. Oren C, Mendelbaum M, Paran D. Vaccination against influenza in rheumatoid arthritis patients: The effect of rituximab on the humoral response. Arthritis Rheum 2006;54(SUPPL. 9).
- 272. Ornetti P, Chevillotte H, Zerrak A, et al. Anti-tumour necrosis factor-alpha therapy for rheumatoid and other inflammatory arthropathies: update on safety in older patients. Drugs Aging. 2006;23(11):855-60.
- 273. Orozco G, Rueda B, Martin J. Genetic basis of rheumatoid arthritis. Biomed Pharmacother. 2006 Dec;60(10):656-62.
- 274. Ory PA. Interpreting radiographic data in rheumatoid arthritis. Ann Rheum Dis. 2003 Jul;62(7):597-604.
- 275. Ostergaard M, Baslund B, Rigby W. Ofatumumab, a human CD20 monoclonal antibody, in the treatment of rheumatoid

- arthritis: Early results from an ongoing, double-blind, randomized, placebo-controlled clinical trial [abstract]. American College of Rheumatology Annual Meeting. 2007.
- 276. Owens DK, Lohr KN, Atkins D, et al. AHRQ series paper 5: grading the strength of a body of evidence when comparing medical interventions--agency for healthcare research and quality and the effective healthcare program. J Clin Epidemiol. 2010 May;63(5):513-23.
- 277. Ozminkowski RJ, Burton WN, Goetzel RZ, et al. The impact of rheumatoid arthritis on medical expenditures, absenteeism, and short-term disability benefits. J Occup Environ Med. 2006 Feb;48(2):135-48.
- 278. Pallavicini FB, Caporali R, Sarzi-Puttini P, et al. Tumour necrosis factor antagonist therapy and cancer development: analysis of the LORHEN registry. Autoimmun Rev 2010;9(3):175-80.
- 279. Papp KA, Caro I, Leung HM, et al. Efalizumab for the treatment of psoriatic arthritis. J Cutan Med Surg. 2007 Mar-Apr;11(2):57-66.
- 280. Pieringer H, Stuby U, Biesenbach G. Patients with Rheumatoid Arthritis Undergoing Surgery: How Should We Deal with Antirheumatic Treatment? Seminars in Arthritis and Rheumatism. 2007;36(5):278-86.
- 281. Pincus T, Marcum SB, Callahan LF. Longterm drug therapy for rheumatoid arthritis in seven rheumatology private practices: II. Second line drugs and prednisone. J Rheumatol. 1992 Dec;19(12):1885-94.
- 282. Pincus T, O'Dell JR, Kremer JM.
 Combination therapy with multiple diseasemodifying antirheumatic drugs in
 rheumatoid arthritis: a preventive strategy.
 Ann Intern Med. 1999 Nov 16;131(10):76874.
- 283. Pincus T, Yazici Y, Bergman M. A practical guide to scoring a Multi-Dimensional Health Assessment Questionnaire (MDHAQ) and Routine Assessment of Patient Index Data

- (RAPID) scores in 10-20 seconds for use in standard clinical care, without rulers, calculators, websites or computers. Best Practice and Research: Clinical Rheumatology. 2007;21(4):755-87.
- 284. Pinzani M, Vizzutti F, Arena U, et al. Technology Insight: Noninvasive assessment of liver fibrosis by biochemical scores and elastography. Nature Clinical Practice Gastroenterology and Hepatology. 2008;5(2):95-106.
- 285. Popovic M, Stefanovic D, Pejnovic N, et al. Comparative study of the clinical efficacy of four DMARDs (leflunomide, methotrexate, cyclosporine, and levamisole) in patients with rheumatoid arthritis. Transplant Proc. 1998 Dec;30(8):4135-6.
- 286. Pouchot J. How can we improve the management of adult-onset Still's disease? Joint Bone Spine. 2007 Mar;74(2):117-9.
- 287. Prevoo ML, van Gestel AM, van THMA, et al. Remission in a prospective study of patients with rheumatoid arthritis. American Rheumatism Association preliminary remission criteria in relation to the disease activity score. Br J Rheumatol. 1996 Nov;35(11):1101-5.
- 288. Pugner KM, Scott DI, Holmes JW, et al. The costs of rheumatoid arthritis: an international long-term view. Semin Arthritis Rheum. 2000 Apr;29(5):305-20.
- 289. Quinn MA, Conaghan PG, O'Connor PJ. Very early treatment with infliximab in addition to methotrexate in early, poorprognosis rheumatoid arthritis reduces magnetic resonance imaging evidence of synovitis and damage, with sustained benefit after infliximab withdrawal: Results from a twelve-month ran-liver disease? Hepatology. 2006;43:352-61.
- 290. Ramey DR, Fries JF, Singh G. The Health Assessment Questionnaire 1995 -- Status and Review. In: Spilker B, ed. Quality of Life and Pharmacoleconomics in Clinical Trials. 2nd ed. Philadelphia: Lippincott-Raven Publischers 1996:227-37.
- 291. Ranganath VK, Furst DE. Disease-modifying antirheumatic drug use in the

- elderly rheumatoid arthritis patient. Rheum Dis Clin North Am. 2007 Feb;33(1):197-217.
- 292. Ravindran V, Scott DL, Choy EH. A systematic review and meta-analysis of efficacy and toxicity of disease modifying anti-rheumatic drugs and biological agents for psoriatic arthritis. Annals of the rheumatic diseases 2008;67(6):855-9.
- 293. Reddy SM, Bingham Iii CO. Outcome measures in psoriatic arthritis clinical trials. Curr Rheumatol Rep 2005;7(4):299-305.
- 294. Reich K, Nestle FO, Papp K, et al. Improvement in quality of life with infliximab induction and maintenance therapy in patients with moderate-to-severe psoriasis: a randomized controlled trial. Br J Dermatol. 2006 Jun;154(6):1161-8.
- 295. Rioda WT, Adorni G. Infliximab treatment in psoriatic arthritis: our experience. Acta Biomed. 2006 Aug;77(2):95-102.
- 296. Ritchie DA, Boyle JA, McInnes JM, et al. Evaluation of a simple articular index for joint tenderness in rheumatoid arthritis. Ann Rheum Dis. 1969 Mar;28(2):196.
- 297. Ritchie DM, Boyle JA, McInnes JM, et al. Clinical studies with an articular index for the assessment of joint tenderness in patients with rheumatoid arthritis. Q J Med. 1968 Jul;37(147):393-406.
- 298. Ritchlin CT, Kavanaugh A, Gladman DD, et al. Treatment recommendations for psoriatic arthritis. Ann Rheum Dis. 2009 Sep;68(9):1387-94.
- 299. Roux CH, Brocq O, Breuil V, et al. Pregnancy in rheumatology patients exposed to anti-tumour necrosis factor (TNF)-α therapy. Rheumatology. 2007;46(4):695-8.
- 300. Ruderman EM, Markenson J.
 Granulomatous infections and tumor necrosis factor antagonists therapy: update through June 2002. Arthritis Rheum. 2003;48(9):S241.
- 301. Saad AA, Ashcroft DM, Watson KD, et al.
 Persistence with anti-tumour necrosis factor

- therapies in patients with psoriatic arthritis: observational study from the British Society of Rheumatology Biologics Register. Arthritis Res Ther 2009;11(2):R52.
- 302. Saag KG, Gim GT, Patkar NM, et al.
 American College of Rheumatology 2008
 recommendations for the use of nonbiologic
 and biologic disease-modifying
 antirheumatic drugs in rheumatoid arthritis.
 Arthritis Care and Research.
 2008;59(6):762-84.
- 303. Salliot C, Gossec L, Ruyssen-Witrand A, et al. Infections during tumour necrosis factor-{alpha} blocker therapy for rheumatic diseases in daily practice: a systematic retrospective study of 709 patients.

 Rheumatology. 2006 July 31, 2006:kel236.
- 304. Salliot C, Gossec L, Ruyssen-Witrand A, et al. Infections during tumour necrosis factorα blocker therapy for rheumatic diseases in daily practice: A systematic retrospective study of 709 patients. Rheumatology 2007:46(2):327-34.
- 305. Samsa G, Edelman D, Rothman ML, et al. Determining clinically important differences in health status measures: a general approach with illustration to the Health Utilities Index Mark II. Pharmacoeconomics 1999;15(2):141-55.
- 306. Sauriol L, Laporta M, Edwardes MD, et al. Meta-analysis comparing newer antipsychotic drugs for the treatment of schizophrenia: evaluating the indirect approach. Clin Ther. 2001 Jun;23(6):942-56.
- 307. Sbeity ZH, Baydoun L, Schmidt S, et al. Visual field changes in methotrexate therapy. Case report and review of the literature. J Med Liban. 2006 Jul-Sep;54(3):164-7.
- 308. Schaible TF. Long term safety of infliximab. Can J Gastroenterol. 2000 Sep;14 Suppl C:29C-32C.
- 309. Schardt C, Adams MB, Owens T, et al.
 Utilization of the PICO framework to
 improve searching PubMed for clinical
 questions. BMC Medical Informatics and
 Decision Making. 2007;7.

- 310. Schiff MH, Burmester GR, Kent JD, et al. Safety analyses of adalimumab (HUMIRA) in global clinical trials and US postmarketing surveillance of patients with rheumatoid arthritis. Ann Rheum Dis. 2006 Jul;65(7):889-94.
- 311. Schuna AA. Rituximab for the treatment of rheumatoid arthritis. Pharmacotherapy. 2007;27(12 I):1702-10.
- 312. Scott DL, Coulton BL, Bacon PA, et al. Methods of X-ray assessment in rheumatoid arthritis: a re-evaluation. Br J Rheumatol. 1985 Feb;24(1):31-9.
- 313. Scott DL, Houssien DA, Laasonen L. Proposed modification to Larsen's scoring methods for hand and wrist radiographs. Br J Rheum. 1995;34:56.
- 314. Setoguchi S, Solomon DH, Weinblatt ME, et al. Tumor necrosis factor alpha antagonist use and cancer in patients with rheumatoid arthritis. Arthritis Rheum. 2006 Sep;54(9):2757-64.
- 315. Sharp JT, Young DY, Bluhm GB, et al. How many joints in the hands and wrists should be included in a score of radiologic abnormalities used to assess rheumatoid arthritis? Arthritis Rheum. 1985
 Dec;28(12):1326-35.
- 316. Shea BJ, Grimshaw JM, Wells GA, et al. Development of AMSTAR: A measurement tool to assess the methodological quality of systematic reviews. BMC Medical Research Methodology. 2007;7.
- 317. Smolen JS, Aletaha D, Keystone E. Superior efficacy of combination therapy for rheumatoid arthritis: fact or fiction? Arthritis Rheum. 2005 Oct;52(10):2975-83.
- 318. Smolen JS, Keystone EC, Emery P, et al. Consensus statement on the use of rituximab in patients with rheumatoid arthritis. Annals of the rheumatic diseases. 2007;66(2):143-50.
- 319. Smolen JS, Landewe R, Breedveld FC, et al. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying

- antirheumatic drugs. Ann Rheum Dis 2010;69(6):964-75.
- 320. Sokka T, Pincus T. Most patients receiving routine care for rheumatoid arthritis in 2001 did not meet inclusion criteria for most recent clinical trials or american college of rheumatology criteria for remission. J Rheumatol. 2003 Jun;30(6):1138-46.
- 321. Sokoll KB, Helliwell PS. Comparison of disability and quality of life in rheumatoid and psoriatic arthritis. J Rheumatol. 2001 Aug;28(8):1842-6.
- 322. Solomon DH. The comparative safety and effectiveness of TNF-alpha antagonists [corrected]. J Manag Care Pharm. 2007 Jan;13(1 Suppl):S7-18.
- 323. Song F, Altman DG, Glenny AM, et al. Validity of indirect comparison for estimating efficacy of competing interventions: empirical evidence from published meta-analyses. Bmj. 2003 Mar 1;326(7387):472.
- 324. Soriano ER, McHugh NJ. Therapies for peripheral joint disease in psoriatic arthritis. A systematic review. J Rheumatol. 2006 Jul;33(7):1422-30.
- 325. Stewart AL, Hays RD, Ware JE, Jr. The MOS short-form general health survey. Reliability and validity in a patient population. Med Care. 1988 Jul;26(7):724-35.
- 326. Stewart AL, Ware JE. Measuring Functioning and Well-Being: The Medical Outcomes Study Approach. Durham, NC: Duke University Press; 1992.
- 327. Strand. Improved health-related quality of life with effective disease-modifying antirheumatic drugs: Evidence from randomized controlled trials (American Journal of Managed Care). American Journal of Managed Care. 2008;14(4):234.
- 328. Strand V, Balbir-Gurman A, Pavelka K, et al. Sustained benefit in rheumatoid arthritis following one course of rituximab: improvements in physical function over 2

- years. Rheumatology (Oxford) 2006;45(12):1505-13.
- 329. Strand V, Tugwell P, Bombardier C, et al. Function and health-related quality of life: results from a randomized controlled trial of leflunomide versus methotrexate or placebo in patients with active rheumatoid arthritis. Leflunomide Rheumatoid Arthritis Investigators Group. Arthritis Rheum. 1999 Sep;42(9):1870-8.
- Szekanecz Z, Koch AE. Macrophages and their products in rheumatoid arthritis.
 Current Opinion in Rheumatology.
 2007;19(3):289-95.
- 331. Tak PP, Thurlings RM, Rossier C, et al. Atacicept in patients with rheumatoid arthritis: Results of a multicenter, phase Ib, double-blind, placebo-controlled, dose-escalating, single- and repeated-dose study. Arthritis and rheumatism. 2008;58(1):61-72.
- 332. Tanaka Y. Biologics: current therapeutic strategies for rheumatoid arthritis. Nippon rinsho Japanese journal of clinical medicine. 2007;65(7):1179-84.
- 333. Taylor W, Gladman D, Helliwell P, et al. Classification criteria for psoriatic arthritis: development of new criteria from a large international study. Arthritis Rheum. 2006 Aug;54(8):2665-73.
- 334. Tilg H, Kaser A, Moschen AR. How to modulate inflammatory cytokines in liver diseases. Liver International. 2006;26(9):1029-39.
- 335. Todd DJ, Costenbader KH, Weinblatt ME. Abatacept in the treatment of rheumatoid arthritis. International Journal of Clinical Practice. 2007;61(3):494-500.
- 336. Tracey D, Klareskog L, Sasso EH, et al. Tumor necrosis factor antagonist mechanisms of action: A comprehensive review. Pharmacology and Therapeutics. 2008;117(2):244-79.
- 337. Tugwell P, Wells G, Strand V, et al. Clinical improvement as reflected in measures of function and health-related quality of life following treatment with leflunomide

- compared with methotrexate in patients with rheumatoid arthritis: sensitivity and relative efficiency to detect a treatment effect in a twelve-month, placebo-controlled trial. Leflunomide Rheumatoid Arthritis Investigators Group. Arthritis Rheum. 2000 Mar;43(3):506-14.
- 338. Turesson C, Schaid DJ, Weyand CM, et al. The impact of HLA-DRB1 genes on extraarticular disease manifestations in rheumatoid arthritis. Arthritis Res Ther. 2005;7(6):R1386-93.
- 339. van der Heijde D. How to read radiographs according to the Sharp/van der Heijde method. J Rheumatol. 1999 Mar;26(3):743-5.
- 340. van der Heijde D. How to read radiographs according to the Sharp/van der Heijde method. J Rheumatol. 2000 Jan;27(1):261-3.
- 341. van der Heijde D, Da Silva JC, Dougados M, et al. Etanercept 50 mg once weekly is as effective as 25 mg twice weekly in patients with ankylosing spondylitis. Ann Rheum Dis. 2006 Dec;65(12):1572-7.
- 342. van der Heijde D, Dankert T, Nieman F, et al. Reliability and sensitivity to change of a simplification of the Sharp/van der Heijde radiological assessment in rheumatoid arthritis. Rheumatology (Oxford). 1999 Oct;38(10):941-7.
- 343. van der Heijde D, Kavanaugh A, Gladman DD, et al. Infliximab inhibits progression of radiographic damage in patients with active psoriatic arthritis through one year of treatment: Results from the induction and maintenance psoriatic arthritis clinical trial 2. Arthritis Rheum 2007;56(8):2698-707.
- 344. van der Heijde D, Klareskog L, Landewe R, et al. Disease remission and sustained halting of radiographic progression with combination etanercept and methotrexate in patients with rheumatoid arthritis. Arthritis Rheum 2007;56(12):3928-39.
- 345. van der Heijde DM. Overview of radiologic efficacy of new treatments. Rheum Dis Clin North Am. 2004 May;30(2):285-93, vi.

- 346. van der Heijde DM, van Leeuwen MA, van Riel PL, et al. Biannual radiographic assessments of hands and feet in a three-year prospective followup of patients with early rheumatoid arthritis. Arthritis Rheum. 1992 Jan;35(1):26-34.
- 347. van Dongen H, van Aken J, Lard LR, et al. Efficacy of methotrexate treatment in patients with probable rheumatoid arthritis: a double-blind, randomized, placebocontrolled trial. Arthritis Rheum. 2007 May;56(5):1424-32.
- 348. van Gestel AM, Anderson JJ, van Riel PL, et al. ACR and EULAR improvement criteria have comparable validity in rheumatoid arthritis trials. American College of Rheumatology European League of Associations for Rheumatology. J Rheumatol 1999;26(3):705-11.
- 349. van Gestel AM, Prevoo ML, van 't Hof MA, et al. Development and validation of the European League Against Rheumatism response criteria for rheumatoid arthritis. Comparison with the preliminary American College of Rheumatology and the World Health Organization/International League Against Rheumatism Criteria. Arthritis Rheum 1996;39(1):34-40.
- 350. van Riel PL, Taggart AJ, Sany J, et al. Efficacy and safety of combination etanercept and methotrexate versus etanercept alone in patients with rheumatoid arthritis with an inadequate response to methotrexate: The ADORE study. Ann Rheum Dis. 2006 Feb 7.
- 351. van Tuyl LH, Vlad SC, Felson DT, et al. Defining remission in rheumatoid arthritis: results of an initial American College of Rheumatology/European League Against Rheumatism consensus conference. Arthritis Rheum 2009;61(5):704-10.
- 352. Verhoeven AC, Boers M, Tugwell P.
 Combination therapy in rheumatoid arthritis: updated systematic review. Br J Rheumatol. 1998 Jun;37(6):612-9.
- 353. Visser K, Katchamart W, Loza E, et al.
 Multinational evidence-based
 recommendations for the use of
 methotrexate in rheumatic disorders with a

- focus on rheumatoid arthritis: Integrating systematic literature research and expert opinion of a broad international panel of rheumatologists in the 3E Initiative. Annals of the rheumatic diseases. 2009;68(7):1086-93
- 354. Visvanathan S, Keenan GF, Baker DG, et al. Response to pneumococcal vaccine in patients with early rheumatoid arthritis receiving infliximab plus methotrexate or methotrexate alone. J Rheumatol. 2007 May;34(5):952-7.
- 355. Visvanathan S, Marini JC, Smolen JS, et al. Changes in biomarkers of inflammation and bone turnover and associations with clinical efficacy following infliximab plus methotrexate therapy in patients with early rheumatoid arthritis. J Rheumatol. 2007 Jul;34(7):1465-74.
- 356. Wailoo A, Brennan A, Bansback N, et al. Modeling the cost effectiveness of etanercept, adalimumab and anakinra compared to infliximab in the treatment of patients with rheumatoid arthritis in the Medicare program. AHRQ Technology Assessment Program. 2006.
- 357. Wallis RS, Broder MS, Wong JY, et al. Granulomatous infectious diseases associated with tumor necrosis factor antagonists. Clin Infect Dis. 2004 May 1;38(9):1261-5.
- 358. Walters SJ, Brazier JE. What is the relationship between the minimally important difference and health state utility values? The case of the SF-6D. Health Qual Life Outcomes 2003;14.
- 359. Ware JE, Jr., Kosinski M, Bayliss MS, et al. Comparison of methods for the scoring and statistical analysis of SF-36 health profile and summary measures: summary of results from the Medical Outcomes Study. Med Care. 1995 Apr;33(4 Suppl):AS264-79.
- Ware JE, Jr., Sherbourne CD. The MOS 36-item short-form health survey (SF-36). I.
 Conceptual framework and item selection.
 Med Care. 1992 Jun;30(6):473-83.

- 361. Ware JE, Snow KK, Kosinski M, et al. SF-36® Health Survey Manual and Interpretation Guide. 1993.
- 362. Weinblatt ME, Bathon JM, Kremer JM, et al. Safety and efficacy of etanercept beyond 10 years of therapy in North American patients with early and long-standing rheumatoid arthritis. Arthritis Care Res (Hoboken) 2010.
- 363. Weinblatt ME, Keystone EC, Furst DE, et al. Long term efficacy and safety of adalimumab plus methotrexate in patients with rheumatoid arthritis: ARMADA 4 year extended study. Ann Rheum Dis. 2006 Jun;65(6):753-9.
- 364. Weinblatt ME, Kremer JM, Coblyn JS, et al. Pharmacokinetics, safety, and efficacy of combination treatment with methotrexate and leflunomide in patients with active rheumatoid arthritis. Arthritis Rheum. 1999 Jul;42(7):1322-8.
- 365. Wells GA, Sultan SA, Chen L. Indirect evidence: Indirect treatment comparisons in meta-analysis. Ottawa (ON): Canadian Agency for Drugs and Technologies in Health. 2009.
- 366. Wells GA, Tugwell P, Kraag GR, et al. Minimum important difference between patients with rheumatoid arthritis: the patient's perspective. J Rheumatol 1993;20(3):557-60.
- 367. Welton NJ, Caldwell DM, Adamopoulos E, et al. Mixed treatment comparison meta-analysis of complex interventions: psychological interventions in coronary heart disease. Am J Epidemiol 2009;169(9):1158-65.
- 368. Westhovens R, Cole JC, Li T, et al.
 Improved health-related quality of life for rheumatoid arthritis patients treated with abatacept who have inadequate response to anti-TNF therapy in a double-blind, placebocontrolled, multicentre randomized clinical trial. Rheumatology (Oxford). 2006
 Oct;45(10):1238-46.
- 369. Whitehead A. Meta-analysis of controlled clinical trials. Chichester, UK: John Wiley & Sons, Ltd.; 2002.

- 370. Willkens RF, Williams HJ, Ward JR, et al. Randomized, double-blind, placebo controlled trial of low-dose pulse methotrexate in psoriatic arthritis. Arthritis Rheum 1984;27(4):376-81.
- 371. Wood AJ. Thrombotic thrombocytopenic purpura and clopidogrel--a need for new approaches to drug safety. N Engl J Med. 2000 Jun 15;342(24):1824-6.
- 372. Woolacott N, Bravo Vergel Y, Hawkins N, et al. Etanercept and infliximab for the treatment of psoriatic arthritis: a systematic review and economic evaluation. Health Technol Assess. 2006 Sep;10(31):1-258.
- 373. Yamamoto M, Takahashi H, Ohara M, et al. A new conceptualization for Mikulicz's disease as an IgG4-related plasmacytic disease. Mod Rheumatol. 2006;16(6):335-40.
- 374. Yamanaka H, Inoue E, Tanaka E, et al. Influence of methotrexate dose on its efficacy and safety in rheumatoid arthritis patients: Evidence based on the variety of prescribing approaches among practicing Japanese rheumatologists in a single institute-based large observational cohort (IORRA). Modern Rheumatology. 2007;17(2):98-105.
- 375. Yelin E. Work disability in rheumatic diseases. Current Opinion in Rheumatology. 2007;19(2):91-6.
- 376. Young MS, Furfaro N. The rheumatology/dermatology collaboration. Dermatol Nurs. 2006 Oct;Suppl:10-22.
- 377. Zachariae H, Zachariae R, Blomqvist K, et al. Quality of life and prevalence of arthritis reported by 5,795 members of the Nordic Psoriasis Associations. Data from the Nordic Quality of Life Study. Acta Derm Venereol. 2002;82(2):108-13.
- 378. Zhao LK, Liao ZT, Li CH, et al. Evaluation of quality of life using ASQoL questionnaire in patients with ankylosing spondylitis in a Chinese population. Rheumatol Int. 2007 May;27(7):605-11.

379. Zink A, Strangfeld A, Schneider M, et al. Effectiveness of tumor necrosis factor inhibitors in rheumatoid arthritis in an observational cohort study: comparison of

patients according to their eligibility for major randomized clinical trials. Arthritis Rheum. 2006 Nov;54(11):3399-407.

.

Reference Source: EMBASE

- 1. Abrahamian H, Endler G, Exner M, et al.
 Association of low-grade inflammation with
 nephropathy in type 2 diabetic patients: role
 of elevated CRP-levels and 2 different genepolymorphisms of proinflammatory
 cytokines. Experimental and clinical
 endocrinology & diabetes: official journal,
 German Society of Endocrinology [and]
 German Diabetes Association 2007(1):3841
- 2. Abrahamyan L, Beyene J, Feng J, et al. Response times follow lognormal or gamma distribution in arthritis patients. Journal of Clinical Epidemiology. 2010;63(12):1363-9.
- 3. Accardo S, Seriolo B, Samanta E, et al. Controlled-Release Naproxen in Rheumatoid Arthritis. CURR THER RES CLIN EXP. 1991;49I(6):936-42.
- 4. Adams J, Burridge J, Mullee M, et al. The clinical effectiveness of static resting splints in early rheumatoid arthritis: A randomized controlled trial. Rheumatology. 2008;47(10):1548-53.
- 5. Agnew-Blais JC, Coblyn JS, Katz JN, et al. Measuring quality of care for rheumatic diseases using an electronic medical record. Annals of the Rheumatic Diseases. 2009;68(5):680-4.
- 6. Aguilar-Chavez EA, Gamez-Nava JI, Lopez-Olivo MA, et al. Circulating leptin and bone mineral density in rheumatoid arthritis. Journal of Rheumatology. 2009;36(3):512-6.
- 7. Ahern MJ, Wetherall M, Leslie A, et al. A Comparison of Ketoprofen Sr and Sulindac in the Elderly With Rheumatoid Arthritis. Br J Clin Pract. 1992;46(4):229-33.
- 8. Alarcon G, Castaneda O, Nair M, et al. Controlled Trial of Methotrexate Versus 10-Deazaaminopterin in the Treatment of Rheumatoid Arthritis. Ann Rheum Dis. 1992;51(5):600-3.
- 9. Alarcon GS, Castaneda O, Ferrandiz M, et al. Efficacy and Safety of 10-Deazaaminopterin in the Treatment of

- Rheumatoid Arthritis. A One-Year Continuation, Double-Blind Study. Arthritis Rheum. 1992;35(11):1318-21.
- 10. Alarcon I, Moreland G, Jaffe L, et al. The Use of Methotrexate Perioperatively in Patients With Rheumatoid Arthritis Undergoing Major Joint Replacement Surgery: Will We Ever Have Consensus About Its Use? J Clin Rheumatol. 1996;2(1):6-8.
- 11. Albert DA, Huang G, Dubrow G, et al. Criteria for Improvement in Rheumatoid Arthritis: Alternatives to the American College of Rheumatology 20. J Rheumatol. 2004;31(5):856-66.
- 12. Aletaha D, Smolen J, Ward MM. Measuring function in rheumatoid arthritis: Identifying reversible and irreversible components.

 Arthritis and Rheumatism. 2006;54(9):2784-92.
- 13. Ali ML, Alam MN, Haq SA, et al. Efficacy of Methotrexate in Rheumatoid Arthritis. Bangladesh Medical Research Council bulletin. 1997;23(3):72-6.
- 14. Allen ZA, Shanahan EM, Crotty M. Does suprascapular nerve block reduce shoulder pain following stroke: A double-blind randomised controlled trial with masked outcome assessment. BMC Neurology. 2010:10.
- 15. Almarzouqi M, Scarsbrook D, Klinkhoff A. Gold therapy in women planning pregnancy: Outcomes in one center. Journal of Rheumatology. 2007;34(9):1827-31.
- 16. Alten R, Doring G, Cutolo M, et al. Hypothalamus-pituitary-adrenal axis function in patients with rheumatoid arthritis treated with nighttime-release prednisone. Journal of Rheumatology. 2010;37(10):2025-31.
- Alten R, Gromnica-Ihle E, Pohl C, et al. Inhibition of Leukotriene B4-Induced Cd11b/Cd18 (Mac-1) Expression by Biil 284, a New Long Acting Ltb4 Receptor Antagonist, in Patients With Rheumatoid

- Arthritis. Annals of the rheumatic diseases. 2004;63(2):170-6.
- 18. Alten RE, Zerbini C, Jeka S, et al. Efficacy and safety of pamapimod in patients with active rheumatoid arthritis receiving stable methotrexate therapy. 2010.
- 19. Anaya JM, Fabre D, Bressolle F, et al. Effect of Etodolac on Methotrexate Pharmacokinetics in Patients With Rheumatoid Arthritis. The Journal of rheumatology. 1994;21(2):293-8.
- Anders HJ, Rihl M, Loch O, et al. Prediction of Creatinine Clearance From Serum
 Creatinine in Patients With Rheumatoid Arthritis: Comparison of Six Formulae and One Nomogram. Clinical rheumatology. 2000;19(1):26-9.
- 21. Andersen LS, Hansen EL, Knudsen JB, et al. Prospectively Measured Red Cell Folate Levels in Methotrexate Treated Patients With Rheumatoid Arthritis: Relation to Withdrawal and Side Effects. The Journal of rheumatology. 1997;24(5):830-7.
- 22. Anderson JJ, O'Neill A, Woodworth T, et al. Health Status Response of Rheumatoid Arthritis to Treatment With Dab486il-2. Arthritis care and research: the official journal of the Arthritis Health Professions Association. 1996;9(2):112-9.
- 23. Anderson KO, Bradley LA, Turner RA, et al. Pain Behavior of Rheumatoid Arthritis Patients Enrolled in Experimental Drug Trials. Arthritis care and research: the official journal of the Arthritis Health Professions Association. 1994;7(2):64-8.
- 24. Andrianakos A, Trontzas P, Christoyannis F, et al. Prevalence and management of rheumatoid arthritis in the general population of Greece The ESORDIG study. Rheumatology. 2006;45(12):1549-54.
- 25. Antoni C, Kalden J. Combination Therapy of the Chimeric Monoclonal Anti-Tumor Necrosis Factor Alpha Antibody (Infliximab) With Methotrexate in Patients With Rheumatoid Arthritis. Clinical and experimental rheumatology. 1999;17(6 Suppl 18):S73-7.

- 26. Appel H, Mertz A, Distler A, et al. The 19 Kda Protein of Yersinia Enterocolitica O:3 Is Recognized on the Cellular and Humoral Level by Patients With Yersinia Induced Reactive Arthritis. J Rheumatol 1999 Sep;26(9):1964-71. 1999;26(9):1964-71.
- 27. April P, Abeles M, Baraf H, et al. Does the Acetyl Group of Aspirin Contribute to the Antiinflammatory Efficacy of Salicylic Acid in the Treatment of Rheumatoid Arthritis? Seminars in arthritis and rheumatism. 1990;19(4 Suppl 2):20-8.
- 28. Arborelius MJ, Konttinen YT, Nordstrom DC, et al. Gly-X-Y Repeat Sequences in the Treatment of Active Rheumatoid Arthritis. Rheumatology international. 1999;18(4):129-35.
- Arendt-Nielsen L, Drewes AM, Svendsen L, et al. Quantitative Assessment of Joint Pain Following Treatment of Rheumatoid Arthritis With Ibuprofen Cream.
 Scandinavian journal of rheumatology.
 1994;23(6):334-7.
- 30. Arnold MH, O'Callaghan J, McCredie M, et al. Comparative Controlled Trial of Low-Dose Weekly Methotrexate Versus Azathioprine in Rheumatoid Arthritis: 3-Year Prospective Study. British journal of rheumatology. 1990;29(2):120-5.
- 31. Arvidson NG, Gudbjornsson B, Larsson A, et al. The Timing of Glucocorticoid Administration in Rheumatoid Arthritis. Annals of the rheumatic diseases. 1997;56(1):27-31.
- 32. Aryaeian N, Shahram F, Djalali M, et al. Effect of conjugated linoleic acids, vitamin E and their combination on the clinical outcome of Iranian adults with active rheumatoid arthritis. International Journal of Rheumatic Diseases. 2009;12(1):20-8.
- 33. Asahina A, Nakagawa H, Etoh T, et al. Adalimumab in Japanese patients with moderate to severe chronic plaque psoriasis: Efficacy and safety results from a Phase II/III randomized controlled study. Journal of Dermatology. 2010;37(4):299-310.
- 34. Assous N, Gossec L, Dougados M, et al. Efficacy of rituximab in patients with

- rheumatoid arthritis refractory or with contra-indication to anti-tumor necrosis factor-alpha drugs in daily practice: An open label observational study [3]. Clinical and Experimental Rheumatology. 2007;25(3).
- 35. Astrauskiene D. Efficacy of Empirically Prescribed Amoxicillin and Amoxicillin + Clavulanic Acid in Children's Reactive Arthritis: a Randomised Trial. Clinical and experimental rheumatology. 2003;21(4):515-21.
- 36. Atkinson M, Khanna V, Menard H, et al. A Comparison of Tenoxicam and Piroxicam in the Treatment of Rheumatoid Arthritis. The Journal of rheumatology. 1992;19(4):538-42.
- 37. Atkinson MH, Buchanan WW, Fitzgerald AA, et al. A Comparison of Flurbiprofen and Naproxen in the Treatment of Rheumatoid Arthritis: a Canadian Multi-Centre Study. Current medical research and opinion. 1990;12(2):76-85.
- 38. Azuma T, Oishi M, Takei M, et al. Tacrolimus-related nocturnal myoclonus of the lower limbs in elderly patients with rheumatoid arthritis. Modern Rheumatology. 2007;17(3):247-50.
- 39. Bacon P, Luqmani RA, Bossingham DH, et al. A Comparison of Two Formulations of Indomethacin ('flexin Continus' Tablets and 'indocid' Capsules) in the Treatment of Rheumatoid Arthritis. Current medical research and opinion. 1990;12(2):128-34.
- 40. Baerwald C, Goebel KM, Krause A, et al. A randomized controlled trial of ciamexon versus placebo in the immunomodulatory treatment of rheumatoid arthritis. Arthritis Rheum. 1990 May;33(5):733-8.
- 41. Bagge E, Geijer M, Tarkowski A. Intra-Articular Administration of Polyclonal Immunoglobulin G in Rheumatoid Arthritis. A Double-Blind, Placebo-Controlled Pilot Study. Scandinavian journal of rheumatology. 1996;25(3):174-6.
- 42. Bahadori B, Uitz E, Thonhofer R, et al. (omega)-3 fatty acids infusions as adjuvant therapy in rheumatoid arthritis. Journal of

- Parenteral and Enteral Nutrition. 2010;34(2):151-5.
- 43. Bakker MF, Jacobs JWG, Welsing PMJ, et al. Are switches from oral to subcutaneous methotrexate or addition of ciclosporin to methotrexate useful steps in a tight control treatment strategy for rheumatoid arthritis? A post hoc analysis of the CAMERA study. Annals of the rheumatic diseases. 2010;69(10):1849-52.
- 44. Barnett ML, Kremer JM, St Clair EW, et al. Treatment of Rheumatoid Arthritis With Oral Type Ii Collagen. Results of a Multicenter, Double-Blind, Placebo-Controlled Trial. Arthritis and rheumatism. 1998;41(2):290-7.
- 45. Barrera P, Boerbooms AM, Demacker PN, et al. Circulating Soluble Tumor Necrosis Factor Receptors, Interleukin-2 Receptors, Tumor Necrosis Factor Alpha, and Interleukin-6 Levels in Rheumatoid Arthritis. Longitudinal Evaluation During Methotrexate and Azathioprine Therapy. Arthritis and rheumatism. 1994;33(11):1017-24.
- 46. Barrera P, Haagsma C, Boerbooms A, et al. Effect of Methotrexate Alone or in Combination With Sulphasalazine on the Production and Circulating Concentrations of Cytokines and Their Antagonists.

 Longitudinal Evaluation in Patients With Rheumatoid Arthritis. British journal of rheumatology. 1995;34(8):747-55.
- 47. Barrera P, Joosten LA, den Broeder AA, et al. Effects of Treatment With a Fully Human Anti-Tumour Necrosis Factor Alpha Monoclonal Antibody on the Local and Systemic Homeostasis of Interleukin 1 and Tnfalpha in Patients With Rheumatoid Arthritis. Annals of the rheumatic diseases. 2001;60(7):660-9.
- 48. Barrera P, van der Maas A, van Ede AE, et al. Drug Survival, Efficacy and Toxicity of Monotherapy With a Fully Human Anti-Tumour Necrosis Factor-a Antibody Compared With Methotrexate in Long-Standing Rheumatoid Arthritis. Rheumatology 2002;41(4):430-9.

- 49. Baslund B, Tvede N, Danneskiold-Samsoe B, et al. Targeting Interleukin-15 in Patients With Rheumatoid Arthritis: a Proof-of-Concept Study. Arthritis and rheumatism. 2005;52(9):2686-92.
- Bateman J, Penfold R, Rigby SP. Comment on: Kidney disease in RA patients: Prevalence and implication on RA-related drugs management: The MATRIX study. Rheumatology. 2008;47(8).
- 51. Battistone MJ, Manaster BJ, Reda DJ, et al. The Prevalence of Sacroilitis in Psoriatic Arthritis: New Perspectives From a Large, Multicenter Cohort. A Department of Veterans Affairs Cooperative Study. Skeletal radiology. 1999;28(4):196-201.
- 52. Bazzani C, Filippini M, Caporali R, et al. Anti-TNFalpha therapy in a cohort of rheumatoid arthritis patients: Clinical outcomes. Autoimmunity Reviews 2009;8(3):260-5.
- 53. Beard AJ, Sleath B, Blalock SJ, et al. Predictors of rheumatoid arthritis patient-physician communication about medication costs during visits to rheumatologists.

 Arthritis Care and Research.
 2010;62(5):632-9.
- 54. Bejarano V, Conaghan PG, Proudman SM, et al. Long-term efficacy and toxicity of ciclosporin A in combination with methotrexate in poor prognosis rheumatoid arthritis. Annals of the Rheumatic Diseases. 2009;68(5):761-3.
- 55. Bejarano V, Conaghan PG, Quinn MA, et al. Benefits 8 years after a remission induction regime with an infliximab and methotrexate combination in early rheumatoid arthritis. Rheumatology. 2010;49(10):1971-4.
- 56. Benenson E, Timina O. Prospidine Versus Methotrexate Pulse in Highly Active Rheumatoid Arthritis: a Controlled 6-Month Clinical Trial. Clinical rheumatology. 1994;13(1):54-9.
- 57. Bengtsson A, Bengtsson M, Nilsson I, et al. Effects of Intravenous Regional Administration of Methylprednisolone Plus Mepivacaine in Rheumatoid Arthritis.

- Scandinavian journal of rheumatology. 1998;27(4):277-80.
- 58. Benitha R, Tikly M. Functional disability and health-related quality of life in South Africans with rheumatoid arthritis and systemic lupus erythematosus. Clinical Rheumatology. 2007;26(1):24-9.
- 59. Bensen W, Weaver A, Espinoza L, et al. Efficacy and Safety of Valdecoxib in Treating the Signs and Symptoms of Rheumatoid Arthritis: a Randomized, Controlled Comparison With Placebo and Naproxen. Rheumatology (Oxford). 2002;41(9):1008-16.
- 60. Berliner MN, Giesecke T, Bornhovd KD. Impact of transdermal fentanyl on quality of life in rheumatoid arthritis. Clinical Journal of Pain. 2007;23(6):530-4.
- 61. Bianchi L, Giunta A, Papoutsaki M, et al. Efficacy and safety of long-term infliximab therapy in moderate to severe psoriasis and psoriatic arthritis. Giornale Italiano di Dermatologia e Venereologia. 2006;141(1):73-8.
- 62. Bianchi Porro G, Montrone F, Lazzaroni M, et al. Clinical and Gastroscopic Evaluation of Amtolmetin Guacyl Versus Diclofenac in Patients With Rheumatoid Arthritis. Ital J Gastroenterol Hepatol. 1999;31(5):378-85.
- 63. Bingham ICO, Looney RJ, Deodhar A, et al. Immunization responses in rheumatoid arthritis patients treated with rituximab: Results from a controlled clinical trial. 2010.
- 64. Bird H, Broggini M. Paroxetine Versus Amitriptyline for Treatment of Depression Associated With Rheumatoid Arthritis: a Randomized, Double Blind, Parallel Group Study. The Journal of rheumatology. 2000;27(12):2791-7.
- 65. Blackburn WDJ, Prupas HM, Silverfield JC, et al. Tenidap in Rheumatoid Arthritis. A 24-Week Double-Blind Comparison With Hydroxychloroquine-Plus-Piroxicam, and Piroxicam Alone. Arthritis and rheumatism. 1995;38(10):1447-56.

- 66. Bluhm GB, Sharp JT, Tilley BC, et al. Radiographic Results From the Minocycline in Rheumatoid Arthritis (Mira) Trial. The Journal of rheumatology. 1997;24(7):1295-302.
- 67. Bombardier C, Laine L, Reicin A, et al. Comparison of upper gastrointestinal toxicity of rofecoxib and naproxen in patients with rheumatoid arthritis. VIGOR Study Group. N Engl J Med. 2000;343(21):1520-8.
- 68. Bombardier C, Peloso P, Goldsmith C. Salsalate, a Nonacetylated Salicylate, Is as Efficacious as Diclofenac in Patients With Rheumatoid Arthritis. Salsalate-Diclofenac Study Group. The Journal of rheumatology. 1995;22(4):617-24.
- 69. Bonilla E, Lee YY, Phillips PE, et al. Hypoglycaemia after initiation of treatment with etanercept in a patient with type 2 diabetes mellitus [5]. Annals of the Rheumatic Diseases. 2007;66(12).
- 70. Borg AA, Davis MJ, Fowler PD, et al. Rifampicin in Early Rheumatoid Arthritis. Scandinavian journal of rheumatology. 1993;22(2):39-42.
- 71. Borg G, Allander E, Berg E, et al. Auranofin Treatment in Early Rheumatoid Arthritis May Postpone Early Retirement. Results From a 2-Year Double Blind Trial. The Journal of rheumatology. 1991;18(7):1015-20
- 72. Borrs-Blasco J, Gracia-Prez A, Rosique-Robles JD, et al. Acceptability of switching adalimumab from a prefilled syringe to an autoinjection pen. Expert Opinion on Biological Therapy. 2010;10(3):301-7.
- 73. Bos WH, Dijkmans BAC, Boers M, et al. Effect of dexamethasone on autoantibody levels and arthritis development in patients with arthralgia: A randomised trial. Annals of the rheumatic diseases. 2010;69(3):571-4.
- 74. Bourikas LA, Sidiropoulos PI, Goulielmos GN, et al. Concomitant onset of Graves disease and rheumatoid arthritis after a serious life event [5]. Journal of Clinical Rheumatology. 2006;12(6):326-7.

- 75. Bradley JD, Dmitrienko AA, Kivitz AJ, et al. A Randomized, Double-Blinded, Placebo-Controlled Clinical Trial of Ly333013, a Selective Inhibitor of Group Ii Secretory Phospholipase A2, in the Treatment of Rheumatoid Arthritis. The Journal of rheumatology. 2005;32(3):417-23
- 76. Breedveld FC, Han C, Bala M, et al. Association Between Baseline Radiographic Damage and Improvement in Physical Function After Treatment of Patients With Rheumatoid Arthritis. Annals of the rheumatic diseases. 2005;64(1):52-5.
- 77. Bressolle F, Kinowski J, Morel J, et al. Folic Acid Alters Methotrexate Availability in Patients With Rheumatoid Arthritis. The Journal of rheumatology. 2000;27(9):2110-4.
- 78. Bridges Jr SL, Causey ZL, Burgos PI, et al. Radiographic severity of rheumatoid arthritis in African Americans: Results from a multicenter observational study. Arthritis Care and Research. 2010;62(5):624-31.
- 79. Brooks PJ, Spruill WJ, Parish RC, et al. Pharmacokinetics of Methotrexate Administered by Intramuscular and Subcutaneous Injections in Patients With Rheumatoid Arthritis. Arthritis & Rheumatism. 1990;33(1):91-4.
- 80. Buchanan WW, Kean WF, St-Jean J, et al. Clinical Evaluation of a Sustained Release Compared to a Standard Formulation of Tiaprofenic Acid (Surgam (R)) in Rheumatoid Arthritis: a Canadian Multicenter Study. J RHEUMATOL. 1991;18(7):1046-54.
- 81. Buckley L, Vacek P, Cooper S.
 Administration of Folinic Acid After Low
 Dose Methotrexate in Patients With
 Rheumatoid Arthritis. The Journal of
 rheumatology. 1990;17(9):1158-61.
- 82. Cacace E, Anedda C, Ruggiero V, et al. Etanercept in rheumatoid arthritis: Long term anti-inflammatory efficacy in clinical practice. European Journal of Inflammation. 2006;4(3):171-6.

- 83. Caldwell J. Comparison of the Efficacy, Safety, and Pharmacokinetic Profiles of Extended-Release Ketoprofen and Piroxicam in Patients With Rheumatoid Arthritis. Clinical therapeutics. 1994;16(2):222-35.
- 84. Calguneri M, Pay S, Caliskaner Z, et al. Combination Therapy Versus Monotherapy for the Treatment of Patients With Rheumatoid Arthritis. Clinical and experimental rheumatology. 1999;17(6):699-704.
- 85. Camp NJ, Cox A, di Giovine FS, et al. Evidence of a Pharmacogenomic Response to Interleukin-L Receptor Antagonist in Rheumatoid Arthritis. Genes Immun. 2005;6(6):467-71.
- 86. Cannon GW, Reading JC, Ward JR, et al. Clinical and Laboratory Outcomes During the Treatment of Rheumatoid Arthritis With Methotrexate. Scandinavian journal of rheumatology. 1990;19(4):285-94.
- 87. Cantatore F, Acquista C, Pipitone V. Evaluation of Bone Turnover and Osteoclastic Cytokines in Early Rheumatoid Arthritis Treated With Alendronate. The Journal of rheumatology. 1999;41(3):247-51.
- 88. Capell H, Maiden N, Madhok R, et al. Intention-to-Treat Analysis of 200 Patients With Rheumatoid Arthritis 12 Years After Random Allocation to Either Sulfasalazine or Penicillamine. The Journal of rheumatology. 1998;25(10):1880-6.
- 89. Capell H, Marabani M, Madhok R, et al.
 Degree and Extent of Response to
 Sulphasalazine or Penicillamine Therapy for
 Rheumatoid Arthritis: Results From a
 Routine Clinical Environment Over a TwoYear Period. The Quarterly journal of
 medicine. 1990;75(276):335-44.
- 90. Caperton E, Heim Duthoy K, Matzke G, et al. Ceftriaxone Therapy of Chronic Inflammatory Arthritis. A Double-Blind Placebo Controlled Trial. Archives of internal medicine. 1990;150(8):1677-82.
- 91. Carmichael S, Beal J, Day R, et al.
 Combination Therapy With Methotrexate

- and Hydroxychloroquine for Rheumatoid Arthritis Increases Exposure to Methotrexate. The Journal of rheumatology. 2002;29(10):2077-83.
- 92. Carpenter M, West S, Vogelgesang S, et al. Postoperative joint infections in rheumatoid arthritis patients on methotrexate therapy. Orthopedics. 1996;19(3):207-10.
- 93. Carpentier N, Bertin P, Marquet P, et al. Is There an Optimal Time to Administer Methotrexate in the Treatment of Rheumatoid Arthritis? The Journal of rheumatology. 1998;25(7):1270-5.
- 94. Cavazzana I, Franceschini F, Quinzanini M, et al. Anti-Ro/SSA antibodies in rheumatoid arthritis: Clinical and immunologic associations. Clinical and Experimental Rheumatology. 2006;24(1):59-64.
- 95. Cazzola M, Antivalle M, Sarzi Puttini P, et al. Oral Type Ii Collagen in the Treatment of Rheumatoid Arthritis. A Six-Month Double Blind Placebo-Controlled Study. Clinical and experimental rheumatology. 2000;18(5):571-7.
- 96. Chan FKL, Hung LCT, Suen BY, et al. Celecoxib versus diclofenac plus omeprazole in high-risk arthritis patients: results of a randomized double-blind trial. Gastroenterology. 2004;127(4):1038-43.
- 97. Chan G, Goh F, Hodgson T, et al. Outpatient follow-up for patients with rheumatoid arthritis in relation to New Zealand Rheumatology Association guidelines at Dunedin Hospital. New Zealand Medical Journal. 2008;121(1274):34-41.
- 98. Chandrashekara S, Syed M, Swapna R. Is three selected parameters adequate to monitor rheumatoid arthritis? Clinical Rheumatology. 2007;26(6):911-4.
- 99. Chard M, Crisp A. Astemizole, an H1
 Antagonist, Has No Additional Therapeutic
 Effect in Rheumatoid Arthritis. The Journal
 of rheumatology. 1991;18(2):203-4.
- 100. Charles P, Elliott MJ, Davis D, et al. Regulation of Cytokines, Cytokine Inhibitors, and Acute-Phase Proteins

- Following Anti-Tnf-Alpha Therapy in Rheumatoid Arthritis. Journal of immunology (Baltimore, Md: 1950). 1999;163(3):1521-8.
- 101. Chen DY, Chou SJ, Hsieh TY, et al.
 Randomized, double-blind, placebocontrolled, comparative study of human
 anti-TNF antibody adalimumab in
 combination with methotrexate and
 methotrexate alone in Taiwanese patients
 with active rheumatoid arthritis. 2009.
- 102. Chiang E, Selhub J, Bagley P, et al.
 Pyridoxine Supplementation Corrects
 Vitamin B6 Deficiency but Does Not
 Improve Inflammation in Patients With
 Rheumatoid Arthritis. Arthritis Res Ther.
 2005;7(6):R1404-11.
- 103. Chijiwa T, Nishiya K, Hashimoto K. Serum Transferrin Receptor Levels in Patients With Rheumatoid Arthritis Are Correlated With Indicators for Anaemia. Clinical rheumatology. 2001;20(5):307-13.
- 104. Chong BF, Wong HK. Treatment of psoriasis with etanercept in a patient with a history of primary B-cell lymphoma.
 Clinical and Experimental Dermatology. 2009;34(5):e11-e3.
- 105. Choy EH, Kingsley GH, Khoshaba B, et al. A Two Year Randomised Controlled Trial of Intramuscular Depot Steroids in Patients With Established Rheumatoid Arthritis Who Have Shown an Incomplete Response to Disease Modifying Antirheumatic Drugs. Ann Rheum Dis. 2005;64(9):1288-93.
- 106. Choy EHS, Scott DL, Kingsley GH, et al. Treating Rheumatoid Arthritis Early With Disease Modifying Drugs Reduces Joint Damage: a Randomised Double Blind Trial of Sulphasalazine Vs Diclofenac Sodium. Clinical and experimental rheumatology. 2002;20(3):351-8.
- 107. Christensen AF, Lottenburger T, Lindegaard H, et al. Differential association of the N-propeptide of collagen IIA (PIIANP) and collagen II C-telopeptide (CTX-II) with synovitis and erosions in early and longstanding rheumatoid arthritis. Clinical and Experimental Rheumatology. 2009;27(2):307-14.

- 108. Ciconelli R, Ferraz M, Visioni R, et al. A Randomized Double-Blind Controlled Trial of Sulphasalazine Combined With Pulses of Methylprednisolone or Placebo in the Treatment of Rheumatoid Arthritis. British journal of rheumatology. 1996;35(2):150-4.
- 109. Claessen SJJ, Hazes JMW, Huisman MAM, et al. Use of risk stratification to target therapies in patients with recent onset arthritis; Design of a prospective randomized multicenter controlled trial. 2009.
- 110. Clark P, Casas E, Tugwell P, et al. Hydroxychloroquine Compared With Placebo in Rheumatoid Arthritis. A Randomized Controlled Trial. Annals of internal medicine. 1993;119(11):1067-71.
- 111. Clegg DO, Reda DJ, Weisman MH, et al. Comparison of Sulfasalazine and Placebo in the Treatment of Psoriatic Arthritis. A Department of Veterans Affairs Cooperative Study. Arthritis and rheumatism. 1996;39(12):2021-7.
- 112. Cohen G, Gossec L, Dougados M, et al. Radiological damage in patients with rheumatoid arthritis on sustained remission. Annals of the Rheumatic Diseases. 2007;66(3):358-63.
- 113. Cohen S, Cannon G, Schiff M, et al. Two-Year, Blinded, Randomized, Controlled Trial of Treatment of Active Rheumatoid Arthritis With Leflunomide Compared With Methotrexate. Utilization of Leflunomide in the Treatment of Rheumatoid Arthritis Trial Investigator Group. Arthritis and rheumatism. 2001;44(9):1984-92.
- 114. Cohen S, Zwillich SH, Chow V, et al. Coadministration of the JAK inhibitor CP-690,550 and methotrexate is well tolerated in patients with rheumatoid arthritis without need for dose adjustment. British Journal of Clinical Pharmacology. 2010;69(2):143-51.
- 115. Cohen SB, Emery P, Greenwald MW, et al.
 Rituximab for rheumatoid arthritis refractory
 to anti-tumor necrosis factor therapy:
 Results of a multicenter, randomized,
 double-blind, placebo-controlled, phase III
 trial evaluating primary efficacy and safety

- at twenty-four weeks. Arthritis and Rheumatism 2006;54(9):2793-806.
- 116. Cojocaru L, Rusali A, Craiu E, et al. The efficacy and safety of simvastatin in patients with rheumatoid arthritis. Archives of the Balkan Medical Union. 2010;45(1):49-53.
- 117. Colombel JF, Sandborn WJ, Rutgeerts P, et al. Adalimumab for maintenance of clinical response and remission in patients with Crohn's disease: the CHARM trial.

 Gastroenterology 2007(1):52-65.
- 118. Combe B, Goupille P, Kuntz J, et al. Sulphasalazine in Psoriatic Arthritis: a Randomized, Multicentre, Placebo-Controlled Study. British journal of rheumatology. 1996;35(7):664-8.
- 119. Combe B, Velicitat P, Garzon N, et al.
 Comparison of Intramuscular and Oral
 Meloxicam in Rheumatoid Arthritis
 Patients. Inflammation research: official
 journal of the European Histamine Research
 Society [et al]. 2001;50(Suppl 1):S10-6.
- 120. Cordero OJ, Salgado FJ, Mera-Varela A, et al. Serum Interleukin-12, Interleukin-15, Soluble Cd26, and Adenosine Deaminase in Patients With Rheumatoid Arthritis. Rheumatology international. 2001;21(2):69-74.
- 121. Corkill MM, Kirkham BW, Chikanza IC, et al. Intramuscular Depot Methylprednisolone Induction of Chrysotherapy in Rheumatoid Arthritis: a 24-Week Randomized Controlled Trial. British journal of rheumatology. 1990;29(4):274-9.
- 122. Corvetta A, Della B, Luchetti M, et al.
 Tenoxicam and Ketoprofen Level
 Monitoring With High Performance Liquid
 Chromatography in Patients Affected by
 Rheumatoid Arthritis. CLIN EXP
 RHEUMATOL. 1991;9(2):143-8.
- 123. Courvoisier N, Dougados M, Cantagrel A, et al. Prognostic factors of 10-year radiographic outcome in early rheumatoid arthritis: A prospective study. Arthritis Research and Therapy. 2008;10(5).

- 124. Crowley B, Hamill J, Lyndon S, et al.
 Controlled-Release Indomethacin and
 Sustained-Release Diclofenac Sodium in the
 Treatment of Rheumatoid Arthritis: a
 Comparative Controlled Clinical Trial.
 Current medical research and opinion.
 1990;12(3):143-50.
- 125. Cush J, Jasin H, Johnson R, et al.
 Relationship Between Clinical Efficacy and
 Laboratory Correlates of Inflammatory and
 Immunologic Activity in Rheumatoid
 Arthritis Patients Treated With Nonsteroidal
 Antiinflammatory Drugs. Arthritis and
 rheumatism. 1990;33(5):623-33.
- 126. Cush J, Lipsky P, Postlethwaite A, et al. Correlation of Serologic Indicators of Inflammation With Effectiveness of Nonsteroidal Antiinflammatory Drug Therapy in Rheumatoid Arthritis. Arthritis & Rheumatism. 1990;33(1):19-28.
- 127. Dalbeth N, Yeoman S, Dockerty JL, et al. A Randomised Placebo Controlled Trial of Delipidated, Deglycolipidated Mycobacterium Vaccae as Immunotherapy for Psoriatic Arthritis. Annals of the rheumatic diseases. 2004;63(6):790-4.
- 128. Danis V, Franic G, Rathjen D, et al.
 Circulating Cytokine Levels in Patients
 With Rheumatoid Arthritis: Results of a
 Double Blind Trial With Sulphasalazine.
 Annals of the rheumatic diseases.
 1992;51(8):946-50.
- 129. Dawczynski C, Schubert R, Hein G, et al. Long-term moderate intervention with n-3 long-chain PUFA-supplemented dairy products: Effects on pathophysiological biomarkers in patients with rheumatoid arthritis. British Journal of Nutrition. 2009;101(10):1517-26.
- 130. de Boer IG, Peeters A, Ronday HK, et al. The usage of functional wrist orthoses in patients with rheumatoid arthritis. Disability and Rehabilitation. 2008;30(4):286-95.
- 131. De Graaf T, Van Ommen E, Van der Stelt M, et al. Effects of Low Dose Methotrexate Therapy on the Concentration and the Glycosylation of Alpha 1-Acid Glycoprotein in the Serum of Patients With Rheumatoid

- Arthritis: a Longitudinal Study. The Journal of rheumatology. 1994;21(12):2209-16.
- 132. Deighton CM, George E, Kiely PDW, et al. Updating the British Society for Rheumatology guidelines for anti-tumour necrosis factor therapy in adult rheumatoid arthritis (again). Rheumatology. 2006;45(6):649-52.
- 133. Dennison W, Loeser R, Turner R, et al. A
 Double Blind Placebo Controlled Trial of
 Low Dose Clotrimazole in Rheumatoid
 Arthritis. The Journal of rheumatology.
 1990;17(8):1003-7.
- 134. DeWitt EM, Glick HA, Albert DA, et al. Medicare coverage of tumor necrosis factor alpha inhibitors as an influence on physicians' prescribing behavior. Archives of Internal Medicine. 2006;166(1):57-63.
- 135. Di Munno O, Mazzantini M, Milani S, et al. Clinical Equivalence Between Deflazacort Oral Drops and Tablets in Active Rheumatoid Arthritis. Clinical rheumatology. 1999;18(2):140-4.
- 136. Dick W, Franchimont P, Veys E. Double-Blind Comparison of Etodolac and Piroxicam in the Treatment of Rheumatoid Arthritis. Clinical therapeutics. 1993;15(1):148-59.
- 137. Dimitrijevic M, Bartlett R. Leflunomide, a Novel Immunomodulating Drug, Inhibits Homotypic Adhesion of Peripheral Blood and Synovial Fluid Mononuclear Cells in Rheumatoid Arthritis. Inflammation research: official journal of the European Histamine Research Society [et al]. 1996;30(8):4132-3.
- 138. Dixon WG, Watson KD, Lunt M, et al.
 Reduction in the incidence of myocardial infarction in patients with rheumatoid arthritis who respond to anti-tumor necrosis factor alpha therapy: Results from the British Society for Rheumatology Biologics Register. Arthritis and Rheumatism 2007;56(9):2905-12.
- 139. Dooley MA, Cush JJ, Lipsky PE, et al. The Effects of Nonsteroidal Antiinflammatory Drug Therapy in Early Rheumatoid Arthritis on Serum Levels of Soluble Interleukin 2

- Receptor, Cd4, and Cd8. The Journal of rheumatology. 1993;20(11):1857-62.
- 140. Dore RK, Cohen SB, Lane NE, et al. Effects of denosumab on bone mineral density and bone turnover in patients with rheumatoid arthritis receiving concurrent glucocorticoids or bisphosphonates. Annals of the rheumatic diseases. 2010;69(5):872-5.
- 141. Dougados M, Combe B, Cantagrel A, et al. Combination Therapy in Early Rheumatoid Arthritis: a Randomised, Controlled, Double Blind 52 Week Clinical Trial of Sulphasalazine and Methotrexate Compared With the Single Components. Annals of the rheumatic diseases. 1999;58(4):220-5.
- 142. Drevlow BE, Lovis R, Haag MA, et al. Recombinant Human Interleukin-1 Receptor Type I in the Treatment of Patients With Active Rheumatoid Arthritis. Arthritis and rheumatism. 1996;39(2):257-65.
- 143. Drewes AM, Andreasen A, Jennum P, et al. Zopiclone as Night Medication in Rheumatoid Arthritis. Scandinavian journal of rheumatology. 1998;27(3):180-7.
- 144. Drosos AA, Tsifetaki N, Tsiakou EK, et al. Influence of Methotrexate on Radiographic Progression in Rheumatoid Arthritis: a Sixty-Month Prospective Study. Clinical and experimental rheumatology. 1997;15(3):263-7.
- 145. Duffy T, Belton O, Bresnihan B, et al.
 Inhibition of PGE2 Production by
 Nimesulide Compared With Diclofenac in
 the Acutely Inflamed Joint of Patients With
 Arthritis. Drugs. 2003;63(Suppl 1):31-6.
- 146. Dugina JL, Petrov VI, Babayeva AR, et al. A Randomized, Open-Label, Comparative, 6-Month Trial of Oral Ultra-Low Doses of Antibodies to Tumor Necrosis Factor-Alpha and Diclofenac in Rheumatoid Arthritis. Int J Tissue React. 2005;27(1):15-21.
- 147. Dupuis LL, Koren G, Shore A, et al. Methotrexate-Nonsteroidal Antiinflammatory Drug Interaction in Children With Arthritis. Journal of Rheumatology. 1990;17(11):1469-73.

- 148. Eastell R, Devogelaer JP, Peel NF, et al.
 Prevention of Bone Loss With Risedronate
 in Glucocorticoid-Treated Rheumatoid
 Arthritis Patients. Osteoporosis international
 : a journal established as result of
 cooperation between the European
 Foundation for Osteoporosis and the
 National Osteoporosis Foundation of the
 USA. 2000;11(4):331-7.
- 149. Eder L, Chandran V, Schentag CT, et al. Time and predictors of response to tumour necrosis factor-(alpha) blockers in psoriatic arthritis: An analysis of a longitudinal observational cohort. Rheumatology. 2010;49(7):1361-6.
- 150. Edwards JCW, Leandro MJ, Cambridge G. B Lymphocyte Depletion in Rheumatoid Arthritis: Targeting of Cd20. Curr Dir Autoimmun. 2005;1422(8):175-92.
- 151. Eggelmeijer F, Papapoulos S, van Paassen H, et al. Clinical and Biochemical Response to Single Infusion of Pamidronate in Patients With Active Rheumatoid Arthritis: a Double Blind Placebo Controlled Study. The Journal of rheumatology. 1994;21(11):2016-20.
- 152. Eggelmeijer F, Papapoulos SE, van Paassen HC, et al. Increased Bone Mass With Pamidronate Treatment in Rheumatoid Arthritis. Results of a Three-Year Randomized, Double-Blind Trial. Arthritis and rheumatism. 1996;39(3):396-402.
- 153. Egsmose C, Lund B, Borg G, et al. Patients With Rheumatoid Arthritis Benefit From Early 2nd Line Therapy: 5 Year Followup of a Prospective Double Blind Placebo Controlled Study. The Journal of rheumatology. 1995;22(12):2208-13.
- 154. Egsmose C, TM H, Andersen LS, et al. Limited Effect of Sulphasalazine Treatment in Reactive Arthritis. A Randomised Double Blind Placebo Controlled Trial. Annals of the rheumatic diseases. 1997;56(1):32-6.
- 155. Eichler HG, Mavros P, Geling O, et al.
 Association Between Health-Related
 Quality of Life and Clinical Efficacy
 Endpoints in Rheumatoid Arthritis Patients
 After Four Weeks Treatment With AntiInflammatory Agents. International journal

- of clinical pharmacology and therapeutics. 2005;43(5):209-16.
- 156. Elewski B, Leonardi C, Gottlieb AB, et al. Comparison of clinical and pharmacokinetic profiles of etanercept 25 mg twice weekly and 50 mg once weekly in patients with psoriasis. The British journal of dermatology 2007(1):138-42.
- 157. Emery P. Disease Modification in Rheumatoid Arthritis With Leflunomide. Scandinavian journal of rheumatology Supplement. 1999;112(9):9-14.
- 158. Emery P, Breedveld FC, Lemmel EM, et al. A Comparison of the Efficacy and Safety of Leflunomide and Methotrexate for the Treatment of Rheumatoid Arthritis. Rheumatology (Oxford). 2000;39(6):655-65.
- 159. Emery P, Clarke A, Williams P, et al.
 Nabumetone Compared With Naproxen in
 the Treatment of Rheumatoid Arthritis: a
 Multicenter, Double Blind, Randomized,
 Parallel Group Trial in Hospital Outpatients.
 The Journal of rheumatology Supplement.
 1992;36:41-7.
- 160. Emery P, Durez P, Dougados M, et al.
 Impact of T-cell costimulation modulation
 in patients with undifferentiated
 inflammatory arthritis or very early
 rheumatoid arthritis: A clinical and imaging
 study of abatacept (the ADJUST trial).
 Annals of the rheumatic diseases.
 2010;69(3):510-6.
- 161. Emery P, Genovese MC, Fleischmann RM, et al. Efficacy of Golimumab, a human anti-TNF(alpha) antibody, by baseline CRP level in patients with rheumatoid arthritis: Results from three phase 3, randomized, double-blind, placebo-controlled studies. Rheumatology 2010;49i101.
- 162. Emery P, Zeidler H, Kvien TK, et al.
 Celecoxib Versus Diclofenac in Long-Term
 Management of Rheumatoid Arthritis:
 Randomised Double-Blind Comparison.
 Lancet. 2000;354(9196):2106-11.
- 163. Ergun T, Inanc N, Tuney D, et al. Skin manifestations of rheumatoid arthritis: A study of 215 Turkish patients. International

- Journal of Dermatology. 2008;47(9):894-902.
- 164. Eriksson LO, Sturfelt G, Thysell H, et al. Effects of Sulindac and Naproxen on Prostaglandin Excretion in Patients With Impaired Renal Function and Rheumatoid Arthritis. The American journal of medicine. 1990;89(3):313-21.
- 165. Faarvang K, Egsmose C, Kryger P, et al. Hydroxychloroquine and Sulphasalazine Alone and in Combination in Rheumatoid Arthritis: a Randomised Double Blind Trial. Annals of the rheumatic diseases. 1993;52(10):711-5.
- 166. Fallatah HI, Akbar HO, Qari YA.
 Autoimmune hepatitis: Single-center experience of clinical presentation, response to treatment and prognosis in Saudi Arabia.
 Saudi Journal of Gastroenterology.
 2010;16(2):95-9.
- 167. Farr M, Kitas G, Waterhouse L, et al. Sulphasalazine in Psoriatic Arthritis: a Double-Blind Placebo-Controlled Study. British journal of rheumatology. 1990;29(1):46-0.
- 168. Fernandez A, Quintana G, Rondon F, et al. Lupus arthropathy: A case series of patients with rhupus. Clinical Rheumatology. 2006;25(2):164-7.
- 169. Ferraz MB, Pinheiro GR, Helfenstein M, et al. Combination Therapy With Methotrexate and Chloroquine in Rheumatoid Arthritis. A Multicenter Randomized Placebo-Controlled Trial. Scandinavian journal of rheumatology. 1994;23(5):231-6.
- 170. Fleischmann R. Safety and efficacy of etanercept in the elderly. Aging Health. 2006;2(2):189-97.
- 171. Flicinski J, Brzosko M, Olewniczak S. Multiple haemangiomas in a psoriatic arthritis patient treated with cyclosporine [13]. Acta Dermato Venereologica. 2006;86(3):271-2.
- 172. Foell D, Kane D, Bresnihan B, et al. Expression of the Pro-Inflammatory Protein S100a12 (En-Rage) in Rheumatoid and

- Psoriatic Arthritis. Rheumatology (Oxford). 2003;42(11):1383-9.
- 173. Foell D, Wulffraat N, Wedderburn LR, et al. Methotrexate withdrawal at 6 vs 12 months in juvenile idiopathic arthritis in remission a randomized clinical trial. JAMA Journal of the American Medical Association. 2010;303(13):1266-73.
- 174. Franck H, Ittel T, Tasch O, et al. Osteocalcin in Patients With Rheumatoid Arthritis. A One-Year Followup Study. The Journal of rheumatology. 1994;21(7):1256-9.
- 175. Fransen J, Visser K, Van Dongen H, et al. Validity of the disease activity score in undifferentiated arthritis. Arthritis Care and Research. 2010;62(10):1392-8.
- 176. Fraser AD, van Kuijk AWR, Westhovens R, et al. A Randomised, Double Blind, Placebo Controlled, Multicentre Trial of Combination Therapy With Methotrexate Plus Ciclosporin in Patients With Active Psoriatic Arthritis. Ann Rheum Dis. 2005;64(6):859-64.
- 177. Fraser S, Hopkins R, Hunter J, et al. Sulphasalazine in the Management of Psoriatic Arthritis. British journal of rheumatology. 1993;32(10):923-5.
- 178. Friedman DM, Llanos C, Izmirly PM, et al. Evaluation of fetuses in a study of intravenous immunoglobulin as preventive therapy for congenital heart block: Results of a multicenter, prospective, open-label clinical trial. Arthritis and rheumatism. 2010;62(4):1138-46.
- 179. Furst D, Erikson N, Clute L, et al. Adverse Experience With Methotrexate During 176 Weeks of a Longterm Prospective Trial in Patients With Rheumatoid Arthritis. The Journal of rheumatology. 1990;12:1628-35.
- 180. Furst D, Felson D, Thoren G, et al.
 Immunoadsorption for the Treatment of
 Rheumatoid Arthritis: Final Results of a
 Randomized Trial. Prosorba Trial
 Investigators. Ther Apher. 2002;6(1):99.
- 181. Furst DE, Kolba KS, Fleischmann R, et al. Dose Response and Safety Study of

- Meloxicam up to 22.5 Mg Daily in Rheumatoid Arthritis: a 12 Week Multicenter, Double Blind, Dose Response Study Versus Placebo and Diclofenac. The Journal of rheumatology. 2002;29(3):436-
- 182. Furuya T, Kotake S, Inoue E, et al. Risk factors associated with incident fractures in Japanese men with rheumatoid arthritis: A prospective observational cohort study. Journal of Bone and Mineral Metabolism. 2008;26(5):499-505.
- 183. Furuya T, Kotake S, Inoue E, et al. Risk factors associated with incident clinical vertebral and nonvertebral fractures in Japanese women with rheumatoid arthritis: A prospective 54-month observational study. Journal of Rheumatology. 2007;34(2):303-10.
- 184. Furuya Y, Ozeki T, Takayanagi R, et al. Theory based analysis of anti-inflammatory effect of infliximab on Crohn's disease.

 Drug metabolism and pharmacokinetics 2007(1):20-5.
- 185. Furuzawa-Carballeda J, Fenutria-Ausmequet R, Gil-Espinosa V, et al. Polymerized-type I collagen for the treatment of patients with rheumatoid arthritis. Effect of intramuscular administration in a double blind placebocontrolled clinical trial. Clinical and Experimental Rheumatology. 2006;24(5):514-20.
- 186. Garnero P, Thompson E, Woodworth T, et al. Rapid and sustained improvement in bone and cartilage turnover markers with the anti-interleukin-6 receptor inhibitor tocilizumab plus methotrexate in rheumatoid arthritis patients with an inadequate response to methotrexate: Results from a substudy of the multicenter double-blind, placebo-controlled trial of tocilizumab in inadequate responders to methotrexate alone. 2010.
- 187. Gasparyan AY, Stavropoulos-Kalinoglou A, Toms TE, et al. Association of mean platelet volume with hypertension in rheumatoid arthritis. Inflammation and Allergy Drug Targets. 2010;9(1):45-50.

- 188. Genant HK. Interleukin-1 Receptor
 Antagonist Treatment of Rheumatoid
 Arthritis Patients: Radiologic Progression
 and Correlation of Genant/Sharp and Larsen
 Scoring Methods. Seminars in arthritis and
 rheumatism. 2001;30(5 Suppl 2):26-32.
- 189. Genant HK, Peterfy CG, Westhovens R, et al. Abatacept inhibits progression of structural damage in rheumatoid arthritis: Results from the long-term extension of the AIM trial. Annals of the Rheumatic Diseases. 2007;67(8):1084-9.
- 190. Genovese MC, McKay JD, Nasonov EL, et al. Interleukin-6 receptor inhibition with tocilizumab reduces disease activity in rheumatoid arthritis with inadequate response to disease-modifying antirheumatic drugs: The tocilizumab in combination with traditional disease-modifying antirheumatic drug therapy study. Arthritis and Rheumatism 2008;58(10):2968-80.
- 191. Genta MS, Kardes H, Gabay C. Clinical evaluation of a cohort of patients with rheumatoid arthritis treated with anti-TNF-alpha in the community. Joint Bone Spine. 2006;73(1):51-6.
- 192. Gerlag DM, Haringman JJ, Smeets TJM, et al. Effects of Oral Prednisolone on Biomarkers in Synovial Tissue and Clinical Improvement in Rheumatoid Arthritis. Arthritis and rheumatism. 2004;50(12):3783-91.
- 193. Gerlag DM, Hollis S, Layton M, et al. Preclinical and clinical investigation of a CCR5 antagonist, AZD5672, in patients with rheumatoid arthritis receiving methotrexate. Arthritis and rheumatism. 2010;62(11):3154-60.
- 194. Geusens P, Alten R, Rovensky J, et al. Efficacy, Safety and Tolerability of Lumiracoxib in Patients With Rheumatoid Arthritis. Int J Clin Pract. 2004;58(11):1033-41.
- 195. Geusens P, Truitt K, Sfikakis P, et al. A
 Placebo and Active Comparator-Controlled
 Trial of Rofecoxib for the Treatment of
 Rheumatoid Arthritis. Scandinavian journal
 of rheumatology. 2002;31(4):230-8.

- 196. Ghosh B, Halder S, Ghosh A, et al. Early rheumatoid arthritis: Clinical and therapeutic evaluation in a tertiary care centre in India. Indian Journal of Rheumatology 2008;3(2):48-51.
- 197. Giannini EH, Ilowite NT, Lovell DJ, et al. Long-term safety and effectiveness of etanercept in children with selected categories of juvenile idiopathic arthritis. 2009.
- 198. Gladman D, Blake R, Brubacher B, et al. Chloroquine Therapy in Psoriatic Arthritis. The Journal of rheumatology. 1992;19(11):1724-6.
- 199. Gladman DD, Mease PJ, Cifaldi MA, et al. Adalimumab improves joint-related and skin-related functional impairment in patients with psoriatic arthritis: patient-reported outcomes of the Adalimumab Effectiveness in Psoriatic Arthritis Trial. Ann Rheum Dis 2007;66(2):163-8.
- 200. Gladman DD, Mease PJ, Ritchlin CT, et al. Adalimumab for long-term treatment of psoriatic arthritis: forty-eight week data from the adalimumab effectiveness in psoriatic arthritis trial. Arthritis Rheum. 2007 Feb;56(2):476-88.
- Godfrey C, Sweeney K, Miller K, et al. The Population Pharmacokinetics of Long-Term Methotrexate in Rheumatoid Arthritis. British journal of clinical pharmacology. 1998;46(4):369-76.
- 202. Goekoop-Ruiterman YPM, De Vries-Bouwstra JK, Allaart CF, et al. Comparison of treatment strategies in early rheumatoid arthritis: A randomized trial. Annals of Internal Medicine 2007;146(6):406-15.
- 203. Goekoop-Ruiterman YPM, De Vries-Bouwstra JK, Kerstens PJSM, et al. DAS-driven therapy versus routine care in patients with recent-onset active rheumatoid arthritis. 2010.
- 204. Gonzalez-Alvaro I, Descalzo MA, Carmona L. Trends towards an improved disease state in rheumatoid arthritis over time: Influence of new therapies and changes in management approach: Analysis of the

- EMECAR cohort. Arthritis Research and Therapy. 2008;10(6).
- 205. Goodnough L, Marcus R. The Erythropoietic Response to Erythropoietin in Patients With Rheumatoid Arthritis. The Journal of laboratory and clinical medicine. 1997;130(4):381-6.
- 206. Gossec L, van der Heijde D, Melian A, et al. Efficacy of Cyclo-Oxygenase-2 Inhibition by Etoricoxib and Naproxen on the Axial Manifestations of Ankylosing Spondylitis in the Presence of Peripheral Arthritis. Annals of the rheumatic diseases. 2005;64(1):1563-7.
- 207. Gøtzsche P, Johansen H. Meta-Analysis of Short-Term Low Dose Prednisolone Versus Placebo and Non-Steroidal Anti-Inflammatory Drugs in Rheumatoid Arthritis. British medical journal. 1998;316(7144):1606-7.
- 208. Gotzsche PC, Hansen M, Stoltenberg M, et al. Randomized, Placebo Controlled Tial of Withdrawal of Slow-Acting Antirheumatic Drugs and of Observer Bias in Rheumatoid Arthritis. Scandinavian Journal of Rheumatology. 1996;25(4):194-0.
- 209. Graell E, Vazquez I, Larrosa M, et al.
 Disability measured by the modified health
 assessment questionnaire in early
 rheumatoid arthritis: Prognostic factors after
 two years of follow-up. Clinical and
 Experimental Rheumatology.
 2009;27(2):284-91.
- 210. Graham DY, White RH, Moreland LW, et al. Duodenal and Gastric Ulcer Prevention With Misoprostol in Arthritis Patients Taking Nsaids. Misoprostol Study Group. Annals of internal medicine. 1993;119(4):257-62.
- 211. Greenberg JD, Bingham ICO, Abramson SB, et al. Assessment of coxib utilization by rheumatologists for nonsteroidal antiinflammatory drug gastroprotection prior to the coxib market withdrawals. Arthritis Care and Research. 2006;55(4):543-50.
- 212. Greenwood MC, Rathi J, Hakim AJ, et al. Regression to the mean using the disease activity score in eligibility and response

- criteria for prescribing TNF-alpha inhibitors in adults with rheumatoid arthritis. Rheumatology. 2007;46(7):1165-7.
- 213. Griffith SM, Fisher J, Clarke S, et al. Do Patients With Rheumatoid Arthritis Established on Methotrexate and Folic Acid 5 Mg Daily Need to Continue Folic Acid Supplements Long Term? Rheumatology (Oxford). 2000;39(10):1102-9.
- 214. Grigor C, Capell H, Stirling A, et al. Effect of a Treatment Strategy of Tight Control for Rheumatoid Arthritis (the Ticora Study): a Single-Blind Randomised Controlled Trial. Lancet. 2004;364(9430):263-9.
- 215. Gulec G, Yenilmez C, Ayranci U. Sulfasalazine plus chloroquine-induced mood disorder in a patient with rheumatoid arthritis. Iranian Journal of Medical Sciences. 2009;34(1):72-5.
- 216. Guler-Yuksel M, Allaart CF, Watt I, et al. Treatment with TNF-(alpha) inhibitor infliximab might reduce hand osteoarthritis in patients with rheumatoid arthritis. Osteoarthritis and Cartilage. 2010;18(10):1256-62.
- 217. Gupta AK, Grober JS, Hamilton TA, et al. Sulfasalazine Therapy for Psoriatic Arthritis: a Double Blind, Placebo Controlled Trial. The Journal of rheumatology. 1996;22(5):894-8.
- 218. Haagsma C, Russel F, Vree T, et al.
 Combination of Methotrexate and
 Sulphasalazine in Patients With Rheumatoid
 Arthritis: Pharmacokinetic Analysis and
 Relationship to Clinical Response. British
 journal of clinical pharmacology.
 1997;36(10):1082-8.
- 219. Haagsma C, van Riel P, de Jong A, et al. Combination of Sulphasalazine and Methotrexate Versus the Single Components in Early Rheumatoid Arthritis: a Randomized, Controlled, Double-Blind, 52 Week Clinical Trial. British journal of rheumatology. 1997;36(10):1082-8.
- Haagsma C, van Riel P, van de Putte L.Combining Sulphasalazine andMethotrexate in Rheumatoid Arthritis: Early

- Clinical Impressions. British journal of rheumatology. 1995;34(Suppl 2):104-8.
- 221. Haagsma CJ, Blom HJ, van Riel PL, et al. Influence of Sulphasalazine, Methotrexate, and the Combination of Both on Plasma Homocysteine Concentrations in Patients With Rheumatoid Arthritis. Annals of the rheumatic diseases. 1999;58(2):79-84.
- 222. Haagsma CJ, van Riel PL, de Rooij DJ, et al. Combination of Methotrexate and Sulphasalazine Vs Methotrexate Alone: a Randomized Open Clinical Trial in Rheumatoid Arthritis Patients Resistant to Sulphasalazine Therapy. British journal of rheumatology. 1994;33(11):1049-55.
- 223. Haar D, Solvkjaer M, Unger B, et al. A
 Double-Blind Comparative Study of
 Hydroxychloroquine and Dapsone, Alone
 and in Combination, in Rheumatoid
 Arthritis. Scandinavian journal of
 rheumatology. 1993;22(3):113-8.
- 224. Hafstrem I, Albertsson K, Boonen A, et al. Remission achieved after 2 years treatment with low-dose prednisolone in addition to diseasemodifying anti-rheumatic drugs in early rheumatoid arthritis is associated with reduced joint destruction still present after 4 years: An open 2-year continuation study. 2009.
- 225. Hakala M, Risteli J, Aman S, et al.
 Combination drug strategy in recent-onset rheumatoid arthritis suppresses collagen I degradation and is associated with retardation of radiological progression.
 Scandinavian Journal of Rheumatology. 2008;37(2):90-3.
- 226. Hamalainen H, Kaarela K, Kroger H, et al. Changes in bone mineral density in premenopausal women with rheumatoid arthritis during a two-year follow-up. Joint Bone Spine. 2007;74(5):482-7.
- 227. Hamilton J, McInnes I, Thomson E, et al. Comparative Study of Intramuscular Gold and Methotrexate in a Rheumatoid Arthritis Population From a Socially Deprived Area. Annals of the rheumatic diseases. 2001;60(6):566-72.

- 228. Hamilton R, Kremer J. Why Intramuscular Methotrexate May Be More Efficacious Than Oral Dosing in Patients With Rheumatoid Arthritis. British journal of rheumatology. 1997;36(1):86-90.
- 229. Hamilton S, Campbell N, Kara M, et al. The Effect of Ingestion of Ferrous Sulfate on the Absorption of Oral Methotrexate in Patients With Rheumatoid Arthritis. The Journal of rheumatology. 2003;30(9):1948-50.
- 230. Hannequin JR. Efficacy of Arthrotec in the Treatment of Rheumatoid Arthritis. Scandinavian journal of rheumatology Supplement. 1992;96:7-14.
- 231. Hannonen P, Mottonen T, Hakola M, et al. Sulfasalazine in Early Rheumatoid Arthritis. A 48-Week Double-Blind, Prospective, Placebo-Controlled Study. Arthritis and rheumatism. 1993;36(11):1501-9.
- 232. Hansen M, Podenphant J, Florescu A, et al. A Randomised Trial of Differentiated Prednisolone Treatment in Active Rheumatoid Arthritis. Clinical Benefits and Skeletal Side Effects. Annals of the rheumatic diseases. 1999;58(11):713-8.
- 233. Hansen TM, Kryger P, Elling H, et al. Double Blind Placebo Controlled Trial of Pulse Treatment With Methylprednisolone Combined With Disease Modifying Drugs in Rheumatoid Arthritis. British medical journal. 1990;301(6749):268-70.
- 234. Hanyuda M, Kasama T, Isozaki T, et al. Activated Leucocytes Express and Secrete Macrophage Inflammatory Protein-1alpha Upon Interaction With Synovial Fibroblasts of Rheumatoid Arthritis Via a Beta2-Integrin/Icam-1 Mechanism. Rheumatology (Oxford). 2003;42(11):1390-7.
- 235. Haringman J, Kraan M, Smeets TJ, et al. Chemokine Blockade and Chronic Inflammatory Disease: Proof of Concept in Patients With Rheumatoid Arthritis. Annals of the rheumatic diseases. 2003;62(8):715-21.
- 236. Hartmann SN, Rordorf CM, Milosavljev S, et al. Lumiracoxib Does Not Affect Methotrexate Pharmacokinetics in

- Rheumatoid Arthritis Patients. The Annals of pharmacotherapy. 2004;38(10):1582-7.
- 237. Hasegawa J, Nagashima M, Yamamoto M, et al. Bone Resorption and Inflammatory Inhibition Efficacy of Intermittent Cyclical Etidronate Therapy in Rheumatoid Arthritis. The Journal of rheumatology. 2004;38(10):1582-7.
- 238. Hatakka K, Martio J, Korpela M, et al. Effects of Probiotic Therapy on the Activity and Activation of Mild Rheumatoid Arthritis--a Pilot Study. Scandinavian journal of rheumatology. 2003;32(4):211-5.
- 239. Haugeberg G, Green MJ, Quinn MA, et al. Hand bone loss in early undifferentiated arthritis: Evaluating bone mineral density loss before the development of rheumatoid arthritis. Annals of the Rheumatic Diseases. 2006;65(6):736-40.
- 240. Haugeberg G, Strand A, Kvien T, et al.
 Reduced Loss of Hand Bone Density With
 Prednisolone in Early Rheumatoid Arthritis:
 Results From a Randomized PlaceboControlled Trial. Archives of internal
 medicine. 2005;165(11):1293-7.
- 241. Hazes JM, Taylor P, Strand V, et al. Physical function improvements and relief from fatigue and pain are associated with increased productivity at work and at home in rheumatoid arthritis patients treated with certolizumab pegol. Rheumatology. 2010;49(10):1900-10.
- 242. Hemmings F, Farhan M, Rowland J, et al. Tolerability and Pharmacokinetics of the Collagenase-Selective Inhibitor Trocade in Patients With Rheumatoid Arthritis. Rheumatology (Oxford). 2001;40(5):537-43.
- 243. Henriksson K, Uribe A, Sandstedt B, et al. Helicobacter Pylori Infection, Abo Blood Group, and Effect of Misoprostol on Gastroduodenal Mucosa in Nsaid-Treated Patients With Rheumatoid Arthritis. Digestive diseases and sciences. 1993;38(9):1688-96.
- 244. Hepburn T, Totoritis M, Davis C. Antibody-Mediated Stripping of Cd4 From Lymphocyte Cell Surface in Patients With

- Rheumatoid Arthritis. Rheumatology (Oxford). 2003;42(1):54-61.
- 245. Hernandez-Cruz B, Ariza-Ariza R, Cardiel-Rios MH. Cost of the standard rheumatology care in active rheumatoid arthritis patients seen in a tertiary care center in Mexico City. Reumatologia Clinica. 2006;2(3):124-30.
- 246. Herrick A, Grennan D, Griffen K, et al. Lack of Interaction Between Flucloxacillin and Methotrexate in Patients With Rheumatoid Arthritis. British journal of clinical pharmacology. 1996;41(3):223-7.
- 247. Hetland ML, Ejbjerg B, Horslev-Petersen K, et al. MRI bone oedema is the strongest predictor of subsequent radiographic progression in early rheumatoid arthritis. Results from a 2-year randomised controlled trial (CIMESTRA). 2009.
- 248. Hetland ML, Lindegaard HM, Hansen A, et al. Do changes in prescription practice in patients with rheumatoid arthritis treated with biological agents affect treatment response and adherence to therapy? Results from the nationwide Danish DANBIO Registry. Annals of the Rheumatic Diseases. 2008;67(7):1023-6.
- 249. Heurkens A, Westedt M, Breedveld F. Prednisone Plus Azathioprine Treatment in Patients With Rheumatoid Arthritis Complicated by Vasculitis. Archives of internal medicine. 1991;151(11):2249-54.
- 250. Hewlett S, Mitchell K, Haynes J, et al. Patient-Initiated Hospital Follow-up for Rheumatoid Arthritis. Rheumatology (Oxford). 2000;39(9):990-7.
- 251. Hickling P, Jacoby R, Kirwan J. Joint Destruction After Glucocorticoids Are Withdrawn in Early Rheumatoid Arthritis. Arthritis and Rheumatism Council Low Dose Glucocorticoid Study Group. British journal of rheumatology. 1994;21(3):435-41.
- 252. Hidaka T, Suzuki K, Kawakami M, et al. Dynamic Changes in Cytokine Levels in Serum and Synovial Fluid Following Filtration Leukocytapheresis Therapy in

- Patients With Rheumatoid Arthritis. J Clin Apher. 2001;16(2):74-81.
- 253. Hidaka T, Suzuki K, Matsuki Y, et al. Changes in Cd4+ T Lymphocyte Subsets in Circulating Blood and Synovial Fluid Following Filtration Leukocytapheresis Therapy in Patients With Rheumatoid Arthritis. Ther Apher. 1999;3(2):178-85.
- 254. Hilliquin P, Chermat Izard V, Menkes CJ. A
 Double Blind, Placebo Controlled Study of a
 Platelet Activating Factor Antagonist in
 Patients With Rheumatoid Arthritis. The
 Journal of rheumatology. 1998;25(8):15027.
- 255. Hoekstra M, Haagsma C, Neef C, et al. Bioavailability of Higher Dose Methotrexate Comparing Oral and Subcutaneous Administration in Patients With Rheumatoid Arthritis. Journal of Rheumatology. 2004;31(4):645-8.
- 256. Hoekstra M, van Ede A, Haagsma C, et al. Factors associated with toxicity, final dose, and efficacy of methotrexate in patients with rheumatoid arthritis. Annals of the rheumatic diseases. 2003;62(5):423-6.
- 257. Hoffman GS, Cid MC, Rendt-Zagar KE, et al. Infliximab for maintenance of glucocorticosteroid-induced remission of giant cell arteritis: a randomized trial. Annals of internal medicine 2007(9):621-30.
- 258. Holm B, Jacobsen S, Skjodt H, et al. Keitel functional test for patients with rheumatoid arthritis: Translation, reliability, validity, and responsiveness. Physical Therapy. 2008;88(5):664-78.
- 259. Hor BTY, Vasoo S, Koh ET. The use of anti-tumour necrosis factor-alpha therapies for rheumatoid arthritis in Singapore.
 APLAR Journal of Rheumatology.
 2006;9(2):157-60.
- 260. Horng MS. Early rheumatoid arthritis: Is there a best treatment? Journal of Clinical Outcomes Management. 2007;14(5):233-4.
- 261. Huang F, Wang L, Zhang J, et al. Risk of tuberculosis in a Chinese registry of rheumatoid arthritis and ankylosing

- spondylitis for tumour necrosis factor-alpha antagonists. APLAR Journal of Rheumatology. 2006;9(2):170-4.
- 262. Huang SC, Wei JCC, Wu DJ, et al. Vitamin B6 supplementation improves proinflammatory responses in patients with rheumatoid arthritis. European Journal of Clinical Nutrition. 2010;64(9):1007-13.
- 263. Huffstutter J, Craig WD, Schimizzi G, et al. A multicenter, randomized, open study to evaluate the impact of an electronic data capture system on the care of patients with rheumatoid arthritis. Current Medical Research and Opinion. 2007;23(8):1967-79.
- 264. Hughes RA, Carr AJ, Carr M, et al. Improving patient safety: Reducing medication errors through use of acceptable, accessible medicines packaging. Pharmaceutical Journal. 2008;280(7484):22-5.
- 265. Huisman AM, Siewertsz van Everdingen AA, Wenting MJG, et al. Glucocorticoid Receptor up-Regulation in Early Rheumatoid Arthritis Treated With Low Dose Prednisone or Placebo. Clinical and experimental rheumatology. 2003;21(2):217-20.
- 266. Hunter J, Parnham M, Balaguer X. Aceclofenac in Rheumatoid Arthritis: a Useful and Novel Anti-Inflammatory. Clinical rheumatology. 1996;15(4):329-34.
- 267. Hurowitz EJ, Gould JS, Fleisig GS, et al. Outcome analysis of agility total ankle replacement with prior adjunctive procedures: Two to six year followup. Foot and Ankle International. 2007;28(3):308-12.
- 268. Huskisson EC. Four Commonly Prescribed Non-Steroidal Anti-Inflammatory Drugs for Rheumatoid Arthritis. European journal of rheumatology and inflammation. 1991;11(2):8-12.
- 269. Hyams J, Crandall W, Kugathasan S, et al. Induction and maintenance infliximab therapy for the treatment of moderate-to-severe Crohn's disease in children.

 Gastroenterology 2007(3):863-73; quiz 1165-6.

- 270. Iagnocco A, Cerioni A, Coari G, et al. Intraarticular methotrexate in the treatment of rheumatoid arthritis and psoriatic arthritis: A clinical and sonographic study. Clinical Rheumatology. 2006;25(2):159-63.
- 271. Ichikawa Y, Saito T, Yamanaka H, et al. Clinical activity after 12 weeks of treatment with nonbiologics in early rheumatoid arthritis may predict articular destruction 2 years later. Journal of Rheumatology. 2010;37(4):723-9.
- 272. Iglehart IWr, Sutton JD, Bender JC, et al. Intravenous Pulsed Steroids in Rheumatoid Arthritis: a Comparative Dose Study. The Journal of rheumatology. 1990;17(2):159-62.
- 273. Ince A, Yazici Y, Hamuryudan V, et al. The Frequency and Clinical Characteristics of Methotrexate (Mtx) Oral Toxicity in Rheumatoid Arthritis (Ra): a Masked and Controlled Study. Clinical rheumatology. 1996;15(5):491-4.
- Iqbal M, Baig J, Ali A, et al. The Effects of Non-Steroidal Anti-Inflammatory Drugs on the Disposition of Methotrexate in Patients With Rheumatoid Arthritis.
 Biopharmaceutics & drug disposition.
 1998;19(3):163-7.
- 275. Ishikawa H, Murasawa A, Nakazono K, et al. The patient-based outcome of upper-extremity surgeries using the DASH questionnaire and the effect of disease activity of the patients with rheumatoid arthritis. Clinical Rheumatology. 2008;27(8):967-73.
- 276. Islam M, Alam M, Haq S, et al. Efficacy of Sulphasalazine Plus Methotrexate in Rheumatoid Arthritis. Bangladesh Medical Research Council bulletin. 2000;26(1):1-7.
- 277. Isozaki T, Sato M, Takahashi R, et al. Effects of low-dose tacrolimus therapy in combination with methotrexate in patients with methotrexate-refractory rheumatoid arthritis. 2010;229-34.
- 278. Izumi Y, Tominaga M, Iwanaga N, et al.
 Twenty-four-week follow-up examination of
 a leukocytapheresis therapy in rheumatoid

- arthritis. Modern Rheumatology. 2006;16(1):20-3.
- 279. Jacobs J, Rasker J, van Riel P, et al.
 Rheumajecta and Vasolastine in the
 Treatment of Rheumatoid Arthritis--the
 Results of a Placebo-Controlled, DoubleBlind Trial of a Complementary Treatment.
 Scandinavian journal of rheumatology.
 1991;20(6):434-40.
- 280. Jahangier ZN, Jacobs JWG, Lafeber FPJG, et al. Is Radiation Synovectomy for Arthritis of the Knee More Effective Than Intraarticular Treatment With Glucocorticoids? Results of an Eighteen-Month, Randomized, Double-Blind, Placebo-Controlled, Crossover Trial. Arthritis and rheumatism. 2005;52(11):3391-402.
- 281. Jakez Ocampo J, Richaud Patin Y, Simon J, et al. Weekly Dose of Leflunomide for the Treatment of Refractory Rheumatoid Arthritis: an Open Pilot Comparative Study. Joint, bone, spine: revue du rhumatisme. 2004;51(1):147-8.
- 282. Jakob A, Porstmann R, Rompel R. Skin ulceration after leflunomide treatment in two patients with rheumatoid arthritis. [German, English]. JDDG Journal of the German Society of Dermatology. 2006;4(4):324-7.
- 283. Jamal S, Patra K, Keystone EC.
 Adalimumab response in patients with early versus established rheumatoid arthritis:
 DE019 randomized controlled trial subanalysis. 2009.
- 284. Jaswal S, Mehta H, Sood A, et al.
 Antioxidant Status in Rheumatoid Arthritis
 and Role of Antioxidant Therapy. 338.
 2003;1-2:international journal of clinical
 chemistry.
- 285. Jelinek G, Will R, Dusci L, et al.
 Intravenous Regional Administration of
 Methylprednisolone in Rheumatoid
 Arthritis. Rheumatology international.
 1991;11(4-5):147-50.
- 286. Jenks K, Stebbings S, Burton J, et al.
 Probiotic therapy for the treatment of
 spondyloarthritis: A randomized controlled

- trial. Journal of Rheumatology. 2010;37(10):2118-25.
- 287. Jessop JD, O'Sullivan MM, Lewis PA, et al. A Long-Term Five-Year Randomized Controlled Trial of Hydroxychloroquine, Sodium Aurothiomalate, Auranofin and Penicillamine in the Treatment of Patients With Rheumatoid Arthritis. British journal of rheumatology. 1998;37(9):992-1002.
- 288. Jeurissen ME, Boerbooms AM, van de Putte LB, et al. Influence of Methotrexate and Azathioprine on Radiologic Progression in Rheumatoid Arthritis. A Randomized, Double-Blind Study. Annals of internal medicine. 1991;114(12):999-1004.
- 289. Jones G, Sebba A, Gu J, et al. Comparison of tocilizumab monotherapy versus methotrexate monotherapy in patients with moderate to severe rheumatoid arthritis: The AMBITION study. 2010.
- 290. Joyce D, Will R, Hoffman D, et al. Exacerbation of Rheumatoid Arthritis in Patients Treated With Methotrexate After Administration of Folinic Acid. Annals of the rheumatic diseases. 1991;50(12):913-4.
- 291. Kafediska I, Spasovski D, Gruev T, et al. Association between Sharp's radiographic index and acute phase reactants in rheumatoid arthritis. Journal of Medical Biochemistry. 2008;27(4):447-53.
- 292. Kageyama Y, Sano M, Ishihara C, et al. Flexor tendon ruptures in both small fingers of a patient with rheumatoid arthritis [2]. Journal of Clinical Rheumatology. 2006;12(2):103-4.
- 293. Kahn KL, MacLean CH, Wong AL, et al. Assessment of American College of Rheumatology quality criteria for rheumatoid arthritis in a pre-quality criteria patient cohort. Arthritis Care and Research. 2007;57(5):707-15.
- 294. Kalden JR, Schattenkirchner M, Sorensen H, et al. The Efficacy and Safety of Leflunomide in Patients With Active Rheumatoid Arthritis: a Five-Year Followup Study. Arthritis and rheumatism. 2003;48(6):1513-20.

- 295. Kalden JR, Scott DL, Smolen JS, et al. Improved Functional Ability in Patients With Rheumatoid Arthritis Longterm Treatment With Leflunomide Versus Sulfasalazine. Journal of Rheumatology. 2001;28(9):1983-91.
- 296. Kalden Nemeth D, Grebmeier J, Antoni C, et al. Nmr Monitoring of Rheumatoid Arthritis Patients Receiving Anti-Tnf-Alpha Monoclonal Antibody Therapy. Rheumatology international. 1997;16(6):249-55.
- 297. Kaltwasser J, Nash P, Gladman D, et al. Efficacy and Safety of Leflunomide in the Treatment of Psoriatic Arthritis and Psoriasis: a Multinational, Double-Blind, Randomized, Placebo-Controlled Clinical Trial. Arthritis and rheumatism. 2004;50(6):1393-50.
- 298. Kamel M, Serafi T. Fucose Concentrations in Sera From Patients With Rheumatoid Arthritis. Clinical and experimental rheumatology. 1995;13(2):243-6.
- 299. Kanbe K, Inoue K. Efficacy of arthroscopic synovectomy for the effect attenuation cases of infliximab in rheumatoid arthritis. Clinical Rheumatology. 2006;25(6):877-81.
- 300. Kanik K, Yarboro C, Naparstek Y, et al. Failure of Low-Dose Intravenous Immunoglobulin Therapy to Suppress Disease Activity in Patients With Treatment-Refractory Rheumatoid Arthritis. Arthritis and rheumatism. 1997;82(4):1279-83.
- 301. Karim A, Tolbert D, Hunt T, et al. Celecoxib, a Specific Cox-2 Inhibitor, Has No Significant Effect on Methotrexate Pharmacokinetics in Patients With Rheumatoid Arthritis. The Journal of rheumatology. 1999;26(12):2539-43.
- 302. Kavanaugh A, Genovese M, Baughman J, et al. Allele and Antigen-Specific Treatment of Rheumatoid Arthritis: a Double Blind, Placebo Controlled Phase 1 Trial. The Journal of rheumatology. 2003;30(3):449-54.
- 303. Kavanaugh A, Menter A, Mendelsohn A, et al. Effect of ustekinumab on physical

- function and health-related quality of life in patients with psoriatic arthritis: A randomized, placebo-controlled, phase II trial. Current Medical Research and Opinion. 2010;26(10):2385-92.
- 304. Kawai S, Uchida E, Kondo M, et al. Efficacy and safety of ketoprofen patch in patients with rheumatoid arthritis: A randomized, double-blind, placebocontrolled study. Journal of Clinical Pharmacology. 2010;50(10):1171-9.
- 305. Kekow J, Moots RJ, Emery P, et al. Patient-reported outcomes improve with etanercept plus methotrexate in active early rheumatoid arthritis and the improvement is strongly associated with remission: The COMET trial. 2010.
- 306. Kerstens P, Boerbooms A, Jeurissen M, et al. Radiological and Clinical Results of Longterm Treatment of Rheumatoid Arthritis With Methotrexate and Azathioprine. The Journal of rheumatology. 2000;27(5):1148-55.
- 307. Kerstens P, Boerbooms A, Jeurissen M, et al. Accelerated Nodulosis During Low Dose Methotrexate Therapy for Rheumatoid Arthritis. An Analysis of Ten Cases. The Journal of rheumatology. 1992;19(6):867-71.
- 308. Kerstens P, Boerbooms A, Jeurissen M, et al. Antiperinuclear Factor and Disease Activity in Rheumatoid Arthritis.

 Longitudinal Evaluation During Methotrexate and Azathioprine Therapy.

 The Journal of rheumatology.
 1994;21(12):2190-4.
- 309. Keystone E, Haraoui B, Bykerk V. Role of Adalimumab in the Treatment of Early Rheumatoid Arthritis. Clinical and experimental rheumatology. 2003;21(5 Suppl 31):S198-9.
- 310. Khan S, Otter S, Springett K. The effects of reflexology on foot pain and quality of life in a patient with rheumatoid arthritis: A case report. Foot. 2006;16(2):112-6.
- 311. Kiely P, Williams R, Walsh D, et al.
 Contemporary patterns of care and disease activity outcome in early rheumatoid

- arthritis: The ERAN cohort. Rheumatology. 2009;48(1):57-60.
- 312. Kim H, Song Y. A Comparison Between Bucillamine and D-Penicillamine in the Treatment of Rheumatoid Arthritis. Rheumatology international. 1997;17(1):5-9.
- 313. Kimball AB, Bensimon AG, Guerin A, et al. Efficacy and safety of adalimumab among patients with moderate to severe psoriasis with co-morbidities: Subanalysis of results from a randomized, double-blind, placebo-controlled, phase III trial. American Journal of Clinical Dermatology 2011;12(1):51-62.
- 314. Kirkham B, Corkill M, Davison S, et al. Response to Glucocorticoid Treatment in Rheumatoid Arthritis: in Vitro Cell Mediated Immune Assay Predicts in Vivo Responses. The Journal of rheumatology. 1991;18(6):821-5.
- 315. Kirkham B, Davison S, Corkill M, et al. Serial Soluble Interleukin 2 Receptor Levels in Rheumatoid Arthritis: Differences in Response to Glucocorticoid Treatment and Chrysotherapy. The Journal of rheumatology. 1993;20(6):935-9.
- 316. Kirkham B, Navarro F, Corkill M, et al. In Vivo Analysis of Disease Modifying Drug Therapy Activity in Rheumatoid Arthritis by Sequential Immunohistological Analysis of Synovial Membrane Interleukin 1 Beta. The Journal of rheumatology. 1994;21(9):1615-9
- 317. Kirwan J, Byron M, Watt I. The Relationship Between Soft Tissue Swelling, Joint Space Narrowing and Erosive Damage in Hand X-Rays of Patients With Rheumatoid Arthritis. Rheumatology (Oxford). 2001;40(3):688-95.
- 318. Kirwan JR, Hallgren R, Mielants H, et al. A Randomised Placebo Controlled 12 Week Trial of Budesonide and Prednisolone in Rheumatoid Arthritis. Annals of the rheumatic diseases. 2004;63-6-688-95.
- 319. Kloppenburg M, Breedveld F, Terwiel J, et al. Minocycline in Active Rheumatoid Arthritis. A Double-Blind, Placebo-Controlled Trial. Arthritis and rheumatism. 1994;37(5):629-36.

- 320. Kloppenburg M, Dijkmans B, Verweij C, et al. Inflammatory and Immunological Parameters of Disease Activity in Rheumatoid Arthritis Patients Treated With Minocycline. Immunopharmacology. 1996;31(2-3):163-9.
- 321. Knijff Dutmer E, Kalsbeek Batenburg E, Koerts J, et al. Platelet Function Is Inhibited by Non-Selective Non-Steroidal Anti-Inflammatory Drugs but Not by Cyclo-Oxygenase-2-Selective Inhibitors in Patients With Rheumatoid Arthritis. Rheumatology (Oxford). 2002;41(4):458-61.
- 322. Knijff Dutmer E, Martens A, vd Laar M. Effects of Nabumetone Compared With Naproxen on Platelet Aggregation in Patients With Rheumatoid Arthritis. Annals of the rheumatic diseases. 1999;58(4):257-9.
- 323. Knijff-Dutmer E, Drossaers-Bakker W, Verhoeven A, et al. Rheumatoid Factor Measured by Fluoroimmunoassay: a Responsive Measure of Rheumatoid Arthritis Disease Activity That Is Associated With Joint Damage. Annals of the rheumatic diseases. 2002;61(7):603-7.
- 324. Knudsen LS, Klarlund M, Skjodt H, et al. Biomarkers of inflammation in patients with unclassified polyarthritis and early rheumatoid arthritis. Relationship to disease activity and radiographic outcome. Journal of Rheumatology. 2008;35(7):1277-87.
- 325. Kollerup G, Hansen M, Horslev Petersen K. Urinary Hydroxypyridinium Cross-Links of Collagen in Rheumatoid Arthritis. Relation to Disease Activity and Effects of Methylprednisolone. British journal of rheumatology. 1994;33(9):816-20.
- 326. Kondo H, Abe T, Hashimoto H, et al. Efficacy and Safety of Tacrolimus (Fk506) in Treatment of Rheumatoid Arthritis: a Randomized, Double Blind, Placebo Controlled Dose-Finding Study. The Journal of rheumatology. 2004;31(2):243-51.
- 327. Kopp S, Akerman S, Nilner M. Short-Term Effects of Intra-Articular Sodium Hyaluronate, Glucocorticoid, and Saline Injections on Rheumatoid Arthritis of the Temporomandibular Joint. Journal of

- craniomandibular disorders : facial & oral pain. 1991;5(4):231-8.
- 328. Kornasoff D, Maisenbacher J, Bowdler J, et al. The Efficacy and Tolerability of Aceclofenac Compared to Indomethacin in Patients With Rheumatoid Arthritis. Rheumatology international. 1996;15(6):225-30.
- 329. Korpela M, Laasonen L, Hannonen P, et al. Retardation of Joint Damage in Patients With Early Rheumatoid Arthritis by Initial Aggressive Treatment With Disease-Modifying Antirheumatic Drugs: Five-Year Experience From the Fin-Raco Study. Arthritis and rheumatism. 2004;50(7):2072-81.
- 330. Korthals-de Bos I, Van Tulder M, Boers M, et al. Indirect and Total Costs of Early Rheumatoid Arthritis: a Randomized Comparison of Combined Step-Down Prednisolone, Methotrexate, and Sulfasalazine With Sulfasalazine Alone. The Journal of rheumatology. 2004;31(9):1709-16.
- 331. Kraan MC, de Koster BM, Elferink JG, et al. Inhibition of Neutrophil Migration Soon After Initiation of Treatment With Leflunomide or Methotrexate in Patients With Rheumatoid Arthritis: Findings in a Prospective, Randomized, Double-Blind Clinical Trial in Fifteen Patients. Arthritis and rheumatism. 2000;43(7):1488-95.
- 332. Kraan MC, Reece RJ, Barg EC, et al.
 Modulation of Inflammation and
 Metalloproteinase Expression in Synovial
 Tissue by Leflunomide and Methotrexate in
 Patients With Active Rheumatoid Arthritis.
 Findings in a Prospective, Randomized,
 Double-Blind, Parallel-Design Clinical Trial
 in Thirty-Nine Patients at Two Centers.
 Arthritis and rheumatism. 2000;43(8):182030.
- 333. Kraan MC, Smeets TJM, van Loon MJ, et al. Differential Effects of Leflunomide and Methotrexate on Cytokine Production in Rheumatoid Arthritis. Annals of the rheumatic diseases. 2004;63(9):1056-61.
- 334. Kremer J, Genovese M, Cannon GW, et al. Combination Leflunomide and Methotrexate

- (Mtx) Therapy for Patients With Active Rheumatoid Arthritis Failing Mtx Monotherapy: Open-Label Extension of a Randomized, Double-Blind, Placebo Controlled Trial. The Journal of rheumatology. 2004;31(8):1521-31.
- 335. Kremer JM, Davies JM, Rynes RI, et al. Every-Other-Week Methotrexate in Patients With Rheumatoid Arthritis. A Double-Blind, Placebo-Controlled Prospective Study. Arthritis and rheumatism. 1995;38(5):601-7.
- 336. Kremer JM, Genovese MC, Cannon GW, et al. Concomitant Leflunomide Therapy in Patients With Active Rheumatoid Arthritis Despite Stable Doses of Methotrexate. A Randomized, Double-Blind, Placebo-Controlled Trial. Annals of internal medicine. 2002;137(9):726-33.
- 337. Kristensen LE, Geborek P, Saxne T. Dose escalation of infliximab therapy in arthritis patients is related to diagnosis and concomitant methotrexate treatment:

 Observational results from the South Swedish Arthritis Treatment Group register. Rheumatology. 2009;48(3):243-5.
- 338. Krug H, Broadwell L, Berry M, et al. Tolerability and Efficacy of Nabumetone and Naproxen in the Treatment of Rheumatoid Arthritis. Clinical therapeutics. 2000;22(1):40-52.
- 339. Kumar K, Gordon C, Toescu V, et al. Beliefs about medicines in patients with rheumatoid arthritis and systemic lupus erythematosus: A comparison between patients of South Asian and White British origin. Rheumatology. 2008;47(5):690-7.
- 340. Kurowski M, Menninger H, Pauli E. The Efficacy and Relative Bioavailability of Diclofenac Resinate in Rheumatoid Arthritis Patients. International journal of clinical pharmacology and therapeutics. 1994;32(8):433-40.
- 341. Kuuliala A, Leirisalo-Repo M, Mottonen T, et al. Serum Soluble Interleukin-2 Receptor Predicts Early Remission in Patients With Recent-Onset Rheumatoid Arthritis Treated With a Single Disease-Modifying Antirheumatic Drug. Clinical and

- experimental rheumatology. 2005;23(2):243-6.
- 342. Kvien TK, Gaston JSH, Bardin T, et al. Three Month Treatment of Reactive Arthritis With Azithromycin: a EULAR Double Blind, Placebo Controlled Study. Annals of the rheumatic diseases. 2004;63(9):1113-9.
- 343. Laan RF, van Riel PL, van de Putte LB, et al. Low-Dose Prednisone Induces Rapid Reversible Axial Bone Loss in Patients With Rheumatoid Arthritis. A Randomized, Controlled Study. Annals of internal medicine. 1993;119(10):963-8.
- 344. Laas K, Peltomaa R, Puolakka K, et al. Early improvement of health-related quality of life during treatment with etanercept and adalimumab in patients with rheumatoid arthritis in routine practice. Clinical and Experimental Rheumatology 2009;27(2):315-20.
- 345. Laasila K, Laasonen L, Leirisalo RM. Antibiotic Treatment and Long Term Prognosis of Reactive Arthritis. Annals of the rheumatic diseases. 2003;62(7):655-8.
- 346. Lacki J, Leszczynski P, Mackiewicz S. Intravenous Cyclophosphamide Combined With Methylprednisolone in the Treatment of Severe Refractory Rheumatoid Arthritis: the Effect on Lymphocytes. Journal of investigational allergology & clinical immunology: official organ of the International Association of Asthmology (INTERASMA) and Sociedad Latinoamericana de Alergia e Inmunología. 1996;6(4):232-6.
- 347. Lacki J, Mackiewicz S, Wiktorowicz K.
 Lymphocyte Phenotype Studies of
 Rheumatoid Arthritis Patients Treated With
 Methotrexate. Archivum immunologiae et
 therapiae experimentalis. 1994;42(4):28790
- 348. Lacki J, Samborski W, Mackiewicz S. Interleukin-10 and Interleukin-6 in Lupus Erythematosus and Rheumatoid Arthritis, Correlations With Acute Phase Proteins. Clinical rheumatology. 1997;16(3):275-8.

- 349. Lacki JK, Schochat T, Sobieska M, et al. Immunological Studies in Patients With Rheumatoid Arthritis Treated With Methotrexate or Cyclophosphamide. Zeitschrift für Rheumatologie. 1994;53(2):76-82.
- 350. Laharie D, Seneschal J, Schaeverbeke T, et al. Assessment of liver fibrosis with transient elastography and FibroTest in patients treated with methotrexate for chronic inflammatory diseases: A casecontrol study. Journal of Hepatology. 2010;53(6):1035-40.
- 351. Laine L, Connors L, Griffin MR, et al. Prescription rates of protective co-therapy for NSAID users at high GI risk and results of attempts to improve adherence to guidelines. 2009.
- 352. Laine L, Curtis SP, Cryer B, et al.
 Assessment of upper gastrointestinal safety
 of etoricoxib and diclofenac in patients with
 osteoarthritis and rheumatoid arthritis in the
 Multinational Etoricoxib and Diclofenac
 Arthritis Long-term (MEDAL) programme:
 a randomised comparison. Lancet.
 2007;369(9560):465-73.
- 353. Laine L, Curtis SP, Cryer B, et al. Risk factors for NSAID-associated upper GI clinical events in a long-term prospective study of 34 701 arthritis patients.

 Alimentary Pharmacology and Therapeutics. 2010;32(10):1240-8.
- 354. Laine L, Goldkind L, Curtis SP, et al. How common is diclofenac-associated liver injury? Analysis of 17,289 arthritis patients in a long-term prospective clinical trial. American Journal of Gastroenterology. 2009;104(2):356-62.
- 355. Lambert CM, Sandhu S, Lochhead A, et al. Dose Escalation of Parenteral Methotrexate in Active Rheumatoid Arthritis That Has Been Unresponsive to Conventional Doses of Methotrexate: a Randomized, Controlled Trial. Arthritis and rheumatism. 2004;50(2):364-71.
- 356. Landewe R, Geusens P, van der Heijde D, et al. Arthritis Instantaneously Causes Collagen Type I and Type Ii Degradation in Patients With Early Rheumatoid Arthritis: a

- Longitudinal Analysis. Ann Rheum Dis. 2006;65(1):40-4.
- 357. Lard LR, Boers M, Verhoeven A, et al. Early and Aggressive Treatment of Rheumatoid Arthritis Patients Affects the Association of Hla Class Ii Antigens With Progression of Joint Damage. Arthritis and rheumatism. 2002;46(4):899-905.
- 358. Larsen A, Kvien TK, Schattenkirchner M, et al. Slowing of Disease Progression in Rheumatoid Arthritis Patients During Long-Term Treatment With Leflunomide or Sulfasalazine. Scandinavian journal of rheumatology. 2001;30(3):135-42.
- 359. Larsen CM, Faulenbach M, Vaag A, et al. Interleukin-1-receptor antagonist in type 2 diabetes mellitus. The New England journal of medicine 2007(15):1517-26.
- 360. Lauhio A, Leirisalo Repo M, Lahdevirta J, et al. Double-Blind, Placebo-Controlled Study of Three-Month Treatment With Lymecycline in Reactive Arthritis, With Special Reference to Chlamydia Arthritis. Arthritis and rheumatism. 1991;34(1):6-14.
- 361. Le Gallez P, Bird H, Wright V. A Comparison of Choline Magnesium Trisalicylate and Acetylsalicylic Acid in Patients With Rheumatoid Arthritis. Current medical research and opinion. 1990;12(2):71-5.
- 362. Lee EY, Lee EB, Park BJ, et al. Tramadol 37.5-mg/acetaminophen 325-mg combination tablets added to regular therapy for rheumatoid arthritis pain: A 1-Week, randomized, double-blind, placebocontrolled trial. Clinical Therapeutics. 2006;28(12):2052-60.
- 363. Lee KKC, You JHS, Ho JTS, et al. Economic Analysis of Celecoxib Versus Diclofenac Plus Omeprazole for the Treatment of Arthritis in Patients at Risk of Ulcer Disease. Alimentary pharmacology & therapeutics. 2003;18(2):217-22.
- 364. Lee VWY, Chan CW, Chan LH, et al. The direct medical cost of rheumatoid arthritis in Hong Kong. Journal of Medical Economics. 2007;10(4):443-53.

- 365. Lehman A, Esdaile J, Klinkhoff A, et al. A
 48-Week, Randomized, Double-Blind,
 Double-Observer, Placebo-Controlled
 Multicenter Trial of Combination
 Methotrexate and Intramuscular Gold
 Therapy in Rheumatoid Arthritis: Results of
 the Metgo Study. Arthritis Rheum.
 2005;52(5):1360-70.
- 366. Lemmel EM. Comparison of Pyritinol and Auranofin in the Treatment of Rheumatoid Arthritis. British Journal of Rheumatology. 1993;32(5):375-82.
- 367. Lemmel EM, Bolten W, Burgos-Vargas R, et al. Efficacy and Safety of Meloxicam in Patients With Rheumatoid Arthritis. The Journal of rheumatology. 1997;24(2):282-90.
- 368. Lerndal T, Svensson B. A Clinical Study of Cph 82 Vs Methotrexate in Early Rheumatoid Arthritis. Rheumatology (Oxford). 2000;39(3):316-20.
- 369. Levalampi T, Korpela M, Vuolteenaho K, et al. Etanercept and adalimumab treatment in patients with rheumatoid arthritis and spondyloarthropathies in clinical practice: Adverse events and other reasons leading to discontinuation of the treatment. Rheumatology International. 2008;28(3):261-9.
- 370. Leventhal L, Boyce E, Zurier R. Treatment of Rheumatoid Arthritis With Gammalinolenic Acid. Annals of internal medicine. 1993;119(9):867-73.
- 371. Levi S, Goodlad RA, Lee CY, et al. Effects of Nonsteroidal Anti-Inflammatory Drugs and Misoprostol on Gastroduodenal Epithelial Proliferation in Arthritis.

 Gastroenterology. 1992;102(5):1609-11.
- 372. Lewandowski B, Bernacka K, Kucharewicz B, et al. Assessment of Beta-2-Microglobulin Concentration in Serum and Urine in Rheumatoid Arthritis. Roczniki Akademii Medycznej w Białymstoku (1995). 1996;41(2):482-91.
- 373. Li LC, Maetzel A, Davis AM, et al. Primary therapist model for patients referred for rheumatoid arthritis rehabilitation: A cost-

- effectiveness analysis. Arthritis Care and Research. 2006;55(3):402-10.
- 374. Li T, Wells G, Westhovens R, et al. Validation of a simple activity participation measure for rheumatoid arthritis clinical trials. Rheumatology. 2009;48(2):170-5.
- 375. Lightfoot R. Comparison of the Efficacy and Safety of Etodolac and Piroxicam in Patients With Rheumatoid Arthritis. Etodolac Study 326 Rheumatoid Arthritis Investigators Group. The Journal of rheumatology Supplement. 1997;47:10-6.
- 376. Lin Q, Gu JR, Li TW, et al. Value of the peripheral blood B-cells subsets in patients with ankylosing spondylitis. 2009.
- 377. Lin Q, Lin Z, Gu J, et al. Abnormal highexpression of CD154 on T lymphocytes of ankylosing spondylitis patients is downregulated by etanercept treatment. 2010.
- 378. Lipsky P, Isakson P. Outcome of Specific Cox-2 Inhibition in Rheumatoid Arthritis. The Journal of rheumatology Supplement. 1997;49:9-14.
- 379. Lisse JR. Clinical Efficacy and Safety of Naprelan Versus Naprosyn in the Treatment of Rheumatoid Arthritis. The American journal of orthopedics. 1996;25(9 Suppl):21-9.
- 380. Litinsky I, Paran D, Levartovsky D, et al. The effects of leflunomide on clinical parameters and serum levels of IL-6, IL-10, MMP-1 and MMP-3 in patients with resistant rheumatoid arthritis. Cytokine. 2006;33(2):106-10.
- 381. Littman B, Drury C, Zimmerer R, et al. Rheumatoid Arthritis Treated With Tenidap and Piroxicam. Clinical Associations With Cytokine Modulation by Tenidap. Arthritis and rheumatism. 1995;38(1):29-37.
- 382. Liu C, Batliwalla F, Li W, et al. Genomewide association scan identifies candidate polymorphisms associated with differential response to anti-TNF treatment in rheumatoid arthritis. Molecular Medicine. 2008;14(9-10):575-81.

- 383. Lonauer G, Tisscher J, Lim H, et al. Double-Blind Comparison of Etodolac and Diclofenac in Patients With Rheumatoid Arthritis. Current medical research and opinion. 1993;13(2):70-7.
- 384. Lopez-Gonzalez R, Hernandez-Garcia C, Abasolo L, et al. Differences between rheumatology attending physicians and training residents in the management of rheumatoid arthritis in Spain. Scandinavian Journal of Rheumatology. 2008;37(6):419-26.
- 385. Lopez-Mendez A, Daniel WW, Reading JC, et al. Radiographic Assessment of Disease Progression in Rheumatoid Arthritis Patients Enrolled in the Cooperative Systematic Studies of the Rheumatic Diseases Program Randomized Clinical Trial of Methotrexate, Auranofin, or a Combination of the Two. Arthritis and rheumatism. 1993;36(10):1364-9.
- 386. Louly PG, Medeiros-Souza P, Santos-Neto L. N-of-1 double-blind, randomized controlled trial of tramadol to treat chronic cough. 2009.
- 387. Lu C, Zha Q, Chang A, et al. Pattern differentiation in traditional chinese medicine can help define specific indications for biomedical therapy in the treatment of rheumatoid arthritis. 2009.
- 388. Luis M, Pacheco-Tena C, Cazarin-Barrientos J, et al. Comparison of Two Schedules for Administering Oral Low-Dose Methotrexate (Weekly Versus Every-Other-Week) in Patients With Rheumatoid Arthritis in Remission: a Twenty-Four Week, Single Blind, Randomized Study. Arthritis and rheumatism. 1999;42(10):2160-5.
- 389. Maccagno A, Di Giorgio E, Roldan E, et al. Double Blind Radiological Assessment of Continuous Oral Pamidronic Acid in Patients With Rheumatoid Arthritis. Scandinavian journal of rheumatology. 1994;23(4):211-4.
- 390. Machold K, Neumann K, Smolen J.
 Recombinant Human Interferon Gamma in
 the Treatment of Rheumatoid Arthritis:
 Double Blind Placebo Controlled Study.

- Annals of the rheumatic diseases. 1992;51(9):1039-43.
- 391. Machold KP, Landewe R, Smolen JS, et al. The Stop Arthritis Very Early (SAVE) trial, an international multicentre, randomised, double-blind, placebo-controlled trial on glucocorticoids in very early arthritis. Annals of the rheumatic diseases. 2010;69(3):495-502.
- 392. Maetzel A, Strand V, Tugwell P, et al. Economic Comparison of Leflunomide and Methotrexate in Patients With Rheumatoid Arthritis: an Evaluation Based on a 1-Year Randomised Controlled Trial. PharmacoEconomics. 2002;20(1):61-70.
- 393. Maillefert JF, Combe B, Goupille P, et al. Long Term Structural Effects of Combination Therapy in Patients With Early Rheumatoid Arthritis: Five Year Follow up of a Prospective Double Blind Controlled Study. Annals of the rheumatic diseases. 2003;62(8):764-6.
- 394. Maksymowych WP, Salonen D, Inman RD, et al. Low-dose infliximab (3 mg/kg) significantly reduces spinal inflammation on magnetic resonance imaging in patients with ankylosing spondylitis: A randomized placebo-controlled study. Journal of Rheumatology. 2010;37(8):1728-34.
- 395. Manorot M, Rojanasathien N, Louthrenoo W, et al. Comparative Studies of Quality and Bioavailability of Methotrexate in Thai Patients With Rheumatoid Arthritis. Journal of the Medical Association of Thailand = Chotmaihet thangphaet. 1998;81(12):978-85
- 396. Mariette X, Tubach F, Bagheri H, et al. Lymphoma in patients treated with anti-TNF: Results of the 3-year prospective French RATIO registry. Annals of the rheumatic diseases 2010;69(2):400-8.
- 397. Marshall D, Hunter J, Capell H. Double Blind, Placebo Controlled Study of Metronidazole as a Disease Modifying Agent in the Treatment of Rheumatoid Arthritis. Annals of the rheumatic diseases. 1992;51(6):758-60.

- 398. Martens H, Sheets P, Tenover J, et al.
 Decreased Testosterone Levels in Men With
 Rheumatoid Arthritis: Effect of Low Dose
 Prednisone Therapy. The Journal of
 rheumatology. 1994;21(8):1427=31.
- 399. Martin Mola E, Gijon Banos J, Ansoleaga J. Aceclofenac in Comparison to Ketoprofen in the Treatment of Rheumatoid Arthritis. Rheumatology international. 1995;15(3):111-6.
- 400. Matsumoto AK, Melian A, Mandel DR, et al. A Randomized, Controlled, Clinical Trial of Etoricoxib in the Treatment of Rheumatoid Arthritis. The Journal of rheumatology. 2002;29(8):1623-30.
- 401. Matsuno H, Yudoh K, Kondo M, et al. Biochemical Effect of Intra-Articular Injections of High Molecular Weight Hyaluronate in Rheumatoid Arthritis Patients. Inflammation research: official journal of the European Histamine Research Society [et al]. 1999;48(3):154-9.
- 402. Matteson EL, Yocum DE, St Clair EW, et al. Treatment of Active Refractory Rheumatoid Arthritis With Humanized Monoclonal Antibody Campath-1h Administered by Daily Subcutaneous Injection. Arthritis and rheumatism. 1995;38(9):1187-93.
- 403. Mayo P, Skeith K, Russell A, et al.
 Decreased Dromotropic Response to
 Verapamil Despite Pronounced Increased
 Drug Concentration in Rheumatoid
 Arthritis. British journal of clinical
 pharmacology. 2000;50(6):605-13.
- 404. Mazzantini M, Di Munno O, Metelli M, et al. Single Infusion of Neridronate (6-Amino-1-Hydroxyhexylidene-1,1-Bisphosphonate) in Patients With Active Rheumatoid Arthritis: Effects on Disease Activity and Bone Resorption Markers. Aging Clin Exp Res. 2002;14(3):197-201.
- 405. McCarey DW, McInnes IB, Madhok R, et al. Trial of Atorvastatin in Rheumatoid Arthritis (Tara): Double-Blind, Randomised Placebo-Controlled Trial. Lancet. 2004;262(9426):2015-21.

- 406. Mcgee B, Small RE, Singh R, et al. B Lymphocytic Clonal Expansion in Rheumatoid Arthritis. The Journal of rheumatology. 1996;23(1):36-43.
- 407. McInnes I, Porter D, Murphy E, et al. Low Dose Desensitisation Does Not Reduce the Toxicity of Sulphasalazine in Rheumatoid Arthritis. Annals of the rheumatic diseases. 1996;55(5):328-30.
- 408. McKendry R, Kraag G, Seigel S, et al. Therapeutic Value of Colchicine in the Treatment of Patients With Psoriatic Arthritis. Annals of the rheumatic diseases. 1993;52(11):826-8.
- 409. McKendry RJ. Azathioprine and Methotrexate as Combination Chemotherapy in Rheumatoid Arthritis. The Journal of rheumatology Supplement. 1990;25:28-33.
- 410. McLachlan A, Tett S, Cutler D, et al.
 Disposition of the Enantiomers of
 Hydroxychloroquine in Patients With
 Rheumatoid Arthritis Following Multiple
 Doses of the Racemate. British journal of
 clinical pharmacology. 1993;36(1):78-81.
- 411. McLachlan A, Tett S, Cutler D, et al. Bioavailability of Hydroxychloroquine Tablets in Patients With Rheumatoid Arthritis. British journal of rheumatology. 1994;33(3):235-9.
- 412. Mease PJ. Cytokine Blockers in Psoriatic Arthritis. Annals of the rheumatic diseases. 2001;60(Suppl 3):iii37-40.
- 413. Mease PJ, Hobbs K, Chalmers A, et al.
 Local delivery of a recombinant
 adenoassociated vector containing a tumour
 necrosis factor alpha antagonist gene in
 inflammatory arthritis: A phase 1 doseescalation safety and tolerability study.
 2009.
- 414. Mease PJ, Signorovitch J, Yu AP, et al. Impact of adalimumab on symptoms of psoriatic arthritis in patients with moderate to severe psoriasis: A pooled analysis of randomized clinical trials. Dermatology. 2010;220(1):1-7.

- 415. Mease PJ, Wei N, Fudman EJ, et al. Safety, tolerability, and clinical outcomes after intraarticular injection of a recombinant adeno-associated vector containing a tumor necrosis factor antagonist gene: Results of a phase 1/2 study. Journal of Rheumatology. 2010;37(4):692-703.
- 416. Mehta S, Dasarathy S, Tandon R, et al. A Prospective Randomized Study of the Injurious Effects of Aspirin and Naproxen on the Gastroduodenal Mucosa in Patients With Rheumatoid Arthritis. The American journal of gastroenterology. 1992;87(8):996-1000.
- 417. Meineke I, Turck D. Population Pharmacokinetic Analysis of Meloxicam in Rheumatoid Arthritis Patients. British journal of clinical pharmacology. 2003;55(1):32-8.
- 418. Melikterminas E, Ranganath V, Furst DE. Treatment of the elderly rheumatoid arthritis patient. Future Rheumatology. 2008;3(3):235-8.
- 419. Menter A, Feldman SR, Weinstein GD, et al. A randomized comparison of continuous vs. intermittent infliximab maintenance regimens over 1 year in the treatment of moderate-to-severe plaque psoriasis. J Am Acad Dermatol. 2007 Jan;56(1):31 e1-15.
- 420. Merkel PA, Dooley MA, Dawson DV, et al. Interleukin-2 Receptor Levels in Sera of Patients With Rheumatoid Arthritis Treated With Sulfasalazine, Parenteral Gold, or Placebo. The Journal of rheumatology. 1996;23(11):1856-61.
- 421. Michaels R, Reading J, Beezhold D, et al. Serum Phospholipase A2 Activity in Patients With Rheumatoid Arthritis Before and After Treatment With Methotrexate, Auranofin, or Combination of the Two. Journal of Rheumatology. 1996;23(2):226-9.
- 422. Mierau M, Schoels M, Gonda G, et al. Assessing remission in clinical practice. Rheumatology. 2007;46(6):975-9.
- 423. Miese FR, Ostendorf B, Wittsack HJ, et al. Metacarpophalangeal joints in rheumatoid arthritis: Delayed gadolinium-enhanced MR

- imaging of cartilage A feasibility study. Radiology. 2010;257(2):441-7.
- 424. Miyake K, Kusunoki M, Shinji Y, et al. Bisphosphonate increases risk of gastroduodenal ulcer in rheumatoid arthritis patients on long-term nonsteroidal antiinflammatory drug therapy. Journal of Gastroenterology. 2009;44(2):113-20.
- 425. Miyake K, Ueki N, Suzuki K, et al. Preventive Therapy for Non-Steroidal Anti-Inflammatory Drug-Induced Ulcers in Japanese Patients With Rheumatoid Arthritis: the Current Situation and a Prospective Controlled-Study of the Preventive Effects of Lansoprazole or Famotidine. Alimentary pharmacology & therapeutics. 2005;21(Suppl 2):67-72.
- 426. Miyamoto S, Kageyama Y, Ozeki T, et al. Effects of Glucocorticoids on Bone Mineral Density in Rheumatoid Arthritis Patients. A Longitudinal Study. Archives of orthopaedic and trauma surgery. 1999;199(1-2):18-21.
- 427. Mladenovic V, Domljan Z, Rozman B, et al. Safety and Effectiveness of Leflunomide in the Treatment of Patients With Active Rheumatoid Arthritis. Results of a Randomized, Placebo-Controlled, Phase Ii Study. Arthritis and rheumatism. 1995;38(11):1595-603.
- 428. Montrone F, Petrillo M, Caruso I, et al. A
 Comparison of Severe Gastric Damage as a
 Result of Pirprofen and Naproxen Treatment
 in Rheumatoid Arthritis: a Controlled
 Endoscopic Study. Journal of internal
 medicine. 1994;236(2):153-9.
- 429. Moore A, Gordon KB, Kang S, et al. A randomized, open-label trial of continuous versus interrupted etanercept therapy in the treatment of psoriasis. Journal of the American Academy of Dermatology 2007(4):598-603.
- 430. Moreland L, R G, King K, et al. Results of a Phase-I/II Randomized, Masked, Placebo-Controlled Trial of Recombinant Human Interleukin-11 (Rhil-11) in the Treatment of Subjects With Active Rheumatoid Arthritis. Arthritis Res. 2001;3(4):247-52.

- 431. Moreland LW. Disease modifiers: Making the right therapeutic choices for our patients. Journal of Rheumatology. 2007;34(SUPPL. 79):21-6.
- 432. Moreland LW, Pratt PW, Mayes MD, et al. Double-Blind, Placebo-Controlled Multicenter Trial Using Chimeric Monoclonal Anti-Cd4 Antibody, Cm-T412, in Rheumatoid Arthritis Patients Receiving Concomitant Methotrexate. Arthritis and rheumatism. 1995;38(11):1581-8.
- 433. Morgan AW, Hale G, Rebello PRUB, et al. A pilot study of combination anti-cytokine and anti-lymphocyte biological therapy in rheumatoid arthritis. Qjm. 2008;101(4):299-306.
- 434. Morris V, Cruwys S, Kidd B.
 Characterisation of Capsaicin-Induced
 Mechanical Hyperalgesia as a Marker for
 Altered Nociceptive Processing in Patients
 With Rheumatoid Arthritis. Pain.
 1997;71(2):179-86.
- 435. Mottonen T, Hannonen P, Korpela M, et al. Delay to Institution of Therapy and Induction of Remission Using Single-Drug or Combination-Disease-Modifying Antirheumatic Drug Therapy in Early Rheumatoid Arthritis. Arthritis Rheum. 2002;46(4):894-8.
- 436. Mottonen T, Hannonen P, Leirisalo-Repo M, et al. Comparison of Combination Therapy With Single-Drug Therapy in Early Rheumatoid Arthritis: a Randomised Trial. Lancet. 1999;353(9164):1568-73.
- 437. Mould DR, Davis CB, Minthorn EA, et al. A Population Pharmacokinetic-Pharmacodynamic Analysis of Single Doses of Clenoliximab in Patients With Rheumatoid Arthritis. Clinical pharmacology and therapeutics. 1999;66(3):246-57.
- 438. Muller Fassbender HR. A 6-Month Randomized Dose Range Study of Om-8980 in Rheumatoid Arthritis. Br J Rheumatol. 1993;32(8):746-50.
- 439. Muller-Ladner U, Rockwitz K, Brandt-Jurgens J, et al. Tolerability and patient/physician satisfaction with

- subcutaneously administered methotrexate provided in two formulations of different drug concentrations in patients with rheumatoid arthritis. Open Rheumatology Journal. 2010;4:15-22.
- 440. Mur E, Hartig F, Eibl G, et al. Randomized Double Blind Trial of an Extract From the Pentacyclic Alkaloid-Chemotype of Uncaria Tomentosa for the Treatment of Rheumatoid Arthritis. The Journal of rheumatology. 2002;29(4):678-81.
- 441. Nagafuchi H, Suzuki N, Kaneko A, et al. Prolactin Locally Produced by Synovium Infiltrating T Lymphocytes Induces Excessive Synovial Cell Functions in Patients With Rheumatoid Arthritis. The Journal of rheumatology. 1999;26(9):1890-900.
- 442. Nair R, Saag KG. The use of low-dose glucocorticoids for the treatment of early rheumatoid arthritis: What can we learn about bone effects of glucocorticoids from randomized controlled trials? Current Rheumatology Reports. 2006;8(1):47-8.
- 443. Nakamura H, Ueki Y, Sakito S, et al. Clinical Effects of Actarit in Rheumatoid Arthritis: Improvement of Early Disease Activity Mediated by Reduction of Serum Concentrations of Nitric Oxide. Clinical and experimental rheumatology. 2000;18(4):455-50.
- 444. Naredo E, Collado P, Cruz A, et al.
 Longitudinal power Doppler
 ultrasonographic assessment of joint
 inflammatory activity in early rheumatoid
 arthritis: Predictive value in disease activity
 and radiologic progression. Arthritis Care
 and Research. 2007;57(1):116-24.
- 445. Nehring AK, Dua U, Mollee P, et al. Epstein-Barr virus T-cell immunity despite rituximab. British journal of haematology 2007(4):628-32.
- 446. Nieto-Colonia AM, Santos WS, Keusseyan SP, et al. Antibodies to citrullinated peptides are not associated with the rate of joint destruction in patients with a wellestablished diagnosis of rheumatoid arthritis. Brazilian Journal of Medical and Biological Research. 2008;41(3):188-92.

- 447. Nikolaisen C, Figenschau Y, Nossent JC. Anemia in early rheumatoid arthritis is associated with interleukin 6-mediated bone marrow suppression, but has no effect on disease course or mortality. Journal of Rheumatology. 2008;35(3):380-6.
- 448. Nisar M, Carlisle L, Amos R. Methotrexate and Sulphasalazine as Combination Therapy in Rheumatoid Arthritis. British journal of rheumatology. 1994;33(7):651-4.
- 449. Nishimoto N, Miyasaka N, Yamamoto K, et al. Long-term safety and efficacy of tocilizumab, an anti-IL-6 receptor monoclonal antibody, in monotherapy, in patients with rheumatoid arthritis (the STREAM study): Evidence of safety and efficacy in a 5-year extension study. 2009.
- 450. Nishimoto N, Yoshizaki K, Miyasaka N, et al. Treatment of Rheumatoid Arthritis With Humanized Anti-Interleukin-6 Receptor Antibody: a Multicenter, Double-Blind, Placebo-Controlled Trial. Arthritis and rheumatism. 2004;50(6):1761-9.
- 451. Nived O, Sturfelt G, Eckernas S, et al. A
 Comparison of 6 Months' Compliance of
 Patients With Rheumatoid Arthritis Treated
 With Tenoxicam and Naproxen. Use of
 Patient Computer Data to Assess Response
 to Treatment. The Journal of rheumatology.
 1994;21(8):1537-41.
- 452. Nobunaga M, Yasuda M. Comparison of Clinical Effects of Bucillamine Between Additive Combination and Single Administration Study in Rheumatoid Arthritis. Agents and actions Supplements. 1993;44:105-9.
- 453. Nomura T, Kodama K, Nishimura M, et al. Animation as a useful tool for assessing functional status in psoriatic arthritis. Journal of Dermatological Science. 2006;44(3):172-4.
- 454. Nourmohammadi I, Athari-Nikazm S, Vafa MR, et al. Effects of antioxidant supplementations on oxidative stress in rheumatoid arthritis patients. Journal of Biological Sciences. 2010;10(1):63-6.
- 455. Numo R. Multicentre Double-Blind Study of the Efficacy, Safety and Tolerance of

- Pirazolac Compared With Sulindac in Patients With Rheumatoid Arthritis. Drugs under experimental and clinical research. 1990;16(1):17-27.
- 456. Nunez M, Nunez E, Yoldi C, et al. Health-related quality of life in rheumatoid arthritis: Therapeutic education plus pharmacological treatment versus pharmacological treatment only. Rheumatology International. 2006;26(8):752-7.
- 457. Ochi T, Hakomori S, Fujimoto M, et al. Therapeutic Effect of Intradermal Injections With Difucosyl Lactosamine (Dimeric Lex) on Patients With Rheumatoid Arthritis. The Journal of rheumatology. 1993;20(12):2038-45.
- 458. O'Connor K, Burke R, Riminton S. Hospital supply of off-label immunomodulatory drugs. 2009.
- 459. O'Dell JR, Blakely KW, Mallek JA, et al. Treatment of Early Seropositive Rheumatoid Arthritis: a Two-Year, Double-Blind Comparison of Minocycline and Hydroxychloroquine. Arthritis and rheumatism. 2001;44(10):2235-41.
- 460. O'Dell JR, Leff R, Paulsen G, et al.
 Treatment of Rheumatoid Arthritis With
 Methotrexate and Hydroxychloroquine,
 Methotrexate and Sulfasalazine, or a
 Combination of the Three Medications:
 Results of a Two-Year, Randomized,
 Double-Blind, Placebo-Controlled Trial.
 Arthritis and rheumatism. 2002;46(5):1164-
- 461. O'Dell JR, Paulsen G, Haire CE, et al.
 Treatment of Early Seropositive Rheumatoid
 Arthritis With Minocycline: Four-Year
 Followup of a Double-Blind, PlaceboControlled Trial. Arthritis and rheumatism.
 1999;42(8):1691-5.
- 462. Odio C, Ramirez T, Arias G, et al. Double Blind, Randomized, Placebo-Controlled Study of Dexamethasone Therapy for Hematogenous Septic Arthritis in Children. The Pediatric infectious disease journal. 2003;22(10):883-8.
- 463. Ogrendik M. Treatment of rheumatoid arthritis with ornidazole: A randomized,

- double-blind, placebo-controlled study. Rheumatology International. 2006;26(12):1132-7.
- 464. Ollendorf DA, Klingman D, Hazard E, et al. Differences in annual medication costs and rates of dosage increase between tumor necrosis factor-antagonist therapies for rheumatoid arthritis in a managed care population. Clinical Therapeutics. 2009;31(4):825-35.
- 465. Olsen N, Teal G, Brooks R. Igm-Rheumatoid Factor and Responses to Second-Line Drugs in Rheumatoid Arthritis. Agents and actions. 1991;34(1-2):124-9.
- 466. Olsen NJ, Brooks RH, Cush JJ, et al. A Double-Blind, Placebo-Controlled Study of Anti-Cd5 Immunoconjugate in Patients With Rheumatoid Arthritis. Arthritis and rheumatism. 1996;39(7):1102-8.
- 467. Osiri M, Deesomchok U, Tugwell P. Disease activity and functional changes of RA patients receiving different DMARDs in clinical practice. Clinical Rheumatology 2006;25(5):721-7.
- 468. Osterhaus JT, Purcaru O, Richard L. Discriminant validity, responsiveness and reliability of the rheumatoid arthritis-specific Work Productivity Survey (WPS-RA). 2009.
- 469. Paleolog E, Young S, Stark A, et al. Modulation of Angiogenic Vascular Endothelial Growth Factor by Tumor Necrosis Factor Alpha and Interleukin-1 in Rheumatoid Arthritis. Arthritis and rheumatism. 1998;41(7):1258-65.
- 470. Paleolog EM, Hunt M, Elliott MJ, et al.
 Deactivation of Vascular Endothelium by
 Monoclonal Anti-Tumor Necrosis Factor
 Alpha Antibody in Rheumatoid Arthritis.
 Arthritis and rheumatism. 1996;39(7):1082-
- 471. Palosaari K, Vuotila J, Takalo R, et al. Bone oedema predicts erosive progression on wrist MRI in early RA A 2-yr observational MRI and NC scintigraphy study. Rheumatology. 2006;45(12):1542-8.

- 472. Pandya S, Aggarwal A, Misra R.
 Methotrexate Twice Weekly Vs Once
 Weekly in Rheumatoid Arthritis: a Pilot
 Double-Blind, Controlled Study.
 Rheumatology international. 2002;22(1):1-4.
- 473. Panicheeva S, Ngsriwongse S, Mokkhavesa C, et al. Original Versus Generic Piroxicams, Their Cost-Effective Evaluation in Rheumatoid Arthritis (Ra) Patients.

 Journal of the Medical Association of Thailand = Chotmaihet thangphaet.
 1992;75(2):104-9.
- 474. Park JY, Kim KA, Lee YH, et al. Pharmacokinetic comparison and bioequivalence of two leflunomide formulations in humans: A single dose, randomized, open-label, two-way crossover study. International Journal of Clinical Pharmacology and Therapeutics. 2010;48(4):291-5.
- 475. Pascual-Ramos V, Contreras-Yanez I, Villa AR, et al. Medication persistence over 2 years of follow-up in a cohort of early rheumatoid arthritis patients: Associated factors and relationship with disease activity and with disability. Arthritis Research and Therapy. 2009;11(1).
- 476. Pasero G, Marcolongo R, Serni U, et al. A
 Multi-Centre, Double-Blind Comparative
 Study of the Efficacy and Safety of
 Aceclofenac and Diclofenac in the
 Treatment of Rheumatoid Arthritis. Current
 medical research and opinion.
 1995;13(6):305-15.
- 477. Paul BJ, Thachil EJ, Jayachandran NV, et al. Clinical efficacy and adverse effects of weekly single dose leflunomide in refractory rheumatoid arthritis. Indian Journal of Rheumatology. 2007;2(1):3-7.
- 478. Paulus H, Egger M, Ward J, et al. Analysis of Improvement in Individual Rheumatoid Arthritis Patients Treated With Disease-Modifying Antirheumatic Drugs, Based on the Findings in Patients Treated With Placebo. The Cooperative Systematic Studies of Rheumatic Diseases Group. Arthritis and rheumatism. 1990;33(4):477-84.

- 479. Pavelka K, Jarosova K, Suchy D, et al. Increasing the infliximab dose in rheumatoid arthritis patients: A randomised, double blind study failed to confirm its efficacy. 2009.
- 480. Pavelka K, Recker D, Verburg K.
 Valdecoxib Is as Effective as Diclofenac in
 the Management of Rheumatoid Arthritis
 With a Lower Incidence of Gastroduodenal
 Ulcers: Results of a 26-Week Trial.
 Rheumatology (Oxford). 2003;42(10):120715.
- 481. Pease C, Pope JE, Thorne C, et al. Canadian variation by province in rheumatoid arthritis initiating anti-tumor necrosis factor therapy: Results from the optimization of adalimumab trial. Journal of Rheumatology. 2010;37(12):2469-74.
- 482. Peeters HR, Jongen-Lavrencic M, Bakker CH, et al. Recombinant Human Erythropoietin Improves Health-Related Quality of Life in Patients With Rheumatoid Arthritis and Anaemia of Chronic Disease; Utility Measures Correlate Strongly With Disease Activity Measures. Rheumatology international. 1999;18(5-6):201-6.
- 483. Peeters HR, Jongen-Lavrencic M,
 Vreugdenhil G, et al. Effect of Recombinant
 Human Erythropoietin on Anaemia and
 Disease Activity in Patients With
 Rheumatoid Arthritis and Anaemia of
 Chronic Disease: a Randomised Placebo
 Controlled Double Blind 52 Weeks Clinical
 Trial. Annals of the rheumatic diseases.
 1996;55(10):739-44.
- 484. Peltomaa R, Paimela L, Helve T, et al. Comparison of Intramuscular Gold and Sulphasalazine in the Treatment of Early Rheumatoid Arthritis. A One Year Prospective Study. Scandinavian journal of rheumatology. 1995;24(6):330-5.
- 485. Pentek M, Kobelt G, Czirjak L, et al. Costs of rheumatoid arthritis in Hungary. Journal of Rheumatology. 2007;34(6):1437-9.
- 486. Peretz A, Siderova V, Neve J. Selenium Supplementation in Rheumatoid Arthritis Investigated in a Double Blind, Placebo-Controlled Trial. Scandinavian journal of rheumatology. 2001;30(4):208-12.

- 487. Perez Ruiz F, Alonso Ruiz A, Ansoleaga J. Comparative Study of the Efficacy and Safety of Aceclofenac and Tenoxicam in Rheumatoid Arthritis. Clinical rheumatology. 1996;15(5):473-7.
- 488. Pettersson T, Soderblom T, Nyberg P, et al. Pleural Fluid Soluble Interleukin 2 Receptor in Rheumatoid Arthritis and Systemic Lupus Erythematosus. The Journal of rheumatology. 1994;21(10):1820-4.
- 489. Pincus T, Swearingen CJ, Luta G, et al. Efficacy of prednisone 1-4 mg/day in patients with rheumatoid arthritis: A randomised, double-blind, placebo controlled withdrawal clinical trial. 2009.
- 490. Pisoni L, Murgo A, Paresce E, et al. Effectiveness and safety of leflunomide in the clinical practice. A different experience [1]. Clinical and Experimental Rheumatology. 2007;25(1).
- 491. Plant M, O'Sullivan MM, Lewis P, et al. What Factors Influence Functional Ability in Patients With Rheumatoid Arthritis. Do They Alter Over Time? Rheumatology (Oxford). 2005;44(9):1181-5.
- 492. Plant MJ, Williams AL, O'Sullivan MM, et al. Relationship Between Time-Integrated C-Reactive Protein Levels and Radiologic Progression in Patients With Rheumatoid Arthritis. Arthritis and rheumatism. 2000;43(7):1473-7.
- 493. Podas T, Nightingale JMD, Oldham R, et al. Is rheumatoid arthritis a disease that starts in the intestine? A pilot study comparing an elemental diet with oral prednisolone. Postgraduate Medical Journal. 2007;83(976):128-31.
- 494. Polisson RP, Dooley MA, Dawson DV, et al. Interleukin-2 Receptor Levels in the Sera of Rheumatoid Arthritis Patients Treated With Methotrexate. Arthritis and rheumatism. 1994;37(1):50-6.
- 495. Popp W, Rauscher H, Ritschka L, et al. Prediction of Interstitial Lung Involvement in Rheumatoid Arthritis; the Value of Clinical Data, Chest Roentgenogram, Lung Function, and Serologic Parameters. CHEST. 1992;102(2):391-4.

- 496. Porter D, Capell H. The 'natural' History of Active Rheumatoid Arthritis Over 3-6 Months--an Analysis of Patients Enrolled Into Trials of Potential Disease-Modifying Anti-Rheumatic Drugs, and Treated With Placebo. British journal of rheumatology. 1993;32(6):423-8.
- 497. Porter D, Madhok R, Hunter J, et al.
 Prospective Trial Comparing the Use of
 Sulphasalazine and Auranofin as Second
 Line Drugs in Patients With Rheumatoid
 Arthritis. Annals of the rheumatic diseases.
 1992;52(6):416-4.
- 498. Porter D, McInnes I, Hunter J, et al. Outcome of second line therapy in rheumatoid arthritis. Annals of the rheumatic diseases. 1994;53(12):812-5.
- 499. Prins AMA, Vos K, Franssen EJF. Instability of topical ciclosporin emulsion for nail psoriasis [4]. Dermatology. 2007;215(4):362-3.
- 500. Prochorec-Sobieszek M, Chelstowska M, Rymkiewicz G, et al. Biclonal T-cell receptor gammadelta+ large granular lymphocyte leukemia associated with rheumatoid arthritis. Leukemia and Lymphoma. 2008;49(4):828-31.
- 501. Pullerits R, D'Elia HF, Tarkowski A, et al. The decrease of soluble RAGE levels in rheumatoid arthritis patients following hormone replacement therapy is associated with increased bone mineral density and diminished bone/cartilage turnover: A randomized controlled trial. 2009.
- 502. Puolakka K, Kautiainen H, Mottonen T, et al. Early Suppression of Disease Activity Is Essential for Maintenance of Work Capacity in Patients With Recent-Onset Rheumatoid Arthritis: Five-Year Experience From the Fin-Raco Trial. Arthritis and rheumatism. 2005;52(1):36-41.
- 503. Puolakka K, Kautiainen H, Mottonen T, et al. Use of the Stanford Health Assessment Questionnaire in estimation of long-term productivity costs in patients with recentonset rheumatoid arthritis. Scandinavian Journal of Rheumatology. 2009;38(2):96-103.

- 504. Puolakka K, Kautiainen H, Mottonen T, et al. Impact of Initial Aggressive Drug Treatment With a Combination of Disease-Modifying Antirheumatic Drugs on the Development of Work Disability in Early Rheumatoid Arthritis: a Five-Year Randomized Followup Trial. Arthritis and rheumatism. 2004;50(1):55-62.
- 505. Puri S, Bery A, Sekhon JS, et al. Prescription practices of general physicians in the treatment of rheumatoid arthritis. Indian Journal of Rheumatology. 2008;3(2):86-7.
- 506. Rao U, Naidu M, Kumar T, et al.
 Comparison of Phenytoin With Auranofin and Chloroquine in Rheumatoid Arthritis--a
 Double Blind Study. The Journal of rheumatology. 1995;22(7):1235-40.
- 507. Raspe H, Deck R, Mattussek S. The Outcome of Traditional or Comprehensive Outpatient Care for Rheumatoid Arthritis (Ra). Results of an Open, Non-Randomized, 2-Year Prospective Study. Zeitschrift für Rheumatologie. 1992;51(Suppl 1):61-6.
- 508. Rau R, Herborn G, Karger T, et al. A
 Double-Blind Comparison of Parenteral
 Methotrexate and Parenteral Gold in the
 Treatment of Early Erosive Rheumatoid
 Arthritis: an Interim Report on 102 Patients
 After 12 Months. Seminars in arthritis and
 rheumatism. 1991;21(2 Suppl 1):13-30.
- 509. Rau R, Herborn G, Menninger H, et al. Comparison of Intramuscular Methotrexate and Gold Sodium Thiomalate in the Treatment of Early Erosive Rheumatoid Arthritis: 12 Month Data of a Double-Blind Parallel Study of 174 Patients. British journal of rheumatology. 2997;36(3):345-52.
- 510. Rau R, Herborn G, Menninger H, et al. Progression in Early Erosive Rheumatoid Arthritis: 12 Month Results From a Randomized Controlled Trial Comparing Methotrexate and Gold Sodium Thiomalate. British journal of rheumatology. 1998;37(11):1220-6.
- 511. Rau R, Wassenberg S, Zeidler H. Low Dose Prednisolone Therapy (LDPT) Retards Radiographically Detectable Destruction in

- Early Rheumatoid Arthritis--Preliminary Results of a Multicenter, Randomized, Parallel, Double Blind Study. Zeitschrift für Rheumatologie. 2000;59(Supple 2):II/90-6.
- 512. Reece RJ, Kraan MC, Radjenovic A, et al. Comparative Assessment of Leflunomide and Methotrexate for the Treatment of Rheumatoid Arthritis, by Dynamic Enhanced Magnetic Resonance Imaging. Arthritis and rheumatism. 2002;46(2):366-72.
- 513. Reginster J, Distel M, Bluhmki E. A
 Double-Blind, Three-Week Study to
 Compare the Efficacy and Safety of
 Meloxicam 7.5 Mg and Meloxicam 15 Mg
 in Patients With Rheumatoid Arthritis.
 British journal of rheumatology.
 1996;35(Suppl 1):17-21.
- 514. Rell Bakalarska M, Filipowicz Sosnowska A, Garwolinska H, et al. Assessment of the Results of Combined Treatment With Cyclophosphamide and Prednisone or Methotrexate and Prednisone in Patients With Rheumatoid Arthritis With Concomitant Vasculitis. Reumatologia. 1998;36(1):15-22.
- 515. Rheumatoid Arthritis Clinical Trial Archive Group. The Effect of Age and Renal Function on the Efficacy and Toxicity of Methotrexate in Rheumatoid Arthritis. . J Rheumatol. 1995;22(2):218-23.
- 516. Rigopoulos D, Gregoriou S, Lazaridou E, et al. Treatment of nail psoriasis with adalimumab: An open label unblinded study: ORIGINAL ARTICLE. Journal of the European Academy of Dermatology and Venereology. 2010;24(5):530-4.
- 517. Robak T, Gladalska A, Stepien H. The Tumour Necrosis Factor Family of Receptors/Ligands in the Serum of Patients With Rheumatoid Arthritis. European cytokine network. 1998;9(2):145-54.
- 518. Robinson AJ, Taylor DH, Wright GD. Infliximab therapy reduces periodontoid rheumatoid pannus formation [5]. Rheumatology. 2008;47(2):225-6.
- 519. Rodriguez de la Serna A, Geli Ferrer C, Diaz Lopez C, et al. Comparative Double-

- Blind Study of Droxicam (New Nsaid) Versus Indomethacin in Rheumatoid Arthritis. European journal of rheumatology and inflammation. 1991;11(4):35-44.
- 520. Rozman B. Clinical Experience With Leflunomide in Rheumatoid Arthritis. The Journal of rheumatology. 1998;52(Suppl):27-32.
- 521. Rubbert-Roth A, Tak PP, Zerbini C, et al. Efficacy and safety of various repeat treatment dosing regimens of rituximab in patients with active rheumatoid arthritis: Results of a Phase III randomized study (MIRROR). Rheumatology. 2010;49(9):1683-93.
- 522. Russell AS, Wallenstein GV, Li T, et al. Abatacept improves both the physical and mental health of patients with rheumatoid arthritis who have inadequate response to methotrexate treatment. Ann Rheum Dis. 2007 Feb;66(2):189-94.
- 523. Sacerdote P, Carrabba M, Galante A, et al. Plasma and Synovial Fluid Interleukin-1, Interleukin-6 and Substance P Concentrations in Rheumatoid Arthritis Patients: Effect of the Nonsteroidal Anti Inflammatory Drugs Indomethacin, Diclofenac and Naproxen. Inflammation research: official journal of the European Histamine Research Society [et al]. 1995;44(11):486-90.
- 524. Salaffi F, Filippucci E, Carotti M, et al. Inter-observer agreement of standard joint counts in early rheumatoid arthritis: A comparison with grey scale ultrasonography A preliminary study. Rheumatology. 2008;47(1):54-8.
- 525. Salemi S, Picchianti-Diamanti A, Germano V, et al. Influenza vaccine administration in rheumatoid arthritis patients under treatment with TNF(alpha) blockers: Safety and immunogenicity. Clinical Immunology. 2010;134(2):113-20.
- 526. Salvarani C, Macchioni P, Manzini C, et al. Infliximab plus prednisone or placebo plus prednisone for the initial treatment of polymyalgia rheumatica: a randomized trial. Annals of internal medicine 2007(9):631-9.

- 527. Sanchez Andrada S, Rodriguez Valverde V. A Double-Blind Randomised Controlled Trial of Droxicam Versus Indomethacin in Rheumatoid Arthritis. European journal of rheumatology and inflammation. 1991;11(4):35-44.
- 528. Sander O, Rau R. Treatment of Refractory Rheumatoid Arthritis With a Tumor Necrosis Factor Alpha Receptor Fusion Protein (Tnfr 55-Igg1) a Monocentric Observation in 80 Patients. Zeitschrift fur Rheumatologie. 1998;57(5):307-11.
- 529. Sands BE, Kozarek R, Spainhour J, et al. Safety and tolerability of concurrent natalizumab treatment for patients with Crohn's disease not in remission while receiving infliximab. Inflammatory bowel diseases 2007(1):2-11.
- 530. Sany J, Anaya JM, Canovas F, et al. Influence of Methotrexate on the Frequency of Postoperative Infectious Complications in Patients With Rheumatoid Arthritis. The Journal of rheumatology. 1993;20(7):1129-32.
- 531. Sarzi Puttini P, Santandrea S, Boccassini L, et al. The Role of Nsaids in Psoriatic Arthritis: Evidence From a Controlled Study With Nimesulide. Clinical and experimental rheumatology. 2001;19(1 Suppl 22):S17-20.
- 532. Sasso E, Merrill C, Furst T.
 Immunoglobulin Binding Properties of the
 Prosorba Immunadsorption Column in
 Treatment of Rheumatoid Arthritis. Ther
 Apher. 2001;5(2):84-91.
- 533. Saul P, Korlipara K. Acemetacin and Indomethacin in the Treatment of Rheumatoid Arthritis: a Double-Blind Comparative Study in General Practice. Current medical research and opinion. 1991;12(5):332-41.
- 534. Savolainen E, Kautiainen H, Koivula MK, et al. Change of diagnoses and outcome of patients with early inflammatory joint diseases during a mean 13-month follow-up. Scandinavian Journal of Rheumatology. 2007;36(3):194-7.
- 535. Schattenkirchner M. Double-Blind Comparison of Etodolac and Piroxicam in

- Patients With Rheumatoid Arthritis. Curr Med Res Opin. 1991;12(8):497-506.
- 536. Scheel AK, Hermann KGA, Ohrndorf S, et al. Prospective 7 year follow up imaging study comparing radiography, ultrasonography, and magnetic resonance imaging in rheumatoid arthritis finger joints. Annals of the Rheumatic Diseases. 2006;65(5):595-600.
- 537. Schiff MH. Role of Interleukin 1 and Interleukin 1 Receptor Antagonist in the Mediation of Rheumatoid Arthritis. Ann Rheum Dis. 2000;59(Suppl 1):i103-8.
- 538. Schirmer M, Mur E, Pfeiffer K, et al. The Safety Profile of Low-Dose Cladribine in Refractory Rheumatoid Arthritis. A Pilot Trial. Scandinavian journal of rheumatology. 1997;26(5):376-9.
- 539. Schlumpf U, Hofmann P. Comparison of Medium- and High-Dose Methylprednisolone Pulse Therapy in Rheumatoid Arthritis. Zeitschrift fur Rheumatologie. 1990;49(3):160-4.
- 540. Schmajuk G, Schneeweiss S, Katz JN, et al. Treatment of older adult patients diagnosed with rheumatoid arthritis: Improved but not optimal. Arthritis Care and Research. 2007;57(6):928-34.
- 541. Schnabel A, Herlyn K, Burchardi C, et al. Long-Term Tolerability of Methotrexate at Doses Exceeding 15 Mg Per Week in Rheumatoid Arthritis. Rheumatology international. 1996;15(5):195-200.
- 542. Schnabel A, Reinhold K, Willmann V, et al. Side Effects and Efficacy of 15 Mg and 25 Mg Methotrexate Per Week in Rheumatoid Arthritis. Z RHEUMATOL. 1994;53(3):142-9.
- 543. Schnabel A, Reinhold Keller E, Willmann V, et al. Tolerability of Methotrexate Starting With 15 or 25 Mg/Week for Rheumatoid Arthritis. Rheumatology international. 1994;14(1):33-8.
- 544. Schnitzer TJ, Truitt K, Fleischmann R, et al. The Safety Profile, Tolerability, and Effective Dose Range of Rofecoxib in the

- Treatment of Rheumatoid Arthritis. Clinical Therapeutics. 1999;21(10):1688-702.
- 545. Schrohenloher R, Koopman W, Woodworth T, et al. Suppression of in Vitro IgM Rheumatoid Factor Production by Diphtheria Toxin Interleukin 2 Recombinant Fusion Protein (Dab 486il-2) in Patients With Refractory Rheumatoid Arthritis. The Journal of rheumatology. 1996;23(11):1845-8
- 546. Schuerwegh AJ, van Offel JF, Bridts CH, et al. Influence of Longterm Therapy With Methotrexate and Low Dose Corticosteroids on Type 1 and Type 2 Cytokine Production in Cd4+ and Cd8+ T Lymphocytes of Patients With Rheumatoid Arthritis. The Journal of rheumatology. 2001;28(8):1793-9.
- 547. Schuerwegh AJ, Van Offel JF, Stevens WJ, et al. Influence of Therapy With Chimeric Monoclonal Tumour Necrosis Factor-Alpha Antibodies on Intracellular Cytokine Profiles of T Lymphocytes and Monocytes in Rheumatoid Arthritis Patients. Rheumatology (Oxford). 2003;42(4):541-8.
- 548. Schwartz JI, Agrawal NG, Wong PH, et al. Lack of Pharmacokinetic Interaction
 Between Rofecoxib and Methotrexate in
 Rheumatoid Arthritis Patients. Journal of clinical pharmacology. 2001;41(10):1120-30.
- 549. Scott BL, Ramakrishnan A, Fosdal M, et al. Anti-thymocyte globulin plus etanercept as therapy for myelodysplastic syndromes (MDS): A phase II study. British Journal of Haematology. 2010;149(5):706-10.
- 550. Scott DL. Leflunomide Improves Quality of Life in Rheumatoid Arthritis. Scandinavian journal of rheumatology Supplement. 1999;112:23-9.
- 551. Scott DL, Smolen JS, Kalden JR, et al.
 Treatment of Active Rheumatoid Arthritis
 With Leflunomide: Two Year Follow up of
 a Double Blind, Placebo Controlled Trial
 Versus Sulfasalazine. Annals of the
 rheumatic diseases. 2001;60(10):913-23.
- 552. Seideman P. Additive Effect of Combined Naproxen and Paracetamol in Rheumatoid

- Arthritis. British journal of rheumatology. 1993;32(12):1077-82.
- 553. Seideman P. Better Effect of Methotrexate on C-Reactive Protein During Daily Compared to Weekly Treatment in Rheumatoid Arthritis. Clinical rheumatology. 1993;12(2):347-9.
- 554. Seideman P, Beck O, Eksborg S, et al. The Pharmacokinetics of Methotrexate and Its 7-Hydroxy Metabolite in Patients With Rheumatoid Arthritis. British journal of clinical pharmacology. 1993;35(4):409-12.
- 555. Seppala E, Nissila M, Isomaki H, et al. Effects of Non-Steroidal Anti-Inflammatory Drugs and Prednisolone on Synovial Fluid White Cells, Prostaglandin E2, Leukotriene B4 and Cyclic Amp in Patients With Rheumatoid Arthritis. Scandinavian journal of rheumatology. 1990;19(1):71-5.
- 556. Sharif M, Salisbury C, Taylor D, et al. Changes in Biochemical Markers of Joint Tissue Metabolism in a Randomized Controlled Trial of Glucocorticoid in Early Rheumatoid Arthritis. Arthritis and rheumatism. 1998;41(7):1203-9.
- 557. Sharp JT, Strand V, Leung H, et al.
 Treatment With Leflunomide Slows
 Radiographic Progression of Rheumatoid
 Arthritis: Results From Three Randomized
 Controlled Trials of Leflunomide in Patients
 With Active Rheumatoid Arthritis. Arthritis
 and rheumatism. 2000;43(3):495-505.
- 558. Shashikumar NS, Shivamurthy MC, Chandrashekara S. Evaluation of efficacy of combination of methotrexate and hydroxychloroquine with leflunomide in active rheumatoid arthritis. Indian Journal of Pharmacology 2010;42(6):358-61.
- 559. Sheeran T, Roobottom C, Wanklyn P, et al. The Effect of Bed Rest and Intra-Articular Steroids on the Acute Phase Response in Rheumatoid Arthritis. Clinical and experimental rheumatology. 1993;11(1):49-52.
- 560. Sheldon P. Ileum-Targeted Steroid Therapy in Rheumatoid Arthritis: Double-Blind, Placebo-Controlled Trial of Controlled-

- Release Budesonide. Rheumatology international. 2003;23(4):154-8.
- 561. Shi W, Wang Y, Li L, et al. Safety and Efficacy of Oral Nonsteroidal Anti-Inflammatory Drugs in Patients With Rheumatoid Arthritis: a Six-Month Randomised Study. Clinical Drug Investigation. 2004;24(2):89-101.
- 562. Shikiar R, Heffernan M, Langley RG, et al. Adalimumab treatment is associated with improvement in health-related quality of life in psoriasis: patient-reported outcomes from a phase II randomized controlled trial. The Journal of dermatological treatment 2007(1):25-31.
- 563. Shiokawa Y, Shichikawa K, Nobunaga M, et al. Clinical Study of a New Anti-Rheumatic Drug, Ms-932 on Rheumatoid Arthritis: Double-Blind Comparative Study With Placebo. Rinsho Iyaku (Journal of Clinical Therapeutics and Medicines). 1991;7(Suppl 2):113-47.
- 564. Shiozawa S, Shiozawa K, Kita M, et al. A Preliminary Study on the Effect of Alpha-Interferon Treatment on the Joint Inflammation and Serum Calcium in Rheumatoid Arthritis. British journal of rheumatology. 1992;31(6):405-8.
- 565. Shiroky J, Neville C, Skelton J. High Dose Intravenous Methotrexate for Refractory Rheumatoid Arthritis. The Journal of rheumatology. 1992;19(2):247-51.
- 566. Shiroky JB, Neville C, Esdaile JM, et al. Low-Dose Methotrexate With Leucovorin (Folinic Acid) in the Management of Rheumatoid Arthritis. Results of a Multicenter Randomized, Double-Blind, Placebo-Controlled Trial. Arthritis and rheumatism. 1993;36(6):795-803.
- 567. Siddiqui AK, Huberfeld SI, Weidenheim KM, et al. Hydroxychloroquine-induced toxic myopathy causing respiratory failure. Chest. 2007;131(2):588-90.
- 568. Sieper J, Fendler C, Laitko S, et al. No Benefit of Long-Term Ciprofloxacin Treatment in Patients With Reactive Arthritis and Undifferentiated Oligoarthritis: a Three-Month, Multicenter, Double-Blind,

- Randomized, Placebo-Controlled Study. Arthritis and rheumatism. 1999;42(7):1386-96
- 569. Sigidin Y, Loukina G, Skurkovich B, et al. Randomized, Double-Blind Trial of Anti-Interferon-Gamma Antibodies in Rheumatoid Arthritis. Scandinavian journal of rheumatology. 2001;30(4):203-7.
- 570. Silverstein FE, Graham DY, Senior JR, et al. Misoprostol Reduces Serious Gastrointestinal Complications in Patients With Rheumatoid Arthritis Receiving Nonsteroidal Anti-Inflammatory Drugs. A Randomized, Double-Blind, Placebo-Controlled Trial. Annals of internal medicine. 1995;123(4):241-9.
- 571. Simon F, Parola P, Grandadam M, et al. Chikungunya infection: An emerging rheumatism among travelers returned from Indian Ocean islands. Report of 47 cases. Medicine. 2007;86(3):123-37.
- 572. Simon L, Robinson D, Basch C. Naproxen Levels in Plasma and Synovial Fluid of Patients With Rheumatoid Arthritis. CLIN THER. 1991;13(Suppl A):35-43.
- 573. Simon LS, Weaver AL, Graham DY, et al. Anti-Inflammatory and Upper Gastrointestinal Effects of Celecoxib in Rheumatoid Arthritis: a Randomized Controlled Trial. JAMA. 1999;282(20):1921-8.
- 574. Slaughter JR, Parker JC, Martens MP, et al. Clinical Outcomes Following a Trial of Sertraline in Rheumatoid Arthritis. Psychosomatics. 2002;43(1):36-41.
- 575. Smieja M, MacPherson DW, Kean W, et al. Randomised, Blinded, Placebo Controlled Trial of Doxycycline for Chronic Seronegative Arthritis. Annals of the rheumatic diseases. 2001;60(12):1088-94.
- 576. Smith AM, Sperling JW, O'Driscoll SW, et al. Arthroscopic shoulder synovectomy in patients with rheumatoid arthritis.

 Arthroscopy Journal of Arthroscopic and Related Surgery. 2006;22(1):50-6.

- 577. Smith DM, Johnson JA, Loeser R, et al. Evaluation of Tenidap (Cp-66,248) on Human Neutrophil Arachidonic Acid Metabolism, Chemotactic Potential and Clinical Efficacy in the Treatment of Rheumatoid Arthritis. Agents and actions. 1990;31(1-2):102-9.
- 578. Smolen J, Emery P. Efficacy and Safety of Leflunomide in Active Rheumatoid Arthritis. Rheumatology. 2000;39(Suppl 1):48-56.
- 579. Smolen JS. Efficacy and Safety of the New Dmard Leflunomide: Comparison to Placebo and Sulfasalazine in Active Rheumatoid Arthritis. Scandinavian journal of rheumatology Supplement. 1999;112:15-21.
- 580. Smolen JS, Kalden JR, Scott DL, et al.
 Efficacy and Safety of Leflunomide
 Compared With Placebo and Sulphasalazine
 in Active Rheumatoid Arthritis: a DoubleBlind, Randomised, Multicentre Trial.
 Lancet. 1999;353(9149):259-66.
- 581. Snowden JA, Biggs JC, Milliken ST, et al. A Randomised, Blinded, Placebo-Controlled, Dose Escalation Study of the Tolerability and Efficacy of Filgrastim for Haemopoietic Stem Cell Mobilisation in Patients With Severe Active Rheumatoid Arthritis. Bone marrow transplantation. 1998;22(11):1035-41.
- 582. Soderlin MK, Geborek P. Changing pattern in the prescription of biological treatment in rheumatoid arthritis. A 7-year follow-up of 1839 patients in southern Sweden. Annals of the Rheumatic Diseases. 2008;67(1):37-42.
- 583. Song YW, Lee EY, Koh EM, et al.
 Assessment of comparative pain relief and tolerability of SKI306X compared with celecoxib in patients with rheumatoid arthritis: A 6-week, multicenter, randomized, double-blind, double-dummy, phase III, noninferiority clinical trial.
 Clinical Therapeutics. 2007;29(5):862-73.
- 584. Spalding SJ, Kent CK, Boudreau R, et al.
 Three-dimensional and thermal surface
 imaging produces reliable measures of joint
 shape and temperature: A potential tool for

- quantifying arthritis. Arthritis Research and Therapy. 2008;10(1).
- 585. Sreekanth V, Handa R, Wali J, et al.
 Doxycycline in the Treatment of
 Rheumatoid Arthritis--a Pilot Study. The
 Journal of the Association of Physicians of
 India. 2000;48(8):804-7.
- 586. St Clair EW, Cohen SB, Lee ML, et al. Treatment of Rheumatoid Arthritis With a Dr4/1 Peptide. The Journal of rheumatology. 2000;27(8):1855-63.
- 587. St Clair EW, Wagner CL, Fasanmade AA, et al. The Relationship of Serum Infliximab Concentrations to Clinical Improvement in Rheumatoid Arthritis: Results From Attract, a Multicenter, Randomized, Double-Blind, Placebo-Controlled Trial. Arthritis and rheumatism. 2002;46(6):1451-9.
- 588. Steen KSS, Nurmohamed MT, Visman I, et al. Decreasing incidence of symptomatic gastrointestinal ulcers and ulcer complications in patients with rheumatoid arthritis. Annals of the Rheumatic Diseases. 2008;67(2):256-9.
- 589. Stenberg VI, Fiechtner JJ, Rice JR, et al. Endocrine Control of Inflammation: Rheumatoid Arthritis Double-Blind, Crossover Clinical Trial. International journal of clinical pharmacology research. 1992;12(1):11-8.
- 590. Stewart C, Fleming R, Arkin C, et al. Coadministration of Naproxen and Low-Dose Methotrexate in Patients With Rheumatoid Arthritis. Clinical Pharmacology & Therapeutics. 1990;47(4):540-6.
- 591. Stichenwirth M, Riedl E, Pehamberger H, et al. Pyoderma Gangrenosum in a patient with seronegative rheumatoid arthritis during therapy with adalimumab: Toxic effects of adalimumab or failure of adalimumab to prevent the onset of this phenomenon? Archives of Dermatology. 2008;144(6):817-8.
- 592. Stoch SA, Saag KG, Greenwald M, et al. Once-weekly oral alendronate 70 mg in patients with glucocorticoid-induced bone

- loss: A 12-month randomized, placebocontrolled clinical trial. 2009.
- 593. Strand V, Cohen S, Schiff M, et al.
 Treatment of Active Rheumatoid Arthritis
 With Leflunomide Compared With Placebo
 and Methotrexate. Archives of Internal
 Medicine. 1999;159(21):2542-50.
- 594. Stubenrauch K, Wessels U, Birnboeck H, et al. Subset analysis of patients experiencing clinical events of a potentially immunogenic nature in the pivotal clinical trials of tocilizumab for rheumatoid arthritis:

 Evaluation of an antidrug antibody ELISA using clinical adverse event-driven immunogenicity testing. Clinical Therapeutics. 2010;32(9):1597-609.
- 595. Suarez Almazor M, Russell A. Parenteral Methotrexate or Gold for Rheumatoid Arthritis: a Follow up. Clinical & Experimental Rheumatology. 1990;8(2):163-6.
- 596. Subbanna PKT, Chandy SJ, Danda D, et al. Correlation between serum methotrexate concentrations and disease remission status in rheumatoid arthritis patients on triple disease-modifying antirheumatic drug therapy [1]. Indian Journal of Pharmacology. 2007;39(2):117-8.
- 597. Sugiura F, Kojima T, Oguchi T, et al. A case of peripheral neuropathy and skin ulcer in a patient with rheumatoid arthritis after a single infusion of tocilizumab. Modern Rheumatology. 2009;19(2):199-203.
- 598. Sundal E, Bertelletti D. Thymopentin
 Treatment of Rheumatoid Arthritis. Progress
 in drug research Fortschritte der
 Arzneimittelforschung Progrès des
 recherches pharmaceutiques.
 1994;44(10):1145-9.
- 599. Suzuki A, Yamada R, Ohtake-Yamanaka M, et al. Anti-Citrullinated Collagen Type I Antibody Is a Target of Autoimmunity in Rheumatoid Arthritis. Biochemical and biophysical research communications. 2005;333(2):418-26.
- 600. Svensson B, Boonen A, Albertsson K, et al. Low-Dose Prednisolone in Addition to the Initial Disease-Modifying Antirheumatic

- Drug in Patients With Early Active Rheumatoid Arthritis Reduces Joint Destruction and Increases the Remission Rate: a Two-Year Randomized Trial. Arthritis and rheumatism. 2005;52(11):3360-70.
- 601. Symmons D, Tricker K, Harrison M, et al. Patients with stable long-standing rheumatoid arthritis continue to deteriorate despite intensified treatment with traditional disease modifying anti-rheumatic drugs Results of the British Rheumatoid Outcome Study Group randomized controlled clinical trial. Rheumatology. 2006;45(5):558-65.
- 602. Symmons D, Tricker K, Roberts C, et al. The British Rheumatoid Outcome Study Group (Brosg) Randomised Controlled Trial to Compare the Effectiveness and Cost-Effectiveness of Aggressive Versus Symptomatic Therapy in Established Rheumatoid Arthritis. Health Technol Assess. 2005;9(34):iii-iv, ix-x, 1-78.
- 603. Szmyrka-Kaczmarek M, Nowak B, Swierkot J, et al. Antinuclear antibodies and anticyclic citrullinated peptide antibodies in patients treated with adalimumab. Central European Journal of Immunology. 2008;33(3):120-6.
- 604. Taha AS, McLaughlin S, Holland PJ, et al. Effect on Gastric and Duodenal Mucosal Prostaglandins of Repeated Intake of Therapeutic Doses of Naproxen and Etodolac in Rheumatoid Arthritis. Annals of the rheumatic diseases. 1990;49(6):354-8.
- 605. Tak PP, Taylor PC, Breedveld FC, et al. Decrease in cellularity and expression of adhesion molecules by anti-tumor necrosis factor alpha monoclonal antibody treatment in patients with rheumatoid arthritis.

 Arthritis and rheumatism. 1996;39(7):1077-81.
- 606. Tak PP, van der Lubbe PA, Cauli A, et al. Reduction of Synovial Inflammation After Anti-Cd4 Monoclonal Antibody Treatment in Early Rheumatoid Arthritis. Arthritis and rheumatism. 1995;38(10):1457-65.
- 607. Takada K, Danning C, Kuroiwa T, et al. Lymphocyte Depletion With Fludarabine in Patients With Psoriatic Arthritis: Clinical

- and Immunological Effects. Annals of the rheumatic diseases. 2003;62(11):1112-5.
- 608. Takahashi M, Suzuki M, Kushida K, et al. Relationship Between Pentosidine Levels in Serum and Urine and Activity in Rheumatoid Arthritis. British journal of rheumatology. 1997;36(6):637-42.
- 609. Tanno M, Nakamura I, Kobayashi S, et al. New-onset demyelination induced by infliximab therapy in two rheumatoid arthritis patients. Clinical Rheumatology. 2006;25(6):929-33.
- 610. Taukumova L, Mouravjoy Y, Gribakin S. Mucocutaneous Side Effects and Continuation of Aurotherapy in Patients With Rheumatoid Arthritis. Advances in experimental medicine and biology. 1999;455:367-73.
- 611. Taylor P, Steuer A, Gruber J, et al. Ultrasonographic and radiographic results from a two-year controlled trial of immediate or one-year-delayed addition of infliximab to ongoing methotrexate therapy in patients with erosive early rheumatoid arthritis. Arthritis and rheumatism. 2006 2006;54(1):47-53.
- 612. Taylor PC, Steuer A, Gruber J, et al.
 Comparison of Ultrasonographic
 Assessment of Synovitis and Joint
 Vascularity With Radiographic Evaluation
 in a Randomized, Placebo-Controlled Study
 of Infliximab Therapy in Early Rheumatoid
 Arthritis. Arthritis and rheumatism.
 2004;50(4):1107-16.
- 613. Tebib J, Mariette X, Bourgeois P, et al.

 Masitinib in the treatment of active rheumatoid arthritis: Results of a multicentre, open-label, dose-ranging, phase 2a study. 2009.
- 614. Tebib JG, Manil LM, Modder G, et al.
 Better Results With Rhenium-186
 Radiosynoviorthesis Than With Cortivazol
 in Rheumatoid Arthritis (Ra): a Two-Year
 Follow-up Randomized Controlled
 Multicentre Study. Clinical and
 experimental rheumatology.
 2004;22(5):609-16.

- 615. Tegelberg A, Kopp S. A 3-Year Follow-up of Temporomandibular Disorders in Rheumatoid Arthritis and Ankylosing Spondylitis. Acta odontologica Scandinavica. 1996;54(1):14-8.
- 616. Teir J, Koduri G, Meadows A, et al. An audit of recording cardiovascular risk factors in patients with rheumatoid arthritis and systemic lupus erythematosus in centres in East Anglia and the South East.

 Rheumatology. 2008;47(8):1252-4.
- 617. ten Klooster PM, Drossaers-Bakker KW, Taal E, et al. Can we assess baseline pain and global health retrospectively? Clinical and Experimental Rheumatology. 2007;25(2):176-81.
- 618. Ten Klooster PM, Veehof MM, Taal E, et al. Changes in priorities for improvement in patients with rheumatoid arthritis during 1 year of anti-tumour necrosis factor treatment. Annals of the Rheumatic Diseases. 2007;66(11):1485-90.
- 619. ten Wolde S, Breedveld FC, Hermans J, et al. Randomised Placebo-Controlled Study of Stopping Second-Line Drugs in Rheumatoid Arthritis. Lancet. 1996;347(8998):347-52.
- 620. Tenembaum SN. Therapy of multiple sclerosis in children and adolescents. Clinical Neurology and Neurosurgery. 2010;112(7):633-40.
- 621. Tesser J, Fleischmann R, Dore R, et al.
 Concomitant Medication Use in a Large,
 International, Multicenter, Placebo
 Controlled Trial of Anakinra, a
 Recombinant Interleukin 1 Receptor
 Antagonist, in Patients With Rheumatoid
 Arthritis. The Journal of rheumatology.
 2004;31(4):649-54.
- 622. Tett S, Cutler D, Beck C, et al.
 Concentration-Effect Relationship of
 Hydroxychloroquine in Patients With
 Rheumatoid Arthritis--a Prospective, Dose
 Ranging Study. The Journal of
 rheumatology. 2000;27(7):1656-60.
- 623. The Australian Multicentre Clinical Trial Group. Sulfasalazine in Early Rheumatoid Arthritis. J Rheumatol. 1992 7;19(11):1672.

- 624. Thurlings RM, Boumans M, Tekstra J, et al. Relationship between the type I interferon signature and the response to rituximab in rheumatoid arthritis patients. Arthritis Care and Research. 2010;62(12):3607-14.
- 625. Tikiz C, Utuk O, Pirildar T, et al. Effects of Angiotensin-Converting Enzyme Inhibition and Statin Treatment on Inflammatory Markers and Endothelial Functions in Patients With Longterm Rheumatoid Arthritis. The Journal of rheumatology. 2005;32(11):2095-101.
- 626. Tilley BC, Alarcon GS, Heyse SP, et al. Minocycline in Rheumatoid Arthritis. A 48-Week, Double-Blind, Placebo-Controlled Trial. Mira Trial Group. Annals of internal medicine. 1995;122(2):81-9.
- 627. Torsteinsdottir I, Groth T, U L. Production and Elimination of Hyaluronan in Rheumatoid Arthritis Patients: Estimation With a Loading Test. Seminars in arthritis and rheumatism. 1999;28(4):268-79.
- 628. Toussirot E, Pertuiset E, Kantelip B, et al. Sarcoidosis occuring during anti-TNF-alpha treatment for inflammatory rheumatic diseases: Report of two cases. Clinical and Experimental Rheumatology. 2008;26(3):471-5.
- 629. Tracy T, Worster T, Bradley J, et al.
 Methotrexate Disposition Following
 Concomitant Administration of Ketoprofen,
 Piroxicam and Flurbiprofen in Patients With
 Rheumatoid Arthritis. British journal of
 clinical pharmacology. 1994;37(5):453-6.
- 630. Tugwell P, Bombardier C, Buchanan WW, et al. Methotrexate in Rheumatoid Arthritis. Impact on Quality of Life Assessed by Traditional Standard-Item and Individualized Patient Preference Health Status Questionnaires. Archives of internal medicine. 1990;150(1):59-62.
- 631. Turiel M, Tomasoni L, Sitia S, et al. Effects of long-term disease-modifying antirheumatic drugs on endothelial function in patients with early rheumatoid arthritis. Cardiovascular Therapeutics. 2010;28(5):e53-e64.

- 632. Tutuncu Z, Kavanaugh A. Treatment of elderly rheumatoid arthritis. Future Rheumatology. 2007;2(3):313-9.
- 633. Uddenfeldt P, Leden I, Rubin B. A Double-Blind Comparison of Oral Ketoprofen 'controlled Release' and Indomethacin Suppository in the Treatment of Rheumatoid Arthritis With Special Regard to Morning Stiffness and Pain on Awakening. Current medical research and opinion. 1993;13(3):127-32.
- 634. Uutela T, Hannonen P, Kautianen H, et al. Positive treatment response improves the health-ralated quality of life of patients with early rheumatiod arthritis. Clinical and Experimental Rheumatology. 2009;27(1):108-11.
- 635. Valleala H, Laasonen L, Koivula M-K, et al. Two Year Randomized Controlled Trial of Etidronate in Rheumatoid Arthritis: Changes in Serum Aminoterminal Telopeptides Correlate With Radiographic Progression of Disease. The Journal of rheumatology. 2003;30(3):468-73.
- 636. Valleala H, Laitinen K, Pylkkanen L, et al. Clinical and Biochemical Response to Single Infusion of Clodronate in Active Rheumatoid Arthritis Double Blind Placebo Controlled Study. Inflammation Research. 2001;50(12):598-601.
- 637. Van Aken J, Van Dongen H, Le Cessie S, et al. Comparison of long term outcome of patients with rheumatoid arthritis presenting with undifferentiated arthritis or with rheumatoid arthritis: An observational cohort study. Annals of the Rheumatic Diseases. 2006;65(1):20-5.
- 638. van Berlo WTM, van de Wiel HBM, Taal E, et al. Sexual functioning of people with rheumatoid arthritis: A multicenter study. Clinical Rheumatology. 2007;26(1):30-8.
- 639. Van Den Bemt BJF, Van Den Hoogen FHJ, Benraad B, et al. Adherence rates and associations with nonadherence in patients with rheumatoid arthritis using disease modifying antirheumatic drugs. 2009.
- 640. Van Der Bijl AE, Teng YKO, Van Oosterhout M, et al. Efficacy of

- intraarticular infliximab in patients with chronic or recurrent gonarthritis: A clinical randomized trial. 2009.
- 641. Van Der Heijde D, Breedveld FC, Kavanaugh A, et al. Disease activity, physical function, and radiographic progression after longterm therapy with adalimumab plus methotrexate: 5-Year results of PREMIER. Journal of Rheumatology. 2010;37(11):2237-46.
- 642. Van Der Kooij SM, Goekoop-Ruiterman YPM, De Vries-Bouwstra JK, et al. Probability of continued low disease activity in patients with recent onset rheumatoid arthritis treated according to the disease activity score. Annals of the Rheumatic Diseases 2008;67(2):266-9.
- otalistics of the following states of the following st
- 644. van der Lubbe PA, Reiter C, Breedveld FC, et al. Chimeric Cd4 Monoclonal Antibody Cm-T412 as a Therapeutic Approach to Rheumatoid Arthritis. Arthritis and rheumatism. 1993;36(10):1375-9.
- 645. van der Lubbe PA, Reiter C, Miltenburg AM, et al. Treatment of Rheumatoid Arthritis With a Chimeric Cd4 Monoclonal Antibody (Cm-T412):

 Immunopharmacological Aspects and Mechanisms of Action. Scandinavian journal of immunology. 1994;39(3):286-94.
- 646. van der Veen M, Bijlsma J. The Effect of Methylprednisolone Pulse Therapy on Methotrexate Treatment of Rheumatoid Arthritis. Clinical rheumatology. 1993;12(4):74-6.
- 647. van Ede AE, Laan RFJM, Blom HJ, et al. Homocysteine and Folate Status in Methotrexate-Treated Patients With Rheumatoid Arthritis. Rheumatology (Oxford). 2002;41(6):658-65.
- 648. Van Eijk Y, Boonen A, Schulpen G, et al. Safety and patient satisfaction of infliximab administration in an extramural setting

- supervised by a rheumatology specialist nurse. Annals of the Rheumatic Diseases. 2006:65(2).
- 649. van Everdingen AA, Jacobs JWG, Siewertsz Van Reesema DR, et al. Low-Dose Prednisone Therapy for Patients With Early Active Rheumatoid Arthritis: Clinical Efficacy, Disease-Modifying Properties, and Side Effects: a Randomized, Double-Blind, Placebo-Controlled Clinical Trial. Annals of internal medicine. 2002;136(1):1-12.
- 650. van Everdingen AA, Siewertsz van Reesema DR, Jacobs JWG, et al. Low-Dose Glucocorticoids in Early Rheumatoid Arthritis: Discordant Effects on Bone Mineral Density and Fractures? Clinical and experimental rheumatology. 2003;21(2):155-60.
- of S1. van Everdingen AA, Siewertsz van Reesema DR, Jacobs JWG, et al. The Clinical Effect of Glucocorticoids in Patients With Rheumatoid Arthritis May Be Masked by Decreased Use of Additional Therapies. Arthritis and rheumatism. 2004;51(2):217-20.
- 652. van Holten J, Pavelka K, Vencovsky J, et al. A Multicentre, Randomised, Double Blind, Placebo Controlled Phase Ii Study of Subcutaneous Interferon Beta-1a in the Treatment of Patients With Active Rheumatoid Arthritis. Ann Rheum Dis. 2005;64(1):64-9.
- 653. van Jaarsveld CH, Jacobs JW, van der Veen MJ, et al. Aggressive Treatment in Early Rheumatoid Arthritis: a Randomised Controlled Trial. Annals of the Rheumatic Diseases. 2000;59(6):468-77.
- 654. van Jaarsveld CH, Jahangier ZN, Jacobs JW, et al. Toxicity of Anti-Rheumatic Drugs in a Randomized Clinical Trial of Early Rheumatoid Arthritis. Rheumatology (Oxford). 2000;39(12):1374-82.
- 655. Van Kuijk AWR, Gerlag DM, Vos K, et al. A prospective, randomised, placebocontrolled study to identify biomarkers associated with active treatment in psoriatic arthritis: Effects of adalimumab treatment on synovial tissue. 2009.

- 656. Van Offel JF, Schuerwegh AJ, Bridts CH, et al. Influence of Cyclic Intravenous Pamidronate on Proinflammatory Monocytic Cytokine Profiles and Bone Density in Rheumatoid Arthritis Treated With Low Dose Prednisolone and Methotrexate. Clinical and experimental rheumatology. 2001;19(1):13-20.
- 657. Van Riel PLCM, Freundlich B, MacPeek D, et al. Patient-reported health outcomes in a trial of etanercept monotherapy versus combination therapy with etanercept and methotrexate for rheumatoid arthritis: The ADORE trial. Annals of the Rheumatic Diseases 2008;67(8):1104-10.
- 658. van Roon J, Wijngaarden S, Lafeber FPJG, et al. Interleukin 10 Treatment of Patients With Rheumatoid Arthritis Enhances Fc Gamma Receptor Expression on Monocytes and Responsiveness to Immune Complex Stimulation. The Journal of rheumatology. 2003;30(4):648-51.
- 659. van Roon JA, van Roy JL, Gmelig-Meyling FH, et al. Prevention and Reversal of Cartilage Degradation in Rheumatoid Arthritis by Interleukin-10 and Interleukin-4. Arthritis and rheumatism. 1996;39(5):829-35.
- of Normal Schaardenburg D, Valkema R, Dijkmans BA, et al. Prednisone Treatment of Elderly-Onset Rheumatoid Arthritis. Disease Activity and Bone Mass in Comparison With Chloroquine Treatment. Arthritis and rheumatism. 1995;38(3):334-42.
- 661. Verdickt W, Moran C, Hantzschel H, et al. A Double-Blind Comparison of the Gastroduodenal Safety and Efficacy of Diclofenac and a Fixed Dose Combination of Diclofenac and Misoprostol in the Treatment of Rheumatoid Arthritis. Scandinavian journal of rheumatology. 1992;21(2):85-91.
- 662. Verhoef J, Toussaint PJ, Zwetsloot-Schonk JHM, et al. Effectiveness of the introduction of an international classification of functioning, disability and health-based rehabilitation tool in multidisciplinary team care in patients with rheumatoid arthritis.

- Arthritis Care and Research. 2007;57(2):240-8.
- 663. Verhoeven AC, Bibo JC, Boers M, et al. Cost-Effectiveness and Cost-Utility of Combination Therapy in Early Rheumatoid Arthritis: Randomized Comparison of Combined Step-Down Prednisolone, Methotrexate and Sulphasalazine With Sulphasalazine Alone. British journal of rheumatology. 1998;37(10):1102-9.
- 664. Verstappen S, Jacobs J, Bijlsma JW. The Utrecht Experience With Different Treatment Strategies in Early Rheumatoid Arthritis. Clinical and experimental rheumatology. 2003;21(5 Suppl 31):S165-8.
- 665. Verstappen S, van Albada Kuipers G,
 Bijlsma J, et al. A Good Response to Early
 Dmard Treatment of Patients With
 Rheumatoid Arthritis in the First Year
 Predicts Remission During Follow up. Ann
 Rheum Dis. 2005;64(1):38-43.
- 666. Verstappen SMM, Jacobs JWG, Bijlsma JWJ, et al. Five-Year Followup of Rheumatoid Arthritis Patients After Early Treatment With Disease-Modifying Antirheumatic Drugs Versus Treatment According to the Pyramid Approach in the First Year. Arthritis and rheumatism. 2003;48(7):1797-807.
- 667. Verstappen SMM, McCoy MJ, Roberts C, et al. Beneficial effects of a 3-week course of intramuscular glucocorticoid injections in patients with very early inflammatory polyarthritis: Results of the STIVEA trial. Annals of the rheumatic diseases. 2010;69(3):503-9.
- 668. Veys E, Menkes C, Emery P. A
 Randomized, Double-Blind Study
 Comparing Twenty-Four-Week Treatment
 With Recombinant Interferon-Gamma
 Versus Placebo in the Treatment of
 Rheumatoid Arthritis. Arthritis and
 rheumatism. 1997;40(1):62-8.
- 669. Vis M, Havaardsholm EA, Haugeberg G, et al. Evaluation of bone mineral density, bone metabolism, osteoprotegerin and receptor activator of the NFkappaB ligand serum levels during treatment with infliximab in patients with rheumatoid arthritis. Annals of

- the Rheumatic Diseases. 2006;65(11):1495-9.
- 670. Vischer TL. Follow-up With Om-8980 After a Double-Blind Study of Om-8980 and Auranofin in Rheumatoid Arthritis. Clinical rheumatology. 1990;9(3):356-61.
- 671. Vlak T, Eldar R. Disability in Rheumatoid Arthritis After Monotherapy With Dmards. International Journal Rehabilitation Research. 2003;26(3):207-12.
- 672. von Scheele B, Pena B, Wong J, et al. Economic Evaluation of Oral Valdecoxib Versus Diclofenac in the Treatment of Patients With Rheumatoid Arthritis in a Randomized Clinical Trial. Rheumatology (Oxford). 2003;42(Suppl 3):iii53-9.
- 673. Wailoo AJ, Bansback N, Brennan A, et al. Biologie drugs for rheumatoid arthritis in the medicare program: A cost-effectiveness analysis. Arthritis and Rheumatism. 2008;58(4):939-46.
- 674. Wakefield D, McCluskey P, Verma M, et al. Ciprofloxacin Treatment Does Not Influence Course or Relapse Rate of Reactive Arthritis and Anterior Uveitis. Arthritis and rheumatism. 1999;42(9):1894-7.
- 675. Walitt B, Pettinger M, Weinstein A, et al. Effects of postmenopausal hormone therapy on rheumatoid arthritis: The women's health initiative randomized controlled trials. Arthritis Care and Research. 2008;59(3):302-10.
- 676. Walsh JK, Muehlbach MJ, Lauter SA, et al. Effects of Triazolam on Sleep, Daytime Sleepiness, and Morning Stiffness in Patients With Rheumatoid Arthritis. The Journal of rheumatology. 1996;23(2):245-52.
- 677. Wassenberg S, Rau R, Steinfeld P, et al. Very Low-Dose Prednisolone in Early Rheumatoid Arthritis Retards Radiographic Progression Over Two Years: a Multicenter, Double-Blind, Placebo-Controlled Trial. Arthritis and rheumatism. 2005;52(11):3371-80.

- 678. Weinblatt M, Maier A, Coblyn J. Low Dose Leucovorin Does Not Interfere With the Efficacy of Methotrexate in Rheumatoid Arthritis: an 8 Week Randomized Placebo Controlled Trial. The Journal of rheumatology. 1993;20(6):950-2.
- 679. Weinblatt M, Maier A, Fraser P, et al.
 Longterm Prospective Study of
 Methotrexate in Rheumatoid Arthritis:
 Conclusion After 132 Months of Therapy.
 The Journal of rheumatology.
 1988;25(2):238-42.
- 680. Weinblatt M, Polisson R, Blotner SD, et al. The Effects of Drug Therapy on Radiographic Progression of Rheumatoid Arthritis. Results of a 36-Week Randomized Trial Comparing Methotrexate and Auranofin. Arthritis and rheumatism. 1993;36(5):613-9.
- 681. Weinblatt M, Schiff M, Goldman A, et al. Selective costimulation modulation using abatacept in patients with active rheumatoid arthritis while receiving etanercept: a randomised clinical trial. Annals of the rheumatic diseases 2007(2):228-34.
- 682. Weinblatt ME, Kaplan H, Germain BF, et al. Methotrexate in Rheumatoid Arthritis. A Five-Year Prospective Multicenter Study. Arthritis and rheumatism. 1994;37(10):1492-8.
- 683. Weinblatt ME, Kaplan H, Germain BF, et al. Low-Dose Methotrexate Compared With Auranofin in Adult Rheumatoid Arthritis. A Thirty-Six-Week, Double-Blind Trial. Arthritis and rheumatism. 1990;33(3):330-8.
- 684. Weinblatt ME, Kaplan H, Germain BF, et al. Methotrexate in Rheumatoid Arthritis: Effects on Disease Activity in a Multicenter Prospective Study. The Journal of rheumatology. 1991;18(3):334-8.
- 685. Weinblatt ME, Kremer JM, Coblyn JS, et al. Zileuton, a 5-Lipoxygenase Inhibitor in Rheumatoid Arthritis. The Journal of rheumatology. 1992;19(10):1537-41.
- 686. Weinblatt ME, Maddison PJ, Bulpitt KJ, et al. Campath-1h, a Humanized Monoclonal Antibody, in Refractory Rheumatoid Arthritis. An Intravenous Dose-Escalation

- Study. Arthritis and rheumatism. 1995;38(11):1589-94.
- 687. Weinblatt ME, Weissman BN, Holdsworth DE, et al. Long-Term Prospective Study of Methotrexate in the Treatment of Rheumatoid Arthritis. 84-Month Update. Arthritis and rheumatism. 1992;35(2):129-37.
- 688. Weitoft T, Larsson A, Saxne T, et al.
 Changes of Cartilage and Bone Markers
 After Intra-Articular Glucocorticoid
 Treatment With and Without Postinjection
 Rest in Patients With Rheumatoid Arthritis.
 Annals of the rheumatic diseases.
 2005;64(12):1750-3.
- 689. Wendling D, Racadot E, Wijdenes J, et al. A Randomized, Double Blind, Placebo Controlled Multicenter Trial of Murine Anti-Cd4 Monoclonal Antibody Therapy in Rheumatoid Arthritis. The Journal of rheumatology. 1998;25(8):1457-61.
- 690. Wendling D, Wijdenes J, Racadot E, et al. Therapeutic use of monoclonal anti-CD4 antibody in rheumatoid arthritis. J Rheumatol. 1991 Mar;18(3):325-7.
- 691. Westhovens R, Robles M, Ximenes AC, et al. Clinical efficacy and safety of abatacept in methotrexate-naive patients with early rheumatoid arthritis and poor prognostic factors. 2009.
- 692. Westhovens R, Verwilghen J, Dequeker J. Total Lymphoid Irradiation in Rheumatoid Arthritis. A Ten-Year Followup. Arthritis and rheumatism. 1997;40(3):426-9.
- 693. Whitehead J, Thomas P. A Sequential Trial of Pain Killers in Arthritis: Issues of Multiple Comparisons With Control and of Interval-Censored Survival Data. Journal of Biopharmaceutical Statistics. 1997;7(3):333-53.
- 694. Wijnands M, van Riel P, van 't Hof M, et al. Longterm Treatment With Nonsteroidal Antiinflammatory Drugs in Rheumatoid Arthritis: a Prospective Drug Survival Study. The Journal of rheumatology. 1991;18(2):184-7.

- 695. Williams HJ, Ward JR, Reading JC, et al. Comparison of Auranofin, Methotrexate, and the Combination of Both in the Treatment of Rheumatoid Arthritis. A Controlled Clinical Trial. Arthritis and rheumatism. 1992;35(3):259-69.
- 696. Willich SN, Rossnagel K, Roll S, et al. Rose hip herbal remedy in patients with rheumatoid arthritis a randomised controlled trial. 2010.
- 697. Willkens R, Sharp J, Stablein D, et al.
 Comparison of Azathioprine, Methotrexate,
 and the Combination of the Two in the
 Treatment of Rheumatoid Arthritis. A FortyEight-Week Controlled Clinical Trial With
 Radiologic Outcome Assessment. Arthritis
 and rheumatism. 1995;38(12):1799-806.
- 698. Willkens R, Stablein D. Combination Treatment of Rheumatoid Arthritis Using Azathioprine and Methotrexate: a 48 Week Controlled Clinical Trial. The Journal of rheumatology Supplement. 1996;44:64-8.
- 699. Willkens RF, Urowitz MB, Stablein DM, et al. Comparison of Azathioprine,
 Methotrexate, and the Combination of Both in the Treatment of Rheumatoid Arthritis. A Controlled Clinical Trial. Arthritis and rheumatism. 1992;35(8):849-56.
- 700. Wojtulewski JA, Schattenkirchner M, Barcelo P, et al. A Six-Month Double-Blind Trial to Compare the Efficacy and Safety of Meloxicam 7.5 Mg Daily and Naproxen 750 Mg Daily in Patients With Rheumatoid Arthritis. British journal of rheumatology. 1996;35(Suppl 1):22-8.
- 701. Wolfe F, Michaud K. Biologic treatment of rheumatoid arthritis and the risk of malignancy: Analyses from a large US observational study. Arthritis and Rheumatism 2007;56(9):2886-95.
- 702. Wong M, Oakley SP, Young L, et al. Infliximab improves vascular stiffness in patients with rheumatoid arthritis. 2009.
- 703. Wood Nd AMDSHSMGRSS. Cartilage Protective Agent (Cpa) Ro 32-3555, a New Matrix Metalloproteinase Inhibitor for the Treatment of Rheumatoid Arthritis. Agents

- and Actions Supplements. 1998;36(8):1087-8
- 704. Woodworth TG. Early Clinical Studies of Il-2 Fusion Toxin in Patients With Severe Rheumatoid Arthritis and Recent Onset Insulin-Dependent Diabetes Mellitus. Clinical and experimental rheumatology. 1993;11(Suppl 8):S177-80.
- 705. Wu E, Chen L, Birnbaum H, et al.
 Retrospective claims data analysis of dosage
 adjustment patterns of TNF antagonists
 among patients with rheumatoid arthritis.
 Current Medical Research and Opinion.
 2008;24(8):2229-40.
- 706. Wylie G, Appelboom T, Bolten W, et al. A Comparative Study of Tenidap, a Cytokine-Modulating Anti-Rheumatic Drug, and Diclofenac in Rheumatoid Arthritis: a 24-Week Analysis of a 1-Year Clinical Trial. British journal of rheumatology. 1995;34(6):554-63.
- 707. Yang ZX, Li ZB, Sun ZC, et al. Correlations between serum macrophage migration inhibitory factor and active rheumatoid arthritis. Journal of Clinical Rehabilitative Tissue Engineering Research. 2008;12(37):7390-3.
- 708. Yasuda M, Sakai K, Oribe M, et al. Efficacy of Additive Dmard Therapy in Patients With Rheumatoid Arthritis. Double Blind Controlled Trial Using Bucillamine and Placebo With Maintenance Doses of Gold Sodium Thiomalate. J Rheumatol. 1994;21(1):33-50.
- 709. Yocum D, Furst D, Kaine JL, et al. Efficacy and Safety of Tacrolimus in Patients With Rheumatoid Arthritis: a Double-Blind Trial. Arthritis Rheum. 2003;48(12):3328-37.
- 710. Yxfeldt A, Wallberg-Jonsson S, Hultdin J, et al. Homocysteine in Patients With Rheumatoid Arthritis in Relation to Inflammation and B-Vitamin Treatment. Scand J Rheumatol. 2003;32(4):205-10.
- 711. Zanette SdA, Born IG, Brenol JCT, et al. A pilot study of acupuncture as adjunctive treatment of rheumatoid arthritis. Clinical Rheumatology. 2008;27(5):627-35.

- 712. Zhang FC, Hou Y, Huang F, et al. Infliximab versus placebo in rheumatoid arthritis patients receiving concomitant methotrexate: A preliminary study from China. APLAR Journal of Rheumatology 2006;9(2):127-30.
- 713. Zhao S, Fiechtner JI, Tindall E, et al.
 Evaluation of Health-Related Quality of Life
 of Rheumatoid Arthritis Patients Treated
 With Celecoxib. Arthritis care and research:
 the official journal of the Arthritis Health
 Professions Association. 2000;13(2):112-21.
- 714. Zhou X, Zhou Z, Jin M, et al. Clinical Study of Qingluo Tongbi Granules in Treating 63 Patients With Rheumatoid Arthritis of the Type of Yin-Deficiency and Heat in Collaterals. J Tradit Chin Med. 2004;24(2):83-7.

Reference Source: Dossiers

- 1. Askling J, Fored CM, Baecklund E, et al. Haematopoietic malignancies in rheumatoid arthritis: lymphoma risk and characteristics after exposure to tumour necrosis factor antagonists. Ann Rheum Dis. 2005 Oct;64(10):1414-20.
- 2. Baecklund E, Iliadou A, Askling J, et al. Association of chronic inflammation, not its treatment, with increased lymphoma risk in rheumatoid arthritis. Arthritis Rheum. 2006 Mar;54(3):692-701.
- 3. Bernstein LE, Berry J, Kim S, et al. Effects of etanercept in patients with the metabolic syndrome. Arch Intern Med. 2006 Apr 24;166(8):902-8.
- 4. Breedveld FC, Kalden JR. Appropriate and effective management of rheumatoid arthritis. Ann Rheum Dis. 2004 Jun;63(6):627-33.
- 5. Brodszky V, Pentek M, Gulacsi L. Efficacy of adalimumab, etanercept, and infliximab in psoriatic arthritis based on ACR50 response after 24 weeks of treatment. Scand J Rheumatol. 2008 Sep-Oct;37(5):399-400.
- 6. Cardiel MH. First Latin American position paper on the pharmacological treatment of

- 715. Ziebland S, Fitzpatrick R, Jenkinson C, et al. Comparison of Two Approaches to Measuring Change in Health Status in Rheumatoid Arthritis: the Health Assessment Questionnaire (Haq) and Modified Haq. Annals of the rheumatic diseases. 1992;51(11):1202-5.
- 716. Zoppi M, Peretti G, Boccard E. Placebo-Controlled Study of the Analgesic Efficacy of an Effervescent Formulation of 500 Mg Paracetamol in Arthritis of the Knee or the Hip. European Journal of Pain. 1995;16(1-2):42-8.
- 717. Zuo X, Duan L, Cao Z, et al. A Clinical Study on Rheumatoid Arthritis Treated by Cu.zn-Sod. Bulletin of Hunan Medical University. 1995;20(3):275-7.
 - rheumatoid arthritis. Rheumatology (Oxford). 2006 Jun;45 Suppl 2:ii7-ii22.
- 7. Cella D, Yount S, Sorensen M, et al. Validation of the Functional Assessment of Chronic Illness Therapy Fatigue Scale relative to other instrumentation in patients with rheumatoid arthritis. J Rheumatol. 2005 May;32(5):811-9.
- 8. Combe BG, Codreanu C, Fiocco U, et al. Double-blind comparison of Etanercept and Sulphasalazine, alone and combined, in patients with active rheumatoid arthritis despite receiving Sulphasalazine. Ann Rheum Dis. 2006 Apr 10.
- 9. Emery P. Role of adalimumab, a novel TNF antagonist in advancing rheumatoid arthritis control. Drugs Today (Barc). 2003;39 Suppl B:17-23.
- 10. Fleischmann RM, Tesser J, Schiff MH, et al. Safety of extended treatment with anakinra in patients with rheumatoid arthritis. Ann Rheum Dis. 2006 Aug;65(8):1006-12.
- 11. Hashimoto J, Garnero P, van der Heijde D, et al. Humanized anti-interleukin-6-receptor antibody (tocilizumab) monotherapy is more effective in slowing radiographic

- progression in patients with rheumatoid arthritis at high baseline risk for structural damage evaluated with levels of biomarkers, radiography, and BMI: data from the SAMURAI study. Mod Rheumatol. 2010 Jun 24.
- 12. Haugeberg G, Conaghan PG, Quinn M, et al. Bone loss in patients with active early rheumatoid arthritis: infliximab and methotrexate compared with methotrexate treatment alone. Explorative analysis from a 12-month randomised, double-blind, placebo-controlled study. Ann Rheum Dis. 2009 Dec;68(12):1898-901.
- 13. Jones G, Crotty M, Brooks P. Psoriatic arthritis: a quantitative overview of therapeutic options. The Psoriatic Arthritis Meta-Analysis Study Group. Br J Rheumatol. 1997 Jan;36(1):95-9.
- 14. Kavanaugh A, Antoni CE, Gladman D, et al. The Infliximab Multinational Psoriatic Arthritis Controlled Trial (IMPACT): results of radiographic analyses after 1 year. Ann Rheum Dis. 2006 Aug;65(8):1038-43.
- 15. Kempeni J. Preliminary results of early clinical trials with the fully human anti-TNFalpha monoclonal antibody D2E7. Ann Rheum Dis. 1999 November 1, 1999;58(90001):70i-2.
- 16. Kempeni J. Update on D2E7: a fully human anti-tumour necrosis factor alpha monoclonal antibody. Ann Rheum Dis. 2000 November 1, 2000;59(90001):44i-5.
- 17. Keystone EC. Appropriate and effective rheumatoid arthritis control: role of TNF antagonists. Drugs Today (Barc). 2003;39 Suppl B:9-15.
- 18. Klareskog L, Gaubitz M, Rodriguez-Valverde V, et al. A Long-Term, Open-Label Trial of the Safety and Efficacy of Etanercept (ENBREL(R)) In Patients With Rheumatoid Arthritis Not Treated With Other DMARDs (3-year Interim Report). Ann Rheum Dis. 2006 Mar 15.
- 19. Machold KP, Smolen JS. Adalimumab a new TNF-alpha antibody for treatment of inflammatory joint disease. Expert Opin Biol Ther. 2003 Apr;3(2):351-60.

- 20. Mease PJ. Adalimumab: an anti-TNF agent for the treatment of psoriatic arthritis. Expert Opin Biol Ther 2005;5(11):1491-504.
- 21. Migliore A, Bizzi E, Lagana B, et al. The safety of anti-TNF agents in the elderly. Int J Immunopathol Pharmacol 2009;22(2):415-26.
- 22. Parekh K, Ching D, Rahman MU, et al.
 Onset of Wegener's granulomatosis during therapy with golimumab for rheumatoid arthritis: a rare adverse event?
 Rheumatology (Oxford). 2010
 Sep;49(9):1785-7.
- 23. Pavelka K. Adalimumab in the treatment of rheumatoid arthritis. Aging Health. 2006;2(4):533-45.
- 24. Rau R. Adalimumab (a fully human antitumour necrosis factor {alpha} monoclonal antibody) in the treatment of active rheumatoid arthritis: the initial results of five trials. Ann Rheum Dis. 2002 November 1, 2002;61(90002):70ii-3.
- 25. Rigopoulos D, Gregoriou S, Stratigos A, et al. Evaluation of the efficacy and safety of infliximab on psoriatic nails: an unblinded, nonrandomized, open-label study. Br J Dermatol. 2008 Aug;159(2):453-6.
- 26. Salfeld JG. Use of new biotechnology to design rational drugs against newly defined targets. Best Pract Res Clin Rheumatol. 2004 Feb;18(1):81-95.
- 27. Saliu OY, Sofer C, Stein DS, et al. Tumornecrosis-factor blockers: differential effects on mycobacterial immunity. J Infect Dis. 2006 Aug 15;194(4):486-92.
- 28. Santora LC, Kaymakcalan Z, Sakorafas P, et al. Characterization of noncovalent complexes of recombinant human monoclonal antibody and antigen using cation exchange, size exclusion chromatography, and BIAcore. Anal Biochem. 2001 Dec 15;299(2):119-29.
- Simpson D, Scott LJ. Adalimumab: in psoriatic arthritis. Drugs. 2006;66(11):1487-96.

- 30. Smolen JS. Objectives and strategies for rheumatoid arthritis therapy: yesterday vs. today. Drugs Today (Barc). 2003;39 Suppl B:3-8.
- 31. Suissa S, Ernst P, Hudson M, et al. Newer disease-modifying antirheumatic drugs and the risk of serious hepatic adverse events in patients with rheumatoid arthritis. Am J Med. 2004 Jul 15;117(2):87-92.
- 32. van de Putte L, Nichol MB. Adalimumab for Rheumatoid Arthritis: Considerations for Reimbursement by Third-Party Payors Disease Management & Health Outcomes. 2004;12(1):1-8.
- 33. Voulgari PV, Venetsanopoulou AI, Epagelis EK, et al. Infliximab in refractory psoriatic arthritis with severe psoriasis: a 2-year experience. Ann Rheum Dis. 2007 Feb;66(2):270-1.
- 34. Weinblatt M, Combe B, Covucci A, et al. Safety of the selective costimulation modulator abatacept in rheumatoid arthritis patients receiving background biologic and nonbiologic disease-modifying antirheumatic drugs: A one-year randomized, placebo-controlled study. Arthritis Rheum. 2006 Aug 31;54(9):2807-16.
- 35. Westhovens R, Yocum D, Han J, et al. The safety of infliximab, combined with background treatments, among patients with rheumatoid arthritis and various comorbidities: a large, randomized, placebo-controlled trial. Arthritis Rheum. 2006 Apr;54(4):1075-86.
- 36. Yazici Y, Adler NM, Yazici H. Most tumour necrosis factor inhibitor trials in rheumatology are undeservedly called 'efficacy and safety' trials: a survey of power considerations. Rheumatology (Oxford). 2008 Jul;47(7):1054-7.

Reference Source: The Cochrane Library

- 1. Aerts NE, Ebo DG, Bridts CH, et al. T cell signal transducer and activator of transcription (STAT) 4 and 6 are affected by adalimumab therapy in rheumatoid arthritis. Clinical and experimental rheumatology 2010(2):208-14.
- 2. Akobeng AK, Thomas AG. Enteral nutrition for maintenance of remission in Crohn's disease. Cochrane Database of Systematic Reviews 2007(3).
- 3. Alfadhli A, McDonald J, Feagan B. Methotrexate for Induction of Remission in Refractory Crohn's Disease. The Cochrane Database of Systematic Reviews. 2004;2004(4).
- 4. Blumenauer B, Judd M, Cranney A, et al. Etanercept for the Treatment of Rheumatoid Arthritis. The Cochrane Database of Systematic Reviews. 2003;2003(3).
- 5. Blumenauer B, Judd M, Wells G, et al. Infliximab for the Treatment of Rheumatoid Arthritis. The Cochrane Database of Systematic Reviews. 2002;2002(3).
- 6. Bongartz T. Tocilizumab for rheumatoid and juvenile idiopathic arthritis. Lancet. 2008(9617):961-3.
- 7. Bravo Vergel Y, Palmer S, Erhorn S, et al. Adalimumab for the treatment of moderate to severe psoriatic arthritis. Health Technology Assessment. 2010.
- 8. Burls A, Clark WK, Jobanputra P. Anakinra for Rheumatoid Arthritis. The Cochrane Database of Systematic Reviews. 2005;2005(1).
- 9. Chen J, Liu C. Methotrexate for Ankylosing Spondylitis. The Cochrane Database of Systematic Reviews. 2003;2003(3).
- 10. Chen J, Liu C. Sulfasalazine for Ankylosing Spondylitis. The Cochrane Database of Systematic Reviews. 2005;2005(2).
- 11. Chen J, Liu C, Lin J. Methotrexate for ankylosing spondylitis. Cochrane Database of Systematic Reviews 2006(4).
- 12. Christensen AF, Hørslev-Petersen K, Christgau S, et al. Uncoupling of collagen II metabolism in newly diagnosed, untreated rheumatoid arthritis is linked to inflammation and antibodies against cyclic citrullinated peptides. The Journal of rheumatology 2010(6):1113-20.
- 13. Clark W, Jobanputra P, Barton P, et al. The clinical and cost-effectiveness of anakinra for the treatment of rheumatoid arthritis in adults: a systematic review and economic analysis (Brief record). Health Technology Assessment. 2004(18):1-118.
- 14. Clarke R, Derry S, Moore RA, et al. Single dose oral etoricoxib for acute postoperative pain in adults. Cochrane Database of Systematic Reviews 2009(2).
- 15. Coombs JH, Bloom BJ, Breedveld FC, et al. Improved pain, physical functioning and health status in patients with rheumatoid arthritis treated with CP-690,550, an orally active Janus kinase (JAK) inhibitor: results from a randomised, double-blind, placebo-controlled trial. Annals of the rheumatic diseases 2010(2):413-6.
- 16. Criswell L, Saag K, Sems KM, et al. Moderate-term, low-dose corticosteroids for rheumatoid arthritis. 1998.

- 17. Criswell L, Saag KG, Sems KM, et al. Moderate-Term, Low-Dose Corticosteroids for Rheumatoid Arthritis. The Cochrane Database of Systematic Reviews. 1998;1998(3).
- 18. de Courten B, Barber Melissa N, Johnston Renea V, et al. Hypolipidemic and antihypertensive drugs for prevention of cardiovascular complications in patients with rheumatoid arthritis. Cochrane Database of Systematic Reviews 2008(3).
- 19. Deodhar A, Dore RK, Mandel D, et al. Denosumab-mediated increase in hand bone mineral density associated with decreased progression of bone erosion in rheumatoid arthritis patients. Arthritis care & research 2010(4):569-74.
- 20. Derry S, Barden J, McQuay Henry J, et al. Single dose oral celecoxib for acute postoperative pain in adults. Cochrane Database of Systematic Reviews 2008(4).
- 21. Egan M, Brosseau L, Farmer M, et al. Splints and Orthosis for Treating Rheumatoid Arthritis. The Cochrane Database of Systematic Reviews. 2001;2001(4).
- 22. Englbrecht M, Wang Y, Ronneberger M, et al. Measuring joint involvement in polyarticular psoriatic arthritis: an introduction of alternatives. Arthritis care & research 2010(7):977-83.
- 23. Flint Wagner HG, Lisse J, Lohman TG, et al. Assessment of a sixteen-week training program on strength, pain, and function in rheumatoid arthritis patients. Journal of clinical rheumatology: practical reports on rheumatic & musculoskeletal diseases. 2009;15(4):165-71.
- 24. Garner S, Fidan D, Frankish R, et al. Celecoxib for Rheumatoid Arthritis. The Cochrane Database of Systematic Reviews. 2002;2002(4).
- 25. Garner S, Fidan DD, Frankish RR, et al. Rofecoxib for Rheumatoid Arthritis. The Cochrane Database of Systematic Reviews. 2005;2005(1).
- 26. Garner Sarah E, Fidan D, Frankish Ruth R, et al. Rofecoxib for rheumatoid arthritis. Cochrane Database of Systematic Reviews 2005(1).
- 27. Gøtzsche P, Johansen H. Short-Term Low-Dose Corticosteroids Vs Placebo and Nonsteroidal Antiinflammatory Drugs in Rheumatoid Arthritis. The Cochrane Database of Systematic Reviews. 2005;2005(1).
- 28. Hashimoto J, Garnero P, van der Heijde D, et al. A combination of biochemical markers of cartilage and bone turnover, radiographic damage and body mass index to predict the progression of joint destruction in patients with rheumatoid arthritis treated with disease-modifying anti-rheumatic drugs. Modern rheumatology / the Japan Rheumatism Association. 2009;19(3):273-82.
- 29. Health Technology A. Adalimumab, etanercept, infliximab, rituximab and abatacept for the treatment of rheumatoid arthritis after the failure of a TNF inhibitor: a systematic review and economic evaluation (Project record). Health Technology Assessment. 2010.
- 30. Health Technology A. The clinical and cost effectiveness of etanercept, infliximab and adalimumab psoriatic arthritis (guidance review 104 and 125) (Project record). Health Technology Assessment. 2010.
- 31. Homer D, Nightingale P, Jobanputra P. Providing patients with information about disease-modifying antirheumatic drugs: Individually or in groups? A pilot randomized controlled trial comparing adherence and satisfaction. Musculoskeletal care. 2009;7(2):78-92.
- 32. Jones G, Crotty M, Brooks P. Interventions for Treating Psoriatic Arthritis. The Cochrane Database of Systematic Reviews. 2000;2000(3).

- 33. Keystone E, Genovese MC, Klareskog L, et al. Golimumab in patients with active rheumatoid arthritis despite methotrexate therapy: 52-week results of the GO-FORWARD study. Annals of the rheumatic diseases 2010(6):1129-35.
- 34. Kirwan J, Shea B, Boers M. Glucocorticoids for Slowing Radiological Progression in Rheumatoid Arthritis. The Cochrane Database of Systematic Reviews. 2005;2005(1).
- 35. Klarenbeek NB, van der Kooij SM, Huizinga TJ, et al. Blood pressure changes in patients with recent-onset rheumatoid arthritis treated with four different treatment strategies: a post hoc analysis from the BeSt trial. Annals of the rheumatic diseases. 2010(7):1342-5.
- 36. Lawson MM, Thomas AG, Akobeng AK. Tumour necrosis factor alpha blocking agents for induction of remission in ulcerative colitis. Cochrane Database of Systematic Reviews 2006(3).
- 37. Lekander I, Borgstrom F, Svarvar P, et al. Cost-effectiveness of real-world infliximab use in patients with rheumatoid arthritis in Sweden. International Journal of Technology Assessment in Health Care. 2010;26(1):54-61.
- 38. Li L, Judd M, Pencharz JN. Comprehensive Physiotherapy for Rheumatoid Arthritis. Li L, Judd M, Pencharz JN Comprehensive physiotherapy for rheumatoid arthritis The Cochrane Database of Systematic Reviews: Protocols 2004 Issue 2 John Wiley & Sons, Ltd Chichester, UK DOI: 101002/14651858CD004802: John Wiley & Sons, Ltd. 2004;2004(2).
- 39. Lin JF, Chen JM, Liu C. A systematic review of methotrexate for ankylosing spondylitis (Brief record). Chinese Journal of Evidence-Based Medicine 2007(4):260-6.
- 40. Little C, Parsons T. Herbal Therapy for Treating Rheumatoid Arthritis. The Cochrane Database of Systematic Reviews. 2000;2000(4).
- 41. Little Christine V, Parsons T, Logan S. Herbal therapy for treating osteoarthritis. 2000. Available at: http://www.mrw.interscience.wiley.com/cochrane/clsysrev/articles/CD002947/frame.html
- 42. Lopez-Olivo Maria A, Amezaga M, McGahan L, et al. Rituximab for rheumatoid arthritis. Cochrane Database of Systematic Reviews 2008(4).
- 43. Lu D, Song H, Shi G. Anti-TNF-α treatment for pelvic pain associated with endometriosis. Cochrane Database of Systematic Reviews 2010(3).
- 44. Lukas C, van der Heijde D, Fatenajad S, et al. Repair of erosions occurs almost exclusively in damaged joints without swelling. Annals of the rheumatic diseases 2010(5):851-5.
- 45. Lv D, Song H, Shi G. Anti-TNF-α treatment for pelvic pain associated with endometriosis. 2009. Available at: http://www.mrw.interscience.wiley.com/cochrane/clsysrev/articles/CD008088/frame.html
- 46. Lv D, Song H, Shi G. Anti-TNF-α treatment for pelvic pain associated with endometriosis. Cochrane Database of Systematic Reviews 2010(3).
- 47. Maxwell L, Singh Jasvinder A. Abatacept for rheumatoid arthritis. Cochrane Database of Systematic Reviews. 2008(3).
- 48. Maxwell L, Singh Jasvinder A. Abatacept for rheumatoid arthritis. Cochrane Database of Systematic Reviews 2009(4).
- 49. Navarro Sarabia F, Ariza Ariza R, Hernandez Cruz B, et al. Adalimumab for Treating Rheumatoid Arthritis. The Cochrane Database of Systematic Reviews. 2005;2005(3).

- 50. Osiri M, Shea B, Robinson V, et al. Leflunomide for Treating Rheumatoid Arthritis. The Cochrane Database of Systematic Reviews 2002;2002(3).
- 51. Osiri M, Shea B, Welch V, et al. Leflunomide for the treatment of rheumatoid arthritis. 2002.
- 52. Ramiro S, Radner H, van der Heijde D, et al. Combination therapy for pain management in inflammatory arthritis. Cochrane Database of Systematic Reviews 2010(12).
- For the Property Roux-Lombard P, Veale DJ, et al. Synovial tissue and serum biomarkers of disease activity, therapeutic response and radiographic progression: analysis of a proof-of-concept randomised clinical trial of cytokine blockade. Annals of the rheumatic diseases 2010(4):706-14.
- 54. Ruiz Garcia V, Burls A, Cabello López Juan CL, et al. Certolizumab pegol (CDP870) for rheumatoid arthritis in adults. Cochrane Database of Systematic Reviews. 2009(1).
- 55. Schiff M, Pritchard C, Huffstutter JE, et al. The 6-month safety and efficacy of abatacept in patients with rheumatoid arthritis who underwent a washout after anti-tumour necrosis factor therapy or were directly switched to abatacept: the ARRIVE trial. Annals of the rheumatic diseases. 2009;68(11):1708-14.
- 56. Sharp JT, Tsuji W, Ory P, et al. Denosumab prevents metacarpal shaft cortical bone loss in patients with erosive rheumatoid arthritis. Arthritis care & research 2010(4):537-44.
- 57. Singh Jasvinder A, Beg S, Lopez Olivo Maria A. Tocilizumab for rheumatoid arthritis. 2010.
- 58. Singh Jasvinder A, Beg S, Lopez-Olivo Maria A. Tocilizumab for rheumatoid arthritis. Cochrane Database of Systematic Reviews 2010(7).
- 59. Singh Jasvinder A, Christensen R, Wells George A, et al. Biologics for rheumatoid arthritis: an overview of Cochrane reviews. Cochrane Database of Systematic Reviews. 2009(2).
- 60. Singh Jasvinder A, Christensen R, Wells George A, et al. Biologics for rheumatoid arthritis: an overview of Cochrane reviews. Cochrane Database of Systematic Reviews 2009(4).
- 61. Smolen JS, Aletaha D, Grisar JC, et al. Estimation of a numerical value for joint damage-related physical disability in rheumatoid arthritis clinical trials. Annals of the rheumatic diseases 2010(6):1058-64.
- 62. Smolen JS, van der Heijde DM, Aletaha D, et al. Progression of radiographic joint damage in rheumatoid arthritis: independence of erosions and joint space narrowing. Annals of the rheumatic diseases. 2009;68(10):1535-40.
- 63. Suarez Almazor M, Belseck E, Shea BJ, et al. Antimalarials for Treating Rheumatoid Arthritis. The Cochrane Database of Systematic Reviews. 2000;2000(4).
- 64. Suarez Almazor M, Belseck E, Shea BJ, et al. Methotrexate for Treating Rheumatoid Arthritis. The Cochrane Database of Systematic Reviews. 1998;1998(2).
- 65. Suarez Almazor M, Belseck E, Shea BJ, et al. Sulfasalazine for Treating Rheumatoid Arthritis. The Cochrane Database of Systematic Reviews. 1998;1998(2).
- 66. Suarez Almazor M, Belseck E, Spooner C. Penicillamine for Treating Rheumatoid Arthritis. The Cochrane Database of Systematic Reviews. 2000;2000(4).
- 67. Suarez Almazor M, Spooner C, Belseck E. Azathioprine for Treating Rheumatoid Arthritis. The Cochrane Database of Systematic Reviews. 2000;2000(4).

- 68. Suarez Almazor M, Spooner CH, Belseck E, et al. Auranofin Versus Placebo in Rheumatoid Arthritis. The Cochrane Database of Systematic Reviews. 2000;2000(2).
- 69. Suarez-Almazor Maria E, Belseck E, Shea B, et al. Sulfasalazine for treating rheumatoid arthritis. Cochrane Database of Systematic Reviews. 1998(2).
- 70. Suarez-Almazor Maria E, Belseck E, Shea B, et al. Cyclophosphamide for treating rheumatoid arthritis. Cochrane Database of Systematic Reviews 2000(4).
- 71. Tirunagari Shravan K, Derry S, Moore RA, et al. Single dose oral etodolac for acute postoperative pain in adults. Cochrane Database of Systematic Reviews 2009(3).
- 72. Towheed T, Hochberg Marc C, Shea B, et al. Analgesia and non-aspirin, non-steroidal anti-inflammatory drugs for osteoarthritis of the hip. Cochrane Database of Systematic Reviews 2006(1).
- van der Heijde D, Burmester G, Melo Gomes J, et al. Inhibition of radiographic progression with combination etanercept and methotrexate in patients with moderately active rheumatoid arthritis previously treated with monotherapy. Annals of the rheumatic diseases 2009;68(7):1113-8.
- 74. van Tuyl LH, Boers M, Lems WF, et al. Survival, comorbidities and joint damage 11 years after the COBRA combination therapy trial in early rheumatoid arthritis. Annals of the rheumatic diseases. 2010(5):807-12.
- 75. Verstappen SM, Bakker MF, Heurkens AH, et al. Adverse events and factors associated with toxicity in patients with early rheumatoid arthritis treated with methotrexate tight control therapy: the CAMERA study. Annals of the rheumatic diseases 2010(6):1044-8.
- 76. Vidal L, Gafter-Gvili A, Leibovici L, et al. Rituximab as maintenance therapy for patients with follicular lymphoma. Cochrane Database of Systematic Reviews 2007(2).
- 77. Wallen Margaret M, Gillies D. Intra-articular steroids and splints/rest for children with juvenile idiopathic arthritis and adults with rheumatoid arthritis. Cochrane Database of Systematic Reviews. 2006(1).
- 78. Westhovens R, Kremer JM, Moreland LW, et al. Safety and efficacy of the selective costimulation modulator abatacept in patients with rheumatoid arthritis receiving background methotrexate: a 5-year extended phase IIB study. The Journal of rheumatology. 2009;36(4):736-42.
- 79. Wienecke T, Gøtzsche P. Paracetamol Versus Nonsteroidal Anti-Inflammatory Drugs for Rheumatoid Arthritis. The Cochrane Database of Systematic Reviews. 2004;2004(1).

Appendix D. Excluded Studies

Excluded Studies

3.

Wrong Language

- Garcia JJ, Lobato JP, Garrido SL, Fernandez ME, Eyaralar JR. Biological therapies in rheumatoid arthritis. Atencion Farmaceutica: European Journal of Clinical Pharmacy. 2008;10(98):100-11.
- Rau R, Wassenberg S, Zeidler H. Low Dose Prednisolone Therapy (LDPT) Retards Radiographically Detectable Destruction in Early Rheumatoid Arthritis--Preliminary Results of a Multicenter, Randomized, Parallel, Double Blind Study. Zeitschrift für Rheumatologie. 2000;59(Supple 2):II/90-6.

Necrosis Factor Alpha Receptor Fusion Protein (Tnfr 55-Igg1) - a Monocentric Observation in 80 Patients. Zeitschrift fur Rheumatologie. 1998;57(5):307-11. 4. Schnabel A, Reinhold K, Willmann V,

Rheumatoid Arthritis With a Tumor

Sander O. Rau R. Treatment of Refractory

4. Schnabel A, Reinhold K, Willmann V, Dihlmann W, Gross W. Side Effects and Efficacy of 15 Mg and 25 Mg Methotrexate Per Week in Rheumatoid Arthritis. Z RHEUMATOL. 1994;53(3):142-9.

Wrong Outcome

- Aletaha D, Funovits J, Breedveld FC, Sharp J, Smolen JS, et al., et al. Rheumatoid Arthritis Joint Progression in Sustained Remission Is Determined by Disease Activity Levels Preceding the Period of Radiographic Assessment. Arthritis and Rheumatism (USA) 2009:1242.
- 2. Aletaha D, Funovits J, Keystone EC, Smolen JS. Disease activity early in the course of treatment predicts response to therapy after one year in rheumatoid arthritis patients. Arthritis Rheum. 2007 Oct;56(10):3226-35.
- 3. Ang DC, Paulus HE, Louie JS. Patient's ethnicity does not influence utilization of effective therapies in rheumatoid arthritis. J Rheumatol. 2006 May;33(5):870-8.
- 4. Aslanidis S, Pyrpasopoulou A, Douma S, Petidis K. Is it safe to readminister tumor necrosis factor alpha antagonists following tuberculosis flare? Arthritis Rheum. 2008 Jan;58(1):327-8.
- 5. Bacquet-Deschryver H, Jouen F, Quillard M, Menard JF, Goeb V, Lequerre T, et al. Impact of three anti-TNFalpha biologics on existing and emergent autoimmunity in rheumatoid arthritis and spondylarthropathy patients. J Clin Immunol. 2008 Sep;28(5):445-55.
- 6. Baskan BM, Sivas F, Alemdaroglu E, Duran S, Ozoran K. Association of bone mineral density and vertebral deformity in patients with rheumatoid arthritis. Rheumatol Int. 2007 Apr;27(6):579-84.
- 7. Baslund B, Tvede N, Danneskiold-Samsoe B, Larsson P, Panayi G, Petersen J, et al.

- Targeting Interleukin-15 in Patients With Rheumatoid Arthritis: a Proof-of-Concept Study. Arthritis and rheumatism. 2005;52(9):2686-92.
- 8. Bendtzen K, Geborek P, Svenson M, Larsson L, Kapetanovic MC, Saxne T. Individualized monitoring of drug bioavailability and immunogenicity in rheumatoid arthritis patients treated with the tumor necrosis factor alpha inhibitor infliximab. Arthritis Rheum. 2006 Dec;54(12):3782-9.
- 9. Bingham ICO, Looney RJ, Deodhar A, Halsey N, Greenwald M, Codding C, et al. Immunization responses in rheumatoid arthritis patients treated with rituximab: Results from a controlled clinical trial. 2010.
- Bobbio-Pallavicini F, Caporali R, Alpini C, Avalle S, Epis OM, Klersy C, et al. High IgA rheumatoid factor levels are associated with poor clinical response to tumour necrosis factor alpha inhibitors in rheumatoid arthritis. Ann Rheum Dis. 2007 Mar;66(3):302-7.
- 11. Breedveld F, Agarwal S, Yin M, Ren S, Li NF, Shaw TM, et al. Rituximab pharmacokinetics in patients with rheumatoid arthritis: B-cell levels do not correlate with clinical response. J Clin Pharmacol. 2007 Sep;47(9):1119-28.
- 12. Breedveld FC, Han C, Bala M, van der Heijde D, Baker D, Kavanaugh AF, et al. Association Between Baseline Radiographic Damage and Improvement in Physical Function After Treatment of Patients With

- Rheumatoid Arthritis. Annals of the rheumatic diseases. 2005;64(1):52-5.
- 13. Buch MH, Seto Y, Bingham SJ, Bejarano V, Bryer D, White J, et al. C-reactive protein as a predictor of infliximab treatment outcome in patients with rheumatoid arthritis: defining subtypes of nonresponse and subsequent response to etanercept. Arthritis Rheum. 2005 Jan;52(1):42-8.
- 14. Buckley LM, Leib ES, Cartularo KS, Vacek PM, Cooper SM. Effects of low dose methotrexate on the bone mineral density of patients with rheumatoid arthritis. J Rheumatol. 1997 Aug;24(8):1489-94.
- 15. Carmona L, Hernandez-Garcia C, Vadillo C, Pato E, Balsa A, Gonzalez-Alvaro I, et al. Increased risk of tuberculosis in patients with rheumatoid arthritis. J Rheumatol. 2003 Jul;30(7):1436-9.
- 16. Cassell S, Kavanaugh AF. Therapies for psoriatic nail disease. A systematic review. J Rheumatol. 2006 Jul;33(7):1452-6.
- 17. Cella D, Yount S, Sorensen M, Chartash E, Sengupta N, Grober J. Validation of the Functional Assessment of Chronic Illness Therapy Fatigue Scale relative to other instrumentation in patients with rheumatoid arthritis. J Rheumatol. 2005 May;32(5):811-9.
- 18. Chung CP, Russell AS, Segami MI, Ugarte CA. The effect of low-dose prednisone on bone mineral density in Peruvian rheumatoid arthritis patients. Rheumatol Int. 2005 Mar;25(2):114-7.
- 19. Chung CP, Thompson JL, Koch GG, Amara I, Strand V, Pincus T. Are American College of Rheumatology 50% response criteria superior to 20% criteria in distinguishing active aggressive treatment in rheumatoid arthritis clinical trials reported since 1997? A meta-analysis of discriminant capacities. Annals of the rheumatic diseases. 2006;65(12):1602-7.
- Coates LC, Helliwell PS. Validation of Minimal Disease Activity Criteria for Psoriatic Arthritis Using Interventional Trial Data. Arthritis Care and Research. 2010;62:965.
- Colwell CW, Jr., Robinson CA, Stevenson DD, Vint VC, Morris BA. Osteonecrosis of the femoral head in patients with inflammatory arthritis or asthma receiving corticosteroid therapy. Orthopedics. 1996 Nov;19(11):941-6.
- 22. Cooper C, Coupland C, Mitchell M. Rheumatoid arthritis, corticosteroid therapy

- and hip fracture. Ann Rheum Dis. 1995 Jan;54(1):49-52.
- 23. Criswell LA, Lum RF, Turner KN, Woehl B, Zhu Y, Wang J, et al. The influence of genetic variation in the HLA-DRB1 and LTA-TNF regions on the response to treatment of early rheumatoid arthritis with methotrexate or etanercept. Arthritis Rheum. 2004 Sep;50(9):2750-6.
- 24. Cui J, Saevarsdottir S, Thomson B, Padyukov L, van der Helm-van Mil AH, Nititham J, et al. Rheumatoid arthritis risk allele PTPRC is also associated with response to anti-tumor necrosis factor alpha therapy. *Arthritis Rheum*. 2010/03/24 ed 2010:1849-61.
- Cunnane G, Madigan A, Murphy E,
 FitzGerald O, Bresnihan B. The effects of
 treatment with interleukin-1 receptor
 antagonist on the inflamed synovial
 membrane in rheumatoid arthritis.
 Rheumatology (Oxford). 2001 Jan;40(1):629.
- Curkendall S, Patel V, Gleeson M,
 Campbell RS, Zagari M, Dubois R.
 Compliance with biologic therapies for
 rheumatoid arthritis: do patient out-of pocket payments matter? Arthritis Rheum.
 2008 Oct 15;59(10):1519-26.
- 27. Cypiene A, Laucevicius A, Venalis A, Ryliskyte L, Dadoniene J, Petrulioniene Z, et al. Non-invasive assessment of arterial stiffness indices by applanation tonometry and pulse wave analysis in patients with rheumatoid arthritis treated with TNF-alpha blocker remicade (infliximab). Proc West Pharmacol Soc. 2007;50:119-22.
- 28. Dahlqvist SR, Engstrand S, Berglin E, Johnson O. Conversion towards an atherogenic lipid profile in rheumatoid arthritis patients during long-term infliximab therapy. Scand J Rheumatol. 2006 Mar-Apr;35(2):107-11.
- 29. de Vries-Bouwstra JK, Goekoop-Ruiterman YP, Verpoort KN, Schreuder GM, Ewals JA, Terwiel JP, et al. Progression of joint damage in early rheumatoid arthritis: association with HLA-DRB1, rheumatoid factor, and anti-citrullinated protein antibodies in relation to different treatment strategies. Arthritis Rheum. 2008 May;58(5):1293-8.
- 30. Dervieux T, Greenstein N, Kremer J.
 Pharmacogenomic and metabolic
 biomarkers in the folate pathway and their
 association with methotrexate effects during

- dosage escalation in rheumatoid arthritis. Arthritis Rheum. 2006 Oct;54(10):3095-103
- 31. di Comite G, Marinosci A, Di Matteo P, Manfredi A, Rovere-Querini P, Baldissera E, et al. Neuroendocrine modulation induced by selective blockade of TNF-alpha in rheumatoid arthritis. Ann N Y Acad Sci. 2006 Jun;1069:428-37.
- 32. Doan QV, Chiou CF, Dubois RW. Review of eight pharmacoeconomic studies of the value of biologic DMARDs (adalimumab, etanercept, and infliximab) in the management of rheumatoid arthritis. Journal of Managed Care Pharmacy (USA). 2006 07/01/;12(Jul):555-69.
- 33. Eklund KK, Leirisalo-Repo M, Ranta P, Maki T, Kautiainen H, Hannonen P, et al. Serum IL-1beta levels are associated with the presence of erosions in recent onset rheumatoid arthritis. Clin Exp Rheumatol. 2007 Sep-Oct;25(5):684-9.
- 34. Ernestam S, Hafstrom I, Werner S, Carlstrom K, Tengstrand B. Increased DHEAS levels in patients with rheumatoid arthritis after treatment with tumor necrosis factor antagonists: evidence for improved adrenal function. J Rheumatol. 2007 Jul;34(7):1451-8.
- 35. Felder M, Ruegsegger P. Bone loss in patients with rheumatoid arthritis--effect of steroids measured by low dose quantitative computed tomography. Rheumatol Int. 1991;11(1):41-4.
- 36. Finckh A, Bansback N, Marra CA, Anis AH, Liang MH, et al., et al. Treatment of Very Early Rheumatoid Arthritis With Symptomatic Therapy, Disease-Modifying Antirheumatic Drugs, or Biologic Agents A Cost-Effectiveness Analysis. Annals of Internal Medicine (USA). 2009;151:612.
- 37. Finckh A, Simard JF, Gabay C, Guerne PA. Evidence for differential acquired drug resistance to anti-tumour necrosis factor agents in rheumatoid arthritis. Ann Rheum Dis. 2006 Jun;65(6):746-52.
- 38. Frey N, Grange S, Woodworth T.
 Population Pharmacokinetic Analysis of
 Tocilizumab in Patients With Rheumatoid
 Arthritis. Journal of Clinical Pharmacology
 (USA). 2010;50:754-66.
- 39. Garnero P, Tabassi NC, Voorzanger-Rousselot N. Circulating dickkopf-1 and radiological progression in patients with early rheumatoid arthritis treated with

- etanercept. J Rheumatol. 2008 Dec;35(12):2313-5.
- 40. Garnero P, Thompson E, Woodworth T, Smolen JS. Rapid and sustained improvement in bone and cartilage turnover markers with the anti-interleukin-6 receptor inhibitor tocilizumab plus methotrexate in rheumatoid arthritis patients with an inadequate response to methotrexate: Results from a substudy of the multicenter double-blind, placebo-controlled trial of tocilizumab in inadequate responders to methotrexate alone. 2010.
- 41. Garnero P, Thompson E, Woodworth T, Smolen JS. Rapid and Sustained Improvement in Bone and Cartilage Turnover Markers With the Anti-Interleukin-6 Receptor Inhibitor Tocilizumab Plus Methotrexate in Rheumatoid Arthritis Patients With an Inadequate Response to Methotrexate Results From a Substudy of the Multicenter Double-Blind, Placebo-Controlled Trial of Tocilizumab in Inadequate Responders to Methotrexate Alone. Arthritis and Rheumatism (USA). 2010;62:33.
- 42. Garton MJ, Reid DM. Bone mineral density of the hip and of the anteroposterior and lateral dimensions of the spine in men with rheumatoid arthritis. Effects of low-dose corticosteroids. Arthritis Rheum. 1993 Feb;36(2):222-8.
- 43. Genant HK. Interleukin-1 Receptor Antagonist Treatment of Rheumatoid Arthritis Patients: Radiologic Progression and Correlation of Genant/Sharp and Larsen Scoring Methods. Seminars in arthritis and rheumatism. 2001;30(5 Suppl 2):26-32.
- 44. Georgiadis AN, Papavasiliou EC, Lourida ES, Alamanos Y, Kostara C, Tselepis AD, et al. Atherogenic lipid profile is a feature characteristic of patients with early rheumatoid arthritis: effect of early treatment—a prospective, controlled study. Arthritis Res Ther. 2006;8(3):R82.
- 45. Gibofsky A, Palmer WR, Goldman JA,
 Lautzenheiser RL, Markenson JA, Weaver
 A, et al. Real-world utilization of DMARDs
 and biologics in rheumatoid arthritis: the
 RADIUS (Rheumatoid Arthritis DiseaseModifying Anti-Rheumatic Drug
 Intervention and Utilization Study) study.
 Curr Med Res Opin. 2006 Jan;22(1):169-83.
- 46. Goekoop-Ruiterman YP, de Vries-Bouwstra JK, Allaart CF, Kerstens PJ, Grillet BA, de Jager MH, et al. Patient preferences for

- treatment: report from a randomised comparison of treatment strategies in early rheumatoid arthritis (BeSt trial). Ann Rheum Dis. 2007 Sep;66(9):1227-32.
- 47. Gonnet-Gracia C, Barnetche T, Richez C, Blanco P, Dehais J, Schaeverbeke T. Antinuclear antibodies, anti-DNA and C4 complement evolution in rheumatoid arthritis and ankylosing spondylitis treated with TNF-alpha blockers. Clin Exp Rheumatol. 2008 May-Jun;26(3):401-7.
- 48. Gonzalez-Alvaro I, Descalzo MA, Carmona L. Trends towards an improved disease state in rheumatoid arthritis over time: Influence of new therapies and changes in management approach: Analysis of the EMECAR cohort. Arthritis Research and Therapy. 2008;10(6).
- 49. Gonzalez-Juanatey C, Llorca J, Garcia-Porrua C, Martin J, Gonzalez-Gay MA.

 Effect of anti-tumor necrosis factor alpha therapy on the progression of subclinical atherosclerosis in severe rheumatoid arthritis. Arthritis and Rheumatism-Arthritis Care and Research. 2006 01/01/:55(Jan):150-3.
- 50. Gotzsche PC, Hansen M, Stoltenberg M, Svendsen A, Beier J, Faarvang KL, et al. Randomized, Placebo Controlled Tial of Withdrawal of Slow-Acting Antirheumatic Drugs and of Observer Bias in Rheumatoid Arthritis. Scandinavian Journal of Rheumatology. 1996;25(4):194-0.
- 51. Grassi W, De Angelis R, Cervini C.
 Corticosteroid prescribing in rheumatoid arthritis and psoriatic arthritis. Clin
 Rheumatol. 1998;17(3):223-6.
- 52. Grijalva CG, Chung CP, Stein CM, Mitchel EF, Jr., Griffin MR. Changing patterns of medication use in patients with rheumatoid arthritis in a Medicaid population. Rheumatology (Oxford). 2008
 Jul;47(7):1061-4.
- 53. Guler-Yuksel M, Allaart CF, Goekoop-Ruiterman YP, de Vries-Bouwstra JK, van Groenendael JH, Mallee C, et al. Changes in hand and generalised bone mineral density in patients with recent-onset rheumatoid arthritis. Ann Rheum Dis. 2009

 Mar;68(3):330-6.
- 54. Guler-Yuksel M, Bijsterbosch J, Goekoop-Ruiterman YP, de Vries-Bouwstra JK, Hulsmans HM, de Beus WM, et al. Changes in bone mineral density in patients with recent onset, active rheumatoid arthritis. Ann Rheum Dis. 2008 Jun;67(6):823-8.

- 55. Guler-Yuksel M, Bijsterbosch J, Goekoop-Ruiterman YP, de Vries-Bouwstra JK, Ronday HK, Peeters AJ, et al. Bone mineral density in patients with recently diagnosed, active rheumatoid arthritis. Ann Rheum Dis. 2007 Nov:66(11):1508-12.
- 56. Haagsma CJ, Blom HJ, van Riel PL, van't Hof MA, Giesendorf BA, van Oppenraaij-Emmerzaal D, et al. Influence of Sulphasalazine, Methotrexate, and the Combination of Both on Plasma Homocysteine Concentrations in Patients With Rheumatoid Arthritis. Annals of the rheumatic diseases. 1999;58(2):79-84.
- 57. Hafstrom I, Rohani M, Deneberg S, Wornert M, Jogestrand T, Frostegard J. Effects of low-dose prednisolone on endothelial function, atherosclerosis, and traditional risk factors for atherosclerosis in patients with rheumatoid arthritis--a randomized study. J Rheumatol. 2007 Sep;34(9):1810-6.
- 58. Hall GM, Daniels M, Doyle DV, Spector TD. Effect of hormone replacement therapy on bone mass in rheumatoid arthritis patients treated with and without steroids. Arthritis Rheum. 1994 Oct;37(10):1499-505.
- 59. Hall GM, Spector TD, Delmas PD. Markers of bone metabolism in postmenopausal women with rheumatoid arthritis. Effects of corticosteroids and hormone replacement therapy. Arthritis Rheum. 1995
 Jul;38(7):902-6.
- 60. Hall GM, Spector TD, Griffin AJ, Jawad AS, Hall ML, Doyle DV. The effect of rheumatoid arthritis and steroid therapy on bone density in postmenopausal women. Arthritis Rheum. 1993 Nov;36(11):1510-6.
- 61. Halpern MT, Cifaldi MA, Kvien TK. Impact of adalimumab on work participation in rheumatoid arthritis: comparison of an openlabel extension study and a registry-based control group. Ann Rheum Dis. 2009 Jun;68(6):930-7.
- 62. Halvorsen EH, Haavardsholm EA, Pollmann S, Boonen A, van der Heijde D, Kvien TK, et al. Serum IgG antibodies to peptidylarginine deiminase 4 predict radiographic progression in patients with rheumatoid arthritis treated with tumour necrosis factor-alpha blocking agents. Ann Rheum Dis. 2009 Feb;68(2):249-52.
- 63. Hansen M, Florescu A, Stoltenberg M, Podenphant J, Pedersen-Zbinden B, Horslev-Petersen K, et al. Bone loss in rheumatoid arthritis. Influence of disease activity, duration of the disease, functional

- capacity, and corticosteroid treatment. Scand J Rheumatol. 1996;25(6):367-76.
- 64. Hashimoto J, Garnero P, van der Heijde D, Miyasaka N, Yamamoto K, Kawai S, et al. A combination of biochemical markers of cartilage and bone turnover, radiographic damage and body mass index to predict the progression of joint destruction in patients with rheumatoid arthritis treated with disease-modifying anti-rheumatic drugs. Modern rheumatology / the Japan Rheumatism Association. 2009;19(3):273-82.
- 65. Hashimoto J, Garnero P, van der Heijde D, Miyasaka N, Yamamoto K, Kawai S, et al. Humanized anti-interleukin-6-receptor antibody (tocilizumab) monotherapy is more effective in slowing radiographic progression in patients with rheumatoid arthritis at high baseline risk for structural damage evaluated with levels of biomarkers, radiography, and BMI: data from the SAMURAI study. Mod Rheumatol. 2010 Jun 24.
- 66. Hatemi G, Melikoglu M, Fresko I,
 Masatlioglu S, Tascilar K, Yazici H.
 Infliximab does not suppress the tuberculin skin test (purified protein derivative). J
 Rheumatol. 2007 Mar;34(3):474-80.
- 67. Haugeberg G, Orstavik RE, Uhlig T, Falch JA, Halse JI, Kvien TK. Bone loss in patients with rheumatoid arthritis: results from a population-based cohort of 366 patients followed up for two years. Arthritis Rheum. 2002 Jul;46(7):1720-8.
- 68. Haugeberg G, Strand A, Kvien T, Kirwan J. Reduced Loss of Hand Bone Density With Prednisolone in Early Rheumatoid Arthritis: Results From a Randomized Placebo-Controlled Trial. Archives of internal medicine. 2005;165(11):1293-7.
- 69. Helliwell PS. Therapies for dactylitis in psoriatic arthritis. A systematic review. J Rheumatol. 2006 Jul;33(7):1439-41.
- 70. Hirano Y, Kojima T, Kanayama Y, Shioura T, Hayashi M, Kida D, et al. Influences of anti-tumour necrosis factor agents on postoperative recovery in patients with rheumatoid arthritis. *Clin Rheumatol*. 2010/01/14 ed 2010:495-500.
- 71. Hornung N, Ellingsen T, Attermann J,
 Stengaard-Pedersen K, Poulsen JH. Patients
 with rheumatoid arthritis treated with
 methotrexate (MTX): concentrations of
 steady-state erythrocyte MTX correlate to

- plasma concentrations and clinical efficacy. J Rheumatol. 2008 Sep;35(9):1709-15.
- 72. Hu CP, Xu ZH, Rahman MU, Davis HM, Zhou HH. A latent variable approach for modeling categorical endpoints among patients with rheumatoid arthritis treated with golimumab plus methotrexate. Journal of Pharmacokinetics and Pharmacodynamics (USA). 2010;37:309-21.
- 73. Imrich R, Vigas M, Rovensky J, Aldag JC, Masi AT. Adrenal plasma steroid relations in glucocorticoid-naive premenopausal rheumatoid arthritis patients during insulininduced hypoglycemia test compared to matched normal control females. Endocr Regul. 2009 Apr;43(2):65-73.
- 74. James HM, Gillis D, Hissaria P, Lester S, Somogyi AA, Cleland LG, et al. Common polymorphisms in the folate pathway predict efficacy of combination regimens containing methotrexate and sulfasalazine in early rheumatoid arthritis. J Rheumatol. 2008 Apr;35(4):562-71.
- 75. Jiang Y, Genant HK, Watt I, Cobby M, Bresnihan B, Aitchison R, et al. A multicenter, double-blind, dose-ranging, randomized, placebo-controlled study of recombinant human interleukin-1 receptor antagonist in patients with rheumatoid arthritis: radiologic progression and correlation of Genant and Larsen scores. Arthritis Rheum. 2000 May;43(5):1001-9.
- 76. Jonsdottir T, Forslid J, van Vollenhoven A, Harju A, Brannemark S, Klareskog L, et al. Treatment with tumour necrosis factor alpha antagonists in patients with rheumatoid arthritis induces anticardiolipin antibodies. Ann Rheum Dis. 2004 Sep;63(9):1075-8.
- 77. Josipovic B. Levels of dehydroepiandrosterone sulfate in female patients with early stage of rheumatoid arthritis. Ann N Y Acad Sci. 1999 Jun 22;876:145-7.
- 78. Kahn KL, MacLean CH, Liu H, Rubenstein LZ, Wong AL, Harker JO, et al. Application of explicit process of care measurement to rheumatoid arthritis: Moving from evidence to practice. Arthritis Rheum. 2006 Dec 15;55(6):884-91.
- 79. Kahn KL, MacLean CH, Wong AL, Rubenstein LZ, Liu H, Fitzpatrick DM, et al. Assessment of American College of Rheumatology quality criteria for rheumatoid arthritis in a pre-quality criteria patient cohort. Arthritis Care and Research. 2007;57(5):707-15.

- 80. Kaine JL, Kivitz AJ, Birbara C, Luo AY. Immune responses following administration of influenza and pneumococcal vaccines to patients with rheumatoid arthritis receiving adalimumab. J Rheumatol. 2007 Feb;34(2):272-9.
- 81. Kalla AA, Meyers OL, Kotze TJ, Laubscher R. Corticosteroid therapy and bone mass-comparison of rheumatoid arthritis and systemic lupus erythematosus. S Afr Med J. 1994 Jul;84(7):404-9.
- 82. Kievit W, Fransen J, Oerlemans AJ, Kuper HH, van der Laar MA, de Rooij DJ, et al. The efficacy of anti-TNF in rheumatoid arthritis, a comparison between randomised controlled trials and clinical practice. Ann Rheum Dis. 2007 Nov;66(11):1473-8.
- 83. Klarenbeek NB, van der Kooij SM,
 Huizinga TJ, Goekoop-Ruiterman YP,
 Hulsmans HM, van Krugten MV, et al.
 Blood pressure changes in patients with
 recent-onset rheumatoid arthritis treated
 with four different treatment strategies: a
 post hoc analysis from the BeSt trial. Annals
 of the rheumatic diseases. 2010(7):1342-5.
- 84. Klimiuk PA, Sierakowski S, Domyslawska I, Chwiecko J. Regulation of serum chemokines following infliximab therapy in patients with rheumatoid arthritis. Clin Exp Rheumatol. 2006 Sep-Oct;24(5):529-33.
- 85. Kobelt G, Eberhardt K, Geborek P. TNF inhibitors in the treatment of rheumatoid arthritis in clinical practice: costs and outcomes in a follow up study of patients with RA treated with etanercept or infliximab in southern Sweden. Ann Rheum Dis. 2004 Jan:63(1):4-10.
- 86. Kopp S, Alstergren P, Ernestam S, Nordahl S, Bratt J. Interleukin-1beta influences the effect of infliximab on temporomandibular joint pain in rheumatoid arthritis. Scand J Rheumatol. 2006 May-Jun;35(3):182-8.
- 87. Korczowska I, Olewicz-Gawlik A, Trefler J, Hrycaj P, Krzysztof Lacki J. Does low-dose and short-term glucocorticoids treatment increase the risk of osteoporosis in rheumatoid arthritis female patients? Clin Rheumatol. 2008 May;27(5):565-72.
- 88. Korthals-de Bos I, Van Tulder M, Boers M, Verhoeven AC, Ader HJ, Bibo J, et al. Indirect and Total Costs of Early Rheumatoid Arthritis: a Randomized Comparison of Combined Step-Down Prednisolone, Methotrexate, and Sulfasalazine With Sulfasalazine Alone. The

- Journal of rheumatology. 2004;31(9):1709-16.
- 89. Kraan MC, Reece RJ, Barg EC, Smeets TJ, Farnell J, Rosenburg R, et al. Modulation of Inflammation and Metalloproteinase Expression in Synovial Tissue by Leflunomide and Methotrexate in Patients With Active Rheumatoid Arthritis. Findings in a Prospective, Randomized, Double-Blind, Parallel-Design Clinical Trial in Thirty-Nine Patients at Two Centers. Arthritis and rheumatism. 2000;43(8):1820-30.
- 90. Kristensen LE, Christensen R, Bliddal H, Geborek P, Danneskiold-SamsÃ, e B, Saxne T. The number needed to treat for adalimumab, etanercept, and infliximab based on ACR50 response in three randomized controlled trials on established rheumatoid arthritis: A systematic literature review. Scandinavian Journal of Rheumatology 2007:411-7.
- 91. Kroot EJ, van Gestel AM, Swinkels HL, Albers MM, van de Putte LB, van Riel PL. Chronic comorbidity in patients with early rheumatoid arthritis: a descriptive study. J Rheumatol. 2001 Jul;28(7):1511-7.
- 92. Kuuliala A, Leirisalo-Repo M, Mottonen T, Hannonen P, Nissila M, Kautiainen H, et al. Serum Soluble Interleukin-2 Receptor Predicts Early Remission in Patients With Recent-Onset Rheumatoid Arthritis Treated With a Single Disease-Modifying Antirheumatic Drug. Clinical and experimental rheumatology. 2005;23(2):243-6.
- 93. Lacroix BD, Lovern MR, Stockis A,
 Sargentini-Maier ML, Karlsson MO, Friberg
 LE. A pharmacodynamic Markov mixedeffects model for determining the effect of
 exposure to certolizumab pegol on the
 ACR20 score in patients with rheumatoid
 arthritis. Clin Pharmacol Ther. 2009
 Oct;86(4):387-95.
- 94. Lau J, Ioannidis JPA, Terrin N, Schmid CH, Olkin I. The case of the misleading funnel plot. British Medical Journal. 2006;333(7568):597-600.
- 95. Lodder MC, de Jong Z, Kostense PJ, Molenaar ET, Staal K, Voskuyl AE, et al. Bone mineral density in patients with rheumatoid arthritis: relation between disease severity and low bone mineral density. Ann Rheum Dis. 2004 Dec;63(12):1576-80.

- 96. Macias I, Garcia-Perez S, Ruiz-Tudela M, Medina F, Chozas N, Giron-Gonzalez JA. Modification of pro- and antiinflammatory cytokines and vascular-related molecules by tumor necrosis factor-a blockade in patients with rheumatoid arthritis. J Rheumatol. 2005 Nov;32(11):2102-8.
- 97. Maetzel A, Strand V, Tugwell P, Wells G, Bombardier C. Economic Comparison of Leflunomide and Methotrexate in Patients With Rheumatoid Arthritis: an Evaluation Based on a 1-Year Randomised Controlled Trial. PharmacoEconomics. 2002;20(1):61-70.
- 98. Marcora SM, Chester KR, Mittal G, Lemmey AB, Maddison PJ. Randomized phase 2 trial of anti-tumor necrosis factor therapy for cachexia in patients with early rheumatoid arthritis. Am J Clin Nutr. 2006 Dec;84(6):1463-72.
- 99. Marotte H, Pallot-Prades B, Grange L, Tebib J, Gaudin P, Alexandre C, et al. The shared epitope is a marker of severity associated with selection for, but not with response to, infliximab in a large rheumatoid arthritis population. Ann Rheum Dis. 2006 Mar;65(3):342-7.
- 100. Maxwell JR, Potter C, Hyrich KL, Barton A, Worthington J, Isaacs JD, et al. Association of the tumour necrosis factor-308 variant with differential response to anti-TNF agents in the treatment of rheumatoid arthritis. Hum Mol Genet. 2008 Nov 15;17(22):3532-8.
- 101. Mease PJ, Wei N, Fudman EJ, Kivitz AJ, Schechtman J, Trapp RG, et al. Safety, tolerability, and clinical outcomes after intraarticular injection of a recombinant adeno-associated vector containing a tumor necrosis factor antagonist gene: Results of a phase 1/2 study. Journal of Rheumatology. 2010;37(4):692-703.
- 102. Ollendorf DA, Klingman D, Hazard E, Ray S. Differences in annual medication costs and rates of dosage increase between tumor necrosis factor-antagonist therapies for rheumatoid arthritis in a managed care population. Clinical Therapeutics. 2009;31(4):825-35.
- 103. Ollendorf DA, Peterson AN, Doyle J, Huse DM. Impact of leflunomide versus biologic agents on the costs of care for rheumatoid arthritis in a managed care population. Am J Manag Care. 2002 May;8(7 Suppl):S203-13.
- 104. Oren C, Mendelbaum M, Paran D. Vaccination against influenza in rheumatoid

- arthritis patients: The effect of rituximab on the humoral response. *Arthritis Rheum* 2006
- 105. Pincus T, Marcum SB, Callahan LF. Longterm drug therapy for rheumatoid arthritis in seven rheumatology private practices: II. Second line drugs and prednisone. J Rheumatol. 1992 Dec;19(12):1885-94.
- 106. Potter C, Hyrich KL, Tracey A, Lunt M, Plant D, Symmons DP, et al. Association of rheumatoid factor and anti-cyclic citrullinated peptide positivity, but not carriage of shared epitope or PTPN22 susceptibility variants, with anti-tumour necrosis factor response in rheumatoid arthritis. Ann Rheum Dis 2009:69-74.
- 107. Quinn MA, Conaghan PG, O'Connor PJ, Karim Z, Greenstein A, Brown A, et al. Very early treatment with infliximab in addition to methotrexate in early, poorprognosis rheumatoid arthritis reduces magnetic resonance imaging evidence of synovitis and damage, with sustained benefit after infliximab withdrawal: results from a twelve-month randomized, double-blind, placebo-controlled trial. Arthritis Rheum. 2005 Jan;52(1):27-35.
- 108. Rajakulendran S, Gadsby K, Deighton C. Rheumatoid arthritis, alcohol, leflunomide and methotrexate. Can changes to the BSR guidelines for leflunomide and methotrexate on alcohol consumption be justified?

 Musculoskeletal Care. 2008 Dec;6(4):233-45.
- 109. Roux CH, Brocq O, Breuil V, Albert C, Euller-Ziegler L. Safety of anti-TNF-alpha therapy in rheumatoid arthritis and spondylarthropathies with concurrent B or C chronic hepatitis. Rheumatology. 2006 10/01/;45(Oct):1294-7.
- 110. Saliu OY, Sofer C, Stein DS, Schwander SK, Wallis RS. Tumor-necrosis-factor blockers: differential effects on mycobacterial immunity. J Infect Dis. 2006 Aug 15;194(4):486-92.
- 111. Sanmarti R, Gomez-Centeno A, Ercilla G, Larrosa M, Vinas O, Vazquez I, et al. Prognostic factors of radiographic progression in early rheumatoid arthritis: a two year prospective study after a structured therapeutic strategy using DMARDs and very low doses of glucocorticoids. Clin Rheumatol. 2007 Jul;26(7):1111-8.
- 112. Scheinberg M, Guedes-Barbosa LS, Mangueira C, Rosseto EA, Mota L, Oliveira

- AC, et al. Yellow fever revaccination during infliximab therapy. *Arthritis Care Res* (*Hoboken*). 2010/06/11 ed 2010:896-8.
- 113. Sennels H, Sorensen S, Ostergaard M, Knudsen L, Hansen M, Skjodt H, et al. Circulating levels of osteopontin, osteoprotegerin, total soluble receptor activator of nuclear factor-kappa B ligand, and high-sensitivity C-reactive protein in patients with active rheumatoid arthritis randomized to etanercept alone or in combination with methotrexate. Scand J Rheumatol. 2008 Jul-Aug;37(4):241-7.
- 114. Seriolo B, Paolino S, Sulli A, Fasciolo D, Cutolo M. Effects of anti-TNF-alpha treatment on lipid profile in patients with active rheumatoid arthritis. Ann N Y Acad Sci. 2006 Jun;1069:414-9.
- 115. Seriolo B, Paolino S, Sulli A, Ferretti V, Cutolo M. Bone metabolism changes during anti-TNF-alpha therapy in patients with active rheumatoid arthritis. Ann N Y Acad Sci. 2006 Jun;1069:420-7.
- 116. Smolen JS, van der Heijde DM, Aletaha D, Xu S, Han J, Baker D, et al. Progression of radiographic joint damage in rheumatoid arthritis: independence of erosions and joint space narrowing. Annals of the rheumatic diseases. 2009;68(10):1535-40.
- 117. Soderlin MK, Geborek P. Changing pattern in the prescription of biological treatment in rheumatoid arthritis. A 7-year follow-up of 1839 patients in southern Sweden. Annals of the Rheumatic Diseases. 2008;67(1):37-42.
- 118. Sokka T, Kautiainen H, Toloza S, Makinen H, Verstappen SM, Lund Hetland M, et al. QUEST-RA: quantitative clinical assessment of patients with rheumatoid arthritis seen in standard rheumatology care in 15 countries. Ann Rheum Dis. 2007 Nov;66(11):1491-6.
- 119. Sokka T, Mottonen T, Hannonen P.
 Mortality in early "sawtooth" treated
 rheumatoid arthritis patients during the first
 8-14 years. Scand J Rheumatol.
 1999;28(5):282-7.
- 120. Sokka T, Pincus T. Contemporary disease modifying antirheumatic drugs (DMARD) in patients with recent onset rheumatoid arthritis in a US private practice: methotrexate as the anchor drug in 90% and new DMARD in 30% of patients. J Rheumatol. 2002 Dec;29(12):2521-4.
- 121. Strand V, Cohen S, Crawford B, Smolen JS, Scott DL, et al. Patient-reported outcomes better discriminate active treatment from

- placebo in randomized controlled trials in rheumatoid arthritis. Rheumatology. 2004 05/01/;43(May):640-7.
- 122. Strober B, Teller C, Yamauchi P, Miller JL, Hooper M, Yang YC, et al. Effects of etanercept on C-reactive protein levels in psoriasis and psoriatic arthritis. Br J Dermatol. 2008 Aug;159(2):322-30.
- 123. Stubenrauch K, Wessels U, Birnboeck H, Ramirez F, Jahreis A, Schleypen J. Subset analysis of patients experiencing clinical events of a potentially immunogenic nature in the pivotal clinical trials of tocilizumab for rheumatoid arthritis: Evaluation of an antidrug antibody ELISA using clinical adverse event-driven immunogenicity testing. Clinical Therapeutics. 2010;32(9):1597-609.
- 124. Suissa S, Ernst P, Hudson M. TNF-alpha antagonists and the prevention of hospitalisation for chronic obstructive pulmonary disease. Pulm Pharmacol Ther. 2008;21(1):234-8.
- 125. Symmons D, Tricker K, Harrison M, Roberts C, Davis M, Dawes P, et al. Patients with stable long-standing rheumatoid arthritis continue to deteriorate despite intensified treatment with traditional disease modifying anti-rheumatic drugs Results of the British Rheumatoid Outcome Study Group randomized controlled clinical trial. Rheumatology. 2006;45(5):558-65.
- 126. Tan RJ, Gibbons LJ, Potter C, Hyrich KL, Morgan AW, Wilson AG, et al. Investigation of rheumatoid arthritis susceptibility genes identifies association of AFF3 and CD226 variants with response to anti-tumour necrosis factor treatment. *Ann Rheum Dis.* 2010/05/07 ed 2010:1029-35.
- 127. Tang B, Rahman M, Waters HC, Callegari P. Treatment persistence with adalimumab, etanercept, or infliximab in combination with methotrexate and the effects on health care costs in patients with rheumatoid arthritis. Clin Ther. 2008 Jul;30(7):1375-84.
- 128. Tascioglu F, Oner C, Armagan O. The effect of low-dose methotrexate on bone mineral density in patients with early rheumatoid arthritis. Rheumatol Int. 2003 Sep;23(5):231-5.
- 129. Tikly M, Zannettou N, Hopley M. A longitudinal study of rheumatoid arthritis in South Africans. MedGenMed. 2003 Feb 5;5(1):2.
- 130. Toms TE, Panoulas VF, John H, Douglas KM, Kitas GD. Methotrexate therapy

- associates with reduced prevalence of the metabolic syndrome in rheumatoid arthritis patients over the age of 60- more than just an anti-inflammatory effect? A cross sectional study. Arthritis Res Ther. 2009;11(4):R110.
- 131. Torikai E, Kageyama Y, Takahashi M, Nagano A. The effect of methotrexate on bone metabolism markers in patients with rheumatoid arthritis. Mod Rheumatol. 2006;16(6):350-4.
- 132. Toubi E, Kessel A, Slobodin G, Boulman N, Pavlotzky E, Zisman D, et al. Changes in macrophage function after rituximab treatment in patients with rheumatoid arthritis. Ann Rheum Dis. 2007

 Jun:66(6):818-20.
- 133. van der Bijl AE, Goekoop-Ruiterman YP, de Vries-Bouwstra JK, Ten Wolde S, Han KH, van Krugten MV, et al. Infliximab and methotrexate as induction therapy in patients with early rheumatoid arthritis. Arthritis Rheum. 2007 Jul;56(7):2129-34.
- 134. van der Heijde D, Landewe R, Klareskog L, Rodriguez-Valverde V, Settas L, Pedersen R, et al. Presentation and analysis of data on radiographic outcome in clinical trials: experience from the TEMPO study. Arthritis Rheum. 2005 Jan;52(1):49-60.
- 135. Verhoeven AC, Bibo JC, Boers M, Engel GL, van der Linden S. Cost-Effectiveness and Cost-Utility of Combination Therapy in Early Rheumatoid Arthritis: Randomized Comparison of Combined Step-Down Prednisolone, Methotrexate and Sulphasalazine With Sulphasalazine Alone. British journal of rheumatology. 1998;37(10):1102-9.
- 136. Verhoeven AC, Boers M, te Koppele JM, van der Laan WH, Markusse HM, Geusens P, et al. Bone turnover, joint damage and bone mineral density in early rheumatoid arthritis treated with combination therapy including high-dose prednisolone.

 Rheumatology (Oxford). 2001

 Nov;40(11):1231-7.
- 137. Visvanathan S, Marini JC, Smolen JS, Clair EW, Pritchard C, Shergy W, et al. Changes in biomarkers of inflammation and bone turnover and associations with clinical efficacy following infliximab plus methotrexate therapy in patients with early rheumatoid arthritis. J Rheumatol. 2007 Jul;34(7):1465-74.
- 138. Visvanathan S, Wagner C, Rojas J, Kay J, Dasgupta B, Matteson EL, et al. E-selectin,

- interleukin 18, serum amyloid a, and matrix metalloproteinase 9 are associated with clinical response to golimumab plus methotrexate in patients with active rheumatoid arthritis despite methotrexate therapy. J Rheumatol. 2009 Jul;36(7):1371-9
- 139. Wallace DJ, Metzger AL, Stecher VJ,
 Turnbull BA, Kern PA. Cholesterollowering effect of hydroxychloroquine in
 patients with rheumatic disease: reversal of
 deleterious effects of steroids on lipids. Am
 J Med. 1990 Sep;89(3):322-6.
- 140. Wells G, Li T, Tugwell P. Investigation into the impact of abatacept on sleep quality in patients with rheumatoid arthritis, and the validity of the MOS-Sleep questionnaire Sleep Disturbance Scale. Ann Rheum Dis. 2010 Oct;69(10):1768-73.
- 141. Wells GA, Boers M, Li T, Tugwell PS. Investigating the validity of the minimal disease activity state for patients with rheumatoid arthritis treated with abatacept. J Rheumatol. 2009 Feb;36(2):260-5.
- 142. Wells GA, Sultan SA, Chen L. Indirect evidence: Indirect treatment comparisons in meta-analysis. Ottawa (ON): Canadian Agency for Drugs and Technologies in Health. 2009.
- 143. Weng HH, Ranganath VK, Khanna D, Oh M, Western Consortium P, et al. Equivalent Responses to Disease-modifying Antirheumatic Drugs Initiated at Any Time During the First 15 Months After Symptom Onset in Patients with Seropositive Rheumatoid Arthritis. Journal of Rheumatology. 2010;37:550-7.
- 144. Wolbink GJ, Vis M, Lems W, Voskuyl AE, Dijkmans B, et al. Development of antiinfliximab antibodies and relationship to clinical response in patients with rheumatoid arthritis. Arthritis and Rheumatism (USA). 2006 03/01/;54(Mar):711-5.
- 145. Wu E, Chen L, Birnbaum H, Yang E, Cifaldi M. Cost of care for patients with rheumatoid arthritis receiving TNF-antagonist therapy using claims data. Curr Med Res Opin. 2007 Aug;23(8):1749-59.
- 146. Wu E, Chen L, Birnbaum H, Yang E, Cifaldi M. Retrospective claims data analysis of dosage adjustment patterns of TNF antagonists among patients with rheumatoid arthritis. Current Medical Research and Opinion. 2008;24(8):2229-40.
- 147. Yamanaka H, Inoue E, Singh G, Tanaka E, Nakajima A, Taniguchi A, et al.

- Improvement of disease activity of rheumatoid arthritis patients from 2000 to 2006 in a large observational cohort study IORRA in Japan. Mod Rheumatol. 2007;17(4):283-9.
- 148. Yazici Y, Krasnokutsky S, Barnes JP, Hines PL, Wang J, Rosenblatt L. Changing patterns of tumor necrosis factor inhibitor use in 9074 patients with rheumatoid arthritis. J Rheumatol. 2009 May;36(5):907-13
- 149. Yee CS, Filer A, Pace A, Douglas K, Situnayake D, Rowe IF. The prevalence of

Drug Not Included in the Report

- 1. Adams J, Burridge J, Mullee M, Hammond A, Cooper C. The clinical effectiveness of static resting splints in early rheumatoid arthritis: A randomized controlled trial. Rheumatology. 2008;47(10):1548-53.
- 2. Anderson JJ, O'Neill A, Woodworth T, Haddad J, Sewell KL, Moreland LW. Health Status Response of Rheumatoid Arthritis to Treatment With Dab486il-2. Arthritis care and research: the official journal of the Arthritis Health Professions Association. 1996;9(2):112-9.
- 3. Bae SC, Corzillius M, Kuntz KM, Liang MH. Cost-effectiveness of low dose corticosteroids versus non-steroidal anti-inflammatory drugs and COX-2 specific inhibitors in the long-term treatment of rheumatoid arthritis. Rheumatology (Oxford). 2003 Jan;42(1):46-53.
- 4. Bakker MF, Jacobs JWG, Welsing PMJ, Van Der Werf JH, Linn-Rasker SP, Van Der Veen MJ, et al. Are switches from oral to subcutaneous methotrexate or addition of ciclosporin to methotrexate useful steps in a tight control treatment strategy for rheumatoid arthritis? A post hoc analysis of the CAMERA study. Annals of the rheumatic diseases. 2010;69(10):1849-52.
- 5. Bejarano V, Conaghan PG, Proudman SM, Buch MH, Brown AK, Emery P. Long-term efficacy and toxicity of ciclosporin A in combination with methotrexate in poor prognosis rheumatoid arthritis. Annals of the Rheumatic Diseases. 2009;68(5):761-3.
- Blyth T, Hunter JA, Stirling A. Pain relief in the rheumatoid knee after steroid injection. A single-blind comparison of hydrocortisone succinate, and triamcinolone acetonide or hexacetonide. Br J Rheumatol. 1994 May;33(5):461-3.

- patients with rheumatoid arthritis in the West Midlands fulfilling the BSR criteria for anti-tumour necrosis factor therapy: an outpatient study. Rheumatology (Oxford). 2003 Jul;42(7):856-9.
- 150. Zink A, Strangfeld A, Schneider M, Herzer P, Listing J, et al. Effectiveness of tumor necrosis factor inhibitors in rheumatoid arthritis in an observational cohort study Comparison of patients according to their eligibility for major randomized clinical trials. Arthritis and Rheumatism (USA). 2006 11/01/;54(Nov):3399-407.
- 7. Capell H, Marabani M, Madhok R, Torley H, Hunter J. Degree and Extent of Response to Sulphasalazine or Penicillamine Therapy for Rheumatoid Arthritis: Results From a Routine Clinical Environment Over a Two-Year Period. The Quarterly journal of medicine. 1990;75(276):335-44.
- 8. Capell HA, Madhok R, Hunter JA, Porter D, Morrison E, Larkin J, et al. Lack of radiological and clinical benefit over two years of low dose prednisolone for rheumatoid arthritis: results of a randomised controlled trial. Ann Rheum Dis. 2004 Jul;63(7):797-803.
- 9. Capell HA, Murphy EA, Hunter JA. Rheumatoid arthritis: workload and outcome over 10 years. Q J Med. 1991 Jun;79(290):461-76.
- 10. Choy EH, Kingsley GH, Khoshaba B, Pipitone N, Scott DL. A Two Year Randomised Controlled Trial of Intramuscular Depot Steroids in Patients With Established Rheumatoid Arthritis Who Have Shown an Incomplete Response to Disease Modifying Antirheumatic Drugs. Ann Rheum Dis. 2005;64(9):1288-93.
- 11. Choy EHS, Scott DL, Kingsley GH,
 Williams P, Wojtulewski J, Papasavvas G,
 et al. Treating Rheumatoid Arthritis Early
 With Disease Modifying Drugs Reduces
 Joint Damage: a Randomised Double Blind
 Trial of Sulphasalazine Vs Diclofenac
 Sodium. Clinical and experimental
 rheumatology. 2002;20(3):351-8.
- 12. Cohen SB, Cheng TT, Chindalore V,
 Damjanov N, Burgos-Vargas R, Delora P, et
 al. Evaluation of the efficacy and safety of
 pamapimod, a p38 MAP kinase inhibitor, in
 a double-blind, methotrexate-controlled
 study of patients with active rheumatoid

- arthritis. Arthritis Rheum. 2009 Feb;60(2):335-44.
- 13. Cohen SB, Dore RK, Lane NE, Ory PA, Peterfy CG, Sharp JT, et al. Denosumab treatment effects on structural damage, bone mineral density, and bone turnover in rheumatoid arthritis: a twelve-month, multicenter, randomized, double-blind, placebo-controlled, phase II clinical trial. Arthritis Rheum. 2008 May;58(5):1299-309.
- 14. Conaghan PG, O'Connor P, McGonagle D, Astin P, Wakefield RJ, Gibbon WW, et al. Elucidation of the relationship between synovitis and bone damage: a randomized magnetic resonance imaging study of individual joints in patients with early rheumatoid arthritis. Arthritis Rheum. 2003 Jan;48(1):64-71.
- 15. Damjanov N, Kauffman RS, Spencer-Green GT. Efficacy, pharmacodynamics, and safety of VX-702, a novel p38 MAPK inhibitor, in rheumatoid arthritis: results of two randomized, double-blind, placebo-controlled clinical studies. Arthritis Rheum. 2009 May;60(5):1232-41.
- 16. Doran MF, Crowson CS, Pond GR, O'Fallon WM, Gabriel SE. Frequency of infection in patients with rheumatoid arthritis compared with controls: a population-based study. Arthritis Rheum. 2002 Sep;46(9):2287-93.
- 17. Eberhardt R, Kruger K, Reiter W, Gross W, Zwingers T. Long-term therapy with the new glucocorticosteroid deflazacort in rheumatoid arthritis. Double-blind controlled randomized 12-months study against prednisone. Arzneimittelforschung. 1994 May;44(5):642-7.
- 18. Egsmose C, TM H, Andersen LS, Beier JM, Christensen L, Ejstrup L, et al. Limited Effect of Sulphasalazine Treatment in Reactive Arthritis. A Randomised Double Blind Placebo Controlled Trial. Annals of the rheumatic diseases. 1997;56(1):32-6.
- 19. Felson DT, Anderson JJ, Meenan RF. The efficacy and toxicity of combination therapy in rheumatoid arthritis. A meta-analysis.

 Arthritis Rheum. 1994 Oct;37(10):1487-91.
- Ferraz MB, Pinheiro GR, Helfenstein M, Albuquerque E, Rezende C, Roimicher L, et al. Combination Therapy With Methotrexate and Chloroquine in Rheumatoid Arthritis. A Multicenter Randomized Placebo-Controlled Trial. Scandinavian journal of rheumatology. 1994;23(5):231-6.
- 21. Finckh A, Liang MH, Van Herckenrode CM, De Pablo P. Long-term impact of early

- treatment on radiographic progression in rheumatoid arthritis: Ameta-analysis. Arthritis and rheumatism. 2006;55(6):86-172.
- 22. Fraser AD, van Kuijk AWR, Westhovens R, Karim Z, Wakefield R, Gerards AH, et al. A Randomised, Double Blind, Placebo Controlled, Multicentre Trial of Combination Therapy With Methotrexate Plus Ciclosporin in Patients With Active Psoriatic Arthritis. Ann Rheum Dis. 2005;64(6):859-64.
- 23. Furtado RN, Oliveira LM, Natour J. Polyarticular corticosteroid injection versus systemic administration in treatment of rheumatoid arthritis patients: a randomized controlled study. J Rheumatol. 2005 Sep;32(9):1691-8.
- 24. Gerlag DM, Hollis S, Layton M, Vencovsky J, Szekanecz Z, Braddock M, et al. Preclinical and clinical investigation of a CCR5 antagonist, AZD5672, in patients with rheumatoid arthritis receiving methotrexate. Arthritis and rheumatism. 2010;62(11):3154-60.
- 25. Gøtzsche P, Johansen H. Short-Term Low-Dose Corticosteroids Vs Placebo and Nonsteroidal Antiinflammatory Drugs in Rheumatoid Arthritis. The Cochrane Database of Systematic Reviews. 2005;2005(1).
- 26. Gough A, Sheeran T, Arthur V, Panayi G, Emery P. Adverse interaction between intramuscular methylprednisolone and sulphasalazine in patients with early rheumatoid arthritis. A pilot study. Scand J Rheumatol. 1994;23(1):46-8.
- 27. Graell E, Vazquez I, Larrosa M, Rodriguez-Cros JR, Hernandez MV, Gratacos J, et al. Disability measured by the modified health assessment questionnaire in early rheumatoid arthritis: Prognostic factors after two years of follow-up. Clinical and Experimental Rheumatology. 2009;27(2):284-91.
- 28. Graudal N, Juergens G. Similar Effects of Disease-Modifying Antirheumatic Drugs, Glucocorticoids, and Biologic Agents on Radiographic Progression in Rheumatoid Arthritis Meta-Analysis of 70 Randomized Placebo-Controlled or Drug-Controlled Studies, Including 112 Comparisons. Arthritis and Rheumatism (USA). 2010;62:2852.
- 29. Gray RE, Doherty SM, Galloway J, Coulton L, de Broe M, Kanis JA. A double-blind

- study of deflazacort and prednisone in patients with chronic inflammatory disorders. Arthritis Rheum. 1991 Mar;34(3):287-95.
- 30. Griffith SM, Fisher J, Clarke S,
 Montgomery B, Jones PW, Saklatvala J, et
 al. Do Patients With Rheumatoid Arthritis
 Established on Methotrexate and Folic Acid
 5 Mg Daily Need to Continue Folic Acid
 Supplements Long Term? Rheumatology
 (Oxford). 2000;39(10):1102-9.
- 31. Hannonen P, Mottonen T, Hakola M, Oka M. Sulfasalazine in Early Rheumatoid Arthritis. A 48-Week Double-Blind, Prospective, Placebo-Controlled Study. Arthritis and rheumatism. 1993;36(11):1501-9.
- 32. Hetland ML, Stengaard-Pedersen K, Junker P, Horslev-Petersen K, Grp CS, et al. Combination treatment with methotrexate, cyclosporine, and intraarticular betamethasone compared with methotrexate and intraarticular betamethasone in early active rheumatoid arthritis An investigatorinitiated, multicenter, randomized, doubleblind, parallel-group, placebo-controlled study. Arthritis and Rheumatism (USA). 2006 05/01/;54(May):1401-9.
- 33. Hetland ML, Stengaard-Pedersen K, Junker P, Lottenburger T, Ellingsen T, Andersen LS, et al. Combination treatment with methotrexate, cyclosporine, and intraarticular betamethasone compared with methotrexate and intraarticular betamethasone in early active rheumatoid arthritis: an investigator-initiated, multicenter, randomized, double-blind, parallel-group, placebo-controlled study. Arthritis Rheum. 2006 May;54(5):1401-9.
- 34. Hetland ML, Stengaard-Pedersen K, Junker P, Lottenburger T, Hansen I, Andersen LS, et al. Aggressive combination therapy with intra-articular glucocorticoid injections and conventional disease-modifying anti-rheumatic drugs in early rheumatoid arthritis: second-year clinical and radiographic results from the CIMESTRA study. Ann Rheum Dis. 2008 Jun;67(6):815-22.
- 35. Hetland ML, Stengaard-Pedersen K, Junker P, Ostergaard M, Ejbjerg BJ, Jacobsen S, et al. Radiographic progression and remission rates in early rheumatoid arthritis MRI bone oedema and anti-CCP predicted radiographic progression in the 5-year extension of the double-blind randomised

- CIMESTRA trial. Ann Rheum Dis. 2010 Oct;69(10):1789-95.
- 36. Hu D, Bao C, Chen S, Gu J, Li Z, Sun L, et al. A comparison study of a recombinant tumor necrosis factor receptor:Fc fusion protein (rhTNFR:Fc) and methotrexate in treatment of patients with active rheumatoid arthritis in China. Rheumatol Int. 2009 Jan;29(3):297-303.
- 37. Ichikawa Y, Saito T, Yamanaka H, Akizuki M, Kondo H, Kobayashi S, et al. Clinical activity after 12 weeks of treatment with nonbiologics in early rheumatoid arthritis may predict articular destruction 2 years later. Journal of Rheumatology. 2010;37(4):723-9.
- 38. Jessop JD, O'Sullivan MM, Lewis PA, Williams LA, Camilleri JP, Plant MJ, et al. A Long-Term Five-Year Randomized Controlled Trial of Hydroxychloroquine, Sodium Aurothiomalate, Auranofin and Penicillamine in the Treatment of Patients With Rheumatoid Arthritis. British journal of rheumatology. 1998;37(9):992-1002.
- 39. Jeurissen ME, Boerbooms AM, van de Putte LB, Doesburg WH, Mulder J, Rasker JJ, et al. Methotrexate versus azathioprine in the treatment of rheumatoid arthritis. A fortyeight-week randomized, double-blind trial. Arthritis Rheum. 1991 Aug;34(8):961-72.
- 40. Johnsen AK, Schiff MH, Mease PJ,
 Moreland LW, Maier AL, Coblyn JS, et al.
 Comparison of 2 doses of etanercept (50 vs
 100 mg) in active rheumatoid arthritis: a
 randomized double blind study. J
 Rheumatol. 2006 Apr;33(4):659-64.
- 41. Katchamart W, Trudeau J, Phumethum V, Bombardier C. Methotrexate monotherapy versus methotrexate combination therapy with non-biologic disease modifying anti-rheumatic drugs for rheumatoid arthritis. Cochrane Database Syst Rev. 2010;4:CD008495.
- 42. Kavanaugh A, Menter A, Mendelsohn A, Shen YK, Lee S, Gottlieb AB. Effect of ustekinumab on physical function and health-related quality of life in patients with psoriatic arthritis: A randomized, placebocontrolled, phase II trial. Current Medical Research and Opinion. 2010;26(10):2385-92.
- 43. Kawai S, Hashimoto H, Kondo H,
 Murayama T, Abe T, et al. Comparison of
 tacrolimus and mizoribine in a randomized,
 double-blind controlled study in patients
 with rheumatoid arthritis. Journal of

- Rheumatology. 2006 11/01/;33(Nov):2153-61.
- 44. Kirwan J, Byron M, Watt I. The Relationship Between Soft Tissue Swelling, Joint Space Narrowing and Erosive Damage in Hand X-Rays of Patients With Rheumatoid Arthritis. Rheumatology (Oxford). 2001;40(3):688-95.
- 45. Kirwan JR. The effect of glucocorticoids on joint destruction in rheumatoid arthritis. The Arthritis and Rheumatism Council Low-Dose Glucocorticoid Study Group. N Engl J Med. 1995 Jul 20;333(3):142-6.
- 46. Kremer J, Ritchlin C, Mendelsohn A, Baker D, Kim L, Xu Z, et al. Golimumab, a new human anti-tumor necrosis factor alpha antibody, administered intravenously in patients with active rheumatoid arthritis: Forty-eight-week efficacy and safety results of a phase III randomized, double-blind, placebo-controlled study. *Arthritis Rheum*. 2010/02/05 ed 2010:917-28.
- 47. Lambert CM, Sandhu S, Lochhead A, Hurst NP, McRorie E, Dhillon V. Dose Escalation of Parenteral Methotrexate in Active Rheumatoid Arthritis That Has Been Unresponsive to Conventional Doses of Methotrexate: a Randomized, Controlled Trial. Arthritis and rheumatism. 2004;50(2):364-71.
- 48. Lard LR, Visser H, Speyer I, vander Horst-Bruinsma IE, Zwinderman AH, Breedveld FC, et al. Early versus delayed treatment in patients with recent-onset rheumatoid arthritis: comparison of two cohorts who received different treatment strategies. Am J Med. 2001 Oct 15;111(6):446-51.
- 49. Lerndal T, Svensson B. A Clinical Study of Cph 82 Vs Methotrexate in Early Rheumatoid Arthritis. Rheumatology (Oxford). 2000;39(3):316-20.
- 50. Lu LJ, Bao CD, Dai M, Teng JL, Fan W, Du F, et al. Multicenter, randomized, doubleblind, controlled trial of treatment of active rheumatoid arthritis with T-614 compared with methotrexate. Arthritis Rheum. 2009 Jul 15;61(7):979-87.
- 51. Ma MH, Kingsley GH, Scott DL. A systematic comparison of combination DMARD therapy and tumour necrosis inhibitor therapy with methotrexate in patients with early rheumatoid arthritis. Rheumatology (Oxford). 2010;49:91-8.
- Messina OD, Barreira JC, Zanchetta JR,
 Maldonado-Cocco JA, Bogado CE,
 Sebastian ON, et al. Effect of low doses of

- deflazacort vs prednisone on bone mineral content in premenopausal rheumatoid arthritis. J Rheumatol. 1992 Oct;19(10):1520-6.
- 53. Migliore A, Bizzi E, Massafra U, Vacca F, Martin Martin LS, Ferlito C, et al. Can Cyclosporine-A associated to methotrexate maintain remission induced by anti-TNF agents in rheumatoid arthritis patients? (Cynar pilot study). Int J Immunopathol Pharmacol. 2010 Jul-Sep;23(3):783-90.
- 54. Mladenovic V, Domljan Z, Rozman B, Jajic I, Mihajlovic D, Dordevic J, et al. Safety and Effectiveness of Leflunomide in the Treatment of Patients With Active Rheumatoid Arthritis. Results of a Randomized, Placebo-Controlled, Phase Ii Study. Arthritis and rheumatism. 1995;38(11):1595-603.
- Moreland L, R G, King K, Chase W, Weisman M, Greco T, et al. Results of a Phase-I/II Randomized, Masked, Placebo-Controlled Trial of Recombinant Human Interleukin-11 (Rhil-11) in the Treatment of Subjects With Active Rheumatoid Arthritis. Arthritis Res. 2001;3(4):247-52.
- 56. Nishimoto N, Yoshizaki K, Miyasaka N, Yamamoto K, Kawai S, Takeuchi T, et al. Treatment of Rheumatoid Arthritis With Humanized Anti-Interleukin-6 Receptor Antibody: a Multicenter, Double-Blind, Placebo-Controlled Trial. Arthritis and rheumatism. 2004;50(6):1761-9.
- Paulus HE, Di Primeo D, Sanda M, Lynch JM, Schwartz BA, Sharp JT, et al.
 Progression of radiographic joint erosion during low dose corticosteroid treatment of rheumatoid arthritis. J Rheumatol. 2000 Jul:27(7):1632-7.
- 58. Peltomaa R, Paimela L, Helve T, Leirisalo-Repo M. Comparison of Intramuscular Gold and Sulphasalazine in the Treatment of Early Rheumatoid Arthritis. A One Year Prospective Study. Scandinavian journal of rheumatology. 1995;24(6):330-5.
- 59. Perdriger A, Mariette X, Kuntz JL, Brocq O, Kara-Terki R, Loet XL, et al. Safety of infliximab used in combination with leflunomide or azathioprine in daily clinical practice. J Rheumatol. 2006 May;33(5):865-9.
- Plant M, O'Sullivan MM, Lewis P, Camilleri J, Coles E, Jessop J. What Factors Influence Functional Ability in Patients With Rheumatoid Arthritis. Do They Alter Over

- Time? Rheumatology (Oxford). 2005;44(9):1181-5.
- 61. Porter D, McInnes I, Hunter J, Capell H. Outcome of second line therapy in rheumatoid arthritis. Annals of the rheumatic diseases. 1994;53(12):812-5.
- 62. Sany J, Kaiser MJ, Jorgensen C, Trape G. Study of the tolerance of infliximab infusions with or without betamethasone premedication in patients with active rheumatoid arthritis. Ann Rheum Dis. 2005 Nov;64(11):1647-9.
- 63. Suarez Almazor M, Belseck E, Shea BJ, Homik J, Wells G, Tugwell P. Antimalarials for Treating Rheumatoid Arthritis. The Cochrane Database of Systematic Reviews. 2000;2000(4).
- 64. Suarez Almazor M, Belseck E, Shea BJ, Tugwell P, Wells G. Methotrexate for Treating Rheumatoid Arthritis. The Cochrane Database of Systematic Reviews. 1998;1998(2).
- 65. Suarez Almazor M, Belseck E, Shea BJ, Tugwell P, Wells G. Sulfasalazine for Treating Rheumatoid Arthritis. The Cochrane Database of Systematic Reviews. 1998;1998(2).
- 66. Suarez Almazor M, Spooner C, Belseck E. Azathioprine for Treating Rheumatoid Arthritis. The Cochrane Database of Systematic Reviews. 2000;2000(4).
- 67. Sugimori S, Watanabe T, Tabuchi M, Kameda N, Machida H, Okazaki H, et al. Evaluation of small bowel injury in patients with rheumatoid arthritis by capsule endoscopy: effects of anti-rheumatoid arthritis drugs. Digestion. 2008;78(4):208-13.
- 68. Tak PP, Thurlings RM, Rossier C, Nestorov I, Dimic A, Mircetic V, et al. Atacicept in patients with rheumatoid arthritis: Results of a multicenter, phase Ib, double-blind, placebo-controlled, dose-escalating, single-and repeated-dose study. Arthritis and rheumatism. 2008;58(1):61-72.
- 69. Tebib JG, Manil LM, Modder G, Verrier P, De Rycke Y, Bonmartin A, et al. Better Results With Rhenium-186
 Radiosynoviorthesis Than With Cortivazol in Rheumatoid Arthritis (Ra): a Two-Year Follow-up Randomized Controlled Multicentre Study. Clinical and experimental rheumatology. 2004;22(5):609-16.

- 70. The Australian Multicentre Clinical Trial Group. Sulfasalazine in Early Rheumatoid Arthritis. J Rheumatol. 1992 7;19(11):1672.
- 71. Tsakonas E, Fitzgerald AA, Fitzcharles MA, Cividino A, Thorne JC, M'Seffar A, et al. Consequences of delayed therapy with second-line agents in rheumatoid arthritis: a 3 year followup on the hydroxychloroquine in early rheumatoid arthritis (HERA) study. J Rheumatol. 2000 Mar;27(3):623-9.
- 72. van der Heide A, Jacobs JW, Bijlsma JW, Heurkens AH, van Booma-Frankfort C, van der Veen MJ, et al. The effectiveness of early treatment with "second-line" antirheumatic drugs. A randomized, controlled trial. Ann Intern Med. 1996 Apr 15;124(8):699-707.
- 73. van Everdingen AA, Jacobs JWG, Siewertsz Van Reesema DR, Bijlsma JWJ. Low-Dose Prednisone Therapy for Patients With Early Active Rheumatoid Arthritis: Clinical Efficacy, Disease-Modifying Properties, and Side Effects: a Randomized, Double-Blind, Placebo-Controlled Clinical Trial. Annals of internal medicine. 2002;136(1):1-12.
- 74. van Everdingen AA, Siewertsz van Reesema DR, Jacobs JWG, Bijlsma JWJ. Low-Dose Glucocorticoids in Early Rheumatoid Arthritis: Discordant Effects on Bone Mineral Density and Fractures? Clinical and experimental rheumatology. 2003;21(2):155-60.
- 75. van Jaarsveld CH, Jacobs JW, van der Veen MJ, Blaauw AA, Kruize AA, Hofman DM, et al. Aggressive Treatment in Early Rheumatoid Arthritis: a Randomised Controlled Trial. Annals of the Rheumatic Diseases. 2000;59(6):468-77.
- 76. van Jaarsveld CH, Jahangier ZN, Jacobs JW, Blaauw AA, van Albada-Kuipers GA, ter Borg EJ, et al. Toxicity of Anti-Rheumatic Drugs in a Randomized Clinical Trial of Early Rheumatoid Arthritis. Rheumatology (Oxford). 2000;39(12):1374-82.
- 77. van Schaardenburg D, Valkema R,
 Dijkmans BA, Papapoulos S, Zwinderman
 AH, Han KH, et al. Prednisone Treatment of
 Elderly-Onset Rheumatoid Arthritis. Disease
 Activity and Bone Mass in Comparison
 With Chloroquine Treatment. Arthritis and
 rheumatism. 1995;38(3):334-42.
- 78. Verhoeven AC, Boers M, Tugwell P.
 Combination therapy in rheumatoid arthritis: updated systematic review. Br J Rheumatol. 1998 Jun;37(6):612-9.

- 79. Verstappen S, van Albada Kuipers G, Bijlsma J, Blaauw A, Schenk Y, Haanen H, et al. A Good Response to Early Dmard Treatment of Patients With Rheumatoid Arthritis in the First Year Predicts Remission During Follow up. Ann Rheum Dis. 2005;64(1):38-43.
- 80. Verstappen SMM, Jacobs JWG, Bijlsma JWJ, Heurkens AHM, van Booma-Frankfort C, Borg EJt, et al. Five-Year Followup of Rheumatoid Arthritis Patients After Early Treatment With Disease-Modifying Antirheumatic Drugs Versus Treatment According to the Pyramid Approach in the First Year. Arthritis and rheumatism. 2003;48(7):1797-807.
- 81. Wallberg-Jonsson S, Ohman ML, Dahlqvist SR. Cardiovascular morbidity and mortality in patients with seropositive rheumatoid arthritis in Northern Sweden. J Rheumatol. 1997 Mar;24(3):445-51.
- 82. Wallen Margaret M, Gillies D. Intraarticular steroids and splints/rest for children with juvenile idiopathic arthritis and adults with rheumatoid arthritis. Cochrane Database of Systematic Reviews. 2006(1).
- 83. Wassenberg S, Rau R, Steinfeld P, Zeidler H. Very Low-Dose Prednisolone in Early

Wrong Population

- 1. Antoni C, Krueger GG, de Vlam K, Birbara C, Beutler A, Guzzo C, et al. Infliximab improves signs and symptoms of psoriatic arthritis: results of the IMPACT 2 trial. Ann Rheum Dis. 2005 Aug;64(8):1150-7.
- 2. Antoni CE, Kavanaugh A, Kirkham B, Tutuncu Z, Burmester GR, Schneider U, et al. Sustained benefits of infliximab therapy for dermatologic and articular manifestations of psoriatic arthritis: results from the infliximab multinational psoriatic arthritis controlled trial (IMPACT). Arthritis Rheum. 2005 Apr;52(4):1227-36.
- 3. Atteno M, Peluso R, Costa L, Padula S, Iervolino S, Caso F, et al. Comparison of effectiveness and safety of infliximab, etanercept, and adalimumab in psoriatic arthritis patients who experienced an inadequate response to previous disease-modifying antirheumatic drugs. *Clin Rheumatol*. 2010/01/13 ed 2010:399-403.
- 4. Boss B, Neeck G, Engelhardt B, Riedel W. Influence of corticosteroids on neutrophils, lymphocytes, their subsets, and T-cell activity markers in patients with active

- Rheumatoid Arthritis Retards Radiographic Progression Over Two Years: a Multicenter, Double-Blind, Placebo-Controlled Trial. Arthritis and rheumatism. 2005;52(11):3371-80.
- 84. Weinblatt ME, Kaplan H, Germain BF, Merriman RC, Solomon SD, Wall B, et al. Methotrexate in Rheumatoid Arthritis: Effects on Disease Activity in a Multicenter Prospective Study. The Journal of rheumatology. 1991;18(3):334-8.
- 85. Wolfe F, Hawley DJ. The comparative risk and predictors of adverse gastrointestinal events in rheumatoid arthritis and osteoarthritis: a prospective 13 year study of 2131 patients. J Rheumatol. 2000 Jul;27(7):1668-73.
- 86. Wolfe F, Michaud K, Li T. Sleep disturbance in patients with rheumatoid arthritis: evaluation by medical outcomes study and visual analog sleep scales. J Rheumatol. 2006 Oct;33(10):1942-51.
- 87. Zhang LL, Wei W, Xiao F, Xu JH, Bao CD, Ni LQ, et al. A randomized, double-blind, multicenter, controlled clinical trial of chicken type II collagen in patients with rheumatoid arthritis. Arthritis Rheum. 2008 Jul 15;59(7):905-10.
 - rheumatoid arthritis, compared to healthy controls. Ann N Y Acad Sci. 1999 Jun 22:876:198-200.
- 5. Cheifetz A, Smedley M, Martin S, Reiter M, Leone G, Mayer L, et al. The incidence and management of infusion reactions to infliximab: a large center experience. Am J Gastroenterol. 2003 Jun;98(6):1315-24.
- 6. Chung ES, Packer M, Lo KH, Fasanmade AA, Willerson JT. Randomized, doubleblind, placebo-controlled, pilot trial of infliximab, a chimeric monoclonal antibody to tumor necrosis factor-alpha, in patients with moderate-to-severe heart failure: results of the anti-TNF Therapy Against Congestive Heart Failure (ATTACH) trial. Circulation. 2003 Jul 1;107(25):3133-40.
- Clegg DO, Reda DJ, Weisman MH, Cush JJ, Vasey FB, Schumacher HRJ, et al. Comparison of Sulfasalazine and Placebo in the Treatment of Psoriatic Arthritis. A Department of Veterans Affairs Cooperative Study. Arthritis and rheumatism. 1996;39(12):2021-7.

- 8. Combe B, Goupille P, Kuntz J, Tebib J, Liote F, Bregeon C. Sulphasalazine in Psoriatic Arthritis: a Randomized, Multicentre, Placebo-Controlled Study. *British journal of rheumatology*. 1996:664-8.
- 9. Dass S, Bowman SJ, Vital EM, Ikeda K, Pease CT, Hamburger J, et al. Reduction of fatigue in Sjogren syndrome with rituximab: results of a randomised, double-blind, placebo-controlled pilot study. Ann Rheum Dis. 2008 Nov;67(11):1541-4.
- 10. Davaine AC, Saraux A, Prigent S, Kupfer-Bessaguet I, Roswag D, Plantin P, et al. Cutaneous events during treatment of chronic inflammatory joint disorders with anti-tumour necrosis factor alpha: a cross-sectional study. J Eur Acad Dermatol Venereol. 2008 Dec;22(12):1471-7.
- 11. Duftner C, Dejaco C, Larcher H, Schirmer M, Herold M. Biologicals in rheumatology: Austrian experiences from a rheumatic outpatient clinic. Rheumatol Int. 2008 Nov;29(1):69-73.
- 12. Feagan BG, Yan S, Bala M, Bao W, Lichtenstein GR. The effects of infliximab maintenance therapy on health-related quality of life. Am J Gastroenterol. 2003 Oct;98(10):2232-8.
- 13. Fernandez-Nebro A, Tomero E, Ortiz-Santamaria V, Castro MC, Olive A, de Haro M, et al. Treatment of rheumatic inflammatory disease in 25 patients with secondary amyloidosis using tumor necrosis factor alpha antagonists. Am J Med. 2005 May;118(5):552-6.
- 14. Fleischmann R, Baumgartner SW, Weisman MH, Liu T, White B, Peloso P. Long term safety of etanercept in elderly subjects with rheumatic diseases. *Ann Rheum Dis* 2006:379-84.
- Fouache D, Goeb V, Massy-Guillemant N, Avenel G, Vittecoq O, et al., et al.
 Paradoxical adverse events of anti-tumour necrosis factor therapy for spondyloarthropathies: a retrospective study. *Rheumatology* 2009:761.
- 16. Franklin J, Lunt M, Bunn D, Symmons D, Silman A. Risk and predictors of infection leading to hospitalisation in a large primary-care-derived cohort of patients with inflammatory polyarthritis. Ann Rheum Dis. 2007 Mar;66(3):308-12.
- 17. Genovese MC, Mease PJ, Thomson GT, Kivitz AJ, Perdok RJ, Weinberg MA, et al. Safety and efficacy of adalimumab in

- treatment of patients with psoriatic arthritis who had failed disease modifying antirheumatic drug therapy. *J Rheumatol* 2007:1040-50.
- 18. Gladman DD, Mease PJ, Cifaldi MA, Perdok RJ, Sasso E, Medich J. Adalimumab improves joint-related and skin-related functional impairment in patients with psoriatic arthritis: patient-reported outcomes of the Adalimumab Effectiveness in Psoriatic Arthritis Trial. *Ann Rheum Dis* 2007:163-8.
- Helliwell PS, Ibrahim G. Ethnic differences in responses to disease modifying drugs. Rheumatology (Oxford). 2003 Oct;42(10):1197-201.
- 20. Jones G, Crotty M, Brooks P. Interventions for Treating Psoriatic Arthritis. The Cochrane Database of Systematic Reviews. 2000;2000(3).
- Jones G, Sebba A, Gu J, Lowenstein MB, Calvo A, Gomez-Reino JJ, et al. Comparison of tocilizumab monotherapy versus methotrexate monotherapy in patients with moderate to severe rheumatoid arthritis: The AMBITION study. 2010.
- 22. Kaltwasser J, Nash P, Gladman D, Rosen C, Behrens F, Jones P, et al. Efficacy and Safety of Leflunomide in the Treatment of Psoriatic Arthritis and Psoriasis: a Multinational, Double-Blind, Randomized, Placebo-Controlled Clinical Trial. Arthritis and rheumatism. 2004;50(6):1393-50.
- 23. Kavanaugh A, Antoni C, Krueger GG, Yan S, Bala M, Dooley LT, et al. Infliximab improves health related quality of life and physical function in patients with psoriatic arthritis. Ann Rheum Dis. 2006 Apr;65(4):471-7.
- 24. Kavanaugh A, Antoni C, Mease P, Gladman D, Yan S, Bala M, et al. Effect of infliximab therapy on employment, time lost from work, and productivity in patients with psoriatic arthritis. *J Rheumatol* 2006:2254-9
- 25. Kavanaugh A, Antoni CE, Gladman D, Wassenberg S, Zhou B, Beutler A, et al. The Infliximab Multinational Psoriatic Arthritis Controlled Trial (IMPACT): results of radiographic analyses after 1 year. Ann Rheum Dis. 2006 Aug;65(8):1038-43.
- 26. Kavanaugh A, McInnes I, Mease P, Krueger GG, Gladman D, Gomez-Reino J, et al. Golimumab, a new human tumor necrosis factor alpha antibody, administered every four weeks as a subcutaneous injection in

- psoriatic arthritis: Twenty-four-week efficacy and safety results of a randomized, placebo-controlled study. *Arthritis Rheum* 2009:976-86.
- 27. Kristensen LE, Gulfe A, Saxne T, Geborek P. Efficacy and tolerability of anti-tumour necrosis factor therapy in psoriatic arthritis patients: results from the South Swedish Arthritis Treatment Group register. *Ann Rheum Dis* 2008:364-9.
- 28. Mease PJ. Adalimumab: an anti-TNF agent for the treatment of psoriatic arthritis. *Expert Opin Biol Ther* 2005:1491-504.
- 29. Mease PJ, Gladman DD, Ritchlin CT, Ruderman EM, Steinfeld SD, Choy EH, et al. Adalimumab for the treatment of patients with moderately to severely active psoriatic arthritis: results of a double-blind, randomized, placebo-controlled trial. *Arthritis Rheum* 2005:3279-89.
- 30. Mease PJ, Goffe BS, Metz J, VanderStoep A, Finck B, Burge DJ. Etanercept in the treatment of psoriatic arthritis and psoriasis: a randomised trial. Lancet. 2000 Jul 29;356(9227):385-90.
- 31. Mease PJ, Kivitz AJ, Burch FX, Siegel EL, Cohen SB, Ory P, et al. Continued inhibition of radiographic progression in patients with psoriatic arthritis following 2 years of treatment with etanercept. *J Rheumatol* 2006:712-21.
- 32. Mease PJ, Kivitz AJ, Burch FX, Siegel EL, Cohen SB, Ory P, et al. Etanercept treatment of psoriatic arthritis: safety, efficacy, and effect on disease progression. *Arthritis Rheum* 2004:2264-72.
- 33. Mease PJ, Woolley JM, Singh A, Tsuji W, Dunn M, Chiou CF. Patient-reported outcomes in a randomized trial of etanercept in psoriatic arthritis. *J Rheumatol*. 2010/04/17 ed 2010:1221-7.
- 34. Nannini C, Cantini F, Niccoli L, Cassara E, Lally EV, et al., et al. Single-Center Series and Systematic Review of Randomized Controlled Trials of Malignancies in Patients With Rheumatoid Arthritis, Psoriatic Arthritis, and Ankylosing Spondylitis Receiving Anti-Tumor Necrosis Factor alpha Therapy: Is There a Need for More Comprehensive Screening Procedures? Arthritis and Rheumatism-Arthritis Care and Research 2009:801.
- 35. Nash P, Thaci D, Behrens F, Falk F, Kaltwasser JP. Leflunomide improves psoriasis in patients with psoriatic arthritis: an in-depth analysis of data from the

- TOPAS study. Dermatology. 2006;212(3):238-49.
- 36. Puechal X, Miceli-Richard C, Mejjad O, Lafforgue P, Marcelli C, Solau-Gervais E, et al. Anti-tumour necrosis factor treatment in patients with refractory systemic vasculitis associated with rheumatoid arthritis. Ann Rheum Dis. 2008 Jun;67(6):880-4.
- 37. Ravindran V, Scott DL, Choy EH. A systematic review and meta-analysis of efficacy and toxicity of disease modifying anti-rheumatic drugs and biological agents for psoriatic arthritis. *Annals of the rheumatic diseases* 2008:855-9.
- 38. Saad AA, Ashcroft DM, Watson KD, Hyrich KL, Noyce PR, Symmons DP. Persistence with anti-tumour necrosis factor therapies in patients with psoriatic arthritis: observational study from the British Society of Rheumatology Biologics Register.

 *Arthritis Res Ther. 2009/04/10 ed 2009:R52.
- Saad AA, Ashcroft DM, Watson KD, Symmons DP, Bsrbr, et al. Efficacy and safety of anti-TNF therapies in psoriatic arthritis: an observational study from the British Society for Rheumatology Biologics Register. Rheumatology (Oxford) 2010:697-705.
- 40. Saad AA, Ashcroft DM, Watson KD, Symmons DP, Noyce PR, Hyrich KL. Improvements in quality of life and functional status in patients with psoriatic arthritis receiving anti-tumor necrosis factor therapies. *Arthritis Care Res (Hoboken)*. 2010/04/15 ed 2010:345-53.
- 41. Salliot C, Gossec L, Ruyssen-Witrand A, Luc M, Duclos M, Guignard S, et al. Infections during tumour necrosis factor-α blocker therapy for rheumatic diseases in daily practice: A systematic retrospective study of 709 patients. *Rheumatology* 2007:327-34.
- 42. Schafer JA, Kjesbo NK, Gleason PP. Formulary review of 2 new biologic agents: tocilizumab for rheumatoid arthritis and ustekinumab for plaque psoriasis. J Manag Care Pharm. 2010 Jul-Aug;16(6):402-16.
- 43. Sichletidis L, Settas L, Spyratos D, Chloros D, Patakas D. Tuberculosis in patients receiving anti-TNF agents despite chemoprophylaxis. Int J Tuberc Lung Dis. 2006 Oct;10(10):1127-32.
- 44. Signorovitch JE, Wu EQ, Yu AP, Gerrits CM, Mulani PM, et al. Comparative Effectiveness Without Head-to-Head Trials A Method for Matching-Adjusted Indirect

- Comparisons Applied to Psoriasis Treatment with Adalimumab or Etanercept. PharmacoEconomics (New Zealand). 2010:28:935-45.
- 45. Tran S, Hooker RS, Cipher DJ, Reimold A, Jul. Patterns of Biologic Agent Use in Older Males with Inflammatory Diseases An Institution-Focused, Observational Post-Marketing Study. Drugs and Aging (New Zealand). 2009;26:607.
- 46. van der Heijde D, Kavanaugh A, Gladman DD, Antoni C, Krueger GG, Guzzo C, et al. Infliximab inhibits progression of radiographic damage in patients with active psoriatic arthritis through one year of treatment: Results from the induction and maintenance psoriatic arthritis clinical trial 2. Arthritis Rheum 2007:2698-707.
- 47. Virkki LM, Sumathikutty BC, Aarnio M, Valleala H, Nordstroem DC, et al.

Wrong Publication Type

- 1. Cochrane Collaboration guidelines.
- 2. Anakinra (Kineret) for rheumatoid arthritis. Med Lett Drugs Ther. 2002 Feb 18;44(1124):18-9.
- 3. Is it true that vaccines may not be safe for people with rheumatoid arthritis (which I have)? Does that mean I shouldn't get a flu shot? Johns Hopkins Med Lett Health After 50. 2004 Oct;17(8):8.
- 4. First Latin American position paper on the pharmacological treatment of rheumatoid arthritis. Rheumatology. 2006 01/01/;45(JUN):7-2.
- 5. Screening for hydroxychloroquine retinopathy. 2006.
- 6. Rituxan (Rituximab) [Package Insert]. 2008.
- Aletaha D, Smolen JS. The definition and measurement of disease modification in inflammatory rheumatic diseases. Rheumatic Disease Clinics of North America. 2006;32(1):9-44.
- 8. Anandacoomarasamy A, Kannangara S, Barnsley L. Cutaneous vasculitis associated with infliximab in the treatment of rheumatoid arthritis. Intern Med J. 2005 Oct;35(10):638-40.
- 9. Andres E, Limbach FX, Goichot B, Sibilia J. Silent thyroiditis associated with etanercept in rheumatoid arthritis. Ann Rheum Dis. 2002 Jun;61(6):565.
- 10. Arend SM, Kuijper EJ, Allaart CF, Muller WH, Van Dissel JT. Cavitating pneumonia after treatment with infliximab and

- Biological Therapy for Psoriatic Arthritis in Clinical Practice: Outcomes Up to 2 Years. *Journal of Rheumatology* 2010:2362-8.
- 48. Wendling D, Streit G, Toussirot E, Prati C. Herpes zoster in patients taking TNFalpha antagonists for chronic inflammatory joint disease. Joint Bone Spine. 2008 Oct;75(5):540-3.
- Willkens RF, Williams HJ, Ward JR, Egger MJ, Reading JC, Clements PJ, et al.
 Randomized, double-blind, placebo controlled trial of low-dose pulse methotrexate in psoriatic arthritis. *Arthritis Rheum*. 1984/04/01 ed 1984:376-81.
- 50. Woolacott N, Bravo Vergel Y, Hawkins N, Kainth A, Khadjesari Z, Misso K, et al. Etanercept and infliximab for the treatment of psoriatic arthritis: a systematic review and economic evaluation. Health Technol Assess. 2006 Sep;10(31):1-258.
 - prednisone. Eur J Clin Microbiol Infect Dis. 2004 Aug;23(8):638-41.
- 11. Armstrong DJ, McCarron MT, Wright GD. Successful treatment of rheumatoid vasculitis-associated foot-drop with infliximab. J Rheumatol. 2005
 Apr;32(4):759; author reply -60.
- 12. Arnold EL, Khanna D, Paulus H, Goodman MP. Acute injection site reaction to intraarticular etanercept administration. Arthritis Rheum. 2003 Jul;48(7):2078-9.
- 13. Ashok D, Ayliffe WH, Kiely PD.

 Necrotizing scleritis associated with rheumatoid arthritis: long-term remission with high-dose infliximab therapy.

 Rheumatology (Oxford). 2005

 Jul:44(7):950-1.
- 14. Asli B, Wechsler B, Lemaitre C. Inhibition of tumor necrosis factor alpha and ankylosing spondylitis. N Engl J Med. 2003 Jan 23;348(4):359-61; author reply -61.
- 15. Assous N, Gossec L, Dougados M, Kahan A, Allanore Y. Efficacy of rituximab in patients with rheumatoid arthritis refractory or with contra-indication to anti-tumor necrosis factor-alpha drugs in daily practice: An open label observational study [3]. Clinical and Experimental Rheumatology. 2007;25(3).
- 16. Bankhurst AD. Etanercept and methotrexate combination therapy. Clin Exp Rheumatol. 1999 Nov-Dec;17(6 Suppl 18):S69-72.

- 17. Bartke U, Venten I, Kreuter A, Gubbay S, Altmeyer P, Brockmeyer NH. Human immunodeficiency virus-associated psoriasis and psoriatic arthritis treated with infliximab. Br J Dermatol. 2004 Apr;150(4):784-6.
- 18. Bennett AN, Wong M, Zain A, Panayi G, Kirkham B. Adalimumab-induced asthma. Rheumatology (Oxford). 2005 Sep;44(9):1199-200.
- Bermas BL. Use of immunosuppressive drugs in pregnancy and lactation. 2007.
- 20. Bleumink GS, ter Borg EJ, Ramselaar CG, Ch Stricker BH. Etanercept-induced subacute cutaneous lupus erythematosus. Rheumatology (Oxford). 2001
 Nov;40(11):1317-9.
- 21. Boatright MD, Wang BW. Clinical infection with Strongyloides sterocoralis following etanercept use for rheumatoid arthritis. Arthritis Rheum. 2005 Apr;52(4):1336-7.
- 22. Bravo Vergel Y, Palmer S, Erhorn S, Young V, Brent S, Dyker A, et al. Adalimumab for the treatment of moderate to severe psoriatic arthritis. Health Technology Assessment. 2010.
- 23. Brocq O, Albert C, Roux C, Gerard D, Breuil V, Ziegler LE. Adalimumab in rheumatoid arthritis after failed infliximab and/or etanercept therapy: experience with 18 patients. Joint Bone Spine. 2004 Nov;71(6):601-3.
- 24. Brodszky V, Pentek M, Gulacsi L. Efficacy of adalimumab, etanercept, and infliximab in psoriatic arthritis based on ACR50 response after 24 weeks of treatment. Scand J Rheumatol. 2008 Sep-Oct;37(5):399-400.
- 25. Bruce SP, Boyce EG. Update on abatacept: A selective costimulation modulator for rheumatoid arthritis. Annals of Pharmacotherapy. 2007;41(7-8):1153-62.
- 26. Burls A, Clark WK, Jobanputra P. Anakinra for Rheumatoid Arthritis. The Cochrane Database of Systematic Reviews. 2005;2005(1).
- 27. Chevillotte-Maillard H, Ornetti P, Mistrih R, Sidot C, Dupuis J, Dellas JA, et al. Survival and safety of treatment with infliximab in the elderly population. Rheumatology (Oxford). 2005 May;44(5):695-6.
- 28. Clelland S, Hunek JR. Etanercept injection site reaction. Dermatol Nurs. 2005 Oct;17(5):375-.
- 29. Clunie G, Voules S, Watts R. Dose reduction of etanercept--can we treat more patients using a fixed budget?

- Rheumatology (Oxford). 2003 Apr;42(4):600-1.
- 30. Cobo Ibanez T, Yehia Tayel M, Balsa Criado A, Hernandez Sanz A, Martin Mola E. Safety and efficacy of leflunomide and infliximab versus methotrexate and infliximab combination therapy in rheumatoid arthritis. Rheumatology (Oxford). 2005 Nov;44(11):1467-8.
- 31. Cocito D, Bergamasco B, Tavella A, Poglio F, Paolasso I, Costa P, et al. Multifocal motor neuropathy during treatment with infliximab. J Peripher Nerv Syst. 2005 Dec;10(4):386-7.
- 32. Cohen CD, Horster S, Sander CA, Bogner JR. Kaposi's sarcoma associated with tumour necrosis factor alpha neutralising therapy. Ann Rheum Dis. 2003
 Jul;62(7):684.
- 33. Cohen JD, Zaltni S, Kaiser MJ, Bozonnat MC, Jorgensen C, Daures JP, et al. Secondary addition of methotrexate to partial responders to etanercept alone is effective in severe rheumatoid arthritis. Ann Rheum Dis. 2004 Feb;63(2):209-10.
- 34. Cohen MD, Conn DL. Benefits of low-dose corticosteroids in rheumatoid arthritis. Bull Rheum Dis. 1997 Jun;46(4):4-7.
- 35. Combe B, Landewe R, Lukas C, Bolosiu HD, Breedveld F, Dougados M, et al. EULAR recommendations for the management of early arthritis: Report of a task force of the European Standing Committee for International Clinical Studies Including Therapeutics (ESCISIT). Annals of the rheumatic diseases, 2007:66(1):34-45.
- 36. Cunnane G, Warnock M, Fye KH, Daikh DI. Accelerated nodulosis and vasculitis following etanercept therapy for rheumatoid arthritis. Arthritis Rheum. 2002 Aug;47(4):445-9.
- 37. Das P, Raghu P, Amit Kumar D, Garg P. Strongyloides hyperinfection in rheumatoid arthritis. Int J Surg Pathol. 2007 Oct;15(4):391-2.
- 38. Day R. Adverse reactions to TNF-alpha inhibitors in rheumatoid arthritis. Lancet. 2002 Feb 16;359(9306):540-1.
- 39. De Bandt M, Vittecoq O, Descamps V, Le Loet X, Meyer O. Anti-TNF-alpha-induced systemic lupus syndrome. Clin Rheumatol. 2003 Feb;22(1):56-61.
- 40. Deighton CM, George E, Kiely PDW, Ledingham J, Luqmani RA, Scott DGI. Updating the British Society for Rheumatology guidelines for anti-tumour

- necrosis factor therapy in adult rheumatoid arthritis (again). Rheumatology. 2006;45(6):649-52.
- 41. Duggan ST, Keam SJ, Jun. Certolizumab Pegol In Rheumatoid Arthritis. BioDrugs (New Zealand). 2009;23:407.
- 42. Dumont-Berset M, Laffitte E, Gerber C, Dudler J, Panizzon RG. Eczematous drug eruption after infliximab. Br J Dermatol. 2004 Dec;151(6):1272-3.
- 43. Emery P. Disease Modification in Rheumatoid Arthritis With Leflunomide. Scandinavian journal of rheumatology Supplement. 1999;112(9):9-14.
- 44. Emery P, Genovese MC, Fleischmann RM, Matteson EL, Hsia EC, Xu S, et al. Efficacy of Golimumab, a human anti-TNF(alpha) antibody, by baseline CRP level in patients with rheumatoid arthritis: Results from three phase 3, randomized, double-blind, placebocontrolled studies. *Rheumatology* 2010:i101.
- 45. Favalli EG, Arreghini M, Arnoldi C, Panni B, Marchesoni A, Tosi S, et al. Anti-tumor necrosis factor alpha switching in rheumatoid arthritis and juvenile chronic arthritis. Arthritis Rheum. 2004 Apr 15:51(2):301-2.
- 46. Fleischmann R. The clinical efficacy and safety of certolizumab pegol in rheumatoid arthritis. Expert Opin Biol Ther. 2010 May;10(5):773-86.
- 47. Franklin CM. Clinical experience with soluble TNF p75 receptor in rheumatoid arthritis. Semin Arthritis Rheum. 1999 Dec;29(3):172-81.
- 48. Furst DE. Anakinra: review of recombinant human interleukin-I receptor antagonist in the treatment of rheumatoid arthritis. Clin Ther. 2004 Dec;26(12):1960-75.
- 49. Furst DE, Keystone EC, Kirkham B, Fleischmann R, Mease P, Breedveld FC, et al. Updated consensus statement on biological agents for the treatment of rheumatic diseases, 2008. Annals of the rheumatic diseases. 2008;67(SUPPL. 3).
- 50. Gadadhar H, Hawkins S, Huffstutter JE, Panda M. Cutaneous mucormycosis complicating methotrexate, prednisone, and infliximab therapy. J Clin Rheumatol. 2007 Dec;13(6):361-2.
- 51. Goekoop-Ruiterman YP, de Vries-Bouwstra JK, Allaart CF, van Zeben D, Kerstens PJ, Hazes JM, et al. Clinical and radiographic outcomes of four different treatment strategies in patients with early rheumatoid

- arthritis (the BeSt study): A randomized, controlled trial. Arthritis Rheum. 2008 Feb;58(2 Suppl):S126-35.
- 52. Goldenberg MM. Etanercept, a novel drug for the treatment of patients with severe, active rheumatoid arthritis. Clin Ther. 1999 Jan;21(1):75-87; discussion 1-2.
- 53. Golding A, Haque UJ, Giles JT. Rheumatoid arthritis and reproduction. Rheum Dis Clin North Am. 2007 May;33(2):319-43, vi-vii.
- 54. Gupta N, Fox CM, Grisolano SW.
 Disseminated histoplasmosis with colonic ulcers in a patient receiving infliximab.
 Gastrointest Endosc. 2009 Sep;70(3):597-8.
- 55. Health Technology A. Adalimumab, etanercept, infliximab, rituximab and abatacept for the treatment of rheumatoid arthritis after the failure of a TNF inhibitor: a systematic review and economic evaluation (Project record). Health Technology Assessment. 2010.
- 56. Health Technology A. The clinical and cost effectiveness of etanercept, infliximab and adalimumab psoriatic arthritis (guidance review 104 and 125) (Project record). Health Technology Assessment. 2010.
- 57. Hewlett S, Hehir M, Kirwan JR. Measuring fatigue in rheumatoid arthritis: A systematic review of scales in use. Arthritis Care and Research. 2007;57(3):429-39.
- 58. Hirche D, Rubbert A, Lunau L, Krieg T, Eming SA. Successful treatment of refractory rheumatoid arthritis-associated leg ulcerations with adalimumab. Br J Dermatol. 2005 May;152(5):1062-4.
- 59. Hong BK, Kumar C, Marottoli RA. "MAC" attack. Am J Med. 2009 Dec;122(12):1096-8.
- 60. Horng MS. Early rheumatoid arthritis: Is there a best treatment? Journal of Clinical Outcomes Management. 2007;14(5):233-4.
- 61. Hoshida Y, Yamamoto S, Wada N, Xu JX, Sasaki T, Aozasa K. Infliximab-associated lymphoproliferative disorders. Int J Hematol. 2005 May;81(4):356-7.
- 62. Hrycaj P, Korczowska I, Lacki JK. Severe Parkinson's disease in rheumatoid arthritis patient treated with infliximab. Rheumatology (Oxford). 2003 May;42(5):702-3.
- 63. Inoue K, Takano H, Yanagisawa R, Yoshikawa T. Effects of tumor necrosis factor-alpha inhibitors on lung lesions with rheumatoid arthritis. Chest. 2003
 Jul;124(1):413-4; author reply 4.

- 64. Josefina M, Ana CJ, Ariel V, Silvio AA. Development of pseudogout during etanercept treatment. J Clin Rheumatol. 2007 Jun;13(3):177.
- 65. Ju JH, Kim SI, Lee JH, Lee SI, Yoo WH, Choe JY, et al. Risk of interstitial lung disease associated with leflunomide treatment in Korean patients with rheumatoid arthritis. *Arthritis Rheum* 2007:2094-6.
- 66. Kaiser MJ, Bozonnat MC, Jorgensen C, Daures JP, Sany J. Effect of etanercept on tenosynovitis and nodules in rheumatoid arthritis. Arthritis Rheum. 2002 Feb:46(2):559-60.
- 67. Kelaidi C, Tulliez M, Lecoq-Lafon C, Pham XV, Kahan A, Dreyfus F, et al. Long-term remission of an EBV-positive B cell lymphoproliferative disorder associated with rheumatoid arthritis under methotrexate with anti-CD20 monoclonal antibody (Rituximab) monotherapy. Leukemia. 2002 Oct;16(10):2173-4.
- 68. Kemp E, Nielsen H, Petersen LJ, Gam AN, Dahlager J, Horn T, et al. Newer immunomodulating drugs in rheumatoid arthritis may precipitate glomerulonephritis. Clin Nephrol. 2001 Jan;55(1):87-8.
- 69. Kempeni J. Preliminary results of early clinical trials with the fully human anti-TNFalpha monoclonal antibody D2E7. Ann Rheum Dis. 1999 November 1, 1999;58(90001):70i-2.
- 70. Kempeni J. Update on D2E7: a fully human anti-tumour necrosis factor alpha monoclonal antibody. Ann Rheum Dis. 2000 November 1, 2000;59(90001):44i-5.
- 71. Kirwan J. Early rheumatoid arthritis: combination therapy with disease-modifying antirheumatic drugs and low-dose glucocorticoids? Nat Clin Pract Rheumatol. 2006 Apr;2(4):182-3.
- 72. Kirwan J, Shea B, Boers M. Glucocorticoids for Slowing Radiological Progression in Rheumatoid Arthritis. The Cochrane Database of Systematic Reviews. 2005;2005(1).
- 73. Korkmaz C, Kasifoglu T, Yasar B. Acceleration of left-ventricular diastolic dysfunction and pulmonary hypertension after TNF-alpha blocker. Ann Pharmacother. 2005 Jun;39(6):1138-9.
- 74. Kramer N, Chuzhin Y, Kaufman LD, Ritter JM, Rosenstein ED. Methotrexate pneumonitis after initiation of infliximab

- therapy for rheumatoid arthritis. Arthritis Rheum. 2002 Dec 15;47(6):670-1.
- 75. Krathen MS, Gottlieb AB, Mease PJ.
 Pharmacologic Immunomodulation and
 Cutaneous Malignancy in Rheumatoid
 Arthritis, Psoriasis, and Psoriatic Arthritis.
 Journal of Rheumatology. 2010;37:2205-15.
- 76. Kremer J, Westhovens R, Luggen M. Longterm efficacy and safety of abatacept through 3 years of treatment in rheumatoid arthritis patients in the AIM and ATTAIN trials [abstract]. American College of Rheumatology Meeting.
- 77. Kremer JM. Safety, efficacy, and mortality in a long-term cohort of patients with rheumatoid arthritis taking methotrexate: followup after a mean of 13.3 years.

 Arthritis Rheum. 1997 May;40(5):984-5.
- 78. Kreuter A, Rose C, Zillikens D, Altmeyer P. Bullous rheumatoid neutrophilic dermatosis. J Am Acad Dermatol. 2005 May;52(5):916-8.
- 79. Kucharz EJ, Gozdzik J, Kopec M, Kotulska A, Lewicki M, Pieczyrak R, et al. A single infusion of infliximab increases the serum endostatin level in patients with rheumatoid arthritis. Clin Exp Rheumatol. 2003 Mar-Apr;21(2):273-4.
- 80. Kurschat P, Rubbert A, Poswig A, Scharffetter-Kochanek K, Krieg T, Hunzelmann N. Treatment of psoriatic arthritis with etanercept. J Am Acad Dermatol. 2001 Jun;44(6):1052.
- 81. Liberopoulos EN, Drosos AA, Elisaf MS. Exacerbation of tuberculosis enteritis after treatment with infliximab. Am J Med. 2002 Nov;113(7):615.
- 82. Lindsay K, Gough A. Psoriatic arthritis, methotrexate and the liver Are rheumatologists putting their patients at risk? Rheumatology. 2008;47(7):939-41.
- 83. Looney RJ. B cell-targeted therapy for rheumatoid arthritis An update on the evidence. Drugs (New Zealand). 2006 05/01/;66(May):625-39.
- 84. Luqmani R, Hennell S, Estrach C, Birrell F, Audit Working G, et al. British society for rheumatology and british health professionals in rheumatology guideline for the management of rheumatoid arthritis (the first two years). Rheumatology. 2006 09/01/;45(Sep):1167-9.
- 85. Manadan AM, Block JA, Sequeira W. Mycobacteria tuberculosis peritonitis associated with etanercept therapy. Clin Exp Rheumatol. 2003 Jul-Aug;21(4):526.

- 86. Mang R, Stege H, Ruzicka T, Krutmann J. Response of severe psoriasis to infliximab. Dermatology. 2002;204(2):156-7.
- 87. Marchesoni A, Puttini PS, Gorla R, Caporali R, Arnoldi C, Atzeni F, et al. Cyclosporine in addition to infliximab and methotrexate in refractory rheumatoid arthritis. Clin Exp Rheumatol. 2005 Nov-Dec;23(6):916-7.
- 88. Matsui T, Komiya A, Shimada K, Nakayama H, Tohma S. Neutrophil CD64 as a marker of infection in patients treated with tocilizumab. Mod Rheumatol. 2009;19(6):696-7.
- 89. Maxwell L, Singh Jasvinder A. Abatacept for rheumatoid arthritis. Cochrane Database of Systematic Reviews. 2008(3).
- 90. McCain ME, Quinet RJ, Davis WE. Etanercept and infliximab associated with cutaneous vasculitis. Rheumatology (Oxford). 2002 Jan;41(1):116-7.
- 91. Mease P. Psoriatic arthritis update. Bulletin of the NYU Hospital for Joint Diseases. 2006;64(1-2):25-31.
- 92. Mease PJ. Cytokine Blockers in Psoriatic Arthritis. Annals of the rheumatic diseases. 2001;60(Suppl 3):iii37-40.
- 93. Michaelsson G, Kajermo U, Michaelsson A, Hagforsen E. Infliximab can precipitate as well as worsen palmoplantar pustulosis: possible linkage to the expression of tumour necrosis factor-alpha in the normal palmar eccrine sweat duct? Br J Dermatol. 2005 Dec;153(6):1243-4.
- 94. Misery L, Perrot JL, Gentil-Perret A, Pallot-Prades B, Cambazard F, Alexandre C.
 Dermatological complications of etanercept therapy for rheumatoid arthritis. Br J
 Dermatol. 2002 Feb:146(2):334-5.
- 95. Molloy E, Ramakrishnan S, Murphy E, Barry M. Morbidity and mortality in rheumatoid patients during treatment with adalimumab and infliximab. Rheumatology (Oxford). 2004 Apr;43(4):522-3.
- 96. Montagna GL, Malesci D, Buono R, Valentini G. Asthenoazoospermia in patients receiving anti-tumour necrosis factor {alpha} agents. Ann Rheum Dis. 2005 Nov:64(11):1667.
- 97. Murphy FT, Enzenauer RJ, Battafarano DF, David-Bajar K. Etanercept-associated injection-site reactions. Arch Dermatol. 2000 Apr;136(4):556-7.
- 98. Musial J, Undas A, Celinska-Lowenhoff M. Polymyositis associated with infliximab treatment for rheumatoid arthritis.

- Rheumatology (Oxford). 2003 Dec;42(12):1566-8.
- 99. Nakelchik M, Mangino JE. Reactivation of histoplasmosis after treatment with infliximab. Am J Med. 2002 Jan;112(1):78.
- 100. Nikas SN, Temekonidis TI, Zikou AK, Argyropoulou MI, Efremidis S, Drosos AA. Treatment of resistant rheumatoid arthritis by intra-articular infliximab injections: a pilot study. Ann Rheum Dis. 2004 Jan;63(1):102-3.
- 101. Nikas SN, Voulgari PV, Takalou IP, Katsimbri P, Drosos AA. Healing of psoriatic skin lesions, and improvement of psoriatic arthritis resistant to immunosuppressive drugs, after infliximab treatment. Ann Rheum Dis. 2005 Nov;64(11):1665-7.
- 102. Novak S, Cikes N. Infliximab-induced lupus or rheumatoid arthritis (RA) overlapping with systemic lupus erythematosus (SLE) unmasked by infliximab. Clin Exp Rheumatol. 2004 Mar-Apr;22(2):268.
- 103. Ornetti P, Solau E, Gaudin P, Sibilia J, Berthelot JM, Puechal X, et al. Increase in methotrexate dose in patients with rheumatoid arthritis who have an inadequate response to infliximab. Ann Rheum Dis. 2005 Sep;64(9):1379-80.
- 104. Ostor AJ, Crisp AJ, Somerville MF, Scott DG. Fatal exacerbation of rheumatoid arthritis associated fibrosing alveolitis in patients given infliximab. BMJ. 2004 Nov 27;329(7477):1266.
- 105. Ostrov BE. Beneficial effect of etanercept on rheumatoid lymphedema. Arthritis Rheum. 2001 Jan;44(1):240-1.
- 106. Pagliano P, Attanasio V, Fusco U, Mohamed DA, Rossi M, Faella FS. Does etanercept monotherapy enhance the risk of Listeria monocytogenes meningitis? Ann Rheum Dis. 2004 Apr;63(4):462-3.
- 107. Parekh K, Ching D, Rahman MU, Stamp LK. Onset of Wegener's granulomatosis during therapy with golimumab for rheumatoid arthritis: a rare adverse event? Rheumatology (Oxford). 2010 Sep;49(9):1785-7.
- 108. Pisoni L, Murgo A, Paresce E, Zeni S, Fantini F. Effectiveness and safety of leflunomide in the clinical practice. A different experience [1]. Clinical and Experimental Rheumatology. 2007;25(1).
- 109. Popovic M, Stefanovic D, Pejnovic N,
 Popovic R, Glisic B, Obradovic S, et al.
 Comparative study of the clinical efficacy of

- four DMARDs (leflunomide, methotrexate, cyclosporine, and levamisole) in patients with rheumatoid arthritis. Transplant Proc. 1998 Dec;30(8):4135-6.
- 110. Provenzano G, Termini A, Le Moli C, Rinaldi F. Efficacy of infliximab in psoriatic arthritis resistant to treatment with disease modifying antirheumatic drugs: an open pilot study. Ann Rheum Dis. 2003

 Jul;62(7):680-1.
- 111. Racunica T, Cassidy D, Cicuttini F, Hall A. Trouble with tumor necrosis factor alpha inhibitors, not just tuberculosis. *Arthritis Care Res (Hoboken)*. 2010/06/11 ed 2010:770-4.
- 112. Radovits BJ, Kievit W, Laan RF. Tumour necrosis factor-alpha antagonists in the management of rheumatoid arthritis in the elderly: a review of their efficacy and safety. Drugs Aging. 2009;26(8):647-64.
- 113. Rahman N, Healy C, Flint SR, Stassen LF. Cautionary note: a possible association between oral squamous cell carcinoma and tumor necrosis factor antagonists; need for oral screening. J Clin Rheumatol. 2010 Jun;16(4):197-9.
- 114. Reddy AR, Backhouse OC. Does etanercept induce uveitis? Br J Ophthalmol. 2003
 Jul;87(7):925.
- 115. Richter C, Wanke L, Steinmetz J, Reinhold-Keller E, Gross WL. Mononeuritis secondary to rheumatoid arthritis responds to etanercept. Rheumatology (Oxford). 2000 Dec;39(12):1436-7.
- 116. Rimar D, Rozenbaum M, Slobodin G, Boulman N, Rosner I. Etanercept related pseudo-empyema in rheumatoid arthritis. *Clin Rheumatol*. 2010/02/04 ed 2010:547-9.
- 117. Rinaldi F, Provenzano G, Termini A, Spinello M, La Seta F. Long term infliximab treatment for severe psoriatic arthritis: evidence of sustained clinical and radiographic response. Ann Rheum Dis. 2005 Sep;64(9):1375-6.
- 118. Robinson V, Boers M, Brooks P, Francis D, Wells GA, et al. Patient-reported pain is central to OMERACT rheumatology core measurement sets. Drug Information Journal (USA). 2006 01/01/;40(Jan):111-6.
- 119. Roux CH, Brocq O, Breuil V, Albert C, Euller-Ziegler L. Pregnancy in rheumatology patients exposed to antitumour necrosis factor (TNF)-α therapy. Rheumatology. 2007;46(4):695-8.
- 120. Rozman B. Clinical Experience With Leflunomide in Rheumatoid Arthritis. The

- Journal of rheumatology. 1998;52(Suppl):27-32.
- 121. Ruiz Garcia V, Burls A, Cabello López Juan CL, Fry- Smith Anne FS, Gálvez Muñoz José G, Jobanputra P, et al. Certolizumab pegol (CDP870) for rheumatoid arthritis in adults. Cochrane Database of Systematic Reviews. 2009(1).
- 122. Russell E, Zeihen M, Wergin S, Litton T. Patients receiving etanercept may develop antibodies that interfere with monoclonal antibody laboratory assays. Arthritis Rheum. 2000 Apr;43(4):944.
- 123. Salli A, Sahin N, Paksoy Y, Kucuksarac S, Ugurlu H. Treatment of periodontoid pannus with infliximab in a patient with rheumatoid arthritis. J Clin Rheumatol. 2009
 Aug;15(5):250-1.
- 124. Scott DL, Kingsley GH. Tumor necrosis factor inhibitors for rheumatoid arthritis. N Engl J Med. 2006 Aug 17;355(7):704-12.
- 125. Sholsberg J, Jackson R. Best evidence topic report. Intra-articular corticosteroid injections in acute rheumatoid monoarthritides. Emerg Med J. 2004 Mar;21(2):204.
- Simpson D, Scott LJ. Adalimumab: in psoriatic arthritis. Drugs. 2006;66(11):1487-96.
- 127. Singh Jasvinder A, Beg S, Lopez Olivo Maria A. Tocilizumab for rheumatoid arthritis. 2010.
- 128. Smith D, Letendre S. Viral pneumonia as a serious complication of etanercept therapy. Ann Intern Med. 2002 Jan 15;136(2):174.
- 129. Smolen JS, Landewe R, Breedveld FC, Dougados M, Emery P, Gaujoux-Viala C, et al. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs. *Ann Rheum Dis* 2010:964-75.
- 130. Soliotis F, Glover M, Jawad AS. Severe skin reaction after leflunomide and etanercept in a patient with rheumatoid arthritis. Ann Rheum Dis. 2002 Sep;61(9):850-1.
- 131. Strand. Improved health-related quality of life with effective disease-modifying antirheumatic drugs: Evidence from randomized controlled trials (American Journal of Managed Care). American Journal of Managed Care. 2008;14(4):234.
- 132. Suresh R, Gupta S, Sathananthan R. Sulphasalazine induced three-week syndrome. J Clin Rheumatol. 2009 Sep;15(6):311-2.

- 133. Sweet BV. Abatacept. American Journal of Health-System Pharmacy (USA). 2006 01/01/;63(Jan):2065-77.
- 134. Tack CJ, Kleijwegt FS, Van Riel PL, Roep BO. Development of type 1 diabetes in a patient treated with anti-TNF-alpha therapy for active rheumatoid arthritis. Diabetologia. 2009 Jul;52(7):1442-4.
- 135. Tateiwa T, Shinmura K, Ko M, Mibe J, Yamamoto K. Iliopectineal bursitis associated with rapid destruction of a rheumatoid hip joint. J Orthop Sci. 2009 Jul;14(4):455-8.
- 136. Van Rijthoven AW, Bijlsma JW, Canninga-Van Dijk M, Derksen RH, Van Roon JA. Onset of systemic lupus erythematosus after conversion of infliximab to adalimumab treatment in rheumatoid arthritis with a preexisting anti-dsDNA antibody level. Rheumatology. 2006 10/01/;45(Oct):1317-9.
- 137. Vis M, Voskuyl AE, Wolbink GJ, Dijkmans BA, Lems WF. Bone mineral density in

Wrong Study Design

- 1. Summaries for patients. Tumor necrosis factor antagonists and heart failure. Ann Intern Med. 2003 May 20;138(10):I48.
- 2. Abramovits W, Arrazola P, Gupta AK. Enbrel (etanercept). Skinmed. 2004 Nov-Dec;3(6):333-5.
- 3. Agarwal S, Zaman T, Handa R. Retention rates of disease-modifying anti-rheumatic drugs in patients with rheumatoid arthritis. *Singapore Med J* 2009:686-92.
- 4. Aggarwal A, Panda S, Misra R. Effect of etanercept on matrix metalloproteinases and angiogenic vascular endothelial growth factor: a time kinetic study. Ann Rheum Dis. 2004 Jul:63(7):891-2.
- Aggarwal R, Manadan AM, Poliyedath A, Sequeira W, Block JA, May. Safety of Etanercept in Patients at High Risk for Mycobacterial Tuberculosis Infections. Journal of Rheumatology. 2009;36:914.
- 6. Alcorn N, Saunders S, Madhok R, Dec. Benefit-Risk Assessment of Leflunomide An Appraisal of Leflunomide in Rheumatoid Arthritis 10 Years After Licensing. Drug Safety (New Zealand). 2009;32:1123.
- 7. Amichai B, Gat A, Grunwald MH.
 Cutaneous hyperpigmentation during
 therapy with hydroxychloroquine. J Clin
 Rheumatol. 2007 Apr;13(2):113.

- patients with rheumatoid arthritis treated with infliximab. Ann Rheum Dis. 2005 Feb;64(2):336-7.
- 138. Vis M, Wolbink GJ, Lodder MC, Kostense PJ, van de Stadt RJ, de Koning MH, et al. Early changes in bone metabolism in rheumatoid arthritis patients treated with infliximab. Arthritis Rheum. 2003 Oct;48(10):2996-7.
- 139. Voulgari PV, Venetsanopoulou AI, Epagelis EK, Alamanos Y, Takalou I, Drosos AA. Infliximab in refractory psoriatic arthritis with severe psoriasis: a 2-year experience. Ann Rheum Dis. 2007 Feb;66(2):270-1.
- 140. Yazici Y, Erkan D, Lockshin MD. Etanercept in the treatment of severe, resistant psoriatic arthritis: continued efficacy and changing patterns of use after two years. Clin Exp Rheumatol. 2002 Jan-Feb;20(1):115.
- 8. Ang HT, Helfgott S. Do the clinical responses and complications following etanercept or infliximab therapy predict similar outcomes with the other tumor necrosis factor-alpha antagonists in patients with rheumatoid arthritis? J Rheumatol. 2003 Nov;30(11):2315-8.
- 9. Antoni C, Dechant C, Hanns-Martin Lorenz PD, Wendler J, Ogilvie A, Lueftl M, et al. Open-label study of infliximab treatment for psoriatic arthritis: clinical and magnetic resonance imaging measurements of reduction of inflammation. Arthritis Rheum. 2002 Oct 15;47(5):506-12.
- Antoni C, Kalden J. Combination Therapy of the Chimeric Monoclonal Anti-Tumor Necrosis Factor Alpha Antibody (Infliximab) With Methotrexate in Patients With Rheumatoid Arthritis. Clinical and experimental rheumatology. 1999;17(6 Suppl 18):S73-7.
- 11. Antoni CE, Kavanaugh A, van der Heijde D, Beutler A, Keenan G, Zhou B, et al. Twoyear efficacy and safety of infliximab treatment in patients with active psoriatic arthritis: findings of the Infliximab Multinational Psoriatic Arthritis Controlled Trial (IMPACT). J Rheumatol. 2008 May;35(5):869-76.
- 12. Argyropoulou MI, Glatzouni A, Voulgari PV, Xydis VG, Nikas SN, Efremidis SC, et

- al. Magnetic resonance imaging quantification of hand synovitis in patients with rheumatoid arthritis treated with infliximab. Joint Bone Spine. 2005 Dec;72(6):557-61.
- 13. Arif S, Cox P, Afzali B, Lombardi G, Lechler RI, Peakman M, et al. Anti-TNFalpha therapy--killing two birds with one stone? *Lancet*. 2010/07/09 ed 2010:2278.
- 14. Augustsson J, Eksborg S, Ernestam S, Gullstrom E, van Vollenhoven R. Low-dose glucocorticoid therapy decreases risk for treatment-limiting infusion reaction to infliximab in patients with rheumatoid arthritis. Ann Rheum Dis. 2007
 Nov;66(11):1462-6.
- 15. Augustsson J, Neovius M, Cullinane-Carli C, Eksborg S, van Vollenhoven RF. Patients with rheumatoid arthritis treated with tumour necrosis factor antagonists increase their participation in the workforce: potential for significant long-term indirect cost gains (data from a population-based registry). *Ann Rheum Dis* 2010:126-31.
- 16. Bansback NJ, Ara R, Barkham N, Brennan A, Emery P, et al. Estimating the cost and health status consequences of treatment with TNF antagonists in patients with psoriatic arthritis. Rheumatology. 2006 08/01/;45(Aug):1029-38.
- 17. Barra L, Pope JE, Payne M. Real-world antitumor necrosis factor treatment in rheumatoid arthritis, psoriatic arthritis, and ankylosing spondylitis: cost-effectiveness based on number needed to treat to improve health assessment questionnaire. J Rheumatol. 2009 Jul;36(7):1421-8.
- 18. Barrera P, van der Maas A, van Ede AE, Kiemeney BALM, Laan RFJM, van de Putte LBA, et al. Drug Survival, Efficacy and Toxicity of Monotherapy With a Fully Human Anti-Tumour Necrosis Factor-a Antibody Compared With Methotrexate in Long-Standing Rheumatoid Arthritis. *Rheumatology* 2002:430-9.
- 19. Bathon JM, Fleischmann RM, van der Heijde DM, Tesser JR, White B, et al. Safety and efficacy of etanercept treatment in elderly subjects with rheumatoid arthritis. Journal of Rheumatology. 2006 02/01/;33(Feb):234-43.
- 20. Baumgartner SW, Fleischmann RM, Moreland LW, Schiff MH, Markenson J, Whitmore JB. Etanercept (Enbrel) in patients with rheumatoid arthritis with

- recent onset versus established disease: improvement in disability. J Rheumatol. 2004 Aug;31(8):1532-7.
- 21. Berends MAM, Snoek J, De Jong EMGJ, Van De Kerkhof PCM, Van Oijen MGH, Van Krieken JH, et al. Liver injury in long-term methotrexate treatment in psoriasis is relatively infrequent. Alimentary Pharmacology and Therapeutics. 2006;24(5):805-11.
- 22. Bibbo C, Goldberg JW. Infectious and healing complications after elective orthopaedic foot and ankle surgery during tumor necrosis factor-alpha inhibition therapy. Foot Ankle Int. 2004
 May;25(5):331-5.
- 23. Bingham CO, Ince A, Haraoui B, Keystone EC, Baumgartner S, et al., et al. Effectiveness and safety of etanercept in subjects with RA who have failed infliximab therapy: 16-week, open-label, observational study. Current Medical Research and Opinion (England) 2009:1131.
- 24. Bliddal H, Terslev L, Qvistgaard E, Konig M, Holm CC, Rogind H, et al. A randomized, controlled study of a single intra-articular injection of etanercept or glucocorticosteroids in patients with rheumatoid arthritis. Scand J Rheumatol. 2006 Sep-Oct;35(5):341-5.
- 25. Blom M, Kievit W, Fransen J, Kuper IH, den Broeder AA, De Gendt CM, et al. The reason for discontinuation of the first tumor necrosis factor (TNF) blocking agent does not influence the effect of a second TNF blocking agent in patients with rheumatoid arthritis. J Rheumatol. 2009
 Oct;36(10):2171-7.
- 26. Blom M, Kievit W, Kuper HH, Jansen TL, Visser H, den Broeder AA, et al. Frequency and effectiveness of dose increase of adalimumab, etanercept, and infliximab in daily clinical practice. Arthritis Care Res (Hoboken). 2010 Sep;62(9):1335-41.
- 27. Bodur H, Ataman S, Akbulut L, Evcik D, Kavuncu V, Kaya T, et al. Characteristics and medical management of patients with rheumatoid arthritis and ankylosing spondylitis. Clin Rheumatol. 2008 Sep;27(9):1119-25.
- 28. Boesen M, Boesen L, Jensen KE, Cimmino MA, Torp-Pedersen S, Terslev L, et al. Clinical outcome and imaging changes after intraarticular (IA) application of etanercept or methylprednisolone in rheumatoid arthritis: magnetic resonance imaging and

- ultrasound-Doppler show no effect of IA injections in the wrist after 4 weeks. J Rheumatol. 2008 Apr;35(4):584-91.
- 29. Bohanec Grabar P, Rozman B, Tomsic M, Suput D, Logar D, Dolzan V. Genetic polymorphism of CYP1A2 and the toxicity of leflunomide treatment in rheumatoid arthritis patients. Eur J Clin Pharmacol. 2008 Sep;64(9):871-6.
- 30. Bologna C, Jorgensen C, Sany J.
 Association of methotrexate and corticosteroids in the treatment of patients with rheumatoid arthritis. Clin Exp Rheumatol. 1996 Jul-Aug;14(4):401-6.
- 31. Bombardieri S, Ruiz AA, Fardellone P, Geusens P, McKenna F, Unnebrink K, et al. Effectiveness of adalimumab for rheumatoid arthritis in patients with a history of TNF-antagonist therapy in clinical practice. Rheumatology (Oxford). 2007 Jul;46(7):1191-9.
- 32. Bongartz T. Tocilizumab for rheumatoid and juvenile idiopathic arthritis. Lancet. 2008(9617):961-3.
- 33. Borah BJ, Huang XY, Zarotsky V, Globe D, Jun. Trends in RA patients' adherence to subcutaneous anti-TNF therapies and costs. *Current Medical Research and Opinion* (England) 2009:1365.
- 34. Boyce EG, Halilovic J, Stan-Ugbene O. Golimumab: Review of the Efficacy and Tolerability of a Recently Approved Tumor Necrosis Factor-alpha Inhibitor. Clinical Therapeutics (USA). 2010;32:1681-703.
- 35. Braun-Moscovici Y, Markovits D, Rozin A, Toledano K, Nahir AM, Balbir-Gurman A. Anti-tumor necrosis factor therapy: 6 year experience of a single center in northern Israel and possible impact of health policy on results. Isr Med Assoc J. 2008 Apr;10(4):277-81.
- 36. Bresnihan B, Newmark R, Robbins S, Genant HK. Effects of anakinra monotherapy on joint damage in patients with rheumatoid arthritis. Extension of a 24-week randomized, placebo-controlled trial. J Rheumatol. 2004 Jun;31(6):1103-11.
- 37. Brocq O, Roux CH, Albert C, Breuil V, Aknouche N, Ruitord S, et al. TNFalpha antagonist continuation rates in 442 patients with inflammatory joint disease. *Joint Bone Spine* 2007:148-54.
- 38. Buch MH, Bingham SJ, Bejarano V, Bryer D, White J, Reece R, et al. Therapy of patients with rheumatoid arthritis: outcome

- of infliximab failures switched to etanercept. Arthritis Rheum. 2007 Apr 15;57(3):448-53.
- Buchbinder R, Barber M, Heuzenroeder L, Wluka AE, Giles G, Hall S, et al. Incidence of melanoma and other malignancies among rheumatoid arthritis patients treated with methotrexate. Arthritis Rheum. 2008 Jun 15:59(6):794-9.
- 40. Buckley LM, Leib ES, Cartularo KS, Vacek PM, Cooper SM. Effects of low dose corticosteroids on the bone mineral density of patients with rheumatoid arthritis. J Rheumatol. 1995 Jun;22(6):1055-9.
- 41. Bukhari MA, Wiles NJ, Lunt M, Harrison BJ, Scott DG, Symmons DP, et al. Influence of disease-modifying therapy on radiographic outcome in inflammatory polyarthritis at five years: results from a large observational inception study. Arthritis Rheum. 2003 Jan;48(1):46-53.
- 42. Burmester GR, Ferraccioli G, Flipo RM, Monteagudo-Saez I, Unnebrink K, Kary S, et al. Clinical remission and/or minimal disease activity in patients receiving adalimumab treatment in a multinational, open-label, twelve-week study. Arthritis Rheum. 2008 Jan 15;59(1):32-41.
- 43. Cacace E, Anedda C, Ruggiero V, Fornasier D, Denotti A, Perpignano G. Etanercept in rheumatoid arthritis: Long term anti-inflammatory efficacy in clinical practice. European Journal of Inflammation. 2006;4(3):171-6.
- 44. Calguneri M, Pay S, Caliskaner Z, Apras S, Kiraz S, Ertenli I, et al. Combination Therapy Versus Monotherapy for the Treatment of Patients With Rheumatoid Arthritis. Clinical and experimental rheumatology. 1999;17(6):699-704.
- 45. Campion GV, Lebsack ME, Lookabaugh J, Gordon G, Catalano M. Dose-range and dose-frequency study of recombinant human interleukin-1 receptor antagonist in patients with rheumatoid arthritis. The IL-1Ra Arthritis Study Group. Arthritis Rheum. 1996 Jul;39(7):1092-101.
- 46. Cantini F, Niccoli L, Nannini C, Cassara E, Pasquetti P, Olivieri I, et al. Frequency and duration of clinical remission in patients with peripheral psoriatic arthritis requiring second-line drugs. *Rheumatology (Oxford)* 2008:872-6.
- 47. Carmona L, Descalzo MÃ, Perez-Pampin E, Ruiz-Montesinos D, Erra A, Cobo T, et al. All-cause and cause-specific mortality in rheumatoid arthritis are not greater than

- expected when treated with tumour necrosis factor antagonists. Annals of the rheumatic diseases. 2007;66(7):880-5.
- 48. Cassano N, Galluccio A, De Simone C, Loconsole F, Massimino SD, Plumari A, et al. Influence of body mass index, comorbidities and prior systemic therapies on the response of psoriasis to adalimumab: an exploratory analysis from the APHRODITE data. J Biol Regul Homeost Agents. 2008 Oct-Dec;22(4):233-7.
- 49. Cauza E, Spak M, Cauza K, Hanusch-Enserer U, Dunky A, Wagner E. Treatment of psoriatic arthritis and psoriasis vulgaris with the tumor necrosis factor inhibitor infliximab. Rheumatol Int. 2002 Nov:22(6):227-32.
- 50. Chambers CD, Johnson DL, Robinson LK, Braddock SR, Xu R, Lopez-Jimenez J, et al. Birth outcomes in women who have taken leflunomide during pregnancy. *Arthritis Rheum*. 2010/02/05 ed 2010:1494-503.
- 51. Chen DY, Chou SJ, Hsieh TY, Chen YH, Chen HH, Hsieh CW, et al. Randomized, double-blind, placebo-controlled, comparative study of human anti-TNF antibody adalimumab in combination with methotrexate and methotrexate alone in Taiwanese patients with active rheumatoid arthritis. 2009.
- 52. Ciconelli R, Ferraz M, Visioni R, Oliveira L, Atra E. A Randomized Double-Blind Controlled Trial of Sulphasalazine Combined With Pulses of Methylprednisolone or Placebo in the Treatment of Rheumatoid Arthritis. British journal of rheumatology. 1996;35(2):150-4.
- 53. Cohen G, Courvoisier N, Cohen JD, Zaltni S, Sany J, Combe B. The efficiency of switching from infliximab to etanercept and vice-versa in patients with rheumatoid arthritis. Clin Exp Rheumatol. 2005 Nov-Dec;23(6):795-800.
- 54. Cohen JD, Dougados M, Goupille P, Cantagrel A, Meyer O, Sibilia J, et al. Health assessment questionnaire score is the best predictor of 5-year quality of life in early rheumatoid arthritis. Journal of Rheumatology. 2006;33(10):1936-41.
- 55. Cole JC, Li T, Lin P, MacLean R,
 Wallenstein GV. Treatment impact on
 estimated medical expenditure and job loss
 likelihood in rheumatoid arthritis: reexamining quality of life outcomes from a
 randomized placebo-controlled clinical trial

- with abatacept. Rheumatology (Oxford). 2008 Jul;47(7):1044-50.
- 56. Contreras-Yanez I, Ponce De Leon S, Cabiedes J, Rull-Gabayet M, Pascual-Ramos V. Inadequate therapy behavior is associated to disease flares in patients with rheumatoid arthritis who have achieved remission with disease-modifying antirheumatic drugs. Am J Med Sci. 2010 Oct;340(4):282-90.
- 57. Covelli M, Scioscia C, Iannone F, Lapadula G. Repeated infusions of low-dose infliximab plus methotrexate in psoriatic arthritis: immediate benefits are not maintained after discontinuation of infliximab. Clin Exp Rheumatol. 2005 MarApr;23(2):145-51.
- 58. Criswell L, Saag K, Sems KM, Welch V, Shea B, Wells George A, et al. Moderate-term, low-dose corticosteroids for rheumatoid arthritis. 1998.
- 59. Cuchacovich M, Ferreira L, Aliste M, Soto L, Cuenca J, Cruzat A, et al. Tumour necrosis factor-alpha (TNF-alpha) levels and influence of -308 TNF-alpha promoter polymorphism on the responsiveness to infliximab in patients with rheumatoid arthritis. Scand J Rheumatol. 2004;33(4):228-32.
- 60. Curtis JR, Martin C, Saag KG, Patkar NM, Kramer J, Shatin D, et al. Confirmation of administrative claims-identified opportunistic infections and other serious potential adverse events associated with tumor necrosis factor alpha antagonists and disease-modifying antirheumatic drugs.

 Arthritis Rheum. 2007 Mar 15;57(2):343-6.
- 61. Davis JM, 3rd, Maradit Kremers H, Crowson CS, Nicola PJ, Ballman KV, Therneau TM, et al. Glucocorticoids and cardiovascular events in rheumatoid arthritis: a population-based cohort study. Arthritis Rheum. 2007 Mar;56(3):820-30.
- 62. De Felice C, Mazzotta A, Esposito M, Bianchi L, Chimenti S. High-dose initiation of etanercept in psoriatic arthritis and plaque psoriasis: efficacy, safety and impact on patients' quality of life. J Dermatolog Treat. 2006:17(6):355-8.
- 63. De Filippis L, Caliri A, Anghelone S, Scibilia G, Lo Gullo R, Bagnato G. Improving outcomes in tumour necrosis factor a treatment: comparison of the efficacy of the tumour necrosis factor a blocking agents etanercept and infliximab in patients with active rheumatoid arthritis. Panminerva Med 2006:129-35.

- 64. De Rycke L, Baeten D, Kruithof E, Van den Bosch F, De Keyser F, et al. Infliximab, but not etanercept, induces IgM anti-double-stranded DNA autoantibodies as main antinuclear reactivity Biologic and clinical implications in autoimmune arthritis.

 Arthritis and Rheumatism (USA). 2005 07/01/;52(Jul):2192-201.
- 65. De Rycke L, Baeten D, Kruithof E, Van den Bosch F, Veys EM, De Keyser F.
 Infliximab, but not etanercept, induces IgM anti-double-stranded DNA autoantibodies as main antinuclear reactivity: biologic and clinical implications in autoimmune arthritis. Arthritis Rheum. 2005
 Jul;52(7):2192-201.
- 66. del Porto F, Aloe L, Lagana B, Triaca V, Nofroni I, D'Amelio R. Nerve growth factor and brain-derived neurotrophic factor levels in patients with rheumatoid arthritis treated with TNF-alpha blockers. Ann N Y Acad Sci. 2006 Jun;1069:438-43.
- 67. Delabaye I, De Keyser F. 74-week followup of safety of infliximab in patients with refractory rheumatoid arthritis. Arthritis Res Ther. 2010;12(3):R121.
- 68. den Broeder A, van de Putte L, Rau R, Schattenkirchner M, Van Riel P, Sander O, et al. A single dose, placebo controlled study of the fully human anti-tumor necrosis factor-alpha antibody adalimumab (D2E7) in patients with rheumatoid arthritis. J Rheumatol. 2002 Nov;29(11):2288-98.
- 69. Dohn UM, Skjodt H, Hetland ML, Vestergaard A, Moller JM, Knudsen LS, et al. No erosive progression revealed by MRI in rheumatoid arthritis patients treated with etanercept, even in patients with persistent MRI and clinical signs of joint inflammation. Clin Rheumatol. 2007 Nov;26(11):1857-61.
- 70. Dore RK, Mathews S, Schechtman J, Surbeck W, Mandel D, Patel A, et al. The immunogenicity, safety, and efficacy of etanercept liquid administered once weekly in patients with rheumatoid arthritis. Clin Exp Rheumatol. 2007 Jan-Feb;25(1):40-6.
- 71. Ducoulombier V, Solau E, Coquerelle P, Houvenagel E, Siame JL, Desprez X, et al. Long-term results of infliximab therapy in rheumatoid arthritis: experience acquired by the North-Pas-de-Calais hospital network. Joint Bone Spine. 2007 Jan;74(1):56-9.
- 72. Dunne CA, Moran CJ, Thompson PW. The effect of regular intramuscular corticosteroid therapy on bone mineral density in

- rheumatoid patients. Scand J Rheumatol. 1995;24(1):48-9.
- 73. Durez P, Malghem J, Nzeusseu Toukap A, Depresseux G, Lauwerys BR, Westhovens R, et al. Treatment of early rheumatoid arthritis: a randomized magnetic resonance imaging study comparing the effects of methotrexate alone, methotrexate in combination with infliximab, and methotrexate in combination with intravenous pulse methylprednisolone. *Arthritis Rheum* 2007:3919-27.
- 74. Durez P, Nzeusseu Toukap A, Lauwerys BR, Manicourt DH, Verschueren P, Westhovens R, et al. A randomised comparative study of the short term clinical and biological effects of intravenous pulse methylprednisolone and infliximab in patients with active rheumatoid arthritis despite methotrexate treatment. Ann Rheum Dis. 2004 Sep;63(9):1069-74.
- 75. Durez P, Van den Bosch F, Corluy L, Veys EM, De Clerck L, Peretz A, et al. A dose adjustment in patients with rheumatoid arthritis not optimally responding to a standard dose of infliximab of 3 mg/kg every 8 weeks can be effective: a Belgian prospective study. Rheumatology (Oxford). 2005 Apr;44(4):465-8.
- 76. Eder L, Chandran V, Schentag CT, Shen H, Cook RJ, Gladman DD. Time and predictors of response to tumour necrosis factor-(alpha) blockers in psoriatic arthritis: An analysis of a longitudinal observational cohort. Rheumatology. 2010;49(7):1361-6.
- 77. Egnatios G, Warthan MM, Pariser R, Hood AF. Pustular psoriasis following treatment of rheumatoid arthritis with TNF-alpha inhibitors. J Drugs Dermatol. 2008 Oct;7(10):975-7.
- 78. Emery P, Genovese MC, van Vollenhoven R, Sharp JT, Sasso EH, et al., et al. Less Radiographic Progression with Adalimumab Plus Methotrexate Versus Methotrexate Monotherapy Across the Spectrum of Clinical Response in Early Rheumatoid Arthritis. *Journal of Rheumatology* 2009:1429.
- 79. Farahani P, Levine M, Gaebel K, Wang EC, Khalidi N. Community-based evaluation of etanercept in patients with rheumatoid arthritis. J Rheumatol. 2006 Apr;33(4):665-70.
- 80. Felson DT, Anderson JJ, Meenan RF. The comparative efficacy and toxicity of second-line drugs in rheumatoid arthritis. Results of

- two metaanalyses. Arthritis Rheum. 1990 Oct;33(10):1449-61.
- 81. Fernandez-Espartero MC, Perez-Zafrilla B, Naranjo A, Esteban C, Ortiz AM, Gomez-Reino JJ, et al. Demyelinating Disease in Patients Treated with TNF Antagonists in Rheumatology: Data from BIOBADASER, a Pharmacovigilance Database, and a Systematic Review. Semin Arthritis Rheum 2010:330-7.
- 82. Ferri C, Ferraccioli G, Ferrari D, Galeazzi M, Lapadula G, Montecucco C, et al. Safety of anti-tumor necrosis factor-alpha therapy in patients with rheumatoid arthritis and chronic hepatitis C virus infection. J Rheumatol. 2008 Oct;35(10):1944-9.
- 83. Fiehn C, Jacki S, Heilig B, Lampe M, Wiesmuller G, Richter C, et al. Eight versus 16-week re-evaluation period in rheumatoid arthritis patients treated with leflunomide or methotrexate accompanied by moderate dose prednisone. Rheumatol Int. 2007 Aug;27(10):975-9.
- 84. Finckh A, Simard JF, Duryea J, Liang MH, Huang J, Daneel S, et al. The effectiveness of anti-tumor necrosis factor therapy in preventing progressive radiographic joint damage in rheumatoid arthritis: a population-based study. Arthritis Rheum. 2006 Jan;54(1):54-9.
- 85. Fischer P. Resolution of treatment-related arthralgias and serologic findings with a switch of TNF antagonist therapies in a patient with psoriatic arthritis. J Clin Rheumatol. 2007 Oct;13(5):294-5.
- 86. Fleischmann R. Safety and efficacy of etanercept in the elderly. Aging Health. 2006;2(2):189-97.
- 87. Fleischmann RM, Cohen SB, Moreland LW, Schiff M, Mease PJ, Smith DB, et al. Methotrexate dosage reduction in patients with rheumatoid arthritis beginning therapy with infliximab: the Infliximab Rheumatoid Arthritis Methotrexate Tapering (iRAMT) trial. Curr Med Res Opin. 2005 Aug;21(8):1181-90.
- 88. Frankel EH, Strober BE, Crowley JJ, Fivenson DP, Woolley JM, Yu EB, et al. Etanercept improves psoriatic arthritis patient-reported outcomes: results from EDUCATE. Cutis. 2007 Apr;79(4):322-6.
- 89. Fries JF, Williams CA, Morfeld D, Singh G, Sibley J. Reduction in long-term disability in patients with rheumatoid arthritis by disease-modifying antirheumatic drug-based

- treatment strategies. Arthritis Rheum. 1996 Apr;39(4):616-22.
- 90. Furst D, Erikson N, Clute L, Koehnke R, Burmeister L, Kohler J. Adverse Experience With Methotrexate During 176 Weeks of a Longterm Prospective Trial in Patients With Rheumatoid Arthritis. The Journal of rheumatology. 1990;12:1628-35.
- 91. Furst DE, Gaylis N, Bray V, Olech E, Yocum D, Ritter J, et al. Open-label, pilot protocol of patients with rheumatoid arthritis who switch to infliximab after an incomplete response to etanercept: the opposite study. *Ann Rheum Dis* 2007:893-9.
- 92. Furuya T, Kotake S, Inoue E, Nanke Y, Yago T, Hara M, et al. Risk factors associated with incident fractures in Japanese men with rheumatoid arthritis: A prospective observational cohort study. Journal of Bone and Mineral Metabolism. 2008;26(5):499-505.
- 93. Furuya T, Kotake S, Inoue E, Nanke Y, Yago T, Kobashigawa T, et al. Risk factors associated with incident clinical vertebral and nonvertebral fractures in Japanese women with rheumatoid arthritis: A prospective 54-month observational study. Journal of Rheumatology. 2007;34(2):303-10.
- 94. Genant HK, Peterfy CG, Westhovens R, Becker JC, Aranda R, Vratsanos G, et al. Abatacept inhibits progression of structural damage in rheumatoid arthritis: Results from the long-term extension of the AIM trial. Annals of the Rheumatic Diseases. 2007;67(8):1084-9.
- 95. Genovese MC, Becker JC, Schiff M, Luggen M, Sherrer Y, Kremer J, et al. Abatacept for rheumatoid arthritis refractory to tumor necrosis factor alpha inhibition. N Engl J Med. 2005 Sep 15;353(11):1114-23.
- 96. Genovese MC, Schiff M, Luggen M, Becker JC, Aranda R, Teng J, et al. Efficacy and safety of the selective co-stimulation modulator abatacept following 2 years of treatment in patients with rheumatoid arthritis and an inadequate response to antitumour necrosis factor therapy. Ann Rheum Dis. 2008 Apr;67(4):547-54.
- 97. George D, Kadlubek P, Batra D, Goldberg G. Infliximab dose and charge escalation patterns in managed care. Manag Care Interface. 2004;Suppl A:5-8.
- 98. Gibson JN, Poyser NL, Morrison WL, Scrimgeour CM, Rennie MJ. Muscle protein synthesis in patients with rheumatoid

- arthritis: effect of chronic corticosteroid therapy on prostaglandin F2 alpha availability. Eur J Clin Invest. 1991 Aug;21(4):406-12.
- 99. Giles JT, Bartlett SJ, Gelber AC, Nanda S, Fontaine K, Ruffing V, et al. Tumor necrosis factor inhibitor therapy and risk of serious postoperative orthopedic infection in rheumatoid arthritis. Arthritis Rheum. 2006 Apr 15;55(2):333-7.
- 100. Gladman DD, Mease PJ, Choy EH, Ritchlin CT, Perdok RJ, Sasso EH. Risk factors for radiographic progression in psoriatic arthritis: subanalysis of the randomized controlled trial ADEPT. Arthritis Res Ther. 2010;12(3):R113.
- 101. Gladman DD, Mease PJ, Ritchlin CT, Choy EH, Sharp JT, Ory PA, et al. Adalimumab for long-term treatment of psoriatic arthritis: forty-eight week data from the adalimumab effectiveness in psoriatic arthritis trial. Arthritis Rheum. 2007 Feb;56(2):476-88.
- 102. Gladman DD, Sampalis JS, Illouz O, Guerette B, Investigators AS. Responses to Adalimumab in Patients with Active Psoriatic Arthritis Who Have Not Adequately Responded to Prior Therapy: Effectiveness and Safety Results From an Open-label Study. Journal of Rheumatology. 2010;37:1898.
- 103. Goekoop-Ruiterman YPM, De Vries-Bouwstra JK, Kerstens PJSM, Nielen MMJ, Vos K, Van Schaardenburg D, et al. DAS-driven therapy versus routine care in patients with recent-onset active rheumatoid arthritis. 2010.
- 104. Goldman JA, Xia HA, White B, Paulus H. Evaluation of a modified ACR20 scoring system in patients with rheumatoid arthritis receiving treatment with etanercept. Ann Rheum Dis. 2006 Dec;65(12):1649-52.
- 105. Gonzalez-Lopez MA, Blanco R, Gonzalez-Vela MC, Fernandez-Llaca H, Rodriguez-Valverde V. Development of sarcoidosis during etanercept therapy. Arthritis Rheum. 2006 Oct 15;55(5):817-20.
- 106. Gottenberg JE, Ravaud P, Bardin T, Cacoub P, Cantagrel A, Combe B, et al. Risk factors for severe infections in patients with rheumatoid arthritis treated with rituximab in the autoimmunity and rituximab registry. Arthritis Rheum. 2010 Sep;62(9):2625-32.
- 107. Gottlieb AB, Kircik L, Eisen D, Jackson JM, Boh EE, Strober BE, et al. Use of etanercept for psoriatic arthritis in the dermatology clinic: the Experience Diagnosing,

- Understanding Care, and Treatment with Etanercept (EDUCATE) study. J Dermatolog Treat. 2006;17(6):343-52.
- 108. Gran JT, Myklebust G. Toxicity of sulphasalazine in rheumatoid arthritis. Possible protective effect of rheumatoid factors and corticosteroids. Scand J Rheumatol. 1993;22(5):229-32.
- 109. Gratacos J, Casado E, Real J, Torre-Alonso JC. Prediction of major clinical response (ACR50) to infliximab in psoriatic arthritis refractory to methotrexate. Ann Rheum Dis. 2007 Apr;66(4):493-7.
- 110. Greenberg JD, Kishimoto M, Strand V, Cohen SB, Olenginski TP, Harrington T, et al. Tumor necrosis factor antagonist responsiveness in a United States rheumatoid arthritis cohort. Am J Med. 2008 Jun;121(6):532-8.
- 111. Grigor C, Capell H, Stirling A, McMahon AD, Lock P, Vallance R, et al. Effect of a Treatment Strategy of Tight Control for Rheumatoid Arthritis (the Ticora Study): a Single-Blind Randomised Controlled Trial. Lancet. 2004;364(9430):263-9.
- 112. Grijalva CG, Kaltenbach L, Arbogast PG, Mitchel EF, Jr., Griffin MR. Adherence to disease-modifying antirheumatic drugs and the effects of exposure misclassification on the risk of hospital admission. *Arthritis Care Res (Hoboken)*. 2010/03/02 ed 2010:730-4.
- 113. Haagsma C, van Riel P, van de Putte L.
 Combining Sulphasalazine and
 Methotrexate in Rheumatoid Arthritis: Early
 Clinical Impressions. British journal of
 rheumatology. 1995;34(Suppl 2):104-8.
- 114. Haagsma CJ, van Riel PL, de Rooij DJ, Vree TB, Russel FJ, van't Hof MA, et al. Combination of Methotrexate and Sulphasalazine Vs Methotrexate Alone: a Randomized Open Clinical Trial in Rheumatoid Arthritis Patients Resistant to Sulphasalazine Therapy. British journal of rheumatology. 1994;33(11):1049-55.
- 115. Hafstrom I, Albertsson K, Boonen A, van der Heijde D, Landewe R, Svensson B. Remission achieved after 2 years treatment with low-dose prednisolone in addition to disease-modifying anti-rheumatic drugs in early rheumatoid arthritis is associated with reduced joint destruction still present after 4 years: an open 2-year continuation study. Ann Rheum Dis. 2009 Apr;68(4):508-13.
- 116. Hall SJ, Hickling P. Failure of etanercept to control extra-articular manifestations of

- rheumatoid arthritis. J Clin Rheumatol. 2007 Feb;13(1):54.
- 117. Hamilton TK. Treatment of psoriatic arthritis and recalcitrant skin disease with combination therapy. J Drugs Dermatol. 2008 Nov;7(11):1089-93.
- 118. Han C, Rahman MU, Doyle MK, Bathon JM, Smolen J, Kavanaugh A, et al.
 Association of anemia and physical disability among patients with rheumatoid arthritis. J Rheumatol. 2007
 Nov;34(11):2177-82.
- 119. Han C, Smolen J, Kavanaugh A, St Clair EW, Baker D, Bala M. Comparison of employability outcomes among patients with early or long-standing rheumatoid arthritis. Arthritis Rheum. 2008 Apr 15;59(4):510-4.
- 120. Harrison MJ, Kim CA, Silverberg M, Paget SA. Does age bias the aggressive treatment of elderly patients with rheumatoid arthritis? J Rheumatol. 2005 Jul;32(7):1243-8.
- 121. Haugeberg G, Conaghan PG, Quinn M, Emery P. Bone loss in patients with active early rheumatoid arthritis: infliximab and methotrexate compared with methotrexate treatment alone. Explorative analysis from a 12-month randomised, double-blind, placebo-controlled study. Ann Rheum Dis. 2009 Dec;68(12):1898-901.
- 122. Hazes JM, Taylor P, Strand V, Purcaru O, Coteur G, Mease P. Physical function improvements and relief from fatigue and pain are associated with increased productivity at work and at home in rheumatoid arthritis patients treated with certolizumab pegol. Rheumatology. 2010;49(10):1900-10.
- 123. Heiberg MS, Kaufmann C, Rodevand E, Mikkelsen K, Koldingsnes W, Mowinckel P, et al. The comparative effectiveness of anti-TNF therapy and methotrexate in patients with psoriatic arthritis: 6 month results from a longitudinal, observational, multicentre study. Ann Rheum Dis. 2007 Aug;66(8):1038-42.
- 124. Heiberg MS, Koldingsnes W, Mikkelsen K, Rodevand E, Kaufmann C, Mowinckel P, et al. The comparative one-year performance of anti-tumor necrosis factor alpha drugs in patients with rheumatoid arthritis, psoriatic arthritis, and ankylosing spondylitis: results from a longitudinal, observational, multicenter study. Arthritis Rheum. 2008 Feb 15:59(2):234-40.
- 125. Helliwell PS, Taylor WJ. Treatment of psoriatic arthritis and rheumatoid arthritis

- with disease modifying drugs -- comparison of drugs and adverse reactions. J Rheumatol. 2008 Mar:35(3):472-6.
- 126. Herenius MM, Hoving JL, Sluiter JK, Raterman HG, Lems WF, Dijkmans BA, et al. Improvement of work ability, quality of life, and fatigue in patients with rheumatoid arthritis treated with adalimumab. J Occup Environ Med. 2010 Jun;52(6):618-21.
- 127. Heytman M, Ahern MJ, Smith MD, Roberts-Thomson PJ. The longterm effect of pulsed corticosteroids on the efficacy and toxicity of chrysotherapy in rheumatoid arthritis. J Rheumatol. 1994 Mar;21(3):435-41
- 128. Higashida J, Wun T, Schmidt S, Naguwa SM, Tuscano JM. Safety and efficacy of rituximab in patients with rheumatoid arthritis refractory to disease modifying antirheumatic drugs and anti-tumor necrosis factor-alpha treatment. J Rheumatol. 2005 Nov;32(11):2109-15.
- 129. Hirose W, Nishikawa K, Hirose M, Nanki T, Sugimoto H. Response of early active rheumatoid arthritis to tumor necrosis factor inhibitors: evaluation by magnetic resonance imaging. Mod Rheumatol. 2009;19(1):20-6.
- 130. Hoekstra M, van Ede A, Haagsma C, van de Laar M, Huizinga T, Kruijsen M, et al. Factors associated with toxicity, final dose, and efficacy of methotrexate in patients with rheumatoid arthritis. Annals of the rheumatic diseases. 2003;62(5):423-6.
- 131. Holman AJ, Ng E. Heart rate variability predicts anti-tumor necrosis factor therapy response for inflammatory arthritis. Auton Neurosci. 2008 Dec 5;143(1-2):58-67.
- 132. Hoshida Y, Xu JX, Fujita S, Nakamichi I, Ikeda J, Tomita Y, et al.
 Lymphoproliferative disorders in rheumatoid arthritis: clinicopathological analysis of 76 cases in relation to methotrexate medication. J Rheumatol. 2007 Feb;34(2):322-31.
- 133. Huang F, Wang L, Zhang J, Deng X, Guo J, Zhang Y. Risk of tuberculosis in a Chinese registry of rheumatoid arthritis and ankylosing spondylitis for tumour necrosis factor-alpha antagonists. APLAR Journal of Rheumatology. 2006;9(2):170-4.
- 134. Hurlimann D, Forster A, Noll G, Enseleit F, Chenevard R, Distler O, et al. Anti-tumor necrosis factor-alpha treatment improves endothelial function in patients with rheumatoid arthritis. Circulation. 2002 Oct 22;106(17):2184-7.

- 135. Huscher D, Thiele K, Gromnica-Ihle E, Hein G, Demary W, Dreher R, et al. Doserelated patterns of glucocorticoid-induced side effects. Ann Rheum Dis. 2009
 Jul;68(7):1119-24.
- 136. Hyrich KL, Deighton C, Watson KD, Symmons DP, Lunt M. Benefit of anti-TNF therapy in rheumatoid arthritis patients with moderate disease activity. *Rheumatology* (Oxford) 2009:1323-7.
- 137. Hyrich KL, Lunt M, Dixon WG, Watson KD, Symmons DP. Effects of switching between anti-TNF therapies on HAQ response in patients who do not respond to their first anti-TNF drug. Rheumatology (Oxford). 2008 Jul;47(7):1000-5.
- 138. Inanc N, Direskeneli H. Serious infections under treatment with TNF-alpha antagonists compared to traditional DMARDs in patients with rheumatoid arthritis.

 Rheumatol Int. 2006 Nov;27(1):67-71.
- 139. Islam M, Alam M, Haq S, Moyenuzzaman M, Patwary M, Rahman M. Efficacy of Sulphasalazine Plus Methotrexate in Rheumatoid Arthritis. Bangladesh Medical Research Council bulletin. 2000;26(1):1-7.
- 140. Iwamoto N, Kawakami A, Fujikawa K, Aramaki T, Kawashiri SY, Tamai M, et al. Prediction of DAS28-ESR remission at 6 months by baseline variables in patients with rheumatoid arthritis treated with etanercept in Japanese population. *Mod Rheumatol* 2009:488-92.
- 141. Jamal S, Patra K, Keystone EC.
 Adalimumab response in patients with early versus established rheumatoid arthritis:
 DE019 randomized controlled trial subanalysis. 2009.
- 142. Jenks KA, Stamp LK, O'Donnell JL, Savage RL, Chapman PT. Leflunomide-associated infections in rheumatoid arthritis. J Rheumatol. 2007 Nov;34(11):2201-3.
- 143. Jung N, Hellmann M, Hoheisel R, Lehmann C, Haase I, Perniok A, et al. An open-label pilot study of the efficacy and safety of anakinra in patients with psoriatic arthritis refractory to or intolerant of methotrexate (MTX). Clin Rheumatol. 2010 Oct;29(10):1169-73.
- 144. Kalden JR, Schattenkirchner M, Sorensen H, Emery P, Deighton C, Rozman B, et al. The Efficacy and Safety of Leflunomide in Patients With Active Rheumatoid Arthritis: a Five-Year Followup Study. Arthritis and rheumatism. 2003;48(6):1513-20.

- 145. Kalden JR, Scott DL, Smolen JS, Schattenkirchner M, Rozman B, Williams BD, et al. Improved Functional Ability in Patients With Rheumatoid Arthritis -Longterm Treatment With Leflunomide Versus Sulfasalazine. Journal of Rheumatology. 2001;28(9):1983-91.
- 146. Kalden Nemeth D, Grebmeier J, Antoni C, Manger B, Wolf F, Kalden J. Nmr Monitoring of Rheumatoid Arthritis Patients Receiving Anti-Tnf-Alpha Monoclonal Antibody Therapy. Rheumatology international. 1997;16(6):249-55.
- 147. Kaplan MJ. Do tumor-necrosis-factor inhibitors prevent first cardiovascular events in patients with rheumatoid arthritis? Nat Clin Pract Rheumatol. 2005 Dec;1(2):74-5.
- 148. Kastbom A, Bratt J, Ernestam S, Lampa J, Padyukov L, Soderkvist P, et al. Fcgamma receptor type IIIA genotype and response to tumor necrosis factor alpha-blocking agents in patients with rheumatoid arthritis. Arthritis Rheum. 2007 Feb;56(2):448-52.
- 149. Katz P, Yelin E, Patel V, Huang XY, Chiou CF. Patient-reported outcomes following biologic therapy in a sample of adults with rheumatoid arthritis recruited from community-based rheumatologists. Arthritis Rheum. 2009 May 15;61(5):593-9.
- 150. Kavanaugh A. Anakinra (interleukin-1 receptor antagonist) has positive effects on function and quality of life in patients with rheumatoid arthritis. Advances in Therapy (USA). 2006 02/01/;23(Feb):208-17.
- 151. Kavanaugh A, Krueger GG, Beutler A, Guzzo C, Zhou B, Dooley LT, et al. Infliximab maintains a high degree of clinical response in patients with active psoriatic arthritis through 1 year of treatment: results from the IMPACT 2 trial. Ann Rheum Dis. 2007 Apr;66(4):498-505.
- 152. Kavanaugh A, Lee SJ, Weng HH, Chon Y, Huang XY, Lin SL. Patient-derived joint counts are a potential alternative for determining Disease Activity Score. *J Rheumatol.* 2010/02/17 ed 2010:1035-41.
- 153. Keystone E, Fleischmann R, Emery P, Furst DE, van Vollenhoven R, Bathon J, et al. Safety and efficacy of additional courses of rituximab in patients with active rheumatoid arthritis: an open-label extension analysis. Arthritis Rheum. 2007 Dec;56(12):3896-908
- 154. Keystone EC, Schiff MH, Kremer JM, Kafka S, Lovy M, DeVries T, et al. Onceweekly administration of 50 mg etanercept

- in patients with active rheumatoid arthritis: results of a multicenter, randomized, double-blind, placebo-controlled trial. Arthritis Rheum. 2004 Feb;50(2):353-63.
- 155. Kielhorn A, Porter D, Diamantopoulos A, Lewis G. UK cost-utility analysis of rituximab in patients with rheumatoid arthritis that failed to respond adequately to a biologic disease-modifying antirheumatic drug. Curr Med Res Opin. 2008 Sep;24(9):2639-50.
- 156. Kimball AB, Bensimon AG, Guerin A, Yu AP, Wu EQ, Okun MM, et al. Efficacy and safety of adalimumab among patients with moderate to severe psoriasis with comorbidities: Subanalysis of results from a randomized, double-blind, placebocontrolled, phase III trial. *American Journal of Clinical Dermatology* 2011:51-62.
- 157. Kimball AB, Jackson JM, Sobell JM, Boh EE, Grekin S, Pharmd EB, et al. Reductions in healthcare resource utilization in psoriatic arthritis patients receiving etanercept therapy: results from the educate trial. J Drugs Dermatol. 2007 Mar;6(3):299-306.
- 158. Kiortsis DN, Mavridis AK, Vasakos S, Nikas SN, Drosos AA. Effects of infliximab treatment on lipoprotein profile in patients with rheumatoid arthritis and ankylosing spondylitis. J Rheumatol. 2006 May;33(5):921-3.
- 159. Klareskog L, Gaubitz M, Rodriguez-Valverde V, Malaise M, Dougados M, Wajdula J. A Long-Term, Open-Label Trial of the Safety and Efficacy of Etanercept (ENBREL(R)) In Patients With Rheumatoid Arthritis Not Treated With Other DMARDs (3-year Interim Report). Ann Rheum Dis. 2006 Mar 15.
- 160. Koeller MD, Aletaha D, Funovits J, Pangan A, Smolen JS, et al., et al. Response of elderly patients with rheumatoid arthritis to methotrexate or TNF inhibitors compared with younger patients. *Rheumatology* 2009:1575.
- 161. Koike T, Harigai M, Inokuma S, Inoue K, Ishiguro N, Ryu J, et al. Postmarketing surveillance of the safety and effectiveness of etanercept in Japan. J Rheumatol. 2009 May;36(5):898-906.
- 162. Komano Y, Harigai M, Koike R, Sugiyama H, Ogawa J, Saito K, et al. Pneumocystis jiroveci pneumonia in patients with rheumatoid arthritis treated with infliximab: a retrospective review and case-control

- study of 21 patients. Arthritis Rheum. 2009 Mar 15;61(3):305-12.
- 163. Kononoff A, Heiskanen J, Lumiaho J, Kautiainen H, Kaipiainen-Seppanen O. Intensifying treatment of rheumatoid arthritis with combinations of traditional disease-modifying anti-rheumatic drugs among patients with persistent disease did not reduce the need for large joint surgery. Scand J Rheumatol. 2007 Nov-Dec;36(6):424-7.
- 164. Kremer J, Genovese M, Cannon GW, Caldwell J, Cush J, Furst DE, et al. Combination Leflunomide and Methotrexate (Mtx) Therapy for Patients With Active Rheumatoid Arthritis Failing Mtx Monotherapy: Open-Label Extension of a Randomized, Double-Blind, Placebo Controlled Trial. The Journal of rheumatology. 2004;31(8):1521-31.
- 165. Kremer JM, Genant HK, Moreland LW, Russell AS, Emery P, Abud-Mendoza C, et al. Results of a two-year followup study of patients with rheumatoid arthritis who received a combination of abatacept and methotrexate. Arthritis Rheum. 2008 Apr;58(4):953-63.
- 166. Kristensen LE, Kapetanovic MC, Gulfe A, Soderlin M, Saxne T, Geborek P. Predictors of response to anti-TNF therapy according to ACR and EULAR criteria in patients with established RA: results from the South Swedish Arthritis Treatment Group Register. Rheumatology (Oxford). 2008 Apr;47(4):495-9.
- 167. Kroesen S, Widmer AF, Tyndall A, Hasler P. Serious bacterial infections in patients with rheumatoid arthritis under anti-TNF-alpha therapy. Rheumatology (Oxford). 2003 May;42(5):617-21.
- 168. Kvalvik AG, Lefsaker L, Dyvik S, Brun JG. Anti-tumor necrosis factor-alpha therapy in the ordinary clinical setting: Three-year effectiveness in patients with rheumatoid arthritis. Joint Bone Spine. 2007 Dec;74(6):606-11.
- 169. Laas K, Peltomaa R, Puolakka K, Kautiainen H, Leirisalo-Repo M. Early improvement of health-related quality of life during treatment with etanercept and adalimumab in patients with rheumatoid arthritis in routine practice. *Clinical and Experimental Rheumatology* 2009:315-20.
- 170. Laivoranta-Nyman S, Mottonen T, Hannonen P, Korpela M, Kautiainen H, Leirisalo-Repo M, et al. Association of

- tumour necrosis factor a, b and c microsatellite polymorphisms with clinical disease activity and induction of remission in early rheumatoid arthritis. Clin Exp Rheumatol. 2006 Nov-Dec;24(6):636-42.
- 171. Landewe R, van der Heijde D, Klareskog L, van Vollenhoven R, Fatenejad S. Disconnect between inflammation and joint destruction after treatment with etanercept plus methotrexate Results from the trial of etanercept and methotrexate with radiographic and patient outcomes. Arthritis and Rheumatism (USA). 2006 10/01/;54(Oct):3119-25.
- 172. Lard LR, Boers M, Verhoeven A, Vos K, Visser H, Hazes JMW, et al. Early and Aggressive Treatment of Rheumatoid Arthritis Patients Affects the Association of Hla Class Ii Antigens With Progression of Joint Damage. Arthritis and rheumatism. 2002;46(4):899-905.
- 173. Lazzerini PE, Acampa M, Hammoud M, Maffei S, Capecchi PL, Selvi E, et al. Arrhythmic risk during acute infusion of infliximab: a prospective, single-blind, placebo-controlled, crossover study in patients with chronic arthritis. J Rheumatol. 2008 Oct;35(10):1958-65.
- 174. Le Loet X, Nordstrom D, Rodriguez M, Rubbert A, Sarzi-Puttini P, Wouters JM, et al. Effect of anakinra on functional status in patients with active rheumatoid arthritis receiving concomitant therapy with traditional disease modifying antirheumatic drugs: evidence from the OMEGA Trial. J Rheumatol. 2008 Aug:35(8):1538-44.
- 175. Lekander I, Borgstrom F, Svarvar P, Ljung T, Carli C, van Vollenhoven RF. Costeffectiveness of real-world infliximab use in patients with rheumatoid arthritis in Sweden. International Journal of Technology Assessment in Health Care. 2010;26(1):54-61.
- 176. Lems WF, Jahangier ZN, Jacobs JW, Bijlsma JW. Vertebral fractures in patients with rheumatoid arthritis treated with corticosteroids. Clin Exp Rheumatol. 1995 May-Jun;13(3):293-7.
- 177. Lequerre T, Vittecoq O, Klemmer N, Goeb V, Pouplin S, Menard JF, et al. Management of infusion reactions to infliximab in patients with rheumatoid arthritis or spondyloarthritis: experience from an immunotherapy unit of rheumatology. J Rheumatol. 2006 Jul;33(7):1307-14.

- 178. Lester SE, Proudman SM, Lee AT, Hall CA, Cleland LG, et al., et al. Treatment-induced stable, moderate reduction in blood cell counts correlate to disease control in early rheumatoid arthritis. Internal Medicine Journal. 2009;39:296.
- 179. Levalampi T, Korpela M, Vuolteenaho K, Moilanen E. Etanercept and adalimumab treatment in patients with rheumatoid arthritis and spondyloarthropathies in clinical practice: Adverse events and other reasons leading to discontinuation of the treatment. Rheumatology International. 2008;28(3):261-9.
- 180. Lindgren P, Geborek P, Kobelt G. Modeling the cost-effectiveness of treatment of rheumatoid arthritis with rituximab using registry data from Southern Sweden. Int J Technol Assess Health Care. 2009 Apr;25(2):181-9.
- 181. Lindqvist E, Saxne T, Geborek P, Eberhardt K. Ten year outcome in a cohort of patients with early rheumatoid arthritis: health status, disease process, and damage. Ann Rheum Dis. 2002 Dec;61(12):1055-9.
- 182. Lisbona MP, Maymo J, Perich J, Almirall M, Carbonell J. Rapid reduction in tenosynovitis of the wrist and fingers evaluated by MRI in patients with rheumatoid arthritis after treatment with etanercept. *Ann Rheum Dis.* 2010/05/08 ed 2010:1117-22.
- 183. Lisbona MP, Maymo J, Perich J, Almirall M, Perez-Garcia C, Carbonell J. Etanercept reduces synovitis as measured by magnetic resonance imaging in patients with active rheumatoid arthritis after only 6 weeks. *J Rheumatol* 2008:394-7.
- 184. Luzi G, Lagana B, Salemi S, Di Rosa R. Are glucocorticoids a consistent risk factor for infections in rheumatoid arthritis patients under treatment with methotrexate and etanercept? Clin Ter. 2009 Mar-Apr;160(2):121-3.
- 185. Lyons JS, Severns ML. Detection of early hydroxychloroquine retinal toxicity enhanced by ring ratio analysis of multifocal electroretinography. Am J Ophthalmol. 2007 May;143(5):801-9.
- 186. Machado P, Santos A, Pereira C, Loureiro C, Silva J, Chieira C, et al. Increased prevalence of allergic sensitisation in rheumatoid arthritis patients treated with anti-TNFalpha. *Joint Bone Spine* 2009:508-13.

- 187. Maignen F, Hauben M, Tsintis P. Modelling the Time to Onset of Adverse Reactions with Parametric Survival Distributions A Potential Approach to Signal Detection and Evaluation. Drug Safety (New Zealand). 2010;33:417-34.
- 188. Malipeddi AS, Rajendran R, Kallarackal G. Disseminated tuberculosis after anti-TNFalpha treatment. Lancet. 2007 Jan 13;369(9556):162.
- 189. Mancarella L, Bobbio-Pallavicini F, Ceccarelli F, Falappone PC, Ferrante A, Malesci D, et al. Good clinical response, remission, and predictors of remission in rheumatoid arthritis patients treated with tumor necrosis factor-alpha blockers: the GISEA study. J Rheumatol. 2007 Aug;34(8):1670-3.
- 190. Marotte H, Arnaud B, Diasparra J, Zrioual S, Miossec P. Association between the level of circulating bioactive tumor necrosis factor alpha and the tumor necrosis factor alpha gene polymorphism at -308 in patients with rheumatoid arthritis treated with a tumor necrosis factor alpha inhibitor.

 Arthritis Rheum. 2008 May;58(5):1258-63.
- 191. Martin N, Innes JA, Lambert CM, Turnbull CM, Wallace WA. Hypersensitivity pneumonitis associated with leflunomide therapy. J Rheumatol. 2007 Sep;34(9):1934-7.
- 192. Mastroianni A, Minutilli E, Mussi A, Bordignon V, Trento E, D'Agosto G, et al. Cytokine profiles during infliximab monotherapy in psoriatic arthritis. Br J Dermatol. 2005 Sep;153(3):531-6.
- 193. Maxwell L, Singh Jasvinder A. Abatacept for rheumatoid arthritis. *Cochrane Database of Systematic Reviews*. Chichester, UK: John Wiley & Sons, Ltd 2009.
- 194. Mazzotta A, Esposito M, Costanzo A, Chimenti S. Efficacy and safety of etanercept in psoriasis after switching from other treatments: an observational study. Am J Clin Dermatol. 2009;10(5):319-24.
- 195. McCluggage LK, Scholtz JM. Golimumab: A Tumor Necrosis Factor Alpha Inhibitor for the Treatment of Rheumatoid Arthritis. Annals of Pharmacotherapy (USA). 2010;44:135-44.
- 196. McGonagle D, Tan AL, Madden J, Taylor L, Emery P. Rituximab use in everyday clinical practice as a first-line biologic therapy for the treatment of DMARD-resistant rheumatoid arthritis. Rheumatology (Oxford). 2008 Jun;47(6):865-7.

- 197. McLean-Tooke A, Aldridge C, Waugh S, Spickett GP, Kay L, Aug. Methotrexate, rheumatoid arthritis and infection riskwhat is the evidence. Rheumatology. 2009;48:867.
- 198. Mease PJ, Cohen S, Gaylis NB, Chubick A, Kaell AT, Greenwald M, et al. Efficacy and safety of retreatment in patients with rheumatoid arthritis with previous inadequate response to tumor necrosis factor inhibitors: results from the SUNRISE trial. *J Rheumatol*. 2010/03/03 ed 2010:917-27.
- 199. Mease PJ, Ory P, Sharp JT, Ritchlin CT, Van den Bosch F, Wellborne F, et al. Adalimumab for long-term treatment of psoriatic arthritis: 2-year data from the Adalimumab Effectiveness in Psoriatic Arthritis Trial (ADEPT). Ann Rheum Dis. 2009 May;68(5):702-9.
- 200. Mease PJ, Signorovitch J, Yu AP, Wu EQ, Gupta SR, Bao Y, et al. Impact of adalimumab on symptoms of psoriatic arthritis in patients with moderate to severe psoriasis: A pooled analysis of randomized clinical trials. Dermatology. 2010;220(1):1-7
- 201. Mittendorf T, Dietz B, Sterz R, Kupper H, Cifaldi MA, von der Schulenburg JM. Improvement and longterm maintenance of quality of life during treatment with adalimumab in severe rheumatoid arthritis. J Rheumatol. 2007 Dec;34(12):2343-50.
- 202. Montecucco C, Caporali R, Caprotti P, Caprotti M, Notario A. Sex hormones and bone metabolism in postmenopausal rheumatoid arthritis treated with two different glucocorticoids. J Rheumatol. 1992 Dec;19(12):1895-900.
- 203. Moreland LW, Alten R, Van den Bosch F, Appelboom T, Leon M, Emery P, et al. Costimulatory blockade in patients with rheumatoid arthritis: a pilot, dose-finding, double-blind, placebo-controlled clinical trial evaluating CTLA-4Ig and LEA29Y eighty-five days after the first infusion. Arthritis Rheum. 2002 Jun;46(6):1470-9.
- 204. Moreland LW, Cohen SB, Baumgartner SW, Tindall EA, Bulpitt K, Martin R, et al. Longterm safety and efficacy of etanercept in patients with rheumatoid arthritis. J Rheumatol. 2001 Jun;28(6):1238-44.
- 205. Moreland LW, Genovese MC, Sato R, Singh A. Effect of etanercept on fatigue in patients with recent or established rheumatoid arthritis. Arthritis Rheum. 2006 Apr 15;55(2):287-93.

- 206. Mori S. A relationship between pharmacokinetics (PK) and the efficacy of infliximab for patients with rheumatoid arthritis: characterization of infliximabresistant cases and PK-based modified therapy. Mod Rheumatol. 2007;17(2):83-91.
- 207. Mroczkowski PJ, Weinblatt ME, Kremer JM. Methotrexate and leflunomide combination therapy for patients with active rheumatoid arthritis. Clin Exp Rheumatol. 1999 Nov-Dec;17(6 Suppl 18):S66-8.
- 208. Nagasawa H, Kameda H, Sekiguchi N, Amano K, Takeuchi T. Normalisation of physical function by infliximab in patients with RA: factors associated with normal physical function. Clin Exp Rheumatol. 2010 May-Jun;28(3):365-72.
- 209. Nawata M, Saito K, Nakayamada S, Tanaka Y. Discontinuation of infliximab in rheumatoid arthritis patients in clinical remission. Mod Rheumatol. 2008;18(5):460-4.
- 210. Niewold TB, Gibofsky A. Concomitant interferon-alpha therapy and tumor necrosis factor alpha inhibition for rheumatoid arthritis and hepatitis C. Arthritis Rheum. 2006 Jul;54(7):2335-7.
- 211. Nishimoto N, Miyasaka N, Yamamoto K, Kawai S, Takeuchi T, Azuma J. Long-term safety and efficacy of tocilizumab, an anti-IL-6 receptor monoclonal antibody, in monotherapy, in patients with rheumatoid arthritis (the STREAM study): Evidence of safety and efficacy in a 5-year extension study. 2009.
- 212. Oei HB, Hooker RS, Cipher DJ, Reimold A. High rates of stopping or switching biological medications in veterans with rheumatoid arthritis. *Clin Exp Rheumatol*. 2010/02/13 ed 2009:926-34.
- 213. Oldfield V, Dhillon S, Plosker GL.
 Tocilizumab A Review of its Use in the
 Management of Rheumatoid Arthritis.
 Drugs. 2009;69:609-32.
- 214. Olivieri I, de Portu S, Salvarani C, Cauli A, Lubrano E, Spadaro A, et al. The psoriatic arthritis cost evaluation study: a cost-of-illness study on tumour necrosis factor inhibitors in psoriatic arthritis patients with inadequate response to conventional therapy. Rheumatology (Oxford). 2008 Nov;47(11):1664-70.
- 215. Ongaro A, De Mattei M, Pellati A, Caruso A, Ferretti S, Masieri FF, et al. Can tumor necrosis factor receptor II gene 676T>G polymorphism predict the response grading

- to anti-TNFalpha therapy in rheumatoid arthritis? Rheumatol Int. 2008 Jul:28(9):901-8.
- 216. Ostensen M, Forger F. Management of RA medications in pregnant patients. Nat Rev Rheumatol. 2009 Jul;5(7):382-90.
- 217. Panoulas VF, Douglas KM, Stavropoulos-Kalinoglou A, Metsios GS, Nightingale P, Kita MD, et al. Long-term exposure to medium-dose glucocorticoid therapy associates with hypertension in patients with rheumatoid arthritis. Rheumatology (Oxford). 2008 Jan:47(1):72-5.
- 218. Pavelka K, Jarosova K, Suchy D, Senolt L, Chroust K, Dusek L, et al. Increasing the infliximab dose in rheumatoid arthritis patients: A randomised, double blind study failed to confirm its efficacy. 2009.
- 219. Perera LC, Tymms KE, Wilson BJ, Shadbolt B, Brook AS, Dorai Raj AK, et al. Etanercept in severe active rheumatoid arthritis: first Australian experience. Intern Med J. 2006 Oct;36(10):625-31.
- 220. Pfeil A, Lippold J, Eidner T, Lehmann G, Oelzner P, Renz DM, et al. Effects of leflunomide and methotrexate in rheumatoid arthritis detected by digital X-ray radiogrammetry and computer-aided joint space analysis. Rheumatol Int. 2009 Jan;29(3):287-95.
- 221. Pisitkun P, Pattarowas C, Siriwongpairat P, Totemchokchyakarn K, Nantiruj K, Janwityanujit S. Reappraisal of cervical spine subluxation in Thai patients with rheumatoid arthritis. Clin Rheumatol. 2004 Feb;23(1):14-8.
- 222. Plushner SL. Tocilizumab: An Interleukin-6 Receptor Inhibitor for the Treatment of Rheumatoid Arthritis. Annals of Pharmacotherapy. 2008;42:1660-8.
- 223. Polinski JM, Mohr PE, Johnson L, Jun. Impact of Medicare Part D on Access to and Cost Sharing for Specialty Biologic Medications for Beneficiaries With Rheumatoid Arthritis. Arthritis and Rheumatism-Arthritis Care and Research. 2009:61:745.
- 224. Prochorec-Sobieszek M, Chelstowska M, Rymkiewicz G, Majewski M, Warzocha K, Maryniak R. Biclonal T-cell receptor gammadelta+ large granular lymphocyte leukemia associated with rheumatoid arthritis. Leukemia and Lymphoma. 2008;49(4):828-31.
- 225. Puolakka K, Kautiainen H, Mottonen T, Hannonen P, Korpela M, Hakala M, et al.

- Early Suppression of Disease Activity Is Essential for Maintenance of Work Capacity in Patients With Recent-Onset Rheumatoid Arthritis: Five-Year Experience From the Fin-Raco Trial. Arthritis and rheumatism. 2005;52(1):36-41.
- 226. Puolakka K, Kautiainen H, Mottonen T, Hannonen P, Korpela M, Hakala M, et al. Use of the Stanford Health Assessment Questionnaire in estimation of long-term productivity costs in patients with recentonset rheumatoid arthritis. Scandinavian Journal of Rheumatology. 2009;38(2):96-103.
- 227. Quartuccio L, Fabris M, Salvin S, Atzeni F, De Vita S, et al., et al. Rheumatoid factor positivity rather than anti-CCP positivity, a lower disability and a lower number of anti-TNF agents failed are associated with response to rituximab in rheumatoid arthritis. *Rheumatology* 2009:1557.
- 228. Quinn MA, Conaghan PG, O'Connor PJ.
 Very early treatment with infliximab in
 addition to methotrexate in early, poorprognosis rheumatoid arthritis reduces
 magnetic resonance imaging evidence of
 synovitis and damage, with sustained benefit
 after infliximab withdrawal: Results from a
 twelve-month ran-liver disease? Hepatology.
 2006;43:352-61.
- 229. Rahman MU, Strusberg I, Geusens P, Berman A, Yocum D, Baker D, et al. Double-blinded infliximab dose escalation in patients with rheumatoid arthritis. Ann Rheum Dis. 2007 Sep;66(9):1233-8.
- 230. Ranganathan P, McLeod HL. Methotrexate pharmacogenetics The first step toward individualized therapy in rheumatoid arthritis. Arthritis and Rheumatism (USA). 2006 05/01/;54(May):1366-77.
- 231. Rantalaiho V, Korpela M, Hannonen P, Kautiainen H, Jarvenpaa S, Leirisalo-Repo M, et al. The good initial response to therapy with a combination of traditional diseasemodifying antirheumatic drugs is sustained over time: the eleven-year results of the Finnish rheumatoid arthritis combination therapy trial. Arthritis Rheum. 2009 May;60(5):1222-31.
- 232. Rau R, Simianer S, van Riel PL, van de Putte LB, Kruger K, Schattenkirchner M, et al. Rapid alleviation of signs and symptoms of rheumatoid arthritis with intravenous or subcutaneous administration of adalimumab in combination with methotrexate. Scand J Rheumatol. 2004;33(3):145-53.

- 233. Reece RJ, Kraan MC, Radjenovic A, Veale DJ, O'Connor PJ, Ridgway JP, et al.
 Comparative Assessment of Leflunomide and Methotrexate for the Treatment of Rheumatoid Arthritis, by Dynamic Enhanced Magnetic Resonance Imaging.
 Arthritis and rheumatism. 2002;46(2):366-72
- 234. Richards BL, Spies J, McGill N, Richards GW, Vaile J, Bleasel JF, et al. Effect of leflunomide on the peripheral nerves in rheumatoid arthritis. Intern Med J. 2007 Feb;37(2):101-7.
- 235. Rozenbaum M, Boulman N, Slobodin G, Ayubkhanov E, Rosner I. Polyarthritis flare complicating rheumatoid arthritis infliximab therapy: a paradoxic adverse reaction. J Clin Rheumatol. 2006 Dec;12(6):269-71.
- 236. Rubbert-Roth A, Tak PP, Zerbini C,
 Tremblay JL, Carreno L, Armstrong G, et al.
 Efficacy and safety of various repeat
 treatment dosing regimens of rituximab in
 patients with active rheumatoid arthritis:
 Results of a Phase III randomized study
 (MIRROR). Rheumatology.
 2010;49(9):1683-93.
- 237. Rudwaleit M, Van den Bosch F, Kron M, Kary S, Kupper H. Effectiveness and safety of adalimumab in patients with ankylosing spondylitis or psoriatic arthritis and history of anti-tumor necrosis factor therapy. Arthritis Res Ther. 2010;12(3):R117.
- 238. Saag KG, Gim GT, Patkar NM, Anuntiyo J, Finney C, Curtis JR, et al. American College of Rheumatology 2008 recommendations for the use of nonbiologic and biologic disease-modifying antirheumatic drugs in rheumatoid arthritis. Arthritis Care and Research. 2008;59(6):762-84.
- 239. Saleem B, Brown AK, Keen H, Nizam S, Freeston J, Karim Z, et al. Disease remission state in patients treated with the combination of tumor necrosis factor blockade and methotrexate or with disease-modifying antirheumatic drugs: A clinical and imaging comparative study. *Arthritis Rheum* 2009:1915-22.
- 240. Salvarani C, Cantini F, Olivieri I, Macchioni P, Padula A, Niccoli L, et al. Efficacy of infliximab in resistant psoriatic arthritis. Arthritis Rheum. 2003 Aug 15;49(4):541-5.
- 241. Sanchez G, Castro JS, Snih SA, Blanco LP, Esteva MH, Macgregor EG, et al. Durability of treatment with methotrexate in Venezuelan patients with rheumatoid

- arthritis. Rheumatol Int. 2007 Apr;27(6):531-6.
- 242. Saunders SA, Capell HA, Stirling A, Vallance R, Kincaid W, McMahon AD, et al. Triple therapy in early active rheumatoid arthritis: a randomized, single-blind, controlled trial comparing step-up and parallel treatment strategies. *Arthritis Rheum* 2008:1310-7.
- 243. Scali JJ, Visentini S, Salomon J, Sevilla D, Ju YC, Morales E, et al. Rapid and deep control of inflammation in rheumatoid arthritis with infliximab and its correlation with acute-phase reactants. Ann N Y Acad Sci. 2007 Sep;1110:389-401.
- 244. Schiff M, Pritchard C, Huffstutter JE, Rodriguez Valverde V, Durez P, Zhou X, et al. The 6-month safety and efficacy of abatacept in patients with rheumatoid arthritis who underwent a washout after antitumour necrosis factor therapy or were directly switched to abatacept: the ARRIVE trial. Annals of the rheumatic diseases. 2009;68(11):1708-14.
- 245. Schiff MH, Yu EB, Weinblatt ME, Moreland LW, Woolley JM, et al. Long-term experience with etanercept in the treatment of rheumatoid arthritis in elderly and younger patients Patient-reported outcomes from multiple controlled and open-label extension studies. Drugs and Aging (New Zealand). 2006 02/01/;23(Feb):167-78.
- 246. Schnabel A, Herlyn K, Burchardi C, Reinhold Keller E, Gross WL. Long-Term Tolerability of Methotrexate at Doses Exceeding 15 Mg Per Week in Rheumatoid Arthritis. Rheumatology international. 1996;15(5):195-200.
- 247. Schnabel A, Reinhold Keller E, Willmann V, Gross W. Tolerability of Methotrexate Starting With 15 or 25 Mg/Week for Rheumatoid Arthritis. Rheumatology international. 1994;14(1):33-8.
- 248. Scrivo R, Conti F, Spinelli FR, Truglia S, Magrini L, Di Franco M, et al. Switching between TNFalpha antagonists in rheumatoid arthritis: personal experience and review of the literature. Reumatismo. 2009 Apr-Jun;61(2):107-17.
- 249. Shashikumar NS, Shivamurthy MC, Chandrashekara S. Evaluation of efficacy of combination of methotrexate and hydroxychloroquine with leflunomide in active rheumatoid arthritis. *Indian Journal of Pharmacology* 2010:358-61.

- 250. Shedd AD, Reddy SG, Meffert JJ, Kraus EW, Usatine RP. Acute onset of rash and oligoarthritis. J Fam Pract. 2007 Oct;56(10):811-4.
- 251. Shergy WJ, Isern RA, Cooley DA,
 Harshbarger JL, Huffstutter JE, Hughes GM,
 et al. Open label study to assess infliximab
 safety and timing of onset of clinical benefit
 among patients with rheumatoid arthritis. J
 Rheumatol. 2002 Apr;29(4):667-77.
- 252. Sheth NU, Hilas O, Charneski L. Abatacept: A novel agent for rheumatoid arthritis. Journal of Pharmacy Technology (USA). 2006 06/01/;22(Jun):336-41.
- 253. Singh Jasvinder A, Christensen R, Wells George A, Suarez-Almazor Maria E, Buchbinder R, Lopez-Olivo Maria A, et al. Biologics for rheumatoid arthritis: an overview of Cochrane reviews. Cochrane Database of Systematic Reviews. 2009(2).
- 254. Sinha A, Patient C. Rheumatoid arthritis in pregnancy: successful outcome with anti-TNF agent (Etanercept). J Obstet Gynaecol. 2006 Oct;26(7):689-91.
- 255. Sinigaglia L, Nervetti A, Mela Q, Bianchi G, Del Puente A, Di Munno O, et al. A multicenter cross sectional study on bone mineral density in rheumatoid arthritis. Italian Study Group on Bone Mass in Rheumatoid Arthritis. J Rheumatol. 2000 Nov;27(11):2582-9.
- 256. Smith N, Ding T, Butt S, Gadsby K,
 Deighton C. The importance of the baseline
 Disease Activity Score 28 in determining
 responders and non-responders to anti-TNF
 in UK clinical practice. Rheumatology
 (Oxford). 2008 Sep;47(9):1389-91.
- 257. Smolen JS, Han C, Bala M, Maini RN, Grp AS, et al. Evidence of radiographic benefit of treatment with infliximab plus methotrexate in rheumatoid arthritis patients who had no clinical improvement A detailed subanalysis of data from the antitumor necrosis factor trial in rheumatoid arthritis with concomitant therapy study. Arthritis and Rheumatism (USA). 2005 04/01/;52(Apr):1020-30.
- 258. Smolen JS, van der Heijde DM, St Clair EW, Emery P, Grp AS, et al. Predictors of joint damage in patients with early rheumatoid arthritis treated with high-dose methotrexate with or without concomitant infliximab Results from the ASPIRE trial. Arthritis and Rheumatism (USA). 2006 03/01/;54(Mar):702-10.

- 259. Soubrier M, Puechal X, Sibilia J, Mariette X, Dougados M, et al., et al. Evaluation of two strategies (initial methotrexate monotherapy <it>vs</it> its combination with adalimumab) in management of early active rheumatoid arthritis: data from the GUEPARD trial. Rheumatology. 2009;48:1429.
- 260. Soubrier M, Puechal X, Sibilia J, Mariette X, Meyer O, Combe B, et al. Evaluation of two strategies (initial methotrexate monotherapy vs its combination with adalimumab) in management of early active rheumatoid arthritis: data from the GUEPARD trial. Rheumatology (Oxford). 2009 Nov;48(11):1429-34.
- 261. Spalding JR, Hay J. Cost effectiveness of tumour necrosis factor-alpha inhibitors as first-line agents in rheumatoid arthritis. Pharmacoeconomics. 2006;24(12):1221-32.
- 262. St Clair EW, Wagner CL, Fasanmade AA, Wang B, Schaible T, Kavanaugh A, et al. The Relationship of Serum Infliximab Concentrations to Clinical Improvement in Rheumatoid Arthritis: Results From Attract, a Multicenter, Randomized, Double-Blind, Placebo-Controlled Trial. Arthritis and rheumatism. 2002;46(6):1451-9.
- 263. Stern R, Wolfe F. Infliximab dose and clinical status: results of 2 studies in 1642 patients with rheumatoid arthritis. J Rheumatol. 2004 Aug;31(8):1538-45.
- 264. Sterry W, Ortonne JP, Kirkham B, Brocq O, Robertson D, Pedersen RD, et al. Comparison of two etanercept regimens for treatment of psoriasis and psoriatic arthritis: PRESTA randomised double blind multicentre trial. Bmj. 2010;340:c147.
- 265. Suarez-Almazor Maria E, Belseck E, Shea B, Tugwell P, Wells George A. Sulfasalazine for treating rheumatoid arthritis. Cochrane Database of Systematic Reviews. 1998(2).
- 266. Suwannalai P, Auethavekiat P, Udomsubpayakul U, Janvitayanujit S. The infectious profiles of anti-tumor necrosis factor agents in a Thai population: a retrospective study a the university-based hospital. *Int J Rheum Dis.* 2010/04/09 ed 2009:118-24.
- 267. Taiwo B, Lee C, Venkat D, Tambar S, Sutton SH. Can tumor necrosis factor alpha blockade predispose to severe babesiosis? Arthritis Rheum. 2007 Feb 15;57(1):179-81.
- 268. Takeuchi T, Miyasaka N, Inoue K, Abe T, Koike T. Impact of trough serum level on

- radiographic and clinical response to infliximab plus methotrexate in patients with rheumatoid arthritis: results from the RISING study. *Mod Rheumatol* 2009:478-87.
- 269. Takeuchi T, Tatsuki Y, Nogami Y, Ishiguro N, Tanaka Y, Yamanaka H, et al. Postmarketing surveillance of the safety profile of infliximab in 5000 Japanese patients with rheumatoid arthritis. Ann Rheum Dis. 2008 Feb;67(2):189-94.
- 270. Takeuchi T, Yamanaka H, Inoue E, Nagasawa H, Nawata M, Ikari K, et al. Retrospective clinical study on the notable efficacy and related factors of infliximab therapy in a rheumatoid arthritis management group in Japan: one-year outcome of joint destruction (RECONFIRM-2J). Mod Rheumatol. 2008;18(5):447-54.
- 271. Tam LS, Griffith JF, Yu AB, Li TK, Li EK. Rapid improvement in rheumatoid arthritis patients on combination of methotrexate and infliximab: clinical and magnetic resonance imaging evaluation. Clin Rheumatol. 2007 Jun;26(6):941-6.
- 272. Tanaka Y, Takeuchi T, Inoue E, Saito K, Sekiguchi N, Sato E, et al. Retrospective clinical study on the notable efficacy and related factors of infliximab therapy in a rheumatoid arthritis management group in Japan: one-year clinical outcomes (RECONFIRM-2). Mod Rheumatol. 2008;18(2):146-52.
- 273. Taniguchi A, Urano W, Tanaka E, Furihata S, Kamitsuji S, Inoue E, et al. Validation of the associations between single nucleotide polymorphisms or haplotypes and responses to disease-modifying antirheumatic drugs in patients with rheumatoid arthritis: a proposal for prospective pharmacogenomic study in clinical practice. Pharmacogenet Genomics. 2007 Jun;17(6):383-90.
- 274. Taylor P, Steuer A, Gruber J, McClinton C, Cosgrove D, Blomley M, et al. Ultrasonographic and radiographic results from a two-year controlled trial of immediate or one-year-delayed addition of infliximab to ongoing methotrexate therapy in patients with erosive early rheumatoid arthritis. Arthritis and rheumatism. 2006 2006;54(1):47-53.
- 275. Taylor PC, Steuer A, Gruber J, McClinton C, Maini RN, et al. Ultrasonographic and radiographic results from a two-year controlled trial of immediate or one-year-

- delayed addition of infliximab to ongoing methotrexate therapy in patients with erosive early rheumatoid arthritis. Arthritis and Rheumatism (USA). 2006 01/01/;54(Jan):47-53.
- 276. Theodoridou A, Kartsios C, Yiannaki E, Markala D, Settas L. Reversible T-large granular lymphocyte expansion and neutropenia associated with adalimumab therapy. Rheumatol Int. 2006 Dec;27(2):201-2.
- 277. Thurlings RM, Vos K, Gerlag DM, Tak PP. Disease activity-guided rituximab therapy in rheumatoid arthritis: the effects of retreatment in initial nonresponders versus initial responders. Arthritis Rheum. 2008 Dec;58(12):3657-64.
- 278. Torii H, Nakagawa H. Infliximab monotherapy in Japanese patients with moderate-to-severe plaque psoriasis and psoriatic arthritis. A randomized, double-blind, placebo-controlled multicenter trial. J Dermatol Sci. 2010 Jul;59(1):40-9.
- 279. Torikai E, Kageyama Y, Suzuki M, Ichikawa T, Nagano A. The effect of infliximab on chemokines in patients with rheumatoid arthritis. Clin Rheumatol. 2007 Jul;26(7):1088-93.
- 280. Torrance GW, Tugwell P, Amorosi S, Chartash E, Sengupta N. Improvement in health utility among patients with rheumatoid arthritis treated with adalimumab (a human anti-TNF monoclonal antibody) plus methotrexate. Rheumatology (Oxford). 2004 Jun;43(6):712-8.
- 281. Tubach F, Ravaud P, Salmon-Ceron D, Petitpain N, Grp R, et al. Emergence of <it>Legionella pneumophila</it> pneumonia in patients receiving tumor necrosis factor-alpha antagonist. Clinical Infectious Diseases. 2006 10/01/:43(Oct):E95-100.
- 282. Tubach F, Salmon D, Ravaud P, Allanore Y, Goupille P, Breban M, et al. Risk of tuberculosis is higher with anti-tumor necrosis factor monoclonal antibody therapy than with soluble tumor necrosis factor receptor therapy: The three-year prospective French Research Axed on Tolerance of Biotherapies registry. Arthritis Rheum. 2009 Jul;60(7):1884-94.
- 283. Tutuncu Z, Kavanaugh A. Treatment of elderly rheumatoid arthritis. Future Rheumatology. 2007;2(3):313-9.
- 284. van den Hout WB, Goekoop-Ruiterman YP, Allaart CF, de Vries-Bouwstra JK, Hazes

- JM, Kerstens PJ, et al. Cost-utility analysis of treatment strategies in patients with recent-onset rheumatoid arthritis. Arthritis Rheum. 2009 Mar 15;61(3):291-9.
- 285. Van Der Heijde D, Breedveld FC, Kavanaugh A, Keystone EC, Landewe R, Patra K, et al. Disease activity, physical function, and radiographic progression after longterm therapy with adalimumab plus methotrexate: 5-Year results of PREMIER. Journal of Rheumatology. 2010;37(11):2237-46.
- 286. van der Heijde D, Burmester G, Melo Gomes J, Codreanu C, Martin Mola E, Pedersen R, et al. Inhibition of radiographic progression with combination etanercept and methotrexate in patients with moderately active rheumatoid arthritis previously treated with monotherapy. *Annals of the rheumatic diseases* 2009:1113-8.
- 287. van der Heijde D, Burmester G, Melo-Gomes J, Codreanu C, Mola EM, Pedersen R, et al. The safety and efficacy of adding etanercept to methotrexate or methotrexate to etanercept in moderately active rheumatoid arthritis patients previously treated with monotherapy. Ann Rheum Dis. 2008 Feb:67(2):182-8.
- van der Kooij SM, de Vries-Bouwstra JK, Goekoop-Ruiterman YP, van Zeben D, Kerstens PJ, Gerards AH, et al. Limited efficacy of conventional DMARDs after initial methotrexate failure in patients with recent onset rheumatoid arthritis treated according to the disease activity score. Ann Rheum Dis. 2007 Oct;66(10):1356-62.
- 289. van der Kooij SM, le Cessie S, Goekoop-Ruiterman YP, de Vries-Bouwstra JK, van Zeben D, Kerstens PJ, et al. Clinical and radiological efficacy of initial vs delayed treatment with infliximab plus methotrexate in patients with early rheumatoid arthritis. Ann Rheum Dis. 2009 Jul;68(7):1153-8.
- 290. van der Veen MJ, Bijlsma JW. The effect of methylprednisolone pulse therapy on methotrexate treatment of rheumatoid arthritis. Clin Rheumatol. 1993 Dec;12(4):500-5.
- 291. Van Kuijk AWR, Gerlag DM, Vos K, Wolbink G, De Groot M, De Rie MA, et al. A prospective, randomised, placebocontrolled study to identify biomarkers associated with active treatment in psoriatic arthritis: Effects of adalimumab treatment on synovial tissue. 2009.

- 292. van Staa TP, Geusens P, Bijlsma JW, Leufkens HG, Cooper C. Clinical assessment of the long-term risk of fracture in patients with rheumatoid arthritis. Arthritis Rheum. 2006 Oct;54(10):3104-12.
- 293. van Tuyl LH, Boers M, Lems WF, Landewé RB, Han H, van der Linden S, et al. Survival, comorbidities and joint damage 11 years after the COBRA combination therapy trial in early rheumatoid arthritis. Annals of the rheumatic diseases. 2010(5):807-12.
- 294. van Vollenhoven RF, Emery P, Bingham CO, 3rd, Keystone EC, Fleischmann R, Furst DE, et al. Longterm safety of patients receiving rituximab in rheumatoid arthritis clinical trials. *J Rheumatol*. 2010/01/30 ed 2010:558-67.
- 295. van Vollenhoven RF, Ernestam S, Harju A, Bratt J, Klareskog L. Etanercept versus etanercept plus methotrexate: a registry-based study suggesting that the combination is clinically more efficacious. Arthritis Res Ther. 2003;5(6):R347-51.
- 296. Vander Cruyssen B, Durez P, Westhovens R, De Keyser F. Seven-year follow-up of infliximab therapy in rheumatoid arthritis patients with severe long-standing refractory disease: attrition rate and evolution of disease activity. Arthritis Res Ther. 2010;12(3):R77.
- 297. Vera-Llonch M, Massarotti E, Wolfe F, Shadick N, Westhovens R, Sofrygin O, et al. Cost-effectiveness of abatacept in patients with moderately to severely active rheumatoid arthritis and inadequate response to methotrexate. Rheumatology (Oxford). 2008 Apr;47(4):535-41.
- 298. Verschueren P, Esselens G, Westhovens R. Daily practice effectiveness of a step-down treatment in comparison with a tight step-up for early rheumatoid arthritis. Rheumatology (Oxford). 2008 Jan;47(1):59-64.
- 299. Verstappen S, Jacobs J, Bijlsma JW. The Utrecht Experience With Different Treatment Strategies in Early Rheumatoid Arthritis. Clinical and experimental rheumatology. 2003;21(5 Suppl 31):S165-8.
- 300. Verstappen SM, Jacobs JW, van der Veen MJ, Heurkens AH, Schenk Y, ter Borg EJ, et al. Intensive treatment with methotrexate in early rheumatoid arthritis: aiming for remission. Computer Assisted Management in Early Rheumatoid Arthritis (CAMERA, an open-label strategy trial). Ann Rheum Dis. 2007 Nov;66(11):1443-9.

- 301. Visser K, Goekoop-Ruiterman YP, de Vries-Bouwstra JK, Ronday HK, Seys PE, Kerstens PJ, et al. A matrix risk model for the prediction of rapid radiographic progression in patients with rheumatoid arthritis receiving different dynamic treatment strategies: post hoc analyses from the BeSt study. Ann Rheum Dis. 2010 Jul;69(7):1333-7.
- 302. Visser K, Katchamart W, Loza E, Martinez-Lopez JA, Salliot C, Trudeau J, et al. Multinational evidence-based recommendations for the use of methotrexate in rheumatic disorders with a focus on rheumatoid arthritis: Integrating systematic literature research and expert opinion of a broad international panel of rheumatologists in the 3E Initiative. Annals of the rheumatic diseases. 2009;68(7):1086-93.
- 303. Vlak T, Eldar R. Disability in Rheumatoid Arthritis After Monotherapy With Dmards. International Journal Rehabilitation Research. 2003;26(3):207-12.
- 304. Voulgari PV, Markatseli TE, Exarchou SA, Zioga A, Drosos AA. Granuloma annulare induced by anti-tumour necrosis factor therapy. Ann Rheum Dis. 2008 Apr;67(4):567-70.
- 305. Wakabayashi H, Sudo A, Hasegawa M, Oka H, Uchida A, Nishioka K. Retrospective clinical study of the efficacy of lower-dose methotrexate and infliximab therapy in patients with rheumatoid arthritis. *Clin Rheumatol*. 2010/03/06 ed 2010:671-5.
- 306. Wakefield RJ, Freeston JE, Hensor EM, Bryer D, Quinn MA, Emery P. Delay in imaging versus clinical response: a rationale for prolonged treatment with anti-tumor necrosis factor medication in early rheumatoid arthritis. Arthritis Rheum. 2007 Dec 15;57(8):1564-7.
- 307. Wasko MC, Hubert HB, Lingala VB, Elliott JR, Luggen ME, Fries JF, et al. Hydroxychloroquine and risk of diabetes in patients with rheumatoid arthritis. Jama. 2007 Jul 11;298(2):187-93.
- 308. Weinblatt ME, Bathon JM, Kremer JM, Fleischmann RM, Schiff MH, Martin RW, et al. Safety and efficacy of etanercept beyond 10 years of therapy in North American patients with early and long-standing rheumatoid arthritis. *Arthritis Care Res (Hoboken)* 2010.
- 309. Weinblatt ME, Kremer JM, Coblyn JS, Maier AL, Helfgott SM, Morrell M, et al.

- Pharmacokinetics, safety, and efficacy of combination treatment with methotrexate and leflunomide in patients with active rheumatoid arthritis. Arthritis Rheum. 1999 Jul;42(7):1322-8.
- 310. Weinblatt ME, Schiff MH, Ruderman EM, Bingham CO, 3rd, Li J, Louie J, et al. Efficacy and safety of etanercept 50 mg twice a week in patients with rheumatoid arthritis who had a suboptimal response to etanercept 50 mg once a week: results of a multicenter, randomized, double-blind, active drug-controlled study. Arthritis Rheum. 2008 Jul;58(7):1921-30.
- 311. Weinblatt ME, Weissman BN, Holdsworth DE, Fraser PA, Maier AL, Falchuk KR, et al. Long-Term Prospective Study of Methotrexate in the Treatment of Rheumatoid Arthritis. 84-Month Update. Arthritis and rheumatism. 1992;35(2):129-37.
- 312. Weisman MH, Moreland LW, Furst DE, Weinblatt ME, Keystone EC, Paulus HE, et al. Efficacy, pharmacokinetic, and safety assessment of adalimumab, a fully human anti-tumor necrosis factor-alpha monoclonal antibody, in adults with rheumatoid arthritis receiving concomitant methotrexate: a pilot study. Clin Ther. 2003 Jun;25(6):1700-21.
- 313. Wells G, Becker JC, Teng J, Dougados M, Schiff M, Smolen J, et al. Validation of the 28-joint Disease Activity Score (DAS28) and European League Against Rheumatism response criteria based on C-reactive protein against disease progression in patients with rheumatoid arthritis, and comparison with the DAS28 based on erythrocyte sedimentation rate. Ann Rheum Dis. 2009 Jun:68(6):954-60.
- 314. Westhovens R, Cole JC, Li T, Martin M, Maclean R, Lin P, et al. Improved health-related quality of life for rheumatoid arthritis patients treated with abatacept who have inadequate response to anti-TNF therapy in a double-blind, placebo-controlled, multicentre randomized clinical trial. Rheumatology (Oxford). 2006 Oct;45(10):1238-46.
- 315. Westhovens R, Houssiau F, Joly J, Everitt DE, Zhu Y, Sisco D, et al. A phase I study assessing the safety, clinical response, and pharmacokinetics of an experimental infliximab formulation for subcutaneous or intramuscular administration in patients with rheumatoid arthritis. J Rheumatol. 2006 May;33(5):847-53.

- 316. Westhovens R, Kremer JM, Moreland LW, Emery P, Russell AS, Li T, et al. Safety and efficacy of the selective costimulation modulator abatacept in patients with rheumatoid arthritis receiving background methotrexate: a 5-year extended phase IIB study. The Journal of rheumatology. 2009;36(4):736-42.
- 317. Westlake SL, Colebatch AN, Baird J, Kiely P, Edwards CJ, et al. The effect of methotrexate on cardiovascular disease in patients with rheumatoid arthritis: a systematic literature review. Rheumatology (Oxford). 2010;49:295.
- 318. White DH, Chapman PT, O'Donnell JL, James J, Stamp LK, et al. Lack of association between elevated mean red cell volume and haematological toxicity in patients receiving long-term methotrexate for rheumatoid arthritis. Internal Medicine Journal. 2010;40:561-5.
- 319. Wislowska M, Jakubicz D. Preliminary evaluation in rheumatoid arthritis activity in patients treated with TNF-alpha blocker plus methotrexate versus methotrexate or leflunomide alone. Rheumatol Int. 2007 May;27(7):641-7.
- 320. Wollina U, Hansel G, Koch A, Schonlebe J, Kostler E, Haroske G. Tumor necrosis factor-alpha inhibitor-induced psoriasis or psoriasiform exanthemata: first 120 cases from the literature including a series of six new patients. Am J Clin Dermatol. 2008;9(1):1-14.
- 321. Yazici Y, Erkan D, Kulman I, Belostocki K, Harrison MJ. Decreased flares of rheumatoid arthritis during the first year of etanercept treatment: further evidence of clinical effectiveness in the "real world". Ann Rheum Dis. 2002 Jul;61(7):638-40.
- 322. Yelin E, Trupin L, Katz P, Lubeck D, Rush S, Wanke L. Association between etanercept use and employment outcomes among patients with rheumatoid arthritis. Arthritis Rheum. 2003 Nov;48(11):3046-54.
- 323. Yount S, Sorensen MV, Cella D, Sengupta N, Grober J, Chartash EK. Adalimumab plus methotrexate or standard therapy is more effective than methotrexate or standard therapies alone in the treatment of fatigue in patients with active, inadequately treated rheumatoid arthritis. Clin Exp Rheumatol. 2007 Nov-Dec;25(6):838-46.
- 324. Yuan Y, Trivedi D, Maclean R, Rosenblatt L. Indirect cost-effectiveness analyses of abatacept and rituximab in patients with

- moderate-to-severe rheumatoid arthritis in the United States. *Journal of Medical Economics (England)* 2010:33-41.
- 325. Yun JE, Lee SW, Kim TH, Jun JB, Jung S, Bae SC, et al. The incidence and clinical characteristics of Mycobacterium tuberculosis infection among systemic lupus erythematosus and rheumatoid arthritis

Unable to Obtain Full Text

1. van der Veen M, Bijlsma J. The Effect of Methylprednisolone Pulse Therapy on Methotrexate Treatment of Rheumatoid

- patients in Korea. Clin Exp Rheumatol. 2002 Mar-Apr;20(2):127-32.
- 326. Zhang W, Bansback N, Guh D, Li X, Nosyk B, Marra CA, et al. Short-term influence of adalimumab on work productivity outcomes in patients with rheumatoid arthritis. J Rheumatol. 2008 Sep;35(9):1729-36.

Arthritis. Clinical rheumatology. 1993;12(4):74-6.

Appendix E. Evidence Tables

Index of Studies by Key Question

KQ1

RCTs and other studies found in Evidence Table 1

Allaart, 2006 – found under Goekoop-Ruiterman, 2005

Bathon, 2000

Boers, 1997

Breedveld, 2006

Capell, 2006

Choy, 2008

Cohen, 2001 – found under Strand 1999

Cohen, 2006

Combe, 2006

Dougados, 1999

Emery, 2000

Emery, 2006

Emery, 2008

Emery, 2008

Emery, 2009

Emery, 2010

Emery, 2010

Fernandez-Nebro, 2007

Finckh, 2007

Finckh, 2009

Fleischmann, 2009

Furst, 2003

Geborek, 2002

Genovese, 2002 – found under Bathon 2000

Genovese, 2004

Genovese, 2005 – found under Bathon 2000

Genovese, 2008

Goekoop-Ruiterman, 2005

Goekoop-Ruiterman, 2007 – found under Goekoop-Ruiterman 2005

Haagsma, 1997

Hetland, 2010

Hoff, 2009

Hyrich, 2006

Hyrich, 2006 [Change ET to say 2006] in 2003 file

Karanikola, 2008

Kavanaugh, 2008 – found under Klareskog 2004

Kay, 2008

Keystone, 2008

Keystone, 2008 – found under Cohen 2006

Keystone, 2009

Keystone, 2009 – found under Cohen 2006

Keystone, 2010

Kievit, 2008

Kim, 2007

Kirwan, 2004

Klareskog, 2004

Korpela, 2004 – found under Mottonen 1999

Kremer, 2006

Kremer, 2010

kristensen, 2006

Kristensen, 2007

Larsen, 2001 – found under Smolen 1999

Lee, 2008

Listing, 2006

Maillefert, 2003 – found under Dougados 1999

Maini, 2006

Miyasaka, 2008

Mottonen, 1999

Mottonen, 2002 – found under Mottonen 1999

Nishimoto, 2009

O'Dell, 1996

O'Dell, 2002

Osiri, 2002

Schiff, 2008

Schipper, 2009

Sharp, 2000 – found under Smolen 1999

Smolen, 1999

Smolen, 1999

Smolen, 2005 – found under Breedveld 2004

Smolen, 2006 - found under St. Clair 2004

Smolen, 2008

Smolen, 2009

Smolen, 2009

St. Clair, 2004

Strand, 1999

Svensson, 2005

van der Heijde, 2005 – found under Klareskog 2004

van der Heijde, 20062005 – found under Klareskog 2004

van der Heijde, 20062005 – found under Klareskog 2004

van der Kooij, 2008

van der Kooij, 2009 – found under Goekoop-Ruiterman 2005

van der Kooij, 2009 – found under Goekoop-Ruiterman 2005

van Riel, 2006

van Vollenhoven, 2009

Weaver, 2006

Weinblatt, 1999

Weinblatt, 2007

Westhovens, 2006

Westhovens, 2009

Zhang, 2006

Zink, 2005

Systematic Reviews and Meta-analyses found in Evidence Table 2

Alonso-Ruiz, 2008

Bergman, 2010

Clark, 2004

Devine, 2011

Gartlehner, 2006

Gaujoux-Viala, 2010

Hochberg, 2003

Kirwan, 2009

Kuriya, 2010

Nam, 2010

Osiri, 2002/9

Singh, 2009

Singh, 2009

Singh, 2010

Singh, 2010

Wailoo, 2006

Wiens, 2010

Does not have Schipper

KQ2

RCTs and other studies found in Evidence Table 1

Allaart, 2006 – found under Goekoop-Ruiterman 2005

Bathon, 2000

Boers, 1997

Breedveld, 2006

Capell, 2006

Choy, 2008

Cohen, 2001 – found under Strand 1999

Combe, 2006

Combe, 2009

Dougados, 1999

Emery, 2000

Emery, 2006

Emery, 2006

Emery, 2008

Emery, 2008

Emery, 2009

Emery, 2010

Fernandez-Nebro, 2007

Finckh, 2009

Genovese, 2002 – found under Bathon 2000

Genovese, 2005 – found under Bathon 2000

Goekoop-Ruiterman, 2005

Goekoop-Ruiterman, 2007 – found under Goekoop-Ruiterman 2005

Haagsma, 1997

Hassett, 2008

Kekow, 2010

Keystone, 2008 – found under Cohen 2006

Kievit, 2008

Kirwan, 2004

Klareskog, 2004

Korpela, 2004 – found under Mottonen 1999

Kosinski, 2002 – found under Bathon 2000

Kremer, 2010

Landewe, 2002 – found under Boers 1997

Li, 2008

Listing, 2006

Maillefert, 2003 – found under Dougados 1999

Mease, 2008

Mottonen, 1999

Nishimoto, 2009

Osiri, 2002

Puolakka, 1487 – found under Mottonen 1999

Schiff, 2008

Scott, 2000 - found under Smolen 1999

Smolen, 1999

Smolen, 2005 - found under Breedveld 1004

Smolen, 2006 - found under St. Clair 2004

St. Clair, 2004

Strand, 1999

Svensson, 2005

van der Heijde, 2005 – found under Klareskog 2004

van der Heijde, 2006 – found under Klareskog 2004

van der Heijde, 2006 – found under Klareskog 2004

van der Kooij, 2009 – found under Goekoop-Ruiterman 2005

van der Kooij, 2009 – found under Goekoop-Ruiterman 2005

van Riel, 2008

Weaver, 2006

Weinblatt, 2007

Wells, 2008 - found under Westhovens 2006

Westhovens, 2006

Westhovens, 2009

Systematic Reviews and Meta-analyses found in Evidence Table 2

Gaujoux-Viala, 2010

Mertens, 2009

Osiri, 2002/9

Singh, 2010

Singh, 2010

KQ3

RCTs and other studies found in Evidence Table 1

Allaart, 2006 – found under Goekoop-Ruiterman 2005

Askling, 2005

Askling, 2005

Askling, 2005

Askling, 2009

Baecklund, 2006

Bathon, 2000

Bergstrom, 2004

Bernatsky, 2007

Boers, 1997

Brassard, 2006

Brassard, 2009

Breedveld, 2006

Brown, 2002

Burmester

Cannon, 2004

Capell, 2006

Chakravarty, 2005

Choy, 2008

Chung, 2003

Cohen, 2001 - found under Strand 1999

Cohen, 2006

Combe, 2006

Combe, 2009

Curtis, 2007

Curtis, 2007

Curtis, 2007

DeBandt, 2005

den Broeder, 2007

Dixon, 2006

Dixon, 2007

Dixon, 2010

Doran, 2002

Dougados, 1999

Duclos, 2006

Edwards, 2007

Emery, 2000

Emery, 2006

Emery, 2008

Emery, 2008

Emery, 2009

Line: y, 2003

Emery, 2010

Emery, 2010

Feltelius, 2005 Fernandez-Nebro, 2007

Fleischmann, 2003

Fleischmann, 2006 – found under Fleischmann 2003

Fleischmann, 2009

Flendrie, 2003

Flendrie, 2005

Fuerst, 2006

Furst, 2003

Galloway, 2011

Geborek, 2002

Geborek, 2005

Genovese, 2002 – found under Bathon 2000

Genovese, 2004

Genovese, 2005 – found under Bathon 2000

Genovese, 2008

Goekoop-Ruiterman, 2005

Goekoop-Ruiterman, 2007 – found under Goekoop-Ruiterman 2005

Gomez-Reino, 2003

Greenberg, 2010

Grijalva, 2007

Grijalva, 2010

Haagsma, 1997

Harley, 2003

Harrison, 2009

Hetland, 2010

Hjardem, 2007

Hyrich, 2006 [Change ET to say 2006] in 2003 file

Hyrich, 2007

Jacobsson, 2005

Karanikola, 2008

Karstila, 2010

Kawakami, 2010

Kay, 2008

Keane, 2001

Keystone, 2008

Keystone, 2009

Kim, 2007

Kirwan, 2004

Klareskog, 2004

Korpela, 2004 – found under Mottonen 1999

Kremer, 2002

Kremer, 2006

Kremer, 2010

kristensen, 2006

kristensen, 2006

Kwon, 2003

Lacaille, 2008

Langer, 2003

Lebwohl, 2005

Lee, 2002

Lee, 2008

Li, 2010

Listing, 2005

Listing, 2008

Maini, 2004 - found under Breedveld 2004

Malyshev, 2008

Marchesoni, 2009

McDonald, 2009

Michaud, 2006

Migliore, 2009

Miyasaka, 2008

Mohan, 2001

Mohan, 2004

Nadareishvili, 2008

Naranjo, 2008

Nishimoto, 2009

Nuki, 2002

O'Dell, 1996

O'Dell, 2002

O'Dell, 2006

Osiri, 2002

Pallavicini, 2010

Pan, 2009

Russell, 2007

Saag, 1994

Salliot, 2006

Schaible, 2000

Schiff, 2006

Schiff, 2008

Schipper, 2009

Schneeweiss, 2007

Setoguchi, 2006

Setoguchi, 2008

Shin, 2006

Slifman, 2003

Smitten, 2007

Smitten, 2008

Smolen, 1999

Smolen, 1999

Smolen, 2008

Smolen, 2009

Sokolove, 2010

Solomon, 2006

St. Clair, 2004

5t. Clair, 200-

Strand, 1999

Strand, 2006

Strangfeld, 2009

Strangfeld, 2010

Suissa, 2004

Suissa, 2006

Suissa, 2006

Svensson, 2003

Svensson, 2005

van der Heijde, 2006 - f ound under Klareskog 2004

van der Heijde, 2006 – found under Klareskog 2004

van der Kooij, 2009 – found under Goekoop-Ruiterman 2005

van Halm, 2006

van Riel, 2006

van Vollenhoven, 2009

Wallis, 2004

Wasserman, 2004

Weinblatt, 1999

Weinblatt, 2006

Weinblatt, 2006

Weinblatt, 2007

Westhovens, 2006

Westhovens, 2009

Wolfe, 2004

Wolfe, 2004

Wolfe, 2004

Wolfe, 2006

Wone, 2000

Wolfe, 2007 Wolfe, 2007

Wolfe, 2007

Zhang, 2006

Zink, 2005

Systematic Reviews and Meta-analyses found in Evidence Table 2

Alonso-Ruiz, 2008

Bernatsky, 2010

Bongartz, 2006

Bongartz, 2009

Gartlehner, 2006

Leombruno, 2009

Maetzel, 2000

Martinez Lopez, 2009

Mertens, 2009

Osiri, 2002, 2009

Salliot, 2009

Schipper, 2009

Singh, 2009

Singh, 2009 Singh, 2010 Singh, 2010 Wiens, 2009 Wiens, 2010

KQ4

RCTs and other studies found in Evidence Table 1

Keystone, 2009 Schiff, 2004

Schiff, 2006 - found under Fleischmann 2003

Solomon, 2006

Tesser, 2004 - found under Fleischmann 2003

Systematic Reviews and Meta-analyses found in Evidence Table 2

Rheumatoid Arthritis Clinical Trial Archive Group, 1995

Abbreviations used in the evidence tables

ACR American College of Rheumatology

ADA adalimumab AEs adverse events

AIDS acquired immunodeficiency syndrome
AIMS Arthritis Impact Measurement Scales

ANA anakinra

ARA American Rheumatism Association criteria (pre-1987)

AS ankylosing spondylitis

ASHI Arthritis-Specific Health Index (Medical Outcomes Study Short Form SF-36 Arthritis-specific

Health Index)

AUC area under the curve

BUD budesonide Ccs corticosteroids

CFS chronic fatigue syndrome
CHF coronary heart failure

Cm centimeters

Combo combination therapy
CI confidence interval
CHD coronary heart disease

COPD Chronic Obstructive Pulmonary Disease

CRP C-reactive protein
CVD cardiovascular disease
CXT cyclophosamide
CYP cyclosporine
Ds days

DM diabetes mellitus
DAS Disease Activity Score

DMARD disease modifying antirheumatic drug

D-HAQ Dutch version of the Health Assessment Questionnaire (HAQ)

EQ-5D- Quality of Life Questionnaire ESR erythrocyte sedimentation rate

ETA etanercept

EULAR European League against Rheumatism EuroQol EQ-5D European Quality of Life Questionnaire

EuroQOL VAS European Quality of Life Visual Analogue Scale

GI gastrointestinal

HAQ Health Assessment Questionnaire

HAQ-DI Disability Index of the Heath Assessment Questionnaire (HAQ)

HIV Human immunodeficiency virus

HLA-DR4 Human immune-response, D-related antigen encoded by the D locus on chromosome 6

HR hazard ratio

HRQOL health related quality of life

ICD International Classification of Diseases

INF infliximab

ISRs injection site reactions ITT intention to treat

JRA juvenile rheumatoid arthritis

HCQ hydroxychloroquine
JSN joint space narrowing

LEF leflunomide MTX methotrexate Mg milligrams

mSharp Scale Modified Sharp Method for Scoring Radiographs

mos months

MHAQ Modified Health Assessment Questionnaire
NSAIDs non-steroidal anti-inflammatory drugs
NSFHS National Survey of Functional Health Status

NA not applicable

NMSC non-melanoma skin cancer

NR not reported NS not significant

NYHA New York Heart Association

OA osteoarthritis OR odds ratio

OMERACT Outcome Measures in Rheumatology Clinical Trials

PASI Psoriasis Area and Severity Index

PNL prednisolone PRED prednisone PsA psoriatic arthritis

PsARC Psoriatic Arthritis Response Scale

Pt patient
PY person-year
QOL quality of life

RCT randomized controlled trial
RAI Ritchie Articular Index
RA rheumatoid arthritis
RDS radiological damage score

RF rheumatoid factor

RIT rituximab RR risk ratio

SAEs serious adverse events

SAARDs slow-acting anti-rheumatic drugs SCC squamous cell carcinoma

SD standard deviation

SF-36 Medical Outcomes Study Short Form 36 Health Survey

SJC swollen joint count

SHS Sharp/van der Heijde Method (SHS) for Scoring Radiographs

SIR standardized incidence ratio
SLE Systemic Lupus Erythematosus
SMR standardized morbidity ratio

SSZ sulfasalazine

SSTG South Swedish Arthritis Treatment Group

TB Tuberculosis

TIM targeted immune modulator TJC tender joint count tumor necrosis factor

Txt treatment

URTI upper respiratory tract infection

UTI urinary tract infection

vs. versus
yrs years
w/ with
w/in with in
w/o with out

Evidence Table 1. Randomized controlled trials and observational studies

S tudy Characteris tics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Bas eline Dis eas e and Treatment Characteris tics	Health Outcomes	Adverse Events (%)	Analysis and Quality Rating
Author, yr: Askling et al., 2005 ¹ Country, Setting: Sweden; registries Funding: Swedish Cancer Society; AFA Insurance Company; Wyeth-Ayerst; Schering-Plough; Abbott Immunology; Bristol-Myers Squibb; King Gustav V; Österlund and Kock Foundations; Reumatikerför-bundet Research Objective: The risk of TB pts with RA Study Design: Retrospective cohort study Overall N: 36,115 w/ RA Study Duration: 467,770 PY	Inclusion Criteria: Diagnosed with RA according to ACR criteria RA inpatient btwn 1964 to 2001 Exclusion Criteria: Psoriatic arthritis, SLE, or AS diagnosis	Interventions, dose: D1: RA inpatient D2: Early RA D3: TNF treated RA N: D1: 31,185 D2: 2430 D3: 2500 Mean age, yrs: D1: 0-39: 19.08%;40-59: 40.80%;60-79: 35.90%;80+: 4.22% D2: 0-39: 15.80%;40-59: 38.40%;60-79: 41.60%;80+: 4.20% D3: 0-39: 18.40%;40-59: 49.44%;60-79: 30.52%;80+: 1.64% Sex, % female: D1: 73.4 D2: 70.2 D3: 73.4 Race, % white: NR	Mean disease duration, yrs: NR TJC, mean: NR SJC, mean: NR DMARD use, %: NR Corticosteroid use, %: NR MTX naive, %: NR Txt resistant %: NR Pts with Early RA (≤3 yrs): NR Baseline DAS, mean: D1: NA D2: 3.6 D3: 5.8 HAQ: D1: NA D2: 0.8 D3: 1.84 TB cases: D1: 27 D2: 2	 RA inpatient vs. General RR 3.9 (95% CI,3.1-5.0) RA inpatient vs. General inpatient RR 1.6 (95% CI,1.3-1.9) 1999 to 2001 RA inpatient vs. General were at increased risk of TB RR 2.0, (95% CI,1.2-3.4) TNF treated RA had a 4-fold increased risk of TB RR 4.0, (95% CI,1.3-12) vs. RA inpatient 	NA	Overall Attrition Rate, %: NA ITT Analysis: NA Quality Rating: Good

Evidence Table 1. Randomized controlled trials and observational studies

S tudy Characteris tics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Advers e Events (%)	Analysis and Quality Rating
Author, yr: Askling et al., 2005 ² Country, Setting: Sweden, Multicenter Funding: Swedish Cancer Society; insurance company AFA; Wyeth Ayerst, Schering-Plough, Abbott, Bristol Myer Squibb; Swedish National Board of Health and Welfare Research Objective: Cancer pattern of contemporary pts with RA and risk of solid cancer after TNF Study Design: Retrospective cohort study Overall N: 60,930 Study Duration: NR	ETA INF or ADA from	Interventions, dose: D1: Inpatient RA Cohort D2: Early Arthritis RA Cohort D3: TNF antagonist cohort N: NR Mean age, yrs: NR Sex, % female: D1: 71.4 D2: 69.9 D3: 74.8 Race, % white: NR	Mean disease duration, yrs: NR TJC, mean: NR SJC, mean: NR DMARD use, %: NR Corticosteroid use, %: NR MTX naive, %: NR Txt resistant %: NR Pts with Early RA (≤3 yrs): NR Baseline DAS, mean: D1: NR D2: 3.5 D3: 5.5 % age 45-74 yrs: D1: 56.3 D2: 65.4 D3: 71.8	Inpatient RA cohort: Based on 3379 observed solid cancers, this cohort had minimally increased overall risk of solid cancer (SIR: 1.05, 95% CI,1.01 to 1.08) Overall RR was 1.19 (95% CI,1.13 to 1.26, N:1311) among men and 0.97 (95% CI,0.93 to 1.02, N:2068) among women GI cancer risk (SIR: 0.85, 95% CI,0.78 to 0.93); Lung cancers (SIR: 1.48, 95% CI,1.33 to 1.65); (SIR: 1.66, 95% CI,1.50 to 1.84); Early Arthritis cohort: 138 solid cancers (SIR: 1.1, 95% CI,0.9 to 1.3), women (SIR: 0.87, 95% CI,0.67 to 1.11, n:64) Men (SIR: 1.42, 95% CI,1.12 to 1.79, n:74) TNF cohort • 67 solid cancers observed (SIR: 0.9, 95% CI,0.7 to 1.2) Women (SIR: 0.87, 95% CI,0.63 to 1.16, N:45) Men 1.06 (95% CI,0.67 to 1.61, N:22) Risk of colorectal cancer		Overall Attrition Rate, %: NR ITT Analysis: NA: retrospective cohort Quality Rating: Fair

Evidence Table 1. Randomized controlled trials and observational studies

S tudy Characteris tics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events (%)	Analysis and Quality Rating
				(SIR: 1.2 lung cancer (SIR: 1.8), breast cancer (SIR: 0.4), NMSC (SIR: 3.6)		

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events (%)	Analysis and Quality Rating
Author, yr: Askling, 2005 ³ Country, Setting: Sweden, Registry data Funding: AFA Insurance Company, Pharmas: Swedish National Board of Health and Welfare; Swedish Cancer Society Research Objective: Risks of hemapoetic malignancies, especially those with associtaed with TNF Study Design: Retrospective cohort study Overall N: Prevalent Cohort (inpatient): 53,067 Study Duration: 4 yrs	• Age: Prevalence:	Interventions, dose: D1: Prevalence D2: Incidence D3: TNF Antagonist N: D1: 53,067 D2: 3,703 D3: 4,160 Mean age, yrs: NR Sex, % female: NR Race, % white: NR	Mean disease duration, yrs: NR TJC, mean: NR SJC, mean: NR DMARD use, %: NR Corticosteroid use, %: NR MTX naive, %: NR Txt resistant %: NR Pts with Early RA (≤3 yrs): NR Baseline DAS, mean: NR	See AEs	Haematopoetic malignancnies: D1: SIR: 1.7 (1.5-1.8) D2: SIR: 1.6 (0.9-2.6) D3: 2.1 (1.1-3.8)	Overall Attrition Rate, %: ITT Analysis: NA Rating: Fair

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
Author, year,	Inclusion Criteria	Comparisons	Mean disease	ACR mean difference/	Overall	Quality rating for
study name, if applicable		(dosage and frequency)	duration, years D1: 10.7	absolute difference (CI/SD/P	NR	efficacy/effectiveness?
Askling et al.,	 RA patients, older than 16 	D1: ETN: dose NR	D1. 10.7 D2: 11.9	Value):	Serious adverse	INIX
2009 ⁴	Vrs	D2: ADA: dose NR	D3: 10.1	NR	events:	Quality rating for
Swedish	Starting	D3: INF: dose NR	Overall: 10.6		NR	observational studies
Biologics	treatment with			HAQ, mean difference/	Malignancies:	Fair
Register	TNF	Number in group	TJC, mean	absolute	Skin cancer (basal	
_	antagonists	D1: 2287	D1: 9.1	difference (CI/SD/P	cell or squamous	
Country and	_	D2: 937	D2: 8.4	Value):	cell) (n):	
setting	Exclusion	D3: 3380	D3: 8.6	NR	D1: 7	
Sweden	Criteria	Overall: 6604	Overall: 8.7	DAS, mean	D2: 2	
Source of		Mean age (years)	SJC, mean	difference/absolute	D3: 23	
funding		D1: 54	D1: 9.8	difference (CI/SD/P	Overall: 32	
Swedish Cancer		D2: 55	D2: 9.1	Value):	Dogniratory cancer:	
Society;		D3: 55	D3: 9.4	NR	Respiratory cancer: D1: 9	
Stockholm		Overall: 55	Overall: 9.5	SF-36, mean	D1: 9 D2: 2	
County Council		Sex, % female	Corticosteroid use, %	difference/absolute	D3: 25	
Research		D1: 77	D1: 57	difference (CI/SD/P	Overall: 36	
objective		D2: 77	D2: 56	Value):		
To assess the		D3: 74	D3: 45	NR ,	GI cancer:	
risk of cancer in		Overall: 75	Overall: 51	Dodiowankie	D1: 8	
RA patients		Race, % white	DMARD use, %:	Radiographic measures, mean	D2: 4 D3: 19	
treated with anti-		NR	D1: 64.3	difference/absolute	Overall: 31	
TNF therapy			D1: 04.3 D2: 76.9	difference (CI/SD/P	Overall. 51	
Study design		Race, % black	D3: 90.7	Value):	Reproductive cancer	
Observational		NR	Overall: 80	NR	D1: 25	
		Ethnicity, Latino			D2: 10	
Overall N		NR	MTX naïve, %:	Quality of life scales,	D3: 40	
6366 (first time		IVIX	D1: 44.3	mean	Overall: 75	
anti-TNF users)			D2: 31.9	difference/absolute	Urogenital cancer:	
Duration of			D3: 12.9	difference (CI/SD/P	D1: 8	
study			Overall: 27	Value): NR	D2: 1	
25,693 person-			Treatment resistant,	INIX	D3: 6	
yrs			%:	Others, (please name);	Overall: 15	
			NR	mean	Hematopoeietic cancer:	
			Patients with early RA,	difference/absolute	D1: 8	
			three years or less, %:	difference (CI/SD/P	D1. 6 D2: 4	
			NR	Value):	D3: 16	

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
			Baseline DAS score D1: 5.6 D2: 5.4 D3: 5.5 Overall: 5.5	NR	Overall: 28 Other cancer: D1: 5 D2: 3 D3: 14 Overall: 22	
			Required treatment for latent TB NR		Respiratory events:	
			Other population characteristics,		Other infections: NR	
			%, (CI/SD/P value): NR		GI: NR	
					Other: Other AEs 1 (n): RR of first primary cancer compared to biologic naive patients: D1: 0.78 (0.61 to 1.00) D2: 1.09 (0.91 to 1.30) D3: 1.32 (0.87 to 1.98) Overall: 1.00 (0.86 to 1.15, P=0.034)	
					Any other AEs: RR of first primary cancer in RA patients first starting anti-TNF therapy versus starting biologic-naive patients: 1.00 (0.87 to 1.17)	
					RR of first primary cancer in RA patients first starting anti-TNF therapy versus starting MTX therapy: 0.99 (0.79 to 1.24)	
					RR of first primary cancer in RA pts first	

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
					starting anti-TNF therapy versus starting DMARD combination therapy: 0.97 (0.69 to 1.36)	

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events (%)	Analysis and Quality Rating
Author, yr: Baecklund et al 2006 ⁵ Country, Setting: Sweden, inpatient Funding: Swedish Rheumatism Society; Lions Cancer Research Foundation of Uppsala; AFA InsuranceSwedish Cancer Society Research Objective: To investigate which RA pts are at highest risk of lymphoma, and whether antirheumatic txt is hazardous or protective Study Design: Cohort Overall N: 756 Study Duration: 1964 to 1995	 Age: ≥ 16 RA and lymphoma All pts receiving inpatient care in Sweden discharged with a diagnosis of RA (ICD) Randomly selected as potential 	Interventions, dose: NR MTX SSZ Other?: steroids N: 756 378 cases 378 controls Mean age, yrs: NR Sex, % female: NR Race, % white: NR	Mean disease duration, yrs: NR TJC, mean: NR SJC, mean: NR DMARD use, %: NR Corticosteroid use, %: NR MTX naive, %: NR Txt resistant %: NR Pts with Early RA (≤3 yrs): NR Baseline DAS, mean: NR	Risk of developing lymphoma is increased in subset of RA with severe disease. (Cases vs. controls) Inflammatory activity Low inflammatory activity: 94 (25%) vs. 278 (74%) OR 1 (referent) Medium: 196 (52%) vs. 94 (25%) OR 7.7 (95% CI,4.8-12.3) High: 86 (23%) vs. 4 (1%) OR 71.3 (95% CI,24.1-211.4) Functional class I 34 (9) vs. 138 (37) OR 1 (referent) II 185 (49) vs. 204 (54) OR 3.9 (95% CI,2.4-6.3) III 105 (28) vs. 31 (8) OR 13.8 (95% CI,7.2-26.2) IV 52 (14) vs. 3 (1) OR 67.5 (95% CI,18.9-239.8) DMARD OR 0.9 (95% CI,0.6-1.2) MTX crude OR 0.8 (95% CI,0.6-1.2) MTX crude OR 0.8 (95% CI,0.4-1.4); adjusted OR 0.7 (95% CI,0.3-1.6) SSZ; crude OR 0.6 (95% CI,0.4-1.0); adjusted OR 0.6 (95% CI,0.4-1.0); adjusted OR 0.6 (95% CI,0.4-1.0); adjusted OR 0.6 (95% CI,0.4-0.9]) and intraarticular steroids (adjusted OR 0.4 [95% CI,0.2-0.6]), calculated with adjustment for disease activity and DMARD use	NA	Overall Attrition Rate, %: NA ITT Analysis: NA: Case contol study Quality Rating: Good

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Txt Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
Author, yr: Bathon et al., 2000 ⁶ ; Genovese et al., 2002 ⁷ ; Kosinski et al., 2002 ⁸ ; Genovese et al., 2005 ⁹ ; ERA Country, Setting: US, clinics Funding: Immunex Research Objective: To compare ETA and MTX in pts with early RA Study Design: RCT Overall N: 632 (468 extension) Study Duration: 12 mos (1 year open label extension; 2 more years, total of 5 yrs)	concentration of at least 2.0 mg per deciliter • Morning stiffness that lasted at least 45 minutes • Stable doses of NSAIDS and PRE	Mean age, yrs:	Mean disease duration, yrs: D1: 12 mos D2: 11 mos D3: 12 mos TJC, mean: D1: 30 (16.1) D2: 31 (15.5) D3: 31 (15.8) SJC, mean: D1: 24 (11.9) D2: 24 (11.7) D3: 24 (11.9) DMARD use, %: NR Corticosteroid use, % D1: 41 D2: 42 D3: 39 MTX naive, %: D1: 100 D2: 100 D3: 100 Txt resistant, %: NR Pts with Early RA (≤3 yrs): D1: 100 D2: 100 D3: 100 Baseline DAS, mean:	First 12 weeks Mean changes in SF-36, HAQ, and ASHI significantly better in with ETA vs. MTX (P < 0.0001) 16 to 52 weeks No significant difference in SF-36, HAQ, and ASHI scores between groups At 6 months Significantly more pts on ETA (25 mg) than on MTX achieved ACR50 and ACR70 responses (data NR, P < 0.05) At 12 months ACR 20 response rates, %: D1: 65 D3: 72 (P = 0.16) Mean increase in Sharp score D1: 1.00 D3: 1.59 (P = 0.11) Erosion score change D1: 1.03 D3: 0.47 (P = 0.002) Despite improvement, QoL measures remained below general population (P < 0.0001); at start QoL measures were significantly below that of general population (P < 0.0001) 24 month open-label extension: ACR20,%	At year 2 SAEs: 20.6 Cardiovascular Events: 1.8 MI Malignancies: 3% overall Total events: 18 Breast: 3 Prostate: 3 Colon: 3 Lung: 12 Malignant melanoma: I2 Leukemia: 1 Kidney: 1 Hodgkins: 1 Adenocarcinoma: 1 URTI: Pnuemonia 2 Overall SAE rate of 0.093 events per ptyear comparable to rate observed in first year of efficacy study, events per ptyear MTX: 0.109 ETA: 0.091	Overall Attrition Rate, %: 19 ITT Analysis: Yes Quality Rating: Fair

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Txt Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
				D3: 72 (P = 0.005);		
				ACR50, % D1: 49 D3: 42		
				ACR 70,% D1: 29 D2: 24		
				HAQ improvement of at least 0.5 units, %: D1: 55 D2: 37 (<i>P</i> < 0.001)		
				Total modified Sharp score change D1: 1.3 D3: 3.2 (P = 0.001)		
				Erosion score change D1: 0.7		
				D3: 1.9 (P = 0.001)		

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
Author, yr: Bergstrom, 2004 ¹⁰ Country, Setting: US, 5 practices Funding: NR Research Objective: To assess if pts who were treated with TNF antagonists have a higher risk of developing coccidioido- mycosis Study Design: Retrospective cohort study Overall N: 985 Study Duration: 3 yrs		Interventions, dose: D1: INF D2: Other Anti-TNF alpha D3: control N: D1: 7 D2: 4 D3: 974 Mean age, yrs: D1: 64.8 D2: 64 D3: 57.8 Sex, % female: D1: 71 D2: 75 D3: 77 Race, % white: D1: 86 D2: 75 D3: NR	Mean disease duration, yrs: NR TJC, mean: NR SJC, mean: NR DMARD use, %: NR Corticosteroid use, %: NR MTX naive, %: NR Txt resistant %: NR Pts with Early RA (≤3 yrs): NR Baseline DAS, mean: NR MTX use: D1: 100 D2: 50 D3: 50	Pts treated with INF are at higher risk for developing symptomatic coccidioidomycosis 7 of 247 pts receiving INF and 4 of 738 pts receiving other therapies developed symptomatic coccidioidomycosis (relative risk 5.23, 95% confidence interval 1.54-17.71; <i>P</i> < 0.01)	NA NA	Overall Attrition Rate, %: NA ITT Analysis: NA: Quality Rating: Fair

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
Author, year, study name, if applicable Bernatsky et al., 2007 ¹¹ Country and setting Canada (Province of Quebec), phDacy and hospital (discharge) databases Source of funding Not reported Research objective Assess risk of severe infections associated with use of traditional DMARDs and glucocorticoid agents Study design Cohort Study – Nested Analysis Overall N 23,733 (RA cohort) For each case of hospitalization for infection that occurred in cohort, they randomly selected 10 controls Duration of study January 1, 1980 and December 31, 2003 Quality rating Fair	Inclusion Criteria Registered in phDacy claims database of Re'gie d'assurance maladie du Que'bec (RAMQ) and Ministry of Health's Maintenance et exploitation des donne'es pour l'e'tude de la cliente`le hospitalie`re (MEDECHO). Diagnosis of RA using physician billing codes (ICD-9 code 714) Were dispensed at least 1 DMARD after January 1, 1980. Exclusion Criteria Record of a hospitalization for infection at any time prior to cohort entry date.	Interventions, Dose D1: MTX: Dosage NR LEF: Dosage NR SSZ: Dosage NR Hydroxychlorquine: Dosage NR ETN: Dosage NR IFX: Dosage NR Glucocorticoids: Dosage NR LEF: Dosage NR LEF: Dosage NR LEF: Dosage NR SSZ: Dosage NR Hydroxychlorquine: Dosage NR ETN: Dosage NR IFX: Dosage NR Hydroxychlorquine: Dosage NR IFX: Dosage NR IFX: Dosage NR IFX: Dosage NR Mumber in group Overall: 23,733 Mean age (years) Overall: 61.7 Sex, % female Overall: 69.9 Race, % white NR Race, % black NR Ethnicity, Latino NR	Mean disease duration, years (SD) NR Patients with early RA, three years or less, % NR Treatment resistant, % NR Tender Joint Count, mean (SD) NR Swollen Joint Count, mean (SD) NR Corticosteroid use, % NR DMARD use, % Overall: Drug exposures at cohort entry for RA subjects (n/%): MTX 7044 (29.7) Anti-malarial agent: 9415 (39.7) Anti-TNF agents: 261 (1.1) All other DMARDs: 6180 (26.0). MTX naïve, % NR Baseline DAS score, mean (SD) NR Required treatment for latent TB NR	ACR NR HAQ, NR DAS NR SF-36 NR Radiographic measures NR Quality of life scales NR Others, (please name); mean difference/absolute difference (CI/SD/P Value) NR	Overall Overall adverse events reported, n: Overall: 1991 from entire RA cohort Serious adverse events NR Malignancies NR Respiratory events Pneumonia, n: Overall: 1,315 Other infections NR GI NR Other Any other AEs: • Entire RA cohort generated 156,520 personyrs of follow-up time, for an average follow-up of 6.3 yrs. During this time, 1970 cases of serious infection occurred, for an incidence rate of 129.1 events per 10 000 person-years. Of these infections, most common event was pneumonia with 1315 cases, for an incidence rate of 83.4 per 10 000 person-years. There were only 21 cases of TB recorded. Risk for all infections requiring hospitalization appeared to be most elevated with

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics Health Outcomes	Adverse Events, %
Characteristics	Criteria	Interventions	characteristics, %, (CI/SD/P value) Avera age at cohort entry Overall: 61.7 yrs We Female Overall: 69.9. Average followup: Overall: 6.3 year follow up After average of 6.3 yrs followup Mean age, Cases: 71.0 yrs Mean age, Controls: 71.5 yrs	current exposures to systemic glucocorticoid agents (RR: 2.6, 95% CI: 2.3 - 2.9) Similar effects were seen with pneumonia as outcome (RR 2.1 (2.4-3.1). For MTX, there was a trend towards increased risk for all infections (RR 1.10 (0.98-1.2), and a moderate increased risk for pneumonia (RR: 1.2, 95% CI: 1.0 - 1.3). For HCQ (and chloroquine) RR
			 % Male, Overall: 65.5 Average yearly number of physician visits: Cases: 5.5 Controls: 5.1 Events occurred at a mean time of 5.5 (S.D. 4.7) yrs after cohort entry. 	1.1 (0.94-1.2) • Anti-TNF 1.9 (0.7-5.3); and for other DMARDs 0.9 (0.8-1.05). Limiting sample to subjects aged 65 yrs and older, estimates were similar, but with suggestion of slightly more pronounced effects, noted particularly for MTX (adjusted RR: 1.3; 95% CI: 1.1-1.5).

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
Author, yr: Boers et al., 1997 ¹² ; Landewe et al., 2002 ¹³ ; COBRA study Country, Setting: Netherlands and Belgium, multicenter Funding: Netherland Research Objective: Comparing efficacy and radiographic outcomes of combination of SSZ, MTX and PNL with SSZ alone Study Design: RCT Overall N: 155 (148) Study Duration: 56 wks; (5 yr followup)	Inclusion Criteria: Age: 18 to 69 Diagnosed with RA according to ACR criteria Duration of condition < 2 yrs NSAID txt at least 3 mos, 6 or more active inflamed joints AND presence of 2 or more (9 or more tender joints, morning stiffness 45 min or more, EST of 28 or more in first hour Exclusion Criteria: Pregnant or lactating: adequate contraception Prior txt with: DMARDS except HCQ or steroids Past TB Impaired renal or hepatic system serious comorbidity surgery in past 3 mos Unable to comply with protocol Allergy to study med Alcohol or substance abuse	Interventions, dose: D1: Combined txt (SSZ, MTX, PNL) D2: SSZ Only SSZ: 2g/d MTX: 7.5 mg/wk, weaned after 40 wks PNL: 60 mg/d wk 1 40 mg/d wk 2 25 mg/d wk 3 20 mg/d wk 4 15 mg/d wk 5 10 mg/d wk 6 then 7.5 mg/d until wk 28 then weaned off N: D1: 76 D2: 79 Mean age, yrs: NR Sex, % female: D1: 66% D2: 52% Race, % white: NR	Mean disease duration, yrs: D1: 4 mos D2: 4 mos TJC, mean: NR SJC, mean: NR Antimalarial use (%): D1: 21 D2: 24 Corticosteroid use, % NR MTX naive, %: NR Txt resistant, %: NR Pts with Early RA (≤3 yrs): NR Baseline DAS, mean: NR Erosions on hand or foot xrays, %: D1: 74 D2: 79	Mean pooled index D1: -1.4 (95% CI, 1.2-1.6) D2: -0.8 (95% CI, 0.6-1.0) (P < 0.0001) ACR20, %: D1: 72 D2: 49 (P = 0.006) ACR50, %: D1: 49 D2: 27 (P = 0.007) DAS median change: D1: -2.1 (SD 1.2) D2: -1.3 (SD 1.2) (P < 0.0001) HAQ mean change: D1: -1.1 (SD 0.8) D2: -0.6 (SD 0.6) (P < 0.0001) Sharp mean change: D1: 1 D2: 4 (P < 0.001) At week 56 Mean pooled index: D1: 1.1 (SD 0.8) D2: 0.9 (SD 0.8) (P = 0.20) DAS median change: D1: 1.4 (SD 1.2) D2: 1.3 (SD 1.4) (P = 0.78) HAQ mean change: D1: 0.8 (SD 0.8) D2: 0.6 (SD 0.7) (P < 0.06) Sharp mean change: D1: 2 D2: 6 (P < 0.004)	Overall: D1: 72.3 D2: 62.0 SAEs: D1: 2.6 D2: 7.6 Infections: D1: 15.8 D2: 7.6 Cardiovascular Events: D1: 7.9 D2: 5.1 Hepatotoxicity: D1: 2.6 D2: 0	Overall Attrition Rate, %: 3.2 ITT Analysis: Yes Quality Rating: Good

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
				At week 80		
				Sharp mean change : D1: 4 D2: 12 (<i>P</i> < 0.01)		
				Five yr follow up Sharp score mean change: D1: 5.6 (95% CI, 4.3, 7.1) (<i>P</i> = 0.001) D2: 8.6 (95%CI, 6.2-11) (<i>P</i> = 0.001)		
				Time averaged DAS28, points/yr: D1: -0.07 D2: -0.17		

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
Author, year, study name, if applicable Brassard et al.,	Inclusion Criteria • Patients	Interventions, Dose D1:	Mean disease duration, years (SD) NR	ACR NR	Overall NR
2009 ¹⁴ Country and setting	registered in provincial phDacy claims	MTX: dosage and frequency NRLEF: dosage and	Patients with early RA, three years or less, %	HAQ, NR	Overall adverse events reported, n: NR
Canada, hospital (inpatient) or	database, which covers residents age ≤ 65 years,	frequency NR Other:	NR Treatment resistant, %	DAS NR	Serious adverse events NR
Source of funding	those who receive social	 Corticosteroids: dosage and frequency NR 	NR Tender Joint Count, mean	SF-36 NR	Malignancies NR
Mentions support by Canadian career award and institutes	assistance, and those who do not have private	All DMARDs included MTX, HCQ,	(SD) NR	Radiographic measures NR	Respiratory events NR
Not reported Research objective	drug insurance through their employer.	chloroquine, SSZ, azathioprine, LEF, cyclophosphamide,	Swollen Joint Count, mean (SD) NR	Quality of life scales NR	Other infections NR
Determine risk of TB and assess whether this risk is associated	 ≥ 1 occurrence of diagnosis of RA using 	cyclosporine, gold compounds, minocycline, or	Corticosteroid use, % D1: 18		GI NR
with exposure to DMARDs	physician billing code for RA	penicillamine D2: • MTXDosage NR	D2: 8.1 P = 0.03		Other Any other AEs:
Study design Cohort – Case / Control	(ICD-9 code 714) during inpatient or	 LEF: dosage and frequency NR 	DMARD use, % D1: 72 D2: 45.6		 RR of TB associated with any nonbiologic DMARD exposure in year prior to
Overall N Cohort consisted of	outpatient visit.Cohort subjects further restricted	 Other: Corticosteroids: dosage and 	P = 0.0004 MTX naïve, %		index date is 3.0 (95% CI 1.6-5.8). • Current use of
24,282 patients with RA; 70.1% were women. mean (SD)	to those who were dispensed ≥ 1 prescription	frequency NR Number in group	NR Baseline DAS score, mean		corticosteroids was also significantly associated with occurrence of TB
subject age at time of cohort entry was	for DMARD therapy.	D1: 50 D2: 1500 Overall: 1550	(SD) NR		(adjusted RR 2.4, 95% CI 1.1-5.4).
61.7 (14.6) years. Duration of study 1980-2003 for cohort	 Cohort entry was defined by date of first 	Mean age (years) D1: 65	Required treatment for latent TB NR		 There were 50 cases of TB identified during followup period. overall sex and
and 1992-2003 for TB incidence rates	DMARD prescription	D2: 67 P=.06	Other population characteristics, %		age-standardized rate of TB in RA cohort for period
Quality rating Fair: Confounding and potential bias in	after 1 year of eligibility in provincial health	Sex, % female D1: 50 D2: 70	Other comorbid clinical conditions and risk factors:		1992-2003 was 45.8 cases per 100,000 person-years of followup compared with

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
population characteristics (older population). Use of case definitions to validate diagnosis of TB and RA conditions.	insurance system. TB as a primary hospitalization diagnosis (ICD-9 codes 010-018) or if TB was part of a medical claim. Had at least 2 classes of usual first-line anti-TB medications prescribed (isoniazid, rifampin, pyrazinamide, or ethambutol) Treatment lasted at least 6 months.	P = 0.002 Race, % white NR Race, % black NR Ethnicity, Latino NR	D1: 2.0 D2: 1.9 Overall: : $P = 0.62$ Diabetes: D1: 12.0 D2: 10.1 $P = 0.67$ Use of COX-2 inhibitors: D1: 8.0 D2: 5.7 $P = 0.53$ Use of NSAIDS: D1: 56.0 D2: 49.9 $P = 0.39$		4.2 cases per 100,000 person-years in general population of Quebec (SIR 10.9, 95% CI 7.9-15.0).
	Exclusion Criteria TB cases that occurred before date of cohort entry were excluded from cohort.				

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
Author, year, study name, if applicable Brassard, P., et al.; 2006; Antirheumatic	Inclusion CriteriaPatients aged 18 years or older with 1 or	Interventions, Dose D1: • MTX: dosage and frequency NR	Mean disease duration, years (SD) NR	ACR NR HAQ	Overall Overall attrition/withdrawal, n: NA
Drugs and Risk of TB ¹⁵ Country and setting	more occurrence of a diagnosis of RA	LEF: dosage and frequency NRSSZ: dosage and	Patients with early RA, three years or less, % NR	NR DAS NR	Overall adverse events reported, n: D1: 386 D2: 0
Canada; Medical and phDaceutical claims data from PhDetrics	Dispensed 1 or more prescriptions for DA	frequency NR • HCQ: dosage and frequency NR	Treatment resistant, % NR Tender Joint Count, mean	SF-36 NR	Serious adverse events NR
Patient-Centric Database were reviewed.	any anti-RA drug during study period were inlcuded in	ETN: dosage and frequency NRIFX: dosage and	(SD) NR	Radiographic measures NR Quality of life scales	Malignancies NR
Source of funding Not reported	cohort. • Cases were	ANK: dosage and frequency NR	Swollen Joint Count, mean (SD) NR	NR Others, (please name);	Respiratory events NR Other infections
Research objective Quantify rate of Mycobacterium TB and assess whether	those patients who were diagnosed with TB during study period.	Other: auronofin, cyclosporin, penacillamine, and cyclophosphamide:	Corticosteroid use, % D1: 46.6 D2: 31.2 P=.001	mean difference/absolute difference NR	NR GI NR
independent use of DMARDs is associated with risk of developing TB	 For each case, 100 controls were matched 	dosage and frequency NR D2: • MTX: dosage and	DMARD use, % D1: biologic DMARDs 17.4%; Traditional DMARDs		Other NR Any other AEs:
Study design Cohort Study with Nested Case / Control	on date of cohort entry and confirmation that they were at risk for TB at time case	frequency NR • LEF: dosage and frequency NR • SSZ: dosage and frequency NR	50.8% D2: biologic DMARDs 11.8% (P = .008); Traditional DMARDs 44.1% (P = .008)		 Crude and Adjusted rate ratio (RR) of developing TB, according to antirheumatoid arthritis medications use
Overall N n: 112,300 patients from which a nested	occurred. Exclusion	HCQ: dosage and frequency NRETN: dosage and	MTX naïve, % NR		(cases: 386, controls: 38,600)Use of biologic DMARDs,
case-control was selected (386 cases, 38,600 controls)	CriteriaPatients who had TB prior to	frequency NR • IFX: dosage and frequency NR	Baseline DAS score, mean (SD) NR		crude RR: 1.5, adjusted RR: 1.5 (1.1 - 1.9); Infliximib, crude RR: 1.7,
Duration of study September 1998 - December 31, 2003	cohort entry were excluded from being cases.	 ANK: dosage and frequency NR Other: auronofin, cyclosporin, 	Required treatment for latent TB NR		adjusted RR: 1.6 (1.0 - 2.6); ETN, crude RR: 1.4, adjusted RR: 1.2 (0.9 - 1.8); ANK, crude RR: 1.5,
Quality rating		penacillamine, and	Other population		adjusted RR: 1.3 (0.8 -

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics Health Outcomes	Adverse Events, %
Fair		cyclophosphamide: dosage and frequency NR Number in group D1: 386 D2: 38,600 Mean age (years) D1: 54 D2: 56 P=.01 Sex, % female D1: 77.2 D2: 73.7 P=.12 Race, % white NR Race, % black NR Ethnicity, Latino NR	characteristics, %, (CI/SD/P value) D1: Diabetes 19.9%; Other comorbid condition (silicosis, chronic renal failure/hemodialysis, solid organ transplantation, and carcinoma) 3.8%; use of corticosteroids 46.6% D2: Diabetes 15% (P = .007)Other comorbid condition (silicosis, chronic renal failure/hemodialysis, solid organ transplantation, and carcinoma) 1.9% (P = .007); Use of corticosteroids 31.2% (P = 0.001)	2.1); • Use of traditional DMARDs, crude RR: 1.3, adjusted RR 1.2 (1.0 - 1.5); study inlcudes a subanalysis of corticosteroid use among cases; crude and adjusted rate ratio (RR) of developing tuberulosis associated with antirheumatoid arthritis medication use stratified by current use of corticosteroids (noncurrent users among cases: 313, current users among cases: 73); • For noncurrent users on any biologic DMARDs, crude RR: 1.8, adjusted RR: 1.7 (1.3 - 2.3); noncurrent users on IFX, crude RR: 2.0, adjusted RR: 1.8 (1.1 - 3.0); noncurrent users on ETN, crude RR: 1.5, adjusted RR: 1.3 (0.9 - 2.0); noncurrent users on ANK, crude RR: 1.7, (1.1 - 2.8) • For noncurrent users on traditional DMARDs, crude RR: 1.5, adjusted RR: 1.5, adjusted RR: 1.5, adjusted RR: 1.7 (1.1 - 2.8) • For current users also on any biologic DMARDs, crude RR: 0.7, adjusted RR: 0.9, adjusted RR: 0.9, adjusted

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
					RR: 1.1 (0.3 - 3.6), for current users also on ETN, crude RR: 0.9, adjusted RR: 0.9 (0.4 - 2.0), for current users also on ANK rates were not estimable; for current users on traditional DMARDs crude RR: 0.6, adjusted RR: 0.6 (0.4 - 1.0).

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events (%)	Analysis and Quality Rating
Author, yr: Breedveld et al. 2004 ¹⁷ , Maini et al. 2004 ¹⁸ and Smolen et al. 2005 ¹⁹ Country, Setting: Multinational Multicenter Funding: Centocor Research Objective: To examine the impact of INF + MTX on the progression of structural damage in pts with early RA. Subanalyses of ATTRACT, early RA and in non-responders. Study Design: RCT Overall N = 428 and 61 of these had available radiographs Study Duration: 102 wks	DMARDs: current MTX 6 or more swollen and tender joints ESR ≥ 28 mm/hour; CRP ≥ 2mg/dl Exclusion Criteria: NR	Interventions (dose): D1: All D2: Early RA D3: Responders placebo/INF D4: Nonresponders placebo/INF MTXINF: 3 mg/kg every 4 or 8 wks and 10 mg/kg every 4 or 8 wks Placebo N = D1: 428 D2: 82 D3: 15/176 D4: 73/164 Mean age (yrs): D1: 54 D2: 50 D3: 49.7/50.6 D4: 51.2/55.2 Sex (% female): D1: 78 D2: 79 D3: 67/77 D4: 82/77 Race (% white): NR	Mean disease duration (yrs): D1: 8.4 D2: 1.7 D3: 9.9/9.5 D4: 10.8/11.2 TJC (mean): D1: 31 D2: 30 D3: 32.5/32.5 D4: 30.4/32.5 SJC (mean): D1: 20 D2: 20 D3: 21.2/22.6 D4: 21.5/22.7 DMARD use (%): NR Corticosteroid use (%) NR MTX naïve (%): NR Txt resistant (%): NR Patients with Early RA (≤3 yrs): NR Baseline DAS (mean): NR Erosion score: D1: 23.5 D2: 8.9	 Early RA at 102 wks- Erosion scores mean Placebo + MTX 12.21 (13.32)vs. INF + MTX - 0.49 (3.89) P < 0.001 JSN Placebo + MTX 12.82 (15.73) vs. INF + MTX - 0.05 (4.30) P < 0.001 Responders vs. non-responders Radiographic progression was much greater in pts receiving MTX + placebo than in pts receiving INF + MTX, (mean change in modified Sharp/van der Heijde score 6.0 in ACR20 responders and 7.2 in ACR20 nonresponders in the MTX + placebo-treated group, vs. 0.1 in ACR20 responders and 1.2 in ACR20 nonresponders in the INF + MTX-treated group (P < 0.01) HAQ median change MTX 0.1 vs. all INF 0.4 P ≤ 0.006 SF-36 median change MTX 2.8 vs. all INF 6.4 P ≤ 0.011 		Overall Attrition Rate (%): 428 randomised, 259 entered 2nd yr and 216 completed. ITT Analysis: Yes Quality Rating: Fair

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events (%)	Analysis and Quality Rating
			JSN score: D1: 28.3 D2: 10.0			

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
Author, yr: Breedveld et al., 2006 16 PREMIER study Country, Setting: Multinational (Europe, North America, Australia), multicenter (133) Funding: Abbott Laboratories Research Objective: To compare efficacy and safety of ADA + MTX vs. MTX or ADA in pts with early, aggressive RA (RA) who had not previously received MTX txt Study Design: RCT Overall N: 799 Study Duration: 2 yrs	and an erythrocyte sedimentation rate of > 28 • Folic acid only other med allowed Exclusion Criteria: • Prior txt with: MTX, cyclophosphamide, cyclosporine, azathioprine	Interventions, dose: D1: MTX (20 mg/wk) D2: ADA (40 mg/biwkly) D3: ADA (40 mg/biwkly) + MTX (20 mg/wk) N: D1: 257 D2: 274 D3: 268 Mean age, yrs: D1: 52 D2: 52.1 D3: 51.9 Sex, % female: D1: 73.9 D2: 77.4 D3: 72 Race, % white: NR	Mean disease duration, yrs: D1: .8 D2: .7 D3: .7 TJC, mean: D1: 32.3 D2: 31.8 D3: 30.7 SJC, mean: D1: 22.1 D2: 21.8 D3: 21.1 DMARD use, %: NR Corticosteroid use, % D1: 35.4 D2: 36.5 D3: 35.8 MTX naive, %: NR Txt resistant, %: NR Pts with Early RA (≤3 yrs): NR Baseline DAS, mean: D1: 6.3 D2: 6.4 D3: 6.3 HAQ: D1: 1.5 D2: 1.6 D3: 1.5 Erosion score: D1: 13.6 D2: 11.3 D3: 11.0	D3: 59 D3 vs. D2 or D1: <i>P</i> < 0.001	SAEs: D1: 18.5 D2: 21.1 D3: 15.9 Infections: D1: 123 D2: 110 D3: 119 Serious Infections: D1: 2.9 D2: 0.7 D3: 1.6 Malignancies: D1: 0.4 D2: 0.9 D3: 0.9 Withdrawal because of adverse events: D1: 7% D2: 10% D3: 12%	Overall Attrition Rate, %: 32% ITT Analysis: Yes Quality Rating: Fair

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
				Withdrawal because of lack of efficacy, %: D1: 18 D2: 19 D3: 4.9		
				HAQ DI improvement, mean units +/- sd: D1: -0.9 +/- 0.6 D2: -0.9 +/- 0.7 D3: -1.0 +/- 0.7 D2 vs. D1, P = NR D3 vs. D1; P < 0.05 D3 vs. D2; P = 0.058		
				% with HAQ DI score of zero: D1: 19 D2: 19 D3: 33 D3 vs. D2, <i>P</i> < 0.001 D3 vs. D1: <i>P</i> < 0.001		
				% with HAQ DI improvement of ≥ 0.22 units from baseline: D1: 63 D2: 58 D3: 72 D3 vs. D2, P < 0.05 D3 vs. D1: P < 0.05		

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
Author, yr: Brown, 2002 ²⁰ Country, Setting: US, NA Funding: Authors are from FDA and National Cancer Institute Research Objective: Occurrence of lympho- proliferative	Inclusion Criteria: Inclusion Criteria: MedWatch reports submitted to FDA for biologic products ETA and INF. All reports citing neoplasms, benign or malignant, were reviewed. Any report with a keyword of lymphoma or		Mean disease duration, yrs: NR TJC, mean: NR SJC, mean: NR DMARD use, %: NR Corticosteroid use, %: NR	Health Outcomes ETA 19 cases per 100,000 treated persons INF • 6.6 cases per 100,000 treated persons • In general, diffuse large B cell lymphoma (non- Hodgkin's) were most common form • (21 of 26 were non- Hodgkin's lymphomas) • Treated person rates of lymphomas in ETA and	NA	
disorders in pts treated with ETA and INF	was investigated further. Cases reported to	Race, % white: NR	MTX naive, %: NR Txt resistant %:	INF users is probably an underestimate based on underreporting, according to authors (Age adjusted		
Study Design: Database analysis; AERS system	base December 2000 comprise basis for current summary rall N: Exclusion Criteria: NA) for	NR Pts with Early RA (≤3 yrs):	rate of lymphomas in US from 1992-1998 18.3 per 100,000 people) • Median time to lymphoma diagnosis was 8 wks (range 2-52 wks) for ETA and 6 wks (range 2-44 wks) for INF	а	
Overall N: 26 cases Study Duration:			NR Baseline DAS, mean: NR			
NA			MTX use: D1: 72.2 D2: 25	·		

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
Author, year, study name, if applicable	Inclusion Criteria • Treatment	Interventions, dose D1: ADA: 40 mg every	Mean disease duration, years (SD)	ACR mean difference/ absolute difference	Attrition/withdrawal NR by arm
Burmester, B. R. et al., 2007 ReAct ²¹	resistant defined as treatment failure with at	other week D2: MTX LEF	D1: 12 (9) D2: 10 (8) 1 DMARD 10 (8)	Response at 12 weeks with ADA+MTX as comparison group, OR (CI):	Serious adverse events, n D1: 126
Country and setting Multinational, multicenter	least one traditional DMARD • Men and	SSZ ADA: 40 mg every other week Antimalarials	2 DMARDs 9 (7) ≥ 3 DMARDs 10 (9) MTX only 10 (8) LEF only 11 (9)	ACR 20: D1: 0.52 (0.45-0.60), P < 0.0001 D2: LEF only 0.69 (0.58-	D2: 260
Source of funding NR	women ≥ 18 years of age with active.	Number in group D1: 1731	SSZ only 11 (8) AM only 8 (7) 1 other DMARD 13 (9)	0.82), $P < 0.0001$, SSZ only 0.61 (0.41-0.89), P = 0.0	
Research objective Evaluate safety and effectiveness of ADA alone or in combination with	adult-onset RA in accordance with1987 revised criteria ofACR	D2: 4879 1 DMARD 4004 2 DMARDs 769 ≥ 3 DMARDs 106 MTX only 2794	MTX+LEF 10 (8) MTX+AM 8 (7) MTX+SSZ 9 (8) MTX+SSZ+AM 9, S	ACR 50: D1: 0.61 (0.53-0.70), P < 0.0001 D2: LEF only 0.72 (0.61-	
standard DMARDs fortreatment of RA.	 Disease duration ≥ 3 	LEF only 842 SSZ only 133 AM only 148	Patients with early RA, three years or less, % NR	0.86), <i>P</i> = 0.0002, SSZ only 0.76 (0.52-1.22), <i>P</i> = 0.1555, AM only 1.14	
Study design Open – label Observational	mos • DAS based on ESR and an	1 other DMARD 84 MTX+LEF 180 MTX+AM 269	Treatment resistant, % D1: 100 D2: 100	P = 0.1533, AlM offly 1.14 (0.81-1.63), $P = 0.4503$; 1 other DMARD 092 (0.57-1.48), $P = 0.7280$,	
Overall N 6610	evaluation of 28 joints (DAS28) of greater than	MTX+SSZ 182 MTX+SSZ+AM 76 Overall: 6610	Overall: 100 Tender Joint Count, mean	MTX+LEF 0.70 (0.50- 0.97), <i>P</i> = 0.0307, MTX+AM 0.94 (0.72-	
Duration of study 12 weeks for main study, 5 years total	or equal to 3.2. Exclusion Criteria	Mean age, years (SD) D1: 55 (13) D2: 55 (13)	D1: 14 (7) D2: 13 (7) 1 DMARD 13 (7)	1.23), <i>P</i> = 0.6590, MTX+SSZ 1.0 (0.73- 1.36), <i>P</i> = 0.9822,	
Quality rating Fair	 Current pregnancy or breast feeding 	1 DMARD 53 (13) 2 DMARDs 53 (13) ≥ 3 DMARDs 52	2 DMARDs 13 (7) ≥ 3 DMARDs 13 (7) MTX only 13 (7)	MTX+SSZ+AM 0.97 (0.59-1.57), P = 0.8849 ACR 70:	
	Any persistent or severe infection within 30 days of baseline	(12) MTX only 53 (13) LEF only 54 (12) SSZ only 56 (13)	LEF only 13 (7) SSZ only 14 (8) AM only 15 (7) 1 other DMARD 14 (7) MTX+LEF 13 (7)	D1: 0.74 (0.62-0.87), P = 0.0004 D2: LEF only 0.67 (0.54- 0.84), P = 0.0006, SSZ	
	 Previous treatment with other TNF antagonists up 	AM only 56 (12) 1 other DMARD 55 (13) MTX+LEF 53 (13) MTX+AM 52 (13)	MTX+AM 14 (7) MTX+SSZ 13 (7) MTX+SSZ+AM	only 0.76 (0.46-1.26), P = 0.2817, AM only 1.11 (0.73-1.68), P = 0.6397, 1 other DMARD 1.08 (0.61- 1.94), P = 0.7871,	

to 2 mos before enrollment Treatment with alkylating agents Total lymphoid irradiation, IV immunoglobulin or any investigational biologic agent History of active	MTX+SSZ 52 (13) Sex, % female D1: 82 D2: 80 1 DMARD 81 2 DMARDs 75 ≥ 3 DMARDs 76 MTX only 82 LEF only 82 SSZ only 81 AM only 83 1 other DMARD 79	Swollen Joint Count, mean D1: 11 (6) D2: 10 (6) 1 DMARD 10 (6) 2 DMARDs 11 (6) ≥ 3 DMARDs 12 (7) MTX only 10 (6) LEF only 11 (6) SSZ only 11 (6) AM only 10 (6) 1 other DMARD 11 (5) MTX+LEF 11 (6)	MTX+LEF 0.72 (0.47- 1.11), $P = 0.1387$, MTX+AM 0.89 (0.64- 1.24), $P = 0.4860$, MTX+SSZ 0.99 (0.67- 1.44), $P = 0.9438$, MTX+SSZ+AM 1.11 (0.62-2.0), $P = 0.7208$ HAQ, D1: Abs change from baseline to 12 weeks: - 0.47 (0.63
arthritis other than RA • Any	MTX+LEF 79 MTX+AM 75 MTX+SSZ 70	MTX+AM 10 (6) MTX+SSZ 11 (6) MTX+SSZ+AM	D2: Abs change from baseline to 12 weeks: - 0.56 (0.60, 1 DMARD -
uncontrolled medical condition History or signs of demyelinating disease Active TB or histoplasmosis, malignancy (except for completely treated squamous or basal cell carcinoma)	MTX+SSZ+AM 78 Overall: 81 Race, % white NR Race, % black NR Ethnicity, Latino NR	Corticosteroid use, % D1: 70 D2: 72 1 DMARD 71 2 DMARDs 75 ≥ 3 DMARDs 67 MTX only 70 LEF only 73 SSZ only 63 AM only 78 1 other DMARD 81 MTX+LEF 81 MTX+AM 74 MTX+SSZ 69 MTX+SSZ+AM	0.56 (0.60, 2 DMARDs - 0.56 (0.60, ≥ 3 DMARDs -0.56 (0.57, MTX only - 0.58 (0.60, LEF only - 0.49 (0.59, AM only -0.72 (0.63, SSZ only -0.52 (0.62, 1 other DMARD - 0.55 (0.55, MTX+LEF - 0.54 (0.58, MTX+AM - 0.63 (0.66, MTX+SSZ - 0.55 (0.52, MTX+SSZ+AM -0.58 (0.59 Overall: Abs change from baseline to 12 weeks: - 0.54 (6.1
		66Overall: 71 DMARD use, % D1: Prior: 3.1 (2.1) D2: Prior: 2.9 (1.7) 1 DMARD 2.8 (1.7) 2 DMARDs 3.3 (1.5) ≥ 3 DMARDs 3.8 (1.2) MTX only 2.7 (1.7) LEF only 3.3 (1.7) SSZ only 3.1 (1.8) AM only 2.8 (1.8) 1 other DMARD 4.1 (2.1) MTX+LEF 3.5 (1.6)	DAS (CI) Abs change from baseline to 12 weeks: D1: -1.9 (1.4, DAS28<2.6 OR for achieving a response at week 12 (ADA+MTX as comparison group): 0.59 (0.49-0.71), P < 0.0001 D2: -2.2, SD 1.3; 1 DMARD - 2.2, SD 1.3; 2 DMARDs - 2.3, SD 1.3; ≥ 3 DMARDs

MTX naïve, % NR	-2.3, SD 1.3; MTX only - 2.3, SD 1.3; LEF only - 2.0, SD 1.3; AM only -
Baseline DAS score D1: 6.2 (1.1) D2: 6.0 (1.1) 1 DMARD 6.0 (1.1) 2 DMARDS 6.0 (1.1) ≥ 3 DMARDS 5.9 (1.1) MTX only 6.0 (1.1) LEF only 6.0 (1.1) SSZ only 6.1 (1.1) AM only 6.2 (1.0) 1 other DMARD 6.3 (1.0) MTX+LEF 6.1 (1.0)	2.4, SD 1.4; SSZ only - 2.1, SD 1.3; 1 other DMARD -2.2, SD 1.2; MTX+LEF -2.2, SD 1.3; MTX+AM -2.4, SD 1.3; MTX+SSZ -2.4, SD 1.3; MTX+SSZ+AM -2.4, SD 1.3; DAS28<2.6 OR for achieving a response at week 12 (ADA+MTX as
MTX+AM 6.0, S Required treatment for latent TB D1: NR D2: NR Overall: 835 Other population characteristics, %, (Cl/SD/value) D1: HAQ DI: 1.73 (0.68) D2: HAQ DI: 1.60 (0.68) 1 DMARD 1.61 (0.68) 2 DMARDs 1.55 (0.69) ≥ 3 DMARDs 1.68 (0.65) MTX only 1.61 (0.68) LEF only 1.58 (0.68)	(0.97-2.36), P= 0.0694; AM only 1.03 (0.65-1.62), P= 0.9107; 1 other DMARD 0.93 (0.48-1.81), P= 0.8365; MTX+LEF 0.82 (0.53-1.25), P= 0.3491; MTX+AM 0.97 (0.69-1.34), P= 0.8310; MTX+SSZ 1.01(0.68- 1.48), P= 0.9729; MTX+SSZ+AM 1.61 (0.91-2.84), P= 0.1006 SF-36, mean
SSZ only 1.70 (0.71) AM only 1.62 (0.69) 1 other DMARD 1.87 (0.69) MTX+LEF 1.55 (0.64) MTX+AM 1.52 (0.70) MTX+SSZ 1.57 (0.70) MTX+SSZ+AM 1.669 (0.66)	Radiographic measures, mean difference/absolute difference NR Quality of life scales, mean difference/absolute difference NR
Overall: HAQ DI: 1.64 (0.68	Others, (please name) Moderate EULAR OR for

achieving a response at week 12 (ADA+MTX as comparison group): D1: 0.45 (0.38-0.53), *P* < 0.0001 D2: LEF only 0.68 (0.54-0.84), P = 0.0004, SSZ only 0.72 (0.44-1.16), P = 0.1756, AM only 0.81 (0.51-1.30), P = 0.3859, 1 other DMARD 0.79 (0.42-1.46), P = 0.4446,MTX+LEF 0.92 (0.59-1.45), P = 0.7183, MTX+AM 1.33 (0.87-2.03), P = 0.1922, MTX+SSZ 1.36 (0.82-2.24), P = 0.2366, MTX+SSZ+AM 2.89 (1.04-8.01), P = 0.0411Good EULAR OR for achieving a response at week 12 (ADA+MTX as comparison group): D1: 0.53 (0.46-0.62), *P* < 0.0001 D2: LEF only 0.77 (0.64-0.93), P = 0.0058, SSZ only 0.95 (0.63-1.43), P = 0.8142, AM only 0.99 (0.67-1.44), P = 0.9420, 1 other DMARD 0.97 (0.57-1.65), P = 0.9157,MTX+LEF 0.72 (0.50-1.02), P = 0.0673, MTX+AM 0.99 (0.75-1.32), P = 0.9493, MTX+SSZ 0.94 (0.67-1.32), P = 0.7336, MTX+SSZ+AM 1.24 (0.74-2.09), P = 0.4180

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
Author, yr: Cannon et al., 2004 ²² Country, Setting: US, claims database Funding: Aventis Pharmaceuticals; Veterans Affairs Research Objective: The incidence of serious adverse events during txt of RA with DMARDs, focusing on LEF Study Design: Retrospective cohort study Overall N: 40594 Study Duration: 2 yrs	Age: 18 and older Diagnosed with	NR	Mean disease duration, yrs: NR TJC, mean: NR SJC, mean: NR DMARD use, %: NR Corticosteroid use, %: NR MTX naive, %: NR Txt resistant %: NR Pts with Early RA (≤3 yrs): NR Baseline DAS, mean: NR	Rates of AE in LEF group, alone and combined with MTX, were lower than or comparable to AE rates seen with MTX and other agents. LEF monotherapy had lowest rate of hepatic events in DMARD monotherapy groups All AE rates: LEF monotherapy (94 events/1000 PY, 95%CI, 84.4-104.8), MTX monotherapy (145 events/1000 PY, 95%CI,136.3-154.3), other DMARD (143 events/1000 PY, 95%CI,137.4-150.3), no DMARD (383 events/1000 PY, 95%CI,365.8-399.6) (P < 0.001). LEF + MTX (42.8/1000 PY, 95%CI, 32.8-55.9), LEF + other DMARD (58.7/1000 PY, 95%CI, 52.0-66.2), DMARD + MTX (69.5/1000 PY, 95%CI, 65.0-74.3; P = 0.002)		Overall Attrition Rate, %: NR ITT Analysis: NA Quality Rating: Fair

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
Author, yr: Capell, 2006 ²³ Country, Setting: Scotland, 8 NHS sites Funding: Wyeth and Pharmacia - drugs Arthritis Research Campaign Research Objective: If a combination of SSZ and MTX is superior to either alone in RA pts with supoptimal response to 6 mos of SSZ Study Design: RCT Overall N: 165 Study Duration: Phase I: 6 mos; Phase 2: 12 additional mos for those with DAS > 2.4 after 6 mos	defined by DAS > 2.4 after 6 mos SSZ txt were eligble for phase II • NSAIDs and other medications were continued • Intra-articular or intramuscular corticosteroid was permitted but not within 1 mo of 6, 12, & 18 mo assessments Exclusion Criteria: • Pregnant or lactating • Prior txt with: MTX or SSZ • Impaired renal or hepatic system: creatinine > 150 mmol/dl, ALT, aspertate	Phase I MTX: 7.5 mg/w (3 x 2.5 mg) increasing by 2.5 mg/mo until max of 25 mg or toxicity SSZ: enteric coated 500 mg/d increased by 500 mg/wkly until 40 mg/kg per d to a max of 4g/d for initial 6 mos Placebo: Folic Acid 5 mg/wk given 3 days after MTX and MTX + placebo N:	Mean disease duration, yrs: D1: 1.9 D2: 1.6 D3: 1.8 TJC, mean: NR SJC, mean: NR DMARD use, %: NR Corticosteroid use, %: NR MTX naive, %: All Txt resistant, %: All Pts with Early RA (≤3 yrs): NR Baseline DAS, mean: D1: 3.63 D2: 3.67 D3: 3.5 Sharp: D1: 17.0 D2: 14.0 D3: 12.0	Median change 18 mos: DAS: D1: -0.67 D2: -0.30 D3: -0.26 (D1 vs. D2; $P = 0.039$) (D1 vs. D3; $P = 0.023$) (D2 vs. D3; $P = 0.79$) HAQ: D1: -0.50 D2: -0.25 D3: -2.00 (D1 vs. D2; $P = 0.51$) (D1 vs. D3; $P = 0.57$) (D2 vs. D3; $P = 0.99$) SJC: D1: -3.00 D2: -3.00 D2: -3.00 D3: -2.00 (D1 vs. D2; $P = 0.94$) (D1 vs. D3; $P = 0.99$) SJC: D1: -3.00 D2: -3.00 D3: -2.00 (D1 vs. D3; $P = 0.94$) (D2 vs. D3; $P = 0.94$) (D1 vs. D3; $P = 0.94$) (D1 vs. D3; $P = 0.94$) (D1 vs. D3; $P = 0.94$) (D2 vs. D3; $P = 0.94$) (D1 vs. D3; $P = 0.94$) (D2 vs. D3; $P = 0.94$) (D1 vs. D3; $P = 0.94$) (D2 vs. D3; $P = 0.94$) (D1 vs. D3; $P = 0.94$) (D2 vs. D3; $P = 0.94$) (D1 vs. D3; $P = 0.94$) (D1 vs. D3; $P = 0.94$) (D2 vs. D3; $P = 0.94$) (D1 vs. D3; $P = 0.94$) (D2 vs. D3; $P = 0.94$) (D3 vs. D3; $P = 0.94$) (D1 vs. D3; $P = 0.94$) (D2 vs. D3; $P = 0.94$) (D3 vs. D3; $P = 0.94$) (D1 vs. D3; $P = 0.94$) (D2 vs. D3; $P = 0.94$) (D3 vs. D3; $P = 0.94$) (D3 vs. D3; $P = 0.94$) (D4 vs. D3; $P = 0.94$) (D3 vs. D3; $P = 0.94$) (D3 vs. D3; $P = 0.94$) (D4 vs. D3; $P = 0.94$) (D4 vs. D3; $P = 0.94$) (D5 vs. D3; $P = 0.94$) (D6 vs. D3; $P = 0.94$) (D1 vs. D3; $P = 0.94$) (D1 vs. D3; $P = 0.94$) (D2 vs. D3; $P = 0.94$) (D3 vs. D3; $P = 0.94$) (D3 vs. D3; $P = 0.94$) (D4 vs. D3; $P = 0.94$) (D4 vs. D3; $P = 0.94$) (D4 vs. D3; $P = 0.94$) (D5 vs. D3; $P = 0.94$) (D6 vs. D3; $P = 0.94$) (D1 vs. D3; $P = 0.94$)	NR	Overall Attrition Rate, %: 28.5 • 687 pts entered phase I (6 mos) • At 6 mos, 165 were not eliglbe to enter phase II (discontinued SSZ because of side effects: 19%, did not attend: 3.6%, died: 0.4%) • Another 191 were not randomized because DAS score was < 2.4 ITT Analysis: Yes Quality Rating: Fair

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
	pulmonary fibrosisUse of oral steroids > 7.5			D2: 2 (OR 1.50 (95% CI, 0.24-9.34), <i>P</i> = 1.00) D3: 2 (OR 3.00 (95% CI, 0.20)		
	mg/d • Known SSZ allergies			0.30-29.78), $P = 0.62$)		

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
Author, yr: Chakravarty, 2005 ²⁴ Country, Setting: US, multicenter Funding: Bristol-Myers- Squibb Research Objective: Rates of NMSC (non-melanoma skin camcer) in a large cohort of pts with RA or OA and to evaluate the role of immunosuppressi ve medications on the development of NMSC Study Design: Retrospective cohort study Overall N: 15,789 (RA); 3,639 (OA) Study Duration: NR	Participants in National Data Bank for Rheumatic Diseases (NDB) Recruited from 908 US rheumatologists; pts who returned at least 2 questionnaires between January 1999 and January 2003 Exclusion Criteria: NR	Interventions, dose: D1: pts with RA D2: pts with OA PRE MTX LEF TNF inhibitors N: D1: 15789 D2: 3639 Mean age, yrs: D1: 62 D2: 67 Sex, % female: D1: 77 D2: 83 Race, % white: D1: 91 D2: 94	Mean disease duration, yrs: NR TJC, mean: NR SJC, mean: NR DMARD use, %: NR Corticosteroid use, %: NR MTX naive, %: NR Txt resistant %: NR Pts with Early RA (≤3 yrs): NR Baseline DAS, mean: NR Skin cancer before NDB: D1: 3.8 D2: 5.8 History of smoking: D1: 56 D2: 46	A total of 738 pts with RA reported new cases of NMSC during followup within the NDB; crude incidence rate: 18.1 / 1000 PY (95% CI, 16.8 -19.4 / 1000 PY) After excluding prevalent cases of NMSC, incidence rate was 15.2 / 1000 PY (95% CI, 14.1 -16.5) Based on multivariate Cox proportional hazard analysis restricted to pts with RA Use of PNL was associated with an increased hazard ratio (HR) (HR: 1.28, P = 0.014) for development of NMSC No association found with use of LEF or MTX alone Use of any anti-TNF (ETA, INF, and ADA) alone showed a slightly increased risk An approximately 2-fold HR for development of NMSC was found among pts with RA using both MTX and any TNF inhibitor (HR 1.97, P = 0.001)	NA	Overall Attrition Rate, %: After initial assessment, ~ 8% of pts decline to participate each yr ITT Analysis: NA Quality Rating: Fair

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
•			Treatment Characteristics Mean disease duration, years D1: 2.7 mos (3.8) D2: 4.2 (5.7) D3: 5.1 (5.8) D4: 3.9 (5.2) Patients with early RA, three years or less, %	ACR mean difference/ absolute difference NR HAQ, mean change, at 2 years (SD) D1: -0.29 (0.07) D2: -0.20 (0.06) D3: -0.28 (0.07) D4: -0.50 (0.06) Overall: NR/ P = 0.02/P = 0.35/P = 0.01 DAS, mean change, at 2 years (SE) D1: -1.42 (0.17) D2: -1.34 (0.15) D3: -1.37 (0.15) D4: -1.67 (0.15) Overall: NR/P = 0.19/P = 0.13/P = 0.06 SF-36, mean change, at 2 years (SE) D1: 5.8 (1.0) D2: 3.9 (1.1) D3: 3.5 (1.0) D4: 8.0 (1.2) Overall: NR/ P = 0.22/P = 0.46/P = 0.001 Radiographic measures at 2 years Cases with new erosions (primary outcome), %: D1: 34 (29) D2: 19 (17) D3: 19 (16) D4: 15 (13) Mean change in Larsen	Overall Overall attrition/withdrawal, n: D1: 49 D2: 62 D3: 54 D4: 55 Overall: 220 Withdrawals due to adverse events, n: D1: 8 D2: 9 D3: 14 D4: 23 Overall: 71 Withdrawals due to lack of efficacy, n: D1: 13 D2: 8 D3: 10 D4: 7 Overall: 71 Other attrition: • n's for various arms reported as "exclusively withdrew for toxicity and lack of effect", but n: 71 totals for each reported intext. Withdrawals from toxicity: D1: 12 D2: 21 D3: 22 D4: 33 Withdrawals lack of effect: D1:19 D2: 17 D3: 13
		other arms	MTX naïve, %	score (SE):	D4: 15

Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events. %
Criteria	Interventions Cyclosporin: same as in arm 2 Number in group D1: 117 D2: 119 D3: 115 D4: 116 Overall: 467 Mean age, years (SD) D1: 54 D2: 53 D3: 54 D4: 55 Overall: NR Sex, % female D1: 67 D2: 65 D3: 66 D4: 67 Overall: 70 Race, % white NR Race, % black NR Ethnicity, Latino NR	Treatment Characteristics NR Baseline mean DAS28 score, mean (SD) D1: 5.8 (1.2) D2: 5.9 (1.3) D3: 5.8 (1.4) D4: 5.6 (1.3) Required treatment for latent TB NR Erosive changes on X-ray, %: D1: 32 D2: 37 D3: 30 D4: 34 Median Larsen score (IQR): D1: 7 (3, 15) D2: 8 (3, 23) D3: 6 (2, 20) D4: 5 (2, 14) HAQ score, mean (SD): D1: 1.5 (0.7) D2: 1.7 (0.7) D3: 1.6 (0.7) D4: 1.6 (0.7) SF-36 PCS, median (IQR): D1: 30 (9) D2: 29 (8) D3: 30 (10) D4: 30 (9)	D1: 7.41 (0.99) D2: 4.53 (0.88) D3: 4.70 (0.69) D4: 2.99 (0.51) Overall: 95% CI: NR (0.36, 0.96), $P = 0.03/$ (0.33,0.88), $P = 0.01$, $P = 0.32/$ (5.47,9.33), $P = 0.003$, $P = 0.008$, $P = 0.45$ Quality of life scales, mean difference/absolute difference NR	NNH for any adverse event leading to withdrawal was 20 (95% CI 8, 1280) with added ciclosporin and 14 (95% CI 665) with added PNL. Estimated NNH for triple therapy, based only on data from patients receiving this therapy was 6 (95% CI 3,23) Overall adverse events reported, n: D1: 21 D2: 18 D3: 19 D4: 23 Overall: 81 Serious adverse events Death, n: D1: 1 D2: 1 D3: 1 D4: 2 Overall: 5 Myocardial infarctions, angina, strokes, n: D1: 1 D2: 2 D3: 2 D4: 4 Overall: 9 Hepatotoxicity/elevated liver enzymes n: D1: 5 D2: 23
		Exclusion Criteria Cyclosporin: same as in arm 2 Number in group D1: 117 D2: 119 D3: 115 D4: 116 Overall: 467 Mean age, years (SD) D1: 54 D2: 53 D3: 54 D4: 55 Overall: NR Sex, % female D1: 67 D2: 65 D3: 66 D4: 67 Overall: 70 Race, % white NR Race, % black NR Ethnicity, Latino	Characteristics and Interventions	Exclusion Criteria Criteria Criteria Criteria Criteria Criteria Criteria Cyclosporin: same as in arm 2 Baseline mean DAS28 D2: 4.53 (0.88) D3: 4.70 (0.69) D4: 2.99 (0.51) D4: 117 D2: 119 D2: 5.9 (1.3) D3: 115 D3: 5.8 (1.4) D4: 116 D4: 5.6 (1.3) D3: 5.8 (1.4) D4: 116 D4: 5.6 (1.3) D3: 5.8 (1.4) D4: 5.6 (1.3) D3: 5.8 (1.4) D4: 5.5 (1.3) D4: 2.5 (0.33, 0.88), P = 0.01, P = 0.032 (5.47,9.33), P = 0.008, P = 0.032 (5.47,9.33), P = 0.008, P

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
					Malignancies, n D1: 5 D2: 2 D3: 0 D4: 1 Overall: 8
					Respiratory events Tuberculosis: NR
					Pneumonia n: D1: NR D2: NR D3: NR D4: NR Overall: 3
					Upper respiratory infection, n D1: 54 D2: 51 D3: 49 D4: 55 Overall: NR
					Other infections Upper GI, n: D1: 1 D2: 2 D3: 0 D4: 1 Overall: 4
					GI Nausea or vomiting, n: D1: 15 D2: 31 D3: 20 D4: 10 Overall: 76
					Abdominal pain, n: D1: 7 D2: 3

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
					D3: 9 D4: 7 Overall: 26
					Gl bleed or ulcer, n: D1: 5 D2: 16 D3: 4 D4: 14 Overall: 39
					Other Headache, n: D1: 6 D2: 17 D3: 10 D4: 15 Overall: 48
					Dizziness, n: D1: 4 D2: 14 D3: 6 D4: 5 Overall: 29
					Diarrhea , n: D1: 5 D2: 10 D3: 10 D4: 3 Overall: 28
					Paraesthesia, n: D1: 3 D2: 5 D3: 8 D4: 11 Overall: 27
					Cough, n: D1: 7 D2: 5 D3: 11

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
					D4: 4 Overall: 27
					Elevated blood pressure, n: D1: 1 D2: 11 D3: 8 D4: 17 Overall: 37

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
Author, yr: Chung, 2003 ²⁶ Country, Setting: US, University clinics (32 centers) Funding: Centocor Research Objective: To assess effectiveness and safety of INF in pts with moderate to severe congestive heart failure Study Design: RCT Overall N: 150 Study Duration: 28 wks	Inclusion Criteria: Age: 18+ Stable New York Heart Association (NYHA) class III or IV heart failure Exclusion Criteria: Prior txt with txt within 3 mos of INF or other therapeutic agents that could interfere with actions of TNF (eg, ETA, pentoxifylline, thalidomide, or D2E7) History of TB: had latent TB or had had TB within 3 yrs NSAID other than aspirin; experienced a serious infection within 2 mos Documented HIV infection	Interventions, dose: D1: placebo D2: INF 5mg/kg D3: INF 10mg/kg N: D1: 49 D2: 50 D3: 51 Mean age, yrs: D1: 60 D2: 62 D3: 62 Sex, % female: D1: 24 D2: 14 D3: 16 Race, % white: D1: 88 D2: 88 D3: 84	Mean disease duration, yrs: NR TJC, mean: NR SJC, mean: NR DMARD use, %: NR Corticosteroid use, %: NR MTX naive, %: NR Txt resistant %: NR Pts with Early RA (≤3 yrs): NR Baseline DAS, mean: NR	10 mg/kg INF group were more likely to die or be hospitalized for heart failure than placebo (hazard ratio 2.84, 95% confidence interval 1.01 to 7.97; nominal $P = 0.043$ using log-rank test);Pts in the 10 mg/kg INF group were more likely to be hospitalized for heart failure or for any reason than pts in the placebo or 5 mg/kg INF groups	Overall: D1: 83.3 D2: 92.2 D3: 84 SAEs: D1: 29.2 D2: 23.5 D3: 44 Serious Infections: D1: 2.1 D2: 5.9 D3: 8 Dizziness: D1: 4.2 D2: 31.4 D3: 20	Overall Attrition Rate, %: NR ITT Analysis: Yes Quality Rating: Fair

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
Author, year, study name, if applicable Cohen et al., 2006, Trial ²⁷ ; Keystone et	Inclusion CriteriaTreatment resistantHad RA for at	Interventions, dose D1: • MethylPNL: 100 mg, 30 minutes before	Mean disease duration, years Note: These data are based on safety population, n:	ACR ACR 20: D1: 18 D2: 51	Attrition/withdrawal Overall, n: D1: 97 D2: 57
al., 2008 ²⁸ ; Keystone et al., 2009 ²⁹ REFLEX	least 6 mos • Had active disease (8 or more tender joints, 8 or more		D1: 11.7 (7.7) D2: 12.1 (8.3) Overall: 517 Patients with early RA, three years or less, %	P = 0.0001 ACR 50: D1: 5 D2: 27 P = 0.0001	Withdrawals due to adverse events, n: D1: 2 D2: 8
Country and setting Mulitnational, multicenter	swollen joints, a CRP level of 1.5 or more, or an erythrocyte sedimentation	mg/week orally or parenterally • Placebo • Folate: 5 or more mg/week	NR Treatment resistant, % D1: 100 D2: 100	ACR 70: D1: 1 D2: 12 P = 0.0001	Withdrawals due to lack of efficacy, n: Required rescue therapy D1: 80 D2: 1
Source of funding Hoffman-La Roche, Biogen Idee, and Genentech	rate of 28 mm/hour or greater, and radiographic	D2: • MethylPNL: 100 mg, 30 minutes before each infusion	Tender Joint Count, mean, (SD) 68 joints assessed D1: 33.0 (15.6)	HAQ NR DAS	Adherent/compliant, n: D1: 112 D2: 254
NIH grant Research objective Determine efficacy and safety of tx with	evidence of at least 1 joint with a definite erosion	 PRED oral: 60 mg on days 2 - 7, 30 mg on days 8 - 14 MTX: 10 - 25 	D2: 33.9 (15.1) Swollen Joint Count, mean (SD)	D1: -0.4 D2: -1.9 P = 0.0001 SF-36	Serious adverse events NR Malignancies NR
RIT + MTX in pts with inadequate responses to anti- tumor necrosis factor	MTX (10 - 25	mg/week orally or parenterally • RIT: 2 infusions of 1,000 mg each	66 joints assessed D1: 22.9 (12.7) D2: 23.4 (11.8) Corticosteroid use, n (%)	NR Radiographic measures D1: N: 177	Respiratory events Tuberculosis: NR
therapies Study design Controlled Trials	mg/week) for at least 12 weeks prior to screening with	Folate: 5 or more mg/week Number in group	D1: 127 (61) D2: 200 (65) Previous DMARD use, n	D2: N: 268 Total Genant-modified Sharp radiographic score, mean	Other infections NR GI NR
Overall N 520 517 received	last 4 weeks at stable dose Experienced an inadequate	D1: 201 D2: 298 Mean age, years (SD) D1: 52.8 (12.6)	(%) D1: 2.4 (1.8) D2: 2.6 (1.8)	change from baseline (SD): D1: 1.2 (3.3) D2: 0.6 (1.9) No worsening of erosions, n	Other AEs • For safety population (N: 517)
treatment and were analyzed as part of "safety population." 499 were analyzed	response to previous or current treatment with	D2: 52.2 (12.2) Based on safety population	MTX naïve, % NR Baseline DAS28 score, mean (SD)	(%): D1: 106 (60%) D2: 176 (66%)	Any adverse event, n: 183 (88)Severe adverse event, n: 49 (23)
as ITT population. (3 never received treatment, some	anti-TNF agents inflixumab,	Sex, % female D1: 81	D1: 6.8 (1.0) D2: 6.9 (1.0)	Quality of life scales NR	• Related adverse event, n: 77 (37)

were treated prior to adalimuman, or D2: 81 Serious adverse event. n: Required treatment for **EULAR** randomization, and ETN Based on safety 21 (10) Moderate Response, %: latent TB others were Were intolerant population • Death, n: 0 (0) NR D1: 20 to at least 1 participants at a Race, % white D2: 50 center where administration of Other population NR blinding of the characteristics, %, (CI/SD/P these agents. Good Response, %: assessor was Race, % black value) D1: 2 Exclusion potentially D2: 15 NR Baseline characteristics are Criteria compromised). reported for safety History of Low disease, %: **Ethnicity, Latino** population, N: 517 - Placebo **Duration of study** rheumatic NR D1: 2 group, N: 209) Results presented autoimmune D2: 15 are at 24 weeks disease other HAQ-D, mean score (SD): Remission, %: REFLEX trial is a 2than RA (except D1: 1.9 (0.5) D1: 0 vear trial. secondary D2: 1.9 (0.6) D2: 9 Sjorgen's Quality rating Total Genant-modified Sharp syndrome) Fair radiographic score Significant D1: 47.9 (36.0) systematic D2: 48.3 (34.9) involvement secondary to Previous anti-TNF agents RA taken (no (%) of patients): ACR functional Inflixumab class IV disease D1: 169 (81) D2: 219 (71) ADA D1: 38 (18) D2: 71 (23) ETN D1: 104 (50) D2: 168 (55) Previous anti-TNF agents taken (mean (±SD)) D1: 1.5 (0.67) D2: 1.5 (0.67) Inadequate efficacy of anti-TNF agents (%) D1: 90 D2: 92

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and in combination, in pts with active RA despite SSZ txt Study Design: RCT Overall N: 260 Study Duration: 24 wks Study Duration: 25 means a control of the factor	D1: 13 D2: 47 D3: 31 D3: 32 D3: 31 D3

advantage to use of ETA in combination with SSZ

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
Author, year, study name, if applicable Combe et al., 2009 ³¹ ; add ³⁰ from old report Country and setting Multinational, multicenter Source of funding Wyeth Research Research objective Determine efficacy and safety of ETN and ETN + SSZ versus SSZ Study design Controlled Trials Overall N 260 Duration of study 2 years Quality rating Fair	older • Disease duration of 20 years or less with active adult onset of RA • Previous use of DMARDs: 2 to 3g SSZ/d for ≥ 4, w/o toxicity • Stable doses of oral corticosteroids	Interventions, dose D1: ETN: 25mg by subcutaneous injection twice daily Placebo Other: Patients in ETN discontinued SSZ D2: SSZ: 2g, 2.5g or 3g daily Placebo D3: SSZ: 25mg by subcutaneous injection twice daily ETN: 2g, 2.5g or 3g daily Number in group D1: 103 D2: 50 D3: 101 Interventions, dose: D1: SSZ (2,2.5, or 3 g /d) + placebo D2: ETA (25 mg SC twice wkly) + placebo D3: ETA (25 mg SC twice wkly) + SSZ (2,2.5, or 3 g /d) N: D1: 50 D2: 103 D3: 101 Overall: 254 Mean age, yrs:	Mean disease duration, years NR Patients with early RA, three years or less, % NR Treatment resistant, % NR Tender Joint Count, mean NR Swollen Joint Count, mean NR Corticosteroid use, % NR DMARD use, % NR MTX naïve, % NR Baseline DAS score NR Required treatment for latent TB NR	ACR At Week 2 ACR 20: D1: 67 D2: 77 D3: 34 P = 0.01 (ETA vs. SSZ) At Week 8 ACR 50: P = 0.01 At Week 12 ACR 70: P = 0.01 HAQ achieved, by % patients D1: 76 D2: 78 D3: 40 P = 0.01 (combination or ETN) DAS mean change at 2 years D1: 2.3 D2: -2.7 D3: -0.6 P = 0.05 for ETA vs. SFS DAS, %: 2.4 at 2 years D1: 45.6 D2: 4.0 D3: 57.0 DAS2.8 vs. 4.5 vs. 2.5 P = 0.01 SF-36 NR Radiographic measures, mean difference/absolute difference	Attrition/withdrawal Overall, n: D1: 38 D2: 34 D3: 24 Overall: 96 Withdrawals due to adverse events, n (%): D1: 8 D2: 9 D3: 10 Overall: NR Withdrawals due to lack of efficacy, n (%): D1: 52 D2: 6 D3: 6 P = 0.001 Overall adverse events reported, n: D1: 166 D2: 53 D3: 140 Overall: 359 Serious adverse events Death, n: Overall: 2 23 patients receiving combination, 27 receiving ETN and 2 receiving SSZ had one or more serious adverse event (SAE). Non-infectious SAE were significantly greater in patients receiving ETN (20.8% for the combination and 20.4% for ETN alone)

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
	or (2) received a DMARD other than SSZ within	D2: 51.3 D3: 50.6		NR Quality of life scales NR	compared with 4% for patients receiving SSZ ($P = 0.01$).
	3 mos. Or any biologic or cyclophosphami de within 6 mos, corticosteroids within 4 wks • Presence of	Overall: 51.4 Sex, % female: D1: 82.0 D2: 78.6 D3: 80.2 Overall: 79.9			Malignancies Lymphoma or leukemia, n: D1: 1 D2: 0 D3: 0 Overall: 1
	relevant comorbidity, including active infections	Race, % white Population described as predominantly white. Race, % black			Skin cancer (basal cell or squamous cell), n: D1: 1 D2: 0 D3: 0 Overall: 1
		NR Ethnicity, Latino NR			Respiratory events Tuberculosis: NR
		NR			Pneumonitis, n: D1: 1 D2: 0 D3: 0 Overall: 1
					Pharyngitis/laryngitis, n: D1: 24 D2: 2 D3: 10 P = 0.01 (combination vs. SFS)
					Sinusitis, n: D1: 12 D2: 0 D3: 3
					Other infections Any treatment-emergent infection, n: D1: 76 D2: 21

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
					D3: 60
					Bronchitis D1: 21 D2: 4 D3: 12
					Gingival/dental infection: D1: 7 D2: 2 D3: 12
					GI Nausea or vomiting, n: D1: 7 D2: 5 D3: 19 Overall: 31
					Abdominal pain, n: D1: 14 D2: 1 D3: 12 Overall: 27
					Dyspepsia, n: D1: 14 D2: 2 D3: 12 Overall: 28
					Diarrhea, n: D1: 11 D2: 0 D3: 6 Overall: 17
					Other Infusion/injection site reactions, n: D1: 34 D2: 2 D3: 2 Overall: 57

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
					Hemorrhage: D1: 9 D2: 3 D3: 14 Overall: 26
					Skin rashes/miscellaneous skin infections, n: D1: 15/19 D2: 3/0 D3: 8/12 Overall: 31
					Headache, n: D1: 11 D2: 4 D3: 25 Overall: 40
					Back pain, n: D1: 9 D2: 5 D3: 20 Overall: 34
					Parathesia , n: D1: 4 D2: 1 D3: 11 Overall: 16
					Flu syndrome, n: D1: 18 D2: 2 D3: 12 Overall: 32
					Leuccopenia, n: D1: 2 D2: 0 D3: 8 Overall: 10

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
Author, year, study name, if applicable Curtis et al., 2007 ³² Country and setting United States, Hospital and administrative claims data Source of funding Maryland Chapter of Arthritis Foundation, Agency for Healthcare Research and Quality and NIH National Institute of Arthritis and Musculoskeletal and Skin Diseases Research objective Evaluate risk of serious bacterial infections associated with TNFα antagonists Study design Retrospective Cohort Overall N n: 5,326 (obtained and abstracted 187 records for analysis) Duration of study 67 months (May 1998 to December 2003), median follow up time 17 months; 3,894 person-years for RA patients	 Inclusion Criteria RA patients older than 18 years with 2 ICD9 codes for RA Either received an infusion or filled a prescription for a TNFα antagonist or filled at least 3 prescriptions for MTX. Exclusion Criteria Individuals with HIV, who had an organ transplant, diagnosed with a malignancy 	Interventions, Dose D1: MTX, ETN, IFX, ADA, patients may have been using more than one biologic and/or other nonbiologic DMARDs or glucocorticoids in addition to a biologic D2: MTXOther (describe)patients may have been using other nonbiologic DMARDs or glucocorticoids in addition to MTX Number in group D1: 2393 D2: 2933 Mean age (years) D1: 50 D2: 55 P = 0.0001 Sex, % female D1: 73 D2: 73 Race, % white NR Race, % black NR Ethnicity, Latino NR	Mean disease duration, years (SD) NR Patients with early RA, three years or less, % NR Treatment resistant, % NR Tender Joint Count, mean (SD) NR Swollen Joint Count, mean (SD) NR Corticosteroid use, % NR DMARD use, % D1: 100 (inferred) D2: NR MTX naïve, % NR Baseline DAS score, mean (SD) NR Required treatment for latent TB NR Other population characteristics, %, (CI/SD/P value) D1: • Mean PRED equivalent dosage: None (referrent), 1,061 (44%) less than or equal to 5mg/day, 252	ACR NR HAQ NR DAS NR SF-36 NR Radiographic measures NR Quality of life scales NR Others, (please name); mean difference/absolute difference (CI/SD/P Value)	Overall Overall attrition/withdrawal, n: D1: 17 records for individuals in exposed Dcould not be accessed, therefore they were not abstracted. number of exposed out of total number of records (217) identified to be abstracted is not given, so a percentage cannot be determined Withdrawals due to adverse events, n: NR Withdrawals due to lack of efficacy, n: NR Adherent/compliant, n: NR Overall adverse events reported, n: D1: 86 (total infections) D2: 82 (total infections) Serious adverse events Death, n: NR Cardiovascular events (specify), n: NR Hepatotoxicity/elevated liver enzymes, n: NR Malignancies Lymphoma or leukemia, n: NR Skin cancer (basal cell or squamous cell), n: NR Other cancer (specify), n: NR Respiratory events Tuberculosis: NR Pneumonia, n: D1: 25 D2: 23

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics Health Outco	omes Adverse Events, %
receving TNFα antagonists and 4,846 person-years			(10%) • 5 - 10 mg/day, 348 (15%) • > 10 mg/day, 732 (31%)	Upper respiratory infection, n: NR
for RA patients receiving MTX.			 Selected medical conditions and drug usage 	Other infections Urinary tract infection, n:
Quality rating Fair			(only that those there were different between groups are abstracted, groups are	kidney/UTI D1: 8 D2: 10
			similar with respect to other conditions investigated):	Other infections (specify), n: NR
			 Severe RA (defined by claims for rheumatoid lung disease, rheumatoid carditis, inflammatory eye disease, or Felty's symdrome), 76 (3%) Joint surgery or deformity, 64 (3%) 	GI Nausea or vomiting, n:NR Abdominal pain, n: NR GI bleed or ulcer, n: NR Bowel obstruction, n: NR Other GI symptoms (specify), n: NR
			 Coronary artery disease (inlcuding CABG, angioplasty), 285 (12%) Number of comorbidities, 	Other AEs, n: Cellulitis/soft tissue, n: D1: 23 D2: 17
			 0.7 ±1 Anti TNFα use: IFX 792 (33%) 	Bacteremia/sepsis, n: D1: 7 D2: 8
			 ETN 1,201 (50%) ADA 118 (5%) ≥ 1 anti TNFα 282 (12%) MTX use 1,677 (70%); 	Postoperative, n: D1: 7 D2: 5
			 M1 A use 1,677 (10%), D2: Mean PRED equivalent dosage: None (referrent), 	Device associated, n: D1: 6 D2: 4
			1,290 (44%) less than or equal to 5mg/day, 294 (10%)	Septic Arthritis: D1: 4 D2: 4
			 5 - 10 mg/day, 418 (14%) > 10 mg/day, 931 (32%) Selected medical conditions (only those that 	Gastroenteritis: D1: 1 D2: 5

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
CHAIACLETISTICS	CITICITA	interventions	were different between groups are abstracted, groups are similar with respect to other conditions investigated): Severe RA (defined by claims for rheumatoid lung disease, rheumatoid carditis, inflammatory eye disease, or Felty's symdrome), 59 (2%) (<i>P</i> = 0.01) Joint surgery or deformity, 37 (1%) (<i>P</i> = 0.001) Coronary artery disease (inlcuding CABG, angioplasty), 43 (15%) (<i>P</i> <0.01) Number of comorbidities, 0.9 ±1.2 (<i>P</i> = 0.0001). MTX use 2,933 (100%) (<i>P</i> = 0.0001)	Treatification of the second o	Abdominal abscess: D1: 1 D2: 2 Osteomyelitis exposed: D1: 1 D2: 3 Bacterial sinusitis: D1: 3 D2: 0 Diverticulitis: D1: 0 D2: 0 Summary results: • 65 infections out of 2,393 exposed individuals (2.7% • 58 infections among 2,933 unexposed individuals (2.0%) • In first 6 months after inded date, there were 32 infections in exposed D(incidence of 2.9 infections per 100 person years) compared with 19 infections in unexposed D(incidence rate of 1.4 infections per 100 person years) • After mulitvariate adjustment, hazard ratios for "risk of hospitilization with a bacterial infection" for those receiving TNF-alpha antagonists was 1.94 (95% CI, 1.32 - 2.83) • Factors Associated hospitalization with a

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
					 (hazard ratio and 95% CI): Anti TNFα treatment crude HR: 1.39 (0.97 - 1.98), Adjusted HR: 1.94 (1.32 - 2.83) Age (5 year increments)Crude HR: 1.22 (1.14 - 1.31), Adjusted HR: 1.14 (1.03 - 1.27) Insurance Type, Medicare, Age: 65 years Crude HR: 2.82 (1.42 - 5.61), Adjusted HR: 2.88 (1.41 - 5.86), Age > 65 years Crude HR: 2.83 (1.89 - 4.22), Adjusted HR 1.88 (1.01 - 3.32) Number of Face to Face physician visits Crude HR: 1.07 (1.05 - 1.10), Adjusted HR: 1.04 (1.01 - 1.07) Prior Infection Crude HR: 1.98 (1.19 - 3.31), Adjusted HR: 1.46 (0.85 - 2.51) Chronic Obstructive Pulmonary Disease Crude HR: 2.68 (1.71 - 4.18) Adjusted HR: 1.90 (1.19 - 3.04) Diabetes mellitus Crude HR: 2.60 (1.66 - 4.06), Adjusted HR: 1.75 (1.10 - 2.78) Kidney Disease crude HR: 6.84 (3.01 - 15.5), Adjusted HR: 3.23 (1.35 - 7.73 Decubitus Ulcer crude

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
					HR: 6.35 (3.22 - 12.52), Adjusted HR: 3.05 (1.50 - 6.19) Number of comorbidities crude HR: 1.50 (1.31 - 1.68), Adjusted HR: NS Mean PRED equivalent doasage > 10 mg per day Crude HR: 1.92 (1.26 - 2.91), Adjusted HR 1.85 (1.21 - 2.85)

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
•	Exclusion Criteria Inclusion Criteria At least 2 International Classification of Diseases, Ninth Revision, Clinical Modification diagnosis codes for RA (714.x, excluding 714.3), receiving either IFX, ADA, ETN or MTX without a TNFα antagonist All patients exposed to TNFα antagonist were new users, defined as having at least 6 months of nonexposure to these drugs prior to first filled prescription. Exclusion Criteria	Interventions	Mean disease duration, years (SD) NR Patients with early RA, three years or less, % NR Treatment resistant, % NR Tender Joint Count, mean (SD) NR Swollen Joint Count, mean (SD) NR Corticosteroid use, % NR DMARD use, % NR MTX naïve, % NR Baseline DAS score, mean (SD) NR Required treatment for latent TB NR Other population	Health Outcomes ACR NR HAQ NR DAS NR SF-36 NR Radiographic measures NR Quality of life scales NR Others, (please name); mean difference/absolute difference (CI/SD/P Value) NR	Overall Overall attrition/withdrawal, n: NR Withdrawals due to adverse events, n: NR Withdrawals due to lack of efficacy, n: NR Adherent/compliant, n: NR Attrition information is not reported as they utilized person-years in their analyses. INF: 372 person-yrs, ETN: 602 person-yrs, ETN: 602 person-yrs, MTX: 1197 person-yrs. Overall adverse events reported, n: NR Serious adverse events NR Malignancies NR Respiratory events NR Other infections D1: Bacterial Infection:: 6 months, n: 16, IR/100 person-yrs: 4.30, 95% CI (2.46 - 6.98), adjusted
Study design Cohort Study Overall N 5195 Duration of study Greater than 6	Patients who were exposed to multiple TNFα antagonists during same window of risk were excluded		characteristics, %, (CI/SD/P value) D1: Physician encounters in 6 months prior to therapy: 8.2 D2: Physician encounters in 6 months prior to therapy: 7.0		(2.46 - 6.98), adjusted IRR: 2.40, 95% CI (1.23-4.68); > 6 months, n: 10, IR/100 person-yrs: 1.61, 95% CI (0.77-2.97), adjusted IRR: 1.14, 95% CI (0.55-2.24); D2: Bacterial Infection:: 6

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
months (specific duration not provided); Personyears: IFX: 372, ETN: 602, MTX: 1197 Quality rating Fair	(within 90 days of most recent filled prescription for drug of interest).		D3: Physician encounters in 6 months prior to therapy: 6.9 Overall: NR		months, n: 12, IR/100 person-yrs: 1.99, 95% CI (1.03-3.48), adjusted IRR: 1.61, 95% CI (0.75- 3.47); > 6 months, n: 19, IR/100 person-yrs: 1.34, 95% CI (0.81-2.10), adjusted IRR: 1.37, 95% CI (0.74-2.53) D3: Bacterial Infection:: 6 months, n: 20, IR/100 person-yrs: 1.67, 95% CI (1.02-2.58), adjusted IRR: referent; > 6 months, n: 34, IR/100 person-yrs: 1.55, 95% CI (1.11-2.22), adjusted IRR: referent Overall: Bacterial Infection:: 6 months, n: 48, > 6 months, n: 63, IR/100 person-yrs: NR
					GI NR
					Other NR

S tudy Characteris tics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Advers e Events, %
Author, year, study name, if applicable Curtis et al., 2007 ³⁴ Country and setting USA Source of funding FDA CBER Award #223-02-1420 Task Order #1, Maryland chapter of Arthritis Foundation, grant HS10389 from AHRQ, K24 AR052361-01 from National Institute of Arthritis and Musculoskeletal and Skin Diseases, and T32 AR47512-03 from NIH Research objective Investigate a possible association between TNF-antagonist use and incident heart failure Study design Observational Overall N 2121 with RA Duration of study Medical and phDacy administrative claims from January 1998 to December 2002 (5 years), with medical record review for	Inclusion Criteria At least two ICD9-CM diagnosis codes for RA (714.X) or CD (555.X) during study period, received an infusion or filled a prescription for a TNF- antagonist or filled at least three prescriptions for one of several selected immunosuppres sive drugs. Exclusion Criteria HIV, organ transplantation, or malignancy in 6 mos prior to index date	to fill at least three prescriptions for MTX. Number in group D1: 330 D2: 808 D3: 983 Mean age (years) D1: 40 D2: 38 D3: 39 Sex, % female D1: 70 D2: 75 D3: 75 Race, % white NR Race, % black	Mean disease duration, years (SD) NR Patients with early RA, three years or less, % NR Treatment resistant, % NR TJC, mean (SD) NR SJC, mean (SD) NR Corticosteroid use, % D1: 53 D2: 45 D3: 42 DMARD use, % D1: non anti-TNF alpha DMARD use 83% D2: non anti-TNF alpha DMARD use 85% D3: non anti-TNF alpha DMARD use 100% MTX naïve, % NR Baseline DAS score, mean (SD) NR Required treatment for latent TB NR Other population characteristics, %, (CI/S D/P value) D1:	ACR mean difference/ absolute difference (CI/S D/P Value) ACR 20: NR ACR 50: NR ACR 70: NR HAQ, mean difference/ absolute difference NR DAS, mean difference/absolute difference NR SF-36, mean difference/absolute difference NR Radiographic measures, mean difference/absolute difference NR Quality of life scales, mean difference/absolute difference NR Others, (please name); mean difference/absolute difference NR	Serious adverse events Cardiovascular events (specify), n: D1: Definite and possible heart failure; N = 1 (in IFX group) D2: Definite and possible heart failure; N = 4 (in ETN group) D3: Definite and possible heart failure; N = 1 (in unexposed group) Any other AEs: Exposed group: patients receiving TNF-alpha antagonists Unexposed Group: patients not receiving TNF-alpha antagonists, these patients did receive MTX, 6-mercaptopurine, azathioprine, or PRED. Cumulative incidence of HF among exposed patients: 4.4 cases per 1000 persons Cumulative incidence of HF among unexposed patients: 1.0 case per 1000 persons in unexposed group. RA exposed compared with RA unexposed, RR = 4.3 (ns) RA exposed (ETN) compared to RA unexposed, RR = 4.9 (ns) RA exposed (IFX) compared to RA unexposed, RR = 3.0 (ns)

	Inclusion and				
Study	Exclusion	Characteristics and	Baseline Disease and		
Characteristics	Criteria	Interventions	Treatment Characteristics	Health Outcomes	Adverse Events, %
identified cases			Exposed D(IFX)		
Quality rating			• N = 330		
Fair			 Age 40 ± 8 years 		
. un			 Women N = 230 (70%) 		
			 Duration of health plan 		
			enrollment 15 ± 10 mos		
			Number of physician visits		
			23 ± 23		
			 Proportion of patients hospitalized N = 36 (11%) 		
			 Comorbidities in 6 mos 		
			prior to index date: extra-		
			articlar disease, N =		
			27(8%)		
			 Joint deformity, N = 16 		
			(5%)		
			 Joint surgery, N = 20 (6%) 		
			 Coronary artery disease, N 		
			= 3 (1%)		
			Medication use in 6 mos		
			prior to index date(mean ± SD of infusions or filled		
			prescriptions): MTX, 9 ± 11		
			Glucocorticoid use, N =		
			176 (53%)		
			• NSAID use, N = 266 (81%)		
			Non anti-TNF-alpha		
			DMARD use, N = 274		
			(83%)		
			 As above, or 		
			glucocorticoids, N = 309		
			(94%)		
			D2:		
			Exposed Drug (ETN)N = 808		
			 N = 808 Age 38 ± 10 years 		
			 Age 36 ± 10 years Women N = 608 (75%) 		
			 Wolfler N = 606 (75%) Duration of health plan 		
			enrollment 21 ± 16 mos		
			Number of physician visits		

Study	Inclusion and Exclusion	Characteristics and	Baseline Disease and		
Characteristics	Criteria	Interventions	Treatment Characteristics	Health Outcomes	Advers e Events, %
			24 ± 32		
			Proportion of patients Proportion of patients Proportion of patients		
			hospitalized N = 95 (12%) • Comorbidities in 6 mos		
			prior to index date: extra-		
			articlar disease, N =		
			36(4%)		
			 Joint deformity, N = 39 		
			(5%)		
			 Joint surgery, N = 68 (7%) 		
			Coronary artery disease, N		
			= 12 (1%)		
			 Medication use in 6 mos prior to index date (mean ± 		
			SD of infusions or filled		
			prescriptions): MTX, 5 ± 10		
			Glucocorticoid use, N =		
			365 (45%)		
			 NSAID use, N = 711 (88%) 		
			 Non anti-TNF-alpha 		
			DMARD use, N = 684		
			(85%)		
			 As above, or glucocorticoids, N = 730 		
			(90%)		
			D3:		
			 Unexposed Group 		
			• N = 983		
			 Age 39 ± 10 years 		
			Women N = 742 (75%)		
			Duration of health plan		
			enrollment 17 ± 14 mos (P		
			< 0.001)		
			 Number of physician visits 19 ± 26 (P < 0.0001) 		
			 Proportion of patients 		
			hospitalized N = 59 (6%)		
			(P < 0.0001)		
			 Comorbidities in 6 mos 		
			prior to index date: extra-		

S tudy Characteris tics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Advers e Events, %
			articlar disease, N = $27(3\%)(P < 0.01)$ Joint deformity, N = 27 $(3\%)(P = < 0.05)$ Joint surgery, N = 31 $(3\%)(P = < 0.0001)$ Coronary artery disease, N = 6 $(1\%)(NS)$ Medication use in 6 mos prior to index date (mean + or - SD of infusions or filled prescriptions): MTX, $13 \pm 13 (P < 0.01)$ Glucocorticoid use, N = $412 (42\%)(P < 0.01)$ NSAID use, N = $874 (89\%)(P < 0.05)$ Non anti-TNF-alpha DMARD use, N = $983 (100\%)(P < 0.001)$ As above, or glucocorticoids, N = $983 (100\%)(P < 0.001)$ - Note: P-values compare pooled IFX and ETN RA patients with unexposed RA patients.		

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
Author, yr: De Bandt et al., 2005 ³⁵ Country, Setting: France, clinical reports Funding: NR Research Objective: To report cases and incidence of anti-TNF-induced SLE from a French national survey Study Design: Case series Overall N: 10,700 (22 cases) Study Duration: varied	Inclusion Criteria: Pts in France given INF or ETA; cases of SLE-like illness during anti-TNF txt were sought; retrospective survey of French rheumatologists and internists between June and October 2003 All French hospital centres prescribing anti-TNF txts (ETA and INF at that time) were surveyed Exclusion Criteria: Improper diagnosis of lupus	Interventions, dose: D1: Limited skin lupus D2: Complete lupus ETA: varied INF: varied N: D1: 10 D2: 12 Mean age, yrs: D1: of RA onset 39 D2: 36 Sex, % female: NR Race, % white: NR	Mean disease duration, yrs: NR TJC, mean: NR SJC, mean: NR DMARD use, %: NR Corticosteroid use, %: NR Txt resistant %: NR Txt resistant %: NR Pts with Early RA (≤3 yrs): NR Baseline DAS, mean: NR INF/ETA: D1: 6 / 4 D2: 9 / 3	Incidence 15/7700: 0.19% with INF and 7/3800: 0.18% with ETA 32 initially reported, 10 were ruled out leaving 22 cases 10 pts only had anti-DNA antibodies and skin manifestations 1 could classify as 'limited skin lupus' or 'toxidermia' in a context of autoimmunity, and 12 pts had more complete drug-induced lupus with systemic manifestations	NA	Overall Attrition Rate, %: NA ITT Analysis: NA Quality Rating: Fair

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
Author, year, study name, if applicable den Broeder et al., 2007 ³⁶ Country and setting The Netherlands, hospital Source of funding NR Research objective Identify risk factors for SSI in RA pts with special attention for anti-TNF tx Study design Observational Overall N 1219 Duration of study January 1997 (at Sint Maartenskliniek, January 2001; Radboud University Nijmegen Medical Centre, January 1997) through September 2004 Quality rating Fair: cohort baseline differences and number of patients between groups 1 and 2 decrease quality in strength of study	between introduction of TNF inhibitors. Exclusion Criteria Patients with no	D1: anti-TNF-naive patients (1) D2: stopped anti-TNF treatment (2A) D3: patients that continued anti-TNF treatment (2B) Number in group D1: 1023 D2: 104 D3: 92 Overall: 1219 Mean age (years) D1: 61 D2: 54 D3: 57 Overall: 60 Sex, % female D1: 77 D2: 75	Mean disease duration, years (SD) D1: 17 yrs (11) D2: 16 (9) D3: 17 (8) Overall: 17 (11) Patients with early RA, three years or less, % NR Treatment resistant, % NR TJC, mean (SD) NR SJC, mean (SD) NR Corticosteroid use, % D1: 30 D2: 40 D3: 42 Overall: 32 DMARD use, % D1: NR D2: NR D3: NR Overall: 16 MTX naïve, % D1: 0 D2: 0 D3: 0 Overall: 0 Baseline DAS score, mean (SD) NR Required treatment for latent TB	ACR mean difference/absolute difference (CI/SD/P Value) NR HAQ, mean difference/absolute difference (CI/SD/P Value) NR DAS, mean difference/absolute difference/absolute difference (CI/SD/P Value) NR SF-36, mean difference/absolute difference (CI/SD/P Value) NR Radiographic measures, mean difference/absolute difference (CI/SD/P Value) NR Quality of life scales, mean difference/absolute difference (CI/SD/P Value) NR Others, (please name); mean difference/absolute difference (CI/SD/P Value) NR	Overall Seventeen cases in cohort 2 were excluded because documentation of anti-TNF treatment was incomplete (9 IFX, 5 ETN, 3 ADA), percentage of missing values was 3%. Due to a logistical error, data on prior SSI/skin infections were missing for cohort 1 patients from Maartenskliniek. For cohort 2, data were complete. Overall adverse events reported, n: D1: Total noninfectious complications: 115 D2: Total noninfectious complications: 13 Overall: Total noninfectious complications: 13 Overall: Total noninfectious complications: 134 Serious adverse events Death, n: D1: 4 D2: 0 D3: 0 Overall: 4 Cardiovascular events (specify), n: NR Hepatotoxicity/elevated liver enzymes, n: NR Malignancies

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
			NR Other population characteristics,		Respiratory events NR
			 %, (CI/SD/P value) D1: Concomitant MTX (%): 34 > 1 DMARD (%): 11 D2: Concomitant MTX (%): 37 > 1 DMARD (%): 54 D3: Concomitant MTX (%): 38 > 1 DMARD (%): 46 		Other infections D1: Surgical site infections: 41 D2: Surgical site infections: D3: Surgical site infections: Overall: Surgical site infections: 55 (22 were backed by positive cultures) GI NR
					Perioperative continuation of anti-TNF was not associated with a significant increase of SS risk, according to entry model (OR, 1.56, 95% CI, 0.52-4.66) and when corrected for potential confounders (OR, 1.50, 95% CI, 0.43-5.2). Wound dehiscence occurred more frequently in patients that continued anti-TNF compared to patients that temporarily discontinued anti-TNF treatment (OR, 11.2, 95% to associate with the continued anti-TNF treatment (OR, 11.2, 95% to associated with the continued anti-TNF treatment (OR, 11.2, 95% to associated with the continued anti-TNF treatment (OR, 11.2, 95% to associated with a significant treatment to a significant treatment to a significant treatment to a significant treatment t
					 CI, 1.4-90). Risk of wound dehiscence was, however, very low in patients that stopped anti TNF treatment. Compared with anti-TNF-naive patients OR for

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
					wound dehiscence was lower but still significant (RR 2.4, 95% CI, 1.1-5.0).

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
Author, yr: Dixon et al., 2006 ³⁷ Country, Setting Britain Multicenter Funding: Schering Plouogh Wyeth, Abbott, and Amgen all fund The British Society for Rheumatology Biologics Register (BSRBR) Research Objective: The rate of serious infection anti-TNF-pts compared with RApts treated with traditional DMARDs Study Design: Prospective cohort study Overall N: 8,973 Study Duration: 11,220 PY	ANTI-TNF cohort: diagnosed by physician w/ RA Treated with ETA, INF, or ADA as first anti-TNF drug, at least 6 mos of followup by September 2005 Comparison cohort: physician diagnosis of RA, active disease (guideline DAS28 > 4.2), current txt with a DMARD, and no previous use of biologic drugs	Interventions, dose: D1: DMARD D2: All anti-TNF D3: ETA D4: INF D5: ADA N: D1: 1354 D2: 7664 D3: 3596 D4: 2878 D5: 1190 Mean age, yrs: D1: 60 D2: 56 D3: 56 D4: 56 D5: 57 Sex, % female: D1: 71 D2: 76 D3: 77 D4: 76 D5: 74 Race, % white: NR	Median disease duration, yrs: D1: 6 D2: 12 D3: 12 D4: 12 D5: 11 TJC (median): D1: 6 D2: 16 D3: 16 D4: 16 D5: 15 SJC (median): D1: 5 D2: 11 D3: 11 D4: 12 D5: 12 DMARD use, %: NR Corticosteroid use, %: NR Corticosteroid use, %: NR Txt resistant %: NR Pts with Early RA (≤3 yrs): NR	:In pts with active RA, anti-TNF therapy was not associated with increased risk of overall serious infection compared with DMARD txt, after adjustment for baseline risk. In contrast, the rate of serious skin and soft tissue infections was increased, suggesting an important physiologic role of TNF in host defense in the skin and soft tissues beyond that in other tissues	Serious Infections: • D1: N:56 (41 events/1000 PY) • D2: N:525 (53 events/1000 PY) UTI: • D1: N:3 (2.2 events/1000 PY) • D2: N:45 (4.6 events/1000 PY)	Overall Attrition Rate, %: NA ITT Analysis: NA: Quality Rating: Fair

D1: 5.1
D2: 6.6
D3: 6.6
D4: 6.6
D4: 6.6
D5: 6.6

Diabetes %:
D1: 5.5
D2: 5.4
D3: 6.0
D4: 4.6
D5: 5.5

COPD/asthma %:
D1: 20
D2: 13
D3: 14
D4: 12
D5: 13

Author, year, study name, if applicable Dixon et al., 2006, 38 British Society for Rheumatoid Biologics Register Country and setting UK, hospitals/general Inclusion Criteria	Mean disease duration, years (SD) D1: 6 yrs (IQR = 1 - 15) D2: 12 yrs (IQR = 6 - 19) Overall: 100 Patients with early RA, three years or less, % NR Treatment resistant, % NR	ACR mean difference/ absolute difference (CI/SD/P Value) ACR 20: ACR 50: ACR 70: HAQ, mean difference/ absolute difference (CI/SD/P Value)	Adverse events reported, n: Urinary tract infection, n: D1: 3; Incidence rate/1,000 person-years: 2.2 (0.5 - 6.5) D2: 45; Incidence rate/1,000 person-yeears: 4.6 (3.3 - 6.1)
who had been treated with ETN, IFX, or ADA as their first anti-TNF drug. Patients had to have completed at least 6 mos of followup by September 2005 Research objective To compare rates of serious infection in RA patients treated with anti-TNF to those treated with traditional DMARDs Study design Observational Who had been treated with ETN, IFX, or ADA as their first anti-TNF drug. Patients had to have completed at least 6 mos of followup by September 2005 Comparison cohort: biologic naive, a physician diagnosis of RA, current treatment with a DMARD. Comparison patients also had to have completed at least 6 mos of followup by September 2005 Comparison patients also had to have completed at least 6 mos of followup by September 2005. Exclusion Criteria Who had been treated with ETN, IFX, or ADA as their first anti-TNF drug. Mean age (years) D1: 60 D2: 56 Sex, % female D1: 71 D2: 76 Race, % white NR Race, % black NR Ethnicity, Latino NR Ethnicity, Latino NR Exclusion Criteria In order to limit	TJC, mean (SD) D1: median = 6 (IQR = 3 - 13) D2: median = 16 (IQR = 10 - 22) SJC, mean (SD) D1: median = 5, (IQR = 2 - 9) D2: median = 11 (IQR = 7 - 16) Corticosteroid use, % D1: 22 D2: 47 DMARD use, % D1: 100 D2: 100 MTX naïve, % NR Baseline DAS score, mean (SD) D1: 5.1 D2: 6.6 Required treatment for latent TB NR Other population	DAS, mean difference/absolute difference (CI/SD/P Value) SF-36, mean difference/absolute difference (CI/SD/P Value) Radiographic measures, mean difference/absolute difference (CI/SD/P Value) Quality of life scales, mean difference/absolute difference (CI/SD/P Value) Others, (please name); mean difference/absolute difference (CI/SD/P Value)	Other infections (specify), n: D1: All serious infections: n = 56 Rate of infections/1,000 person-years (95% CI) = 41.4 (31.4 - 53.5) D2: All serious infections: n = 525 Rate of infections/1,000 person-years (95% CI) = 53.2 (48.9 - 57.8) Overall: All serious infections, IRR, DMARD = ref, adjusted for age and sex: 1.47 (1.07 - 2.01) Adjusted for aged, sex, disease severity, comorbidity, extraarticular manifestations, steroid use, and smoking: 1.03 (0.68 - 1.57) D1: Lower respiratory tract: 36 Incidence rate/1,000 person-years: 26.6 (18.7 - 36.7) D2:

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
Duration of study December 2001 to September 2005 Quality rating Fair	problems associated with recall and left censorship • Patients who had been registered > 6 mos after start of biologic therapy were excluded.		characteristics, %, (CI/SD/P value) D1: HAQ score, mean: 1.5 Extraarticular disease: 21% Current smoker: 26% Former smoker: 39% Never a smoker: 35% COPD/asthma: 20% D2: HAQ score, mean: 2.1 Extraarticular disease: 30% Current smoker: 22% Former smoker: 38% Never a smoker: 40% Diabetes: 5.4% COPD/asthma: 13%		 Lower respiratory tract: 203 Incidence rate/1,000 person-years: 20.6 (17.9 - 23.6) D1: Skin and soft tissue: 4; Incidence rate/1,000 person-years: 3.0 (0.8 - 7.6) D2: Skin and soft tissue: 118; Incidence rate/1,000 person-years: 12.0 (9.9 - 14.3) D1: Bone and joint: 4; Incidence rate/1,000 person-years: 3.0 (0.8 - 7.6) D2: Bone and joint: 68; Incidence rate/1,000 person-years: 6.9 (5.4 - 8.7) D1: Bacterial intrcellular infections: 0 D2: Bacterial intrcellular infections: 19 (10 Mycobacterium TB, 2 Legionella pneumophila, 3 Listeria monocytogenes, 1 Mycobacterium fortuitum, and 3 Salmonella) Subanalysis: No. of infections: DMARD = 56, ETN = 209, IFX = 255, ADA = 61; Rate of infections/1,000 person-years (95% CI):

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
					DMARD = 41.4 (31.4-53.5), ETN = 51.3 (44.7-58.5), IFX = 55.2 (48.8-62.2), ADA = 51.9 (39.9-66.2); • Adjusted IRR (DMARD = ref): ETN = 0.97 (0.63-1.50), IFX = 1.04 (0.68-1.61), ADA = 1.07 (0.67-1.72); • TB, crude IR: ETN = 0.5, IFX = 1.5, • ADA = 0.9; adjusted IRRs for TB (ETN = ref): IFX = 4.9 (95% CI, 0.5-49.8) and ADA = 3.5 (0.3-47.3)

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
Author, year, study name, if applicable Dixon et al., 2007 ³⁸ ; British Society for Rheumatology Biologics Register (BSRBR). Country and setting United Kingdom (UK) Source of funding British Society for Rheumatology is indirectly funded by Schering-Plough, Whety Laboratories, Abbot Laboratories, and Amgen Research objective Determine whether incidence of myocardial infarction (MI) was lower in pts treated with anti-TNFα than traditional DMARDs; to explore impact of response to tx on rates of MI in anti-TNFalpha cohort Study design Prospective Cohort Study Overall N N: 10,755; 74 individuals switched groups during course	 Inclusion Criteria Registered with BSRBR Diagnosed with RA Followed up for more than 6 months by July 31, 2006 Anti-TNFalpha cohort: treated with an anti-TNFalpha drug Registered with BSRBR within 6 months of starting biologic therapy. UK national guidelines require that patients to whom anti-TNFa drugs are prescribed have a Disease Activity Score in 28 joints > 5.1 despite previous therapy with at least 2 DMARDs, one of which must have been MTX. DMARDs cohort: never 	Interventions, Dose D1: Unspecified DMARDs: dose and frequency NR D2: ETN IFX ADA In anti-TNFalpha group, 3,844 pts received ETN, 2,944 pts received infliximib, and 1,871 pts received ADA. Dosages and frequencies were not reported. Number in group D1: 2,170 D2: 8,659 Mean age (years) D1: 60 D2: 56 Sex, % female D1: 72 D2: 76 Race, % white NR Race, % black NR Ethnicity, Latino NR	Mean disease duration, years (SD) D1: 7 years (IQR, 1 - 15) D2: 12 years (IQR, 6 - 19) Patients with early RA, three years or less, % NR Treatment resistant, % NR Tender Joint Count, mean (SD) NR Swollen Joint Count, mean (SD) NR Corticosteroid use, % D1: 19.3 D2: 43.7 DMARD use, % D1: 100% D2: NR MTX naïve, % D1: NR D2: 0 (inferred) Baseline DAS score, mean (SD) D1: 5.0 (SD 1.4) D2: 6.6 (SD 1.0) Required treatment for latent TB NR Other population	ACR NR HAQ NR DAS NR SF-36 NR Radiographic measures NR Quality of life scales NR Others, (please name); mean difference/absolute difference (CI/SD/P Value)	Overall Overall attrition/withdrawal, n: In general for BSRBR only 2.2% of all patients enrolled > 12 months before July 31, 2006 had no returned rheumatologist questionnaires and 17.2% had no returned patient diaries. Only 0.6% had no follow up information from either source. Patients with no returned information from rheumatologist were not included in this analysis. Overall adverse events reported, n: D1: 17 D2: 63; In subanalysis, nonresponders had 17 AEs and responders had 35 AEs. Serious adverse events Cardiovascular events (specify), n: D1: MI, 17 D2: MI, 63; In subanalysis, nonresponders had 17 MIs (n: 1,638), and responders had 35 MIs (n: 5,877). Malignancies NR
of study and were counted in both	taken biologic agents, diagnosed as		characteristics, %, (CI/SD/P value)		Respiratory events NR

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
TNFalpha groups. Duration of study Anti-TNFalpha Drepresented 13,233 person-years of follow up. DMARDs Drepresented 2,893 person-years of follow up. Median follow up for anti- TNFalpha cohort was 1.66 years; median follow up for DMARDs cohort was 1.34 years. Quality rating Fair: Drug specific data not reported	Exclusion Criteria NR		 BMI, mean ±SD kg/m2: 26.9 (5.7) Smoking History, no. (%), current smoker 537 (25), Former Smoker 849 (39), Never Smoked 767 (35) Prior MI, no (%), 116 (5.3) Angina, no (%), 183 (8.4) Hypertension, no (%), 672 (31.0) Diabetes, no. (%), 132 (6.1) Corticosteriods, no. (%), 418 (19.3) Lipid-lowering Drugs, no. (%), 338 (15.6) Antiplatelet Drugs. no (%), 291 (13.4) NSAIDs, no. (%), 1344 (61.9) D2: BMI, mean ±SD kg/m2: 26.7 ± 5.8) Smoking History, no. (%), current smoker 1886 (22), Former Smoker 3298 (38), Never Smoked 3431 (40) Prior MI, no (%), 250 (2.9) Angina, no (%), 381 (4.4) Hypertension, no (%), 2581 (29.8) Diabetes, no. (%), 470 (5.4) Corticosteriods, no. (%), 3793 (43.7) Lipid-lowering Drugs, no. (%), 768 (8.9) Antiplatelet Drugs. no (%), 648 (7.5) NSAIDs, no. (%), 5705 		Other In DMARD group, Personyears, 2893 Number of Reported Mls: 17 Rate of Mls per 1000 person-years (95% CI): 5.9 (3.4-9.4) Incident rate ratio, referent Incidence rate ratio adjusted for age and sex, referent Incidence rate ratio multivariate analysis, referent In anti-TNFalpha DPersonyears, 13323 Number of Reported Mls, 63 Rate of Mls per 1000 person-years (95% CI), 4.8 (3.7 - 6.1) Incident rate ratio, 0.81 (0.47 - 1.38) Incidence rate ratio adjusted for age and sex, 1.13 (0.65 - 1.96) Incidence rate ratio multivariate analysis, 1.44 (0.56 - 3.67) In subanalysis, results among nonresponders, Person-years 1,815, Number of reported Mls: 17, rate of Mls per 1,000 person years was

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics Health Outcome	s Adverse Events, %
			 (65.9) A sub-analysis was done of non-responders and responders Anti-TNFalpha Nonresponders, N: 1,638 Mean Age (Y), 57 Sex, female (%), 79 Race, white (%), NR Race, black (%), NR Ethnicity, Latino (%) NR Disease Duration (mean & SD), 11 (IQR, 6-19) DMARD use (%), NR Corticosteroid use (%) 45.3 MTX naïve (%), 0 (inferred) Treatment resistant (%) NR Patients with early RA, three years or less, (%), NR Baseline DAS score, mean (SD), 6.4 (SD 1.1) Tender joint count, NR Swollen joint count, NR Required treatment for latent TB, NR Other BMI, mean ±SD kg/m2: 26.9 (6.2) Smoking History, no. (%) Current smoker 382 (23) Former Smoker 625 (38) Never Smoked 621 (38) Prior MI, no (%), 48 (2.9) Angina, no (%), 85 (5.2) Hypertension, no (%), 506 (30.9) 	9.4 (95% CI, 5.5 - 15.0), Incident rate ratio, referent Incidence rate ratio adjusted for age and sex, referent Incidence rate ratio multivariate analysis, referent Amon responders, Person years 9,886, Number of reported MIs: 35, rate of MIs per 1,000 person-years (95% CI): 3.5 (2.5 - 4.9), Incident rate ratio, 0.38 (2.5 - 4.0) Incidence rate ratio adjusted for age and sex, 0.38 (0.21 - 0.68) Incidence rate ratio multivariate analysis, 0.36 (0.19 - 0.69), incidence rate ratio by sex, multivariate analysis (male) 0.31 (0.12 - 0.81), (female) 0.46 (0.20 - 1.06)

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
			 Diabetes, no. (%), 110 		
			(6.7)		
			 Corticosteriods% 		

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
Author, year, study name, if applicable Dixon WG et al., 2010 ³⁹ British Society for Rheumatology Biologics Register (BSRBR) Country and setting UK Source of funding the University of Manchester Research objective To compare directly the risk between drugs, to explore time to event, site of infection and the role of ethnicity. Study design Observational	Inclusion Criteria Inclusion Criteria Patient with doctor's dx of RA At least 1 returned consultant follow-up questionnaire before 3/31/08 Anti-TNF cohort the anti-TNF drug must have been their first biolgical drug DMARD cohort they must have been biologic naive Exclusion Criteria		Treatment	ACR mean difference/absolute difference (CI/SD/P Value): NR HAQ, mean difference/absolute difference (CI/SD/P Value): NR DAS, mean difference/absolute difference (CI/SD/P Value): NR SF-36, mean difference/absolute difference (CI/SD/P Value): NR RF-36, mean difference/absolute difference (CI/SD/P Value): NR Radiographic measures, mean difference/absolute difference (CI/SD/P Value): NR Quality of life scales, mean difference/absolute	Adverse Events, % Overall NR Serious adverse events: NR Malignancies: NR Respiratory events: Tuberculosis (n): D1: 0 D2: 40 (118/100,000 pys; 95% CI, 84- 160) D3: 8 (53/100,000 pys; 95% CI, 23-105) D4: 12 (123/100,000 pys; 95% CI, 64- 215) D5: 20 (217/100,000 pys; 95% CI, 132- 335) Rates of TB D1: NR D2: NR D3: 39 events/100,000 person-yrs D4: 136 events/100,000 person-yrs D5: 144 events/100,000 person-yrs	
Overall N 13739 Duration of study Total follow-up time (person- yrs): DMARD: 7345		Overall: DMARD vs. All anti-TNF, P<0.001; Between the three anti-TNF drugs, P=0.012 Sex, % female D1: 72 D2: 76	Required treatment for latent TB NR Other population characteristics, %, (CI/SD/P value):	difference (CI/SD/P Value): NR Others, (please name); mean difference/absolute difference (CI/SD/P Value):	IRR for active TB Non-white vs. white patients=6.5 (2.8-15.3). UK population rate of TB: 12.3-14.7 events/100,000 person- yrs from 2001-2005).	

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
Anti-TNF: 34025 Median duration of follow- up/patient (yrs): DMARD: 2.30 Anti-TNF: 3.21		D3: 77 D4: 76 D5: 75 Overall: DMARD vs. All anti-TNF, P<0.001; Between the three anti-TNF drugs, P=0.108	205 patients switched from the DMARD cohort to the anti-TNF cohort		Other infections: NR GI: NR Other: NR	
		Race, % white D1: 78 D2: 83 D3: 82 D4: 82 D5: 84 Overall: DMARD vs. All anti-TNF, P<0.001				
		Between the three anti-TNF drugs, <i>P</i> =0.363				
		Race, % black D1: Non-white: 2 D2: Non-white: 3 D3: Non-white: 3 D4: Non-white: 4 D5: Non-white: 3				
		Ethnicity, Latino NR				

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
Author, year: Doran et al., 2002 ⁴⁰ Country, Setting: US, Minnessota cohort Funding: Immunnex; NIH Research Objective: Identify predictors of serious infections amnong pts with RA Study Design: Retrospective Cohort Overall N: 609 Study Duration: 39 yrs	 Diagnosed with RA according to ACR criteria Exclusion Criteria: NR 	Interventions, dose: DMARDS N: NR Mean age, yrs: NR Sex, % female: NR Race, % white: NR	Mean disease duration, yrs: NR TJC, mean: NR SJC, mean: NR DMARD use, %: NR Corticosteroid use, %: NR MTX naive, %: NR Txt resistant %: NR Pts with Early RA (≤3 yrs): NR Baseline DAS, mean: NR	Age, /10-yr increment OR 1.49 95% CI,1.33-1.67 <i>P</i> < 0.001 • Alcoholism OR 2.00 95%CI,1.27-3.16 <i>P</i> = 0.003 • Leukopenia OR 2.17 95%CI,1.58-2.98 <i>P</i> < 0.001 • Organic brain disease OR 2.94 95%CI,2.08-4.16 <i>P</i> < 0.001 • DM OR 2.45 95%CI,1.84-3.27 <i>P</i> < 0.001 • Chronic lung disease OR 2.83 95%CI,2.15-3.72 <i>P</i> < 0.001 • Extraarticular RA OR 3.22 95%CI,2.17-4.77 <i>P</i> < 0.001 • RF OR 1.65 95%CI,1.24-2.20 <i>P</i> < 0.001 • RA nodules OR 1.76 95%CI,1.32-2.33 <i>P</i> < 0.001 • ESR OR 1.63 95%CI,1.25-2.13 <i>P</i> < 0.001 • ESR OR 1.63 95%CI,1.25-2.13 <i>P</i> < 0.001 • Cyclophosphamide OR 6.14 95%CI,2.44-10.3 <i>P</i> < 0.001 • Cyclosporine OR 1.99 95%CI,1.25-3.16 <i>P</i> = 0.004 • Corticosteroids OR 1.90 95%CI,1.47-2.47 <i>P</i> < 0.001	NA	Overall Attrition Rate, %: NR ITT Analysis: NA Quality Rating: Fair

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
Author, yr: Dougados et al., 1999 ⁴¹ and Maillefert et al., 2003 ⁴² Country, Setting: Finland, France, Germany (France only for 5 yr), multicenter Funding: Pharmacia Upjohn Research Objective: Clinical benefit of MTX + SSZ compared to either drug alone early, active RA pts fulfilling some criteria of poor potential long term outcome Study Design: RCT Overall N: 209 (146) Study Duration: 52 wks (5 yrs)	according to ACR criteria Duration < 1 yr Presence of active disease as defined by DAS ≥ 3 (calculation based on Ritchie articular index, 44 SJC, and ESR) and presence of RF and/or HLA DR 1/4 Concommitant drugs allowed were analgesics and NSAIDS Exclusion Criteria: Prior txt with steroids, DMARDS, or any drugs to treat RA other than analgesic or NSAIDS Pts with contraindications to use of SSZ or MTX	Interventions, dose: D1: SSZ + placebo D2: MTX + placebo D3: SSZ + MTX MTX: 7.5 mg wkly (2.5 mg 3 times per wk). After wk 16, could be increased to 15 mg wkly if efficacy inadequate SSZ: increased to 2 grams daily by d #9. Could be increased to 3 grams daily after wk 16 of study if efficacy was inadequate Other?: combo MTX + SSZ N: D1: 68 D2: 69 D3: 68 Mean age, yrs: D1: 52 D2: 50 D3: 52 Sex, % female: D1: 71 D2: 74 D3: 77 Race, % white: NR	Mean disease duration, yrs: D1: 2.9 mos since diagnosis, 10.8 since onset D2: 2.3 mos from diagnosis, 18.4 from onset D3: 3.4 mos from diagnosis, 10.6 from onset TJC, mean: NR SJC, mean: D1: 10.5 D2: 9.4 D3: 9.4 DMARD use, %: All groups: 0 Corticosteroid use, % All groups: 0 MTX naive, %: All groups: 100 Txt resistant, %: NR Pts with Early RA (≤3 yrs): All groups: 100	DAS change: D1: -1.15 D2: -0.87 D3: -1.26 ($P = 0.019$ from inter-group comparisons using analysis of variance) RAI changes: D1: -7.1 D2: -4.2 D3: -9.4 ($P = 0.001$) ACR response, %: D1: 59 D2: 59 D3: 65 ($P = NR$) At 5 years Txt of pts with early RA with combination therapy of MTX and SSZ during first yr did not result in any long term differences in disease activity, quality of life, or structural damage compared to monotherapy with either drug used alone Mean DAS (SD): D1 or D2: 2.2 (1) D3: 2.2 (1) Overall: ($P = 0.9$) HAQ:	Overall: D1: 75 D2: 75 D3: 91 Abdominal Pain: D1: 9 D2: 6 D3: 13 Dizziness: D1: 6 D2: 1 D3: 3 Headache: D1: 9 D2: 4 D3: 12 Nausea: D1: 32 D2: 23 D3: 49	Overall Attrition Rate, %: 27% (28.8) ITT Analysis: Yes Quality Rating: Fair

Characteristics C	Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
name, if applicable Duclos, 2006 ⁴³ Country and setting Monocenter French C	nclusion Criteria Received a TNF blocker Exclusion Criteria NR	Interventions, Dose D1: ETN: dosage and frequency NR IFX: dosage and frequency NR ADA: dosage and frequency NR ETN: dosage and frequency NR ETN: dosage and frequency NR IFX: dosage and frequency NR ADA: dosage and frequency NR ADA: dosage and frequency NR Mumber in group D1: 440 D2: 290 Overall: 770 Mean age (years) D1: 55.1 D2: 41.6 Overall: 49.3 Sex, % female D1: 80.5 D2: 29.7 Overall: 60.4 Race, % white NR Race, % black NR Ethnicity, Latino NR	Mean disease duration, years (SD) D1: 13.5 yrs (9.5) D2: 13.6 (10.0) Overall: 13.4 (9.7) Patients with early RA, three years or less, % NR Treatment resistant, % NR Tender Joint Count, mean (SD) NR Swollen Joint Count, mean (SD) NR Corticosteroid use, % NR Overall: 16.1 (21.5) DMARD use, % NR Overall: 3.0 (2.1) MTX naïve, % NR Baseline DAS score, mean (SD) NR Required treatment for latent TB NR Other population characteristics, %, NR	ACR NR HAQ, DAS SF-36 Radiographic measures Quality of life scales Others, (please name); mean difference/absolute difference (CI/SD/P Value)	 Overall Percentage of patients who did not interrupt treatment due to inefficacy or intolerance was 82.5%: 1.3 at 6 months, 64.0% ± 1.8 at 12 months, 50.3% ± 2.1 at 24 months, and 39.4% ± 2.4 at 36 months. Retention rates were similar for 3 TNF blockers. At 1 year, rates were 63.2% ± 2.9, 63.9% ± 2.6, and 68.2% ± 4.6, and at 2 years, rates were 47.5% ± 3.2, 50.8% ± 3.0, and 60.2% ± 5.6 for IFX, ETN, and ADA, respectively (P = 0.48). Analyses according to reason for interruption did not find any difference in efficacy between 3 agents (P = 0.33), but showed a trend for a better tolerance with ETN and ADA versus with IFX (P = 0.06) Overall adverse events reported, n: Serious adverse events NR Malignancies NR Respiratory events NR Other infections

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
					GI NR
					Other NR

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
-	Exclusion	Interventions Interventions, Dose D1: PNL: Dosage NR MTX: Dosage NR LEF: Dosage NR SSZ: Dosage NR Hydroxychlorquine: Dosage NR Other: Any combination D2: PNL: Dosage NR MTX: Dosage NR MTX: Dosage NR MTX: Dosage NR LEF: Dosage NR SSZ: Dosage NR Hydroxychlorquine: Dosage NR Chydroxychlorquine: Dosage NR Hydroxychlorquine: Dosage NR Other: Any combination Number in group D1: 102,747 D2: 34,250 Mean age (years) D1: 55.3 D2: 55.6 P=.001 Sex, % female D1: 71.4 D2: 71.4 P=1.0 Race, % white NR	Mean disease duration, years (SD) NR Patients with early RA, three years or less, % NR Treatment resistant, % NR Tender Joint Count, mean (SD) NR Swollen Joint Count, mean (SD) NR Corticosteroid use, % D1: NR D2: 40 Overall: NR D4: NR D2: 50 Overall: NR MTX naïve, % NR Raseline DAS score, mean (SD) NR Required treatment for latent TB NR	ACR NR HAQ NR DAS NR SF-36 NR Radiographic measures NR Quality of life scales NR Others, (please name); mean difference/absolute difference (CI/SD/P Value) NR	Overall NR Overall adverse events reported, n: NR Serious adverse events NR Malignancies NR Respiratory events NR Other infections NR GI NR Other • SA incidence (1992-1997): 0.29 (95% confidence interval [95% CI] 0.27– 0.31) per 1,000 person- years for entire population studied (including RA cases and controls) and 0.11 (95% CI 0.09–0.12) per 1,000 person-years for control population. • In RA population, SA incidence was increased at 1.31 (95% CI 1.22–1.41) per 1,000 person-years. incidence rate of SA was 12.9 times greater among
2002 Quality rating Fair		Race, % black NR Ethnicity, Latino NR	Other population characteristics, %, (CI/SD/P value) Smoking (ever vs. never), %: D1: 37.5		patients with RA than among RA controls (95% CI 10.1–16.5, $P = 0.001$). • A diagnosis of RA,

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
			D2: 41.6 P = 0.001 Diabetes %: D1: 5.55 D2: 5.50 P = 0.7 Hypertension %: D1: 23.5 D2: 22.8 P = 0.01 Heart Failure: D1: 6.39 D2: 9.38 P = 0.001 Renal Failure %: D1: 0.86 D2: 1.83 P = 0.001 BMI IQR in kg meters squared: D1: 25.2 (22.7-28.2) D2: 24.9 (22.3-28.0) P = 0.001		hypertension, heart failure, or renal failure significantly increased risk of future SA and incidence of SA was significantly higher while experiencing one or more of these risk factors than while not. SA incidence rate while receiving a DMARD or PNL was 2.17 (95% CI 1.68–2.80, P = 0.001) times greater than while receiving no drugs, even after adjustment for RA. Incident rate of SA in patients with RA receiving DMARDs was 2.14 (95% CI 1.64–2.78, P = .001) times greater than in patients with RA not receiving DMARDs, and corresponding rate ratio for RA controls was 2.80 (95% CI 1.03–, P = 0.045). Incident rate ratios (IRRs) for developing SA while receiving DMARDs compared with receiving no DMARDs were different for different medications: SSZ (adjusted IRR 1.74, 95% CI 1.04–2.91, P 0.03) and PNL (adjusted IRR 2.94, 95% CI 1.93–4.46, P = 0.001) were associated with an increased incidence of SA when compared with not receiving any DMARD. use of other DMARDs including

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
					MTX showed no such effect; adjusted IRR HCQ 0.59 (0.08-4.25); LEF no events; MTX 1.01 (0.44-2.34).

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
Author, yr: Emery, 2000 ⁴⁵ Country, Setting: Multinational, 117 centers Funding: NR Research Objective: To compare both short and long-term (up to 2 yr) clinical efficacy and safety of LEF and MTX for txt of RA Study Design: RCT Overall N: 999 Study Duration: 1 yr, optional second yr	Inclusion Criteria: Age: 18+ Diagnosed with RA according to ACR criteria: Active Disease Previous use of DMARDs: only if discontinued 28 ds before trial Duration of condition: for at least 4 mos, but no longer than 10 yrs NSAIDs and steroids were allowed provided a stable dose of NSAIDs or steroid (≤ 10 mg/d) PNL for at least 28 ds prior to study entry Women of childbearing age were required to use adequate contraception Exclusion Criteria: Pregnant or lactating Prior txt with: Intraarticular corticosteriod injections w/in 6 wks of efficacy assessment	Interventions, dose: D1: LEF Yr 1 D2: MTX Yr 1 D3: LEF Yr 2 D4: MTX Yr 2 MTX: 7.5 to 15 mg/wk LEF: loading dose of 100 mg/d for 3 ds, followed by maintenance dose 20/ mg/d N: D1: 501 D2: 498 D3: 292 D4: 320 Mean age, yrs: D1: 58.3 D2: 57.8 D3: 57.7 D4: 57.0 Sex, % female: D1: 70.7 D2: 71.3 D3: 71.2 D4: 71.3 Race, % white: NR	duration, yrs: D1: 3.7 D2: 3.8 D3: 3.5 D4: 3.8 TJC, mean:	At year 1 ACR20: D1: 50.5% D2: 64.8% (P < 0.001) HAQ improvement: Minimal quantitative difference between groups, but statistically significant (shown in figure only; P < 0.05) Radiograph change, Larsen Scores: D1 and D2: 0.03 increase (P = NS, NR) Primary clinical efficacy endpoints: TJC: D1: -8.3 D2: -9.7 SJC: D1: -6.8 D2: -9.0 Physician global assessment: D1: -0.9 D2: -1.2 Pt global assessment: D1: -0.9 D2: -1.2 At year 2 ACR20, %: D1: 64.3 D2: 71.7 (P = NS, NR)	SAEs: D1: 7% D2: 8% Headache: D1: 6.2 D2: 4.8 Hepatotoxicity: D1: 5.4 D2: 16.3 D3: 2.7 D4: 5.9 Nausea: D1: 11.2 D2: 15.7 URTI: D1: 5.2 D2: 5.0 D3: 4.5 D4: 5.6 Deaths MTX: 2	Overall Attrition Rate, %: • 26.3% (263/999) during yr 1 • Combined 2 yrs, attrition 50.3% (502/999) of those initially starting study at baseline • During yr 2, attrition 18.8% (115/612) of those agreeing to continue study for 2nd yr ITT Analysis: Yes Quality Rating: Fair

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
Author, year, study name, if applicable Emery et al., 2006,	Inclusion Criteria • Treatment resistant,	Interventions, dose D1: • MethylPNL Placebo	Mean disease duration, years 10.8	ACR mean difference/ absolute difference ACR 20:	Attrition/withdrawal Overall, n: D1: 52
DANCER trial ⁴⁶ Country and setting	outpatients between ages of 18 - 80 years	methyIPNL IV: 30 - 60 minutes before infusion on days 1	Patients with early RA, three years or less, %	D1: 28 D2: 55 ($P \le 0.001$) D3: 54 ($P \le 0.001$)	D2: 11 D3: 27
Multinational, multicenter	who had presented at	and 15 - or - premed methylPNL 100 mg IV	NR Treatment resistant, %	ACR 50: D1: 13	Withdrawals due to adverse events, n: D1: 0
Source of funding Roche primarily, also support from	least 6 mos prior to randomization	on days 1 and 15 - or - premed methylPNL 100 mg IV on days 1	D1: 100 D2: 100 D3: 100	D1: 13 D2: 33 ($P \le 0.001$) D3: 34 ($P \le 0.001$)	D2: 3 D3: 6
Genentech and Biogen Idec Research objective	with severe RA despite ongoing treatment with	and 15 plus 60 mg of oral PRED on days 2 - 7 and 30 mg on	Tender Joint Count, mean D1: 35 D2: 33	ACR 70: D1: 5 D2: 13 (<i>P</i> = 0.029)	Withdrawals due to lack of efficacy, n: D1: 46
Examine efficacy and safety of	MTX for at least 12 weeks • Must have failed	days 8 – 14 • PRED see "methylPNL"	D3: 32	D3: $20 (P = 0.0001$ HAQ-DI, mean change from	D2: 8 D3: 16
different RIT doses + MTX with or without glucocorticoids in pts resistant to	prior treatment with at least 1 but not more than 5 DMARDs	 MTX: weekly regimen 10 - 25 mg orally Placebo placebo RIT: on days 1 and 15 	D2: 22	baseline D1: -0.16 D2: -0.43 D3: -0.49	Adherent/compliant, n: NR 13 RF+ pts (out of 380) were exlcuded from analyses because of unblinding, drug
DMARDs, including biologics	(other than MTX) and/or	Folate: dosage and frequency NR	Corticosteroid use, % NR	DAS (P Value) Adjusted mean change:	dispensing errors, and unverifiable data.
Study design Controlled Trials	biologic response modifiers	D2: • MethylPNL Placebo	DMARD use, % NR	D1: -0.67 D2: -1.79 (P = 0.0001)	Serious adverse events NR
Overall N 465 (Note: 465 pts	Pts taking glucocorticoids	methylPNL IV: 30 - 60 minutes before infusion on days 1	MTX naïve, % NR	D3: -2.05 (<i>P</i> = 0.0001) SF-36, mean	Malignancies NR
were randomized adverse event and baseline data analyses usewhole	were included ifdosage had been stable for at least 4 weeks	and 15 - or - premed methylPNL 100 mg IV on days 1 and 15 - or - premed methylPNL	Baseline DAS score D1: 6.8 D2: 6.8	difference/absolute difference NR	Respiratory events Tuberculosis: NR Other infections
population, efficacy analyses use an "ITT efficacy population" of N: 367.ITT	before trial entryPts who received	100mg IV on days 1 and 15 plus 60 mg of oral PRED on days 2	D3: 6.7 Required treatment for latent TB	Radiographic measures, mean difference/absolute difference NR	NR GI NR
population is limited toRF+ pts who were not exlcuded (13	intraarticular or parenteral glucocorticoids were included if	- 7 and 30 mg on days 8 – 14 • PRED see	NR Other population characteristics, %, (CI/SD/P	Quality of life scales NR	Other Data are from Safety Population N: 465
RF+ pts were exclu	most recent	"methylPNL" MTX: weekly	value) D1:	EULAR (%) No response:	Adverse events affecting 5%

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
Duration of study 24 weeks	administration was more than 4 weeks before	regimen: 10 - 25 mg orally • RITIn RF+ positive	Data presented in table above are baseline disease characteristics for	D1: 63 D2: 28 D3: 34	or more of patients in any one Dare reported, values are %.
Quality rating Fair	Exclusion Criteria Significant systematic involvement secondary to RA Evidence of significant other illness or laboratory adnormalities History of severe allergic or anaphylactic reactions to humanized or murine monoclonal antibodies Previous treatment with RIT or any lymphocyte- depleting therapies History of recurrent significant infection.	patients: 500 mg on days 1 and 15 Other: folate: dosage and frequency NR D3: MethylPNL Placebo methylPNL IV: 30 - 60 minutes before infusion on days 1 and 15 - or - premed methylPNL 100 mg IV on days 1 and 15 -or - premed methylPNL 100mg IV on days 1 and 15 plus 60 mg of oral PRED on days 2 - 7 and 30 mg on days 8 - 14 PRED see "methylPNL" MTX: weekly regimen: 10 - 25mg orally RITIn RF+ pts: 1,000 mg on days 1 and 15; In RF- pts: 1,000 mg on days 1 and 15; In RF- pts: 1,000 mg on days 1 and 15 Other: folate: dosage and frequency NR Number in group D1: 122 D2: 123 D3: 122	years: 9.3, Previous DMARDs, mean number: 2.2 prior anti-tnf alpha treatment: 26%, MTX dose, mean mg/week: 15.6 D2:	Moderate/good response: D1: 37 D2: 73 D3: 67 Good response: D1. 4% D2: 14% D3: 28% P = 0.0001 for D2 and D4 vs. D1.	D1: All Events: 105, Exacerbations of RA: 44, Headache: 19, Nausea: 13, URI: 9, Nasopharyngitis: 8, Arthralgia: 5, Diarrhea: 8, Fatigue: 8, Hypertension: 4, Rigors: 3, Dizziness: 6, Serious noninfection adverse events: 2, Serious infections: 2; Arm 2: All Events: 100, Exacerbations of RA: 21, Headache: 14, Nausea: 8, URI: 10, Nasopharyngitis: 7, Arthralgia: 5, Diarrhea: 7, Fatigue: 5, Hypertension: 5, Rigors: 5, Dizziness: 4, Serious noninfection adverse events: 9, Serious infections: 0; Arm 3 All Events: 164, Exacerbations of RA: 27, Headache: 21, Nausea: 19, URI: 12, Nasopharyngitis: 10, Arthralgia: 11, Diarrhea: 6, Fatigue: 8, Hypertension: 12, Rigors: 13, Dizziness: 10, Serious noninfection adverse events: 9, Serious infections: 4
		Mean age, years (%) 51.1 Sex, % female	Other population characteristics as follows are for "safety population"		

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
		80	N: 465:		
		Race, % white NR	 Prior anti-tnf alpha treatment: 28%, MTX dose, mean 		
		Race, % black NR	mg/week: 14.9		
		Ethnicity, Latino NR			

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
Author, year, study name, if applicable Emery et al., 2006 ⁴⁷ Country and setting UK, US, Canada Source of funding Bristol-Myers Squibb Research objective Examine effect of ABA on HRQOL Study design Controlled Trials Overall N 339 Duration of study 1 year Quality rating Fair	Inclusion Criteria American Rheumatism Association criteria for RA while meeting functional class I, II, or III according to revised criteria of ACR Have > 10 swollen, > 12 tender joints, and CRP level > 1 mg/dl signifying active disease Have been treated with MTX for at least 6 mos and on a stable dose for 28 days prior to enrollment Be washed-out of all DMARD other than Exclusion Criteria NR	Interventions, Dose D1: MTX: 15.8 (SD 4.1) Abatacept: 2 mg/kg administered at baseline, every two weeks for first month, then monthly thereafter D2: MTX: 15.8 (SD 4.8) Abatacept: 10 mg/kg administered at baseline, every two weeks for first month, then monthly thereafter D3: MTX: 15.0 (SD 4.4) Placebo Number in group D1: 105 D2: 115 D3: 119 Overall: 339 Mean age (years) D1: 54.4 D2: 55.8 D3: 54.7 Sex, % female D1: 62.9 D2: 74.8 D3: 66.4 Race, % white D1: 86.7 D2: 86.9 D3: 87.4	Mean disease duration, years (SD) D1: 9.7 (8.1) D2: 9.7 (9.8) D3: 8.9 (8.3) Patients with early RA, three years or less, % NR Treatment resistant, % NR TJC, mean (SD) D1: 28.2 D2: 30.8 D3: 29.2 SJC, mean (SD) D1: 20.2 D2: 21.3 D3: 21.8 Corticosteroid use, % NR DMARD use, % NR MTX naïve, % D1: 0 D2: 0 D3: 0 Overall: 0 Baseline DAS score, mean (SD) NR Required treatment for latent TB NR Other population	ACR NR HAQ NR DAS NR SF-36, mean Changes in 8 categories of SF-36 scale PF (SE) Physical functioning D1: 4.7 (0.9) D2: 7.2 (0.8) D3: 2.1 (0.8) Role limitations due to physical health (RP): D1: 5.3 (1.1) D2: 8.2 (1.0) D3: 4.1 (1.0) Bodily pain (BP): D1: 6.5 (0.9) D2: 9.3 (0.8) D3: 3.5 (0.8) General health perceptions (GH): D1: 4.1 (0.7) D2: 5.8 (0.7 D3: 2.3 (0.7) Vitality (VT): D1: 3.5 (0.8) D2: 7.9 (0.8) D3: 2.1 (0.8) Social functioning (SF): D1: 4.6 (1.0) D2: 7.6 (0.9) D3: 3.6 (0.9)	Overall Overall attrition/withdrawal, n: D1: 31 D2: 25 D3: 48 Overall: 104 Overall adverse events reported, n: NR Serious adverse events NR Malignancies NR Respiratory events NR Other infections NR GI NR

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
		Race, % black NR Ethnicity, Latino NR	value) D1: All reported characteristics were similar at baseline including mean MTX dose and HRQOL score	Role limitations due to emotional health (RE): D1: 5.0 (1.4) D2: 6.8 (0.9) D3: 3.8 (1.0)	
			D2: All reported characteristics were similar at baseline including mean MTX dose and HRQOL score	naracteristics were D1: 3.5 (0.9) milar at baseline D2: 5.3 (0.8) cluding mean MTX D3: 2.6 (0.8)	
			D3: All reported characteristics were similar at baseline including mean MTX dose and HRQOL score [Mean Changes in SF-36 summary measures, physical summary measure (SE) Physical summary measure (PCS): D1: 5.2 (0.8) D2: 8.0 (0.8) D3: 2.6 (0.7)	
				Mental summary measure (MCS): D1: 3.5 (1.0) D2: 5.7 (0.9) D3: 2.8 (0.9)	
				Radiographic measures NR	
				Quality of life scales D1: See SF-36 results D2: See SF-36 results D3: See SF-36 results Overall: See SF-36 results	
				Others, (please name) Differences in Mean Change Scores in 8 categories of SF- 36 scale: • Placebo vs. Abatacept 2mg/kg - Physical Functioning (PF) = 2.6	

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
				 (P = 0.05) Role limitations due to physical health (RP) = 1.2 Bodily pain (BP) = 3.0 (P = 0.05) General health perceptions (GH) = 1.8 Vitality (VT) = 1.4 Social functioning (SF) = 1.0 Role limitations due to emotional health (RE) = 1.8 Mental health (MH) = 0.9 	
				Differences in Mean Change Scores in SF-36 summary measures: • Physical summary measure (PCS) = 2.6 (P = 0.05) • Mental summary measure (MCS) = 0.7 • Difference in Mean Change Score in SF-36 Utility Index: SF-6D = 0.00 Abatacept 2mg/kg vs. Abatacept 10 mg/kg - Physical Functioning (PF) = 2.5 (P = 0.05) • Role limitations due to physical health (RP) = 2.9 (P = 0.05) • Bodily pain (BP) = 2.8	
				 (P = 0.05) General health perceptions (GH) = 1.7 Vitality (VT) = 4.4 (P = 0.001) Social functioning (SF) = 3.0 (P = 0.05) 	

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
				 Role limitations due to emotional health (RE) = 1.8 Mental health (MH) = 1.8 	
				Differences in Mean Change Scores in SF-36 summary measures: • Physical summary measure (PCS) = 2.8 (P = 0.05) • Mental summary measure (MCS) = 1.9 • Difference in Mean Change Score in SF-36 Utility Index: SF-6D = 0.05 (P = 0.05) - Placebo vs. Abatacept 10 mg/kg - Physical Functioning (PF) = 5.1 (P = 0.0001) • Role limitations due to physical health (RP) = 4.1 (P < 0.01) • Bodily pain (BP) = 5.8 (P < 0.0001) • General health perceptions (GH) = 2.5 (P = 0.001) • Vitality (VT) = 5.8 (P = 0.0001) • Vitality (VT) = 5.8 (P = 0.0001) • Social functioning (SF) = 4.0 (P = 0.01) • Role limitations due to emotional health (RE) = 3.0 (P = 0.001) • Mental health (MH) = 2.7 (P = 0.05)	
				Differences in Mean Change Scores in SF-36 summary measures: • Physical summary	

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
				measure (PCS) = 5.4 (P = 0.0001)	
				 Mental summary measure (MCS) = 2.9 (P = 0.05) 	
				 Difference in Mean Change Score in SF-36 Utility Index: SF-6D = 0.05 (P = 0.001) 	

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
Author, year, study name, if applicable Emery et al., 2008, COMET ⁴⁸	Inclusion Criteria MTX Naïve Early RA defined as at	Interventions, dose D1: • MTX: 7.5 mg orally once a week	Mean disease duration, months D1: 9.3 (0.4) D2: 8.8 (0.4)	ACR mean difference/ absolute difference (%) Week 52: ACR 20:	Attrition/withdrawal Overall, n: D1: 79 D2: 53
Country and setting Multinational, multicenter	least 3 mos but less than 2 yrs • Age 18 years or older with	 Placebo ETN- matching placebo injections subcutaneously: once 	Overall: 9.0 (0.3) Patients with early RA, three years or less, % D1: 100	D1: 67 (61-73) D2: 86 (82-90) Overall: Week 52: <i>P</i> = .0001 ACR 50:	Withdrawals due to adverse events, n: D1: 34 D2: 28
Source of funding Wyeth Research Research objective	diagnosis of adult-onset RA • Disease duration of at	 a week for 52 weeks Other: In patients with tender or swollen joints, dose was 	D2: 100 Overall: 100 Treatment resistant, %	D1: 49 (43-55) D2: 71 (66-76) P=.0001	Withdrawals due to lack of efficacy, n: D1: 24
Compare remission and radiographic non-progression in pts treated with MTX	least 3 mos but not more than 2 years	titrated up over 8 weeks to a maximum of 20 mg a week	NR Tender Joint Count, mean D1: 24.8 (14.5)	ACR 70: D1: 28 (22-34) D2: 48 (41-55) P = 0001	D2: 9 Adherent/compliant, n: D1: 221
monotherapy or MTX + ETN Study design	 DAS28 of 3·2 or more Either Westergren 	 MTX: 7.5 mg orally once a week ETN: 50 mg by 	D2: 25.1 (14.6) Overall: 25.0 (14.5) Swollen Joint Count, mean	HAQ, Week 52 difference: D1: 0.7	D2: 189 Overall adverse events reported, n:
Controlled Trials Overall N 542	ESR of 28 mm/h or more or CRP of 20 mg/L or more.	subcutaneous injection once a week for 52 weeks Other: In patients with	D1: 17.6 (10.0) D2: 17.1 (10.5) Overall: 17.3 (10.2)	D1: 0.7 D2: 1.0 P = 0.0001 Remission DAS28: 2.6 (CI)	D1: 246 D2: 247 Overall: 493
Duration of study 52 weeks	Exclusion Criteria	tender or swollen joints, dose was titrated up over 8	Corticosteroid use, % D1: 50 D2: 49 Overall: 49	At week 52: D1: - 73 [28%] of 263 (23- 33%)	Serious adverse events Death, n: NR Overall: 1
Quality rating Fair	 Previous treatment with MTX, ETN, or another TNF 	weeks to a maximum of 20 mg a week Number in group	DMARD use, % D1: 24 D2: 18	D2: -132 [50%] of 265 (44- 56%) Overall: Week 4: DAS 44- effect	Cardiovascular events (specify), n: D1: 2 D2: 2
	antagonist at any timeHad received	D1: 263 D2: 265 Overall: 528	Overall: 21 MTX naïve, %	difference 9.07% (95% CI 4.84-13.31%, P = 0.0001)	
	treatment with other DMARDs or corticosteroid	Mean age, years (SD) D1: 52.3 D2: 50.5	D1: 100 D2: 100 Overall: 100	Week 52: DAS 28 22.05%, 95% CI 13.96- 30.15%, P <0.0001)/	enzymes, n: D1: 0 D2: 3
	injections in4 weeks before baseline visits. Important	Overall: 51.4 Sex, % female D1: 73	Baseline DAS28 mean (SD) D1: 6.5 (1.0) D2: 6.5 (1.0)	Week 52: DAS 44: effect difference-23.56% (95% CI: 15.47-31.66%)	Overall: 3 Malignancies Lymphoma or leukemia, n:
	concurrent	D2: 74	Overall: 6.5 (1.0)	SF-36	D1: CLL: 0

Characteristics	Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
	medical diseases and/or other relevant comorbidities.	Overall: 73 Race, % white D1: 88 D2: 87 Overall: 88 Race, % black NR Ethnicity, Latino NR	Required treatment for latent TB NR HAQ mean (SD) D1: 1.6 (0.7) D2: 1.7 (0.7) Overall: 1.7 (0.7)	Radiographic measures (CI) Week 52: mTSS change from baseline D1: - 2.44 (1.45 -3.43) D2: - 0.27 (-0.13- 0.68) Overall: mTSS-effect difference 20.98%, (12.97-29.09%, P = 0.0001) Quality of life scales NR Mean DAS 28 swollen joint count- Week (CI/SD/P Value) D1: 8 D2: 10.6 P = 0.0108 Radiographic nonprogression: mTSS:: 0.5 (%) D1: 59 (53-65) D2: 80 (75-85), P = 0.0001	D2: CLL: 1 Overall: CLL: 1 Skin cancer (basal cell or

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
					D1: 50 D2: 53 Overall: 103
					Not specified, n: D1: 4 D2: 1 Overall: 5
					Other Infusion/injection site reactions, n: D1: 1 D2: 2 Overall: 3
					Demyelenation or multiple sclerosis, n: D1: 0 D2: 0 Overall: 0
					Worsening of RA, n: D1: 5 D2: 2 Overall: 7
					Cholelithiasis, n: D1: 0 D2: 2 Overall: 2
					Intervertebral disc protrusion, n: D1: 0 D2: 2 Overall: 2
					Osteoarthritis, n: D1: 2 D2: 0 Overall: 2
					Any other AEs: Interstitial lung disease (2

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
					incombined-treatment group) and hip arthroplasty (2 in MTX group).

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
Author, year, study name, if applicable Emery el al., 2008, RADIATE Study ⁴⁹ Country and setting Multinational multicenter Source of funding Hoffmann-La Roche Ltd, Chugai Pharma KK Research objective Examine safety and efficacy of Tocilizumab in pts refractory to TNF	Inclusion Criteria Treatment resistant inadequate response to 1 or more TNF antagonist withinpast year 18 years old or older with moderate to severe RA for 6 mos or more Swollen joint count of 6 or more CRP of more than 1.0 mg/dl or ESR of more than 28	every 4 weeks D3: MTX10-25 mg/week Placebo every 4 weeks	D2: 11.0 (8.5) D3: 11.4 (9.2) Patients with early RA, three years or less, % NR Treatment resistant, % D1: 100 D2: 100 D3: 100 Overall: 10 Tender Joint Count, mean D1: 31.7 (15.4) D2: 31.3 (15.1)	ACR mean difference/ absolute difference (P Value) ACR 20: D1: 50 D2: 30.4 D3: 10.1 (P = 0.001) ACR 50: D1: 28.8 (P = 0.001) D2: 16.8 (P = 0.001) D3: 3.8 ACR 70: D1: 12.4 (P = 0.001) D2: 5.0 (P = 0.1) D3: 1.3	Attrition/withdrawal Overall, n: D1: 23 D2: 25 D3: 33 Overall: 82 Withdrawals due to adverse events, n: D1: 11 D2: 10 D3: 10 Overall: 31 Withdrawals due to lack of efficacy, n: D1: 4 D2: 6 D3: 19
antagonist therapy Study design Controlled Trials Overall N 499	mm/h • Treatment with MTX for 12 weeks or more Exclusion Criteria	Overall: 498 Mean age, years (SD) D1: 53.9 D2: 50.9 D3: 53.9	D3: 30.4 (16.8) Swollen Joint Count, mean D1: 18.9 (10.9) D2: 19.5 (10.4) D3: 18.9 (11.1)	D1: -0.39 (<i>P</i> = 0.001) D2: -0.31 (<i>P</i> = 0.003) D3: -0.05 DAS (%) Low disease activity (DAS: 3.2):	Overall: 29 1 control withdrew after randomization but before receiving study treatment due to latex allergy
Duration of study 24 weeks Quality rating Fair	 Treatment with cell depleting agents Uncontrolled medical conditions History of other 		Corticosteroid use, % Receiving oral steroids: D1: 52 D2: 58 D3: 58 Overall: 54.6	D1: 51.2 D2: 15.2 D3: 4.9% Remission (DAS: 2.6): D1: 30.1% (<i>P</i> = 0.001)	Patients received rescue therapy (8 mg/kg of tocilizumab plus MTX at week 16 in case of treatment failure defined as less than 20%
	inflammatory diseases or functional class 4 RA • History of malignancies or recurrent infections • Primary or secondary immunodeficiency	Race, % white NR Race, % black NR Ethnicity, Latino NR	DMARD use, % D1: 100 D2: 100 D3: 100 Overall: 100 MTX naïve, % D1: 0 D2: 0 D3: 0 Overall: 0	D2: 7.6% ($P = 0.053$) D3: 1.6% SF-36, mean difference/absolute difference NR Radiographic measures Swollen joint count: D1: -7.8 ($P = 0.001$) D2: -6.8 ($P = 0.001$) D3: -0.5	improvement in both SJC and TJC): D1:20 D2:30 D3: 63 Overall adverse events reported, n: D1: 147 D2: 142 D3: 129 Overall: 418

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
	 Hemoglobin less than 8.5 g/dl Leucopenia Neutropenia Thrombocytopenia Baseline DAS score D1: 6.79 (0.93) D2: 6.78 (0.97) D3: 6.80 (1.06) 	Tender joint count: D1: -14.8 (<i>P</i> = 0.001) D2: -10.5 (<i>P</i> = 0.001) D3: -0.3	Serious adverse events Death, n: D1: 0 D2: 0 D3: 0		
	 Abnormal liver function Ttriglycerides greater than 10 mmol/l Recognized active TB, hepatitis B, or the setting of th		Required treatment for latent TB NR Other population characteristics, %, (CI/SD/P value) D1: HAQ-D1: 1.7 (0.6)	Quality of life scales, mean difference/absolute difference NR Good or moderate EULAR responses D1: 67.7% (P = 0.001)	Overall: 0 Myocardial infarction, n: D1: 0 D2: 0 D3:1 Overall: 1
	hepatitis C		D2: 1.7 (0.6) D3: 1.7 (0.6)	D2: 46.5% (<i>P</i> = 0.001) D3: 16.5%	Hepatotoxicity/elevated liver enzymes, n: D1: 4 D2: 0 4 D3: 0 1 Overall: 0 9
					Malignancies NR
					Respiratory events Tuberculosis: NR
					Other infections Infections: D1: 86 D2: 76 D3: 66 Overall: 228
					Serious infections: D1: 8 D2: 3 D3: 5 Overall: 16
					GI Other GI event (not specified n: D1: 64 D2: 53 D3: 31

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
					Overall: 90
					Other Infusion/injection site reactions, n: D1: 15 D2: 15 D3: 10 Overall: 40
					HDL > 60 mg/dl, n: D1: 29 D2: 22 D3: 6 Overall: 57
					LDL > 160 mg/dl, n: D1: 21 D2: 25 D3: 6 Overall: 52
					Severe AE (resulting in inability to work or perform daily activities), n: D1: 24 D2: 22 D3: 31 Overall: 77
					Serious AE (primarily related to complications of RA), n: D1: 11 D2: 12 D3: 18 Overall: 41
					AE leading to discontinuation n: D1: 10 D2: 10 D3: 8
					AE leading to dose modification, n:

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
					D1: 12 D2: 24 D3: 1
					Note that AE occurring in those receiving rescue therapy excluded from AE analysis

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
-	Criteria Inclusion Criteria MTX naïve Adults with ACR diagnosis of RA for at least 3 mos Not received more than 3 wkly doses of MTX as RA tx ≥ 4 swollen and tender joints met ≥ 2 of the following	Interventions Interventions, Dose D1: • MTX: 10 mg/wk escalated to 20 mg/wk • Placebo D2: • GOL: 100 mg every 4 wks • Placebo D3: • MTX: 10 mg/wk escalated to 20 mg/wk • GOL: 50 mg every 4 wks D4: • MTX: 10 mg/wk escalated to 20 mg/wk • GOL: 100 mg every 4 wks Number in group D1: 160		ACR: ACR 20: ITT pop D1: 49.4 D2: 51.6 D3: 61.6 (<i>P</i> = 0.028) D4: 61.6 (<i>P</i> = 0.028) ACR 50: ITT pop D1: 29.4 D2: 32.7 D3: 40.3 (<i>P</i> = 0.042) D4: 36.5 (<i>P</i> = 0.177) mITT pop D1: 29.4 D2: 33.1 D3: 40.5 (<i>P</i> = 0.177) ACR 70: ITT pop D1: 15.6 D2: 13.8 D3: 23.9 (<i>P</i> = 0.064) D4: 18.2 (<i>P</i> = 0.535) HAQ: DAS: SF-36: Radiographic measures: Quality of life scales: Others:	Adverse Events, % Overall Overall attrition/withdrawal (n): D1: 10 D2: 11 D3: 9 D4: 8 Withdrawals due to adverse events (n): Unclear Withdrawals due to lack of efficacy (n): Unclear Adherent/compliant (n): Unclear Other attrition related comments? Figure 1 describes the number of patients that discontinued a study agent and stratifies by SC and oral agents. The lists are not mutually exclusive, so it is unclear how many of the total withdrawals were due to adverse events or for reasons of efficacy. Overall adverse events reported (n): D1: 116 D2: 107 D3: 129 D4: 121 Serious adverse events: Death (n): D1: 0 D2: 0
	criteria	D4: 78.6	D2: 58.5		D3: 1

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
	Exclusion	Interventions Overall: NR Race, % white D1: 71.3 D2: 69.8 D3: 74.8 D4: 73.6		Health Outcomes	Adverse Events, % D4: 1 Cardiovascular events (specify) (n): HTN D1: 3 D2: 4 D3: 8 D4: 6 Hepatotoxicity/elevated liver enzymes (n): ALT D1: 10 D2: 7 D3: 20 D4: 12 AST D1: 6 D2: 6 D3: 13 D4: 10 Malignancies: Lymphoma or leukemia (n): D1: 0
					D2: 0 D3: 0 D4: 1 Skin cancer (basal cell or squamous cell) (n): D1: 1 D2: 0 D3: 0 D4: 0 Other cancer (specify) (n): Malignancy D1: 2 D2: 0

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
					Breast cancer D1: 1 D2: 0 D3: 1 D4: 0
					Respiratory events: Tuberculosis (n): D1: 0 D2: 0 D3: 1 D4: 0
					Pneumonia (n): D1: NR D2: NR D3: NR D4: 2
					Upper respiratory infection (n): D1: 14 D2: 9 D3: 13 D4: 19
					Other infections: Infections D1: 52 D2: 55 D3: 54 D4: 50
					Serious infections D1: 3 D2: 2 D3: 2 D4: 7
					GI: Nausea D1: 16 D2: 11 D3: 22

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
					Vomiting D1: 3 D2: 2 D3: 4 D4: 7
					Abdominal pain (n): D1: 1 D2: 6 D3: 9 D4: 5
					Dyspepsia D1: 7 D2: 5 D3: 10 D4: 8
					Other: Infusion/injection site reactions (n): D1: 3 D2: 17 D3: 7 D4: 14
					Skin rash (n): D1: 7 D2: 6 D3: 8 D4: 5
					Headache (n): D1: 10 D2: 7 D3: 6 D4: 11
					Dizziness (n): D1: 1 D2: 3 D3: 7

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
					D4: 3
					Serious AEs D1: 11
					D2: 5 D3: 10 D4: 10

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
Author, year, study name, if applicable Emery, 2010 ⁵¹ COMET trial (do not combine with other COMET REF IDs) Country and setting multinational; multicenter Source of funding Wyeth Pharmaceuticals; Pfizer Research objective To evaluate how continuation of and alterations to initial year 1 combination ETN + MTX therapy and MTX monotherapy regimens affect long-term remission and radiograhic progression in early active RA Study design RCT Overall N 411	Inclusion Criteria Early RA Disease duration of 3-24 mos Included in year 2 of study Completed COMET trial by end of year Texclusion Criteria Previous treatment with MTX, ETN, or another TNF antagonist at any time Had received treatment with other DMARDs or corticosteroid injections in4 weeks before baseline visits Important concurrent medical diseases and/or other relevant comorbidities.	Comparisons (dosage and frequency) D1: • MTX: avg. of 16.2 mg once weekly • ETN: 50 mg once weekly • (ETN+MTX in year 1) D2: • ETN: 50 mg once weekly • (ETN+MTX in year 1) D3: • MTX: avg. 17.8 mg once a week • ETN: 50 mg once weekly • (MTX in year 1) D4: • MTX: avg. 18.0 mg once weekly • (MTX in year 1) Number in group D1: 108 D2: 108 D3: 88 D4: 94 Overall: 398 Mean age (years) D1: 52.4 D2: 52.2 D3: 55.6 D4: 53.2 Overall: 53.2	Mean disease duration, years D1: 8.4 mos (5.7) D2: 9.1 mos (5.6) D3: 9.1 mos (6.0) D4: 8.7 mos (5.4)	ACR mean difference/absolute difference (CI/SD/P Value): ACR 20: D1: 86 (P<0.001 compared to MTX/MTX) D2: 80 (P=0.004, compared to MTX/MTX) D3: 81 D4: 61 ACR 50: D1: 70 (P<0.001 compared to MTX/MTX) D2: 64 (P=0.007 compared to MTX/MTX) D3: 66 D4: 46 ACR 70: D1: 57 (P<0.001 copmared to MTX/MTX) D3: 46 ACR 70: D1: 57 (P<0.001 copmared to MTX/MTX) D3: 46 ACR 70: D1: 57 (P<0.001 copmared to MTX/MTX) D3: 48 ACR 70: D4: 40 (P=0.034 compared to MTX/MTX) D5: 44 (P=0.034 compared to MTX/MTX) D6: 44 (P=0.034 compared to MTX/MTX) D7: 48 D8: 48 D8: 32 HAQ, mean difference/absolute difference (CI/SD/P Value): NR DAS, mean	Overall Overall attrition/withdrawal (n): D1: 7 D2: 18 D3: 16 D4: 23 Overall: 64 Withdrawals due to adverse events (n): D1: 3 D2: 5 D3: 7 D4: 9 Overall: 24 Withdrawals due to lack of efficacy (n): D1: 0 D2: 7 D3: 1 D4: 7 Overall: 15 Overall adverse events reported (n): D1: 91 D2: 89 D3: 71 D4: 79 Overall: 330 Serious adverse events: Death (n): D1: 0 D2: 0 D3: 0 D4: 1 Overall: 1	Quality rating for efficacy/effectiveness? Fair Quality rating for observational studies NR
		Sex, % female	Baseline DAS score	difference/absolute	Malignancy	

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
Duration of study total of 2 yrs (results from this study from wk 52 to wk 104)		D1: 72.2 D2: 75.9 D3: 59.1 D4: 81.9 Overall: 72.6 Race, % white D1: 87.0 D2: 88.0 D3: 88.6 D4: 88.3 D5Overall: 87.9 Race, % black NR Ethnicity, Latino NR	D1: 2.7 (1.2) D2: 2.6 (1.2) D3: 3.3 (1.4) D4: 3.4 (1.4) Overall: 3.0 (1.4) Required treatment for latent TB NR Other population characteristics, %, (CI/SD/P value): NR	difference (CI/SD/P Value): Diff from wk 104 and wk 52 D1: 0.00 D2: -0.5 (P<0.001 versus MTX/MTX) D3: 0.5 (P<0.05 versus ETN + MTX/ETN + MTX) D4: 0.1 SF-36, mean difference/absolute difference (CI/SD/P Value): NR Radiographic measures, mean difference/absolute difference (CI/SD/P Value): SHS change from wk 52 to wk 104, mean (95% CI) D1: -0.02 (-0.32 to 0.29; P=0.006 vs ETN + MTX/ETN) D2: 0.11 (-0.54 to 0.77) D3: 0.78 (-0.06 to 1.61) D4: 2.07 (0.42 to 3.72)	D1: 0 D2: 1 D3: 5 D4: 3 Overall: 9 Respiratory events: NR Other infections: Serious Infections D1: 1 D2: 2 D3: 1 D4: 2 Overall: 6 GI: NR Other: NR	
				Quality of life scales, mean difference/absolute difference (CI/SD/P Value): NR		
				Others, (please name); mean difference/absolute		

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
				difference (CI/SD/P		
				Value):		
				NR		

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
Author, year, study name, if	Inclusion Criteria	Comparisons (dosage and	Mean disease duration, years	ACR mean difference/	Overall Overall	Quality rating for efficacy/effectiveness?
applicable	Treatment	frequency)	D1: 7.48 (7.642)	difference (CI/SD/P	attrition/withdrawal (n):	Fair
Emery et al., 2010 ⁵² SERENE	resistant resistant to 10-25 mg	D1: • MTX: 10-25 mg/wk	D2: 7.10 (6.969) D3: 6.61 (7.294)	Value): ACR 20: Wk 24	D1: 13 D2: 6 D3: 6	Quality rating for observational studies
Country and setting multinational;	MTX/wk for 12 wks or more	PlaceboD2:	TJC, mean D1: 30.2 (15.94) D2: 27.1 (14.10)	D1: 23.3 D2: 54.5 (<i>P</i> <0.0001)	Withdrawals due to adverse events (n):	NR
multicenter	18-80 yrs oldRA according	 MTX: 10-25 mg/wk 	D3: 28.7 (14.98)	D3: 50.6 (<i>P</i> <0.0001)	D1: 2	
Source of funding	to ACR (SJC and TJC of	RTX: 500 mg IV infusion on day 1	SJC, mean D1: 20.9 (11.26)	Wk 48: D1: NR D2: 55.7	D2: 2 D3: 3	
Hoffmann-La Roche,	both at least 8 • CRP at least	and 15 D3:	D2: 18.6 (9.62) D3: 19.5 (10.32)	D3: 57.6 (<i>P</i> =NR)	Other attrition related comments?	
Genentech, Biogen Idec	0.6 mg/dl or ESR at least	 MTX: 10-25 mg/week 	Corticosteroid use, % D1: 47.7	ACR 50:	Reported for 24 wksWithdrawals due to	
Research objective	28 mm/h) for 6 mos or more • Absolute	RTX: 1000 mg IV infusion on day 1	D2: 47.9 D3: 39.4	Wk 24 D1: 9.3 D2: 26.3 (<i>P</i> <0.0001)	 AE exclude RA flare Study reports that Study reports that 	
To study the efficacy and	neutrophil count of 1500	and 15 Number in group	DMARD use, %: NR	D3: 25.9 (<i>P</i> <0.0001)	over 90% of patients completed 48 wks of study.	
safety of RTX 2 x 500 mg and 2 x	mcg/mcl or	D1: 172 D2: 167	MTX naïve, %:	Wk 48 D1: NR	Overall adverse events	
1000 mg with	more • Hemoglobin of	D3: 170	NR	D2: 32.9	reported (n):	
MTX in active RA patients who	8 g/dl or more	Mean age (years)	Treatment resistant,	D3: 34.1 (<i>P</i> =NR)	D1: 128 D2: 128	
had inadequate response to MTX	 IgM of 40 mg/dl or more 	D1: 52.16 D2: 51.91	%: NR	ACR 70:	D3: 138	
and no prior biologic	 IgG of 500 mg/dl or more 	D3: 51.30	Patients with early RA,	Wk 24 D1: 5.2	Serious adverse events:	
treatment	Exclusion	Sex, % female D1: 85.5	three years or less, %: NR	D2: 9.0 (<i>P</i> =NR) D3: 10.0 (<i>P</i> =NR)	Death (n): D1: 0 D2: 0	
Study design Controlled Trials	Criteria • Previous	D2: 79.6 D3: 81.2	Baseline DAS score	D1: NR	D3: 0	
Overall N	treatment with	Race, % white	DAS28-ESR D1: 6.54 (1.015)	D2: 12.6 D3: 13.5	Any Cardiac Disorder	
511	biologic	D1: 82.6 D2: 80.2	D2: 6.40 (0.951) D3: 6.49 (1.061)	(<i>P</i> =NR)	Events D1: 4	
Duration of		D3: 80.6	DAS28-CRP	HAQ, mean difference/	D2: 5 D3: 7	
study 48 wks		Race, % black NR	D1: 5.95 (0.972) D2: 5.81 (0.912)	difference (CI/SD/P Value):	Serious Cardiac Disorder Events	

Ethnicity, Latino	D3: 5.86 (0.967)	NR	D1: 2
NR	Required treatment for latent TB	DAS, mean difference/absolute	D2: 2 D3: 1
	NR	difference (CI/SD/P Value): population cteristics, VSD/P value): difference (CI/SD/P Value): VSD/P value):	Malignancies:
	Other population characteristics, %, (CI/SD/P value): NR		Malignancy D1: 1 D2: 1 D3: 2
		D2: -1.76 (<i>P</i> <0.0001) D3: -1.69 (<i>P</i> <0.0001) Wk 48	Respiratory events: NR
		D1: NR D2: -1.96 (<i>P</i> =NR) D3: -2.02 (<i>P</i> =NR)	Other infections: Any Infection D1: 74
		SF-36, mean difference/absolute	D2: 69 D3: 61
		difference (CI/SD/P Value): NR	Serious Infection D1: 4 D2: 1
		Radiographic measures, mean difference/absolute difference (CI/SD/P Value): NR	D3: 2 GI: Any lower GI events D1: 20 D2: 16
		Quality of life scales, mean difference/absolute difference (CI/SD/P Value):	D3: 16 Any serious GI Events D1: 3 D2: 1 D3: 1
		NR	Other: Infusion/injection site
		Others, (please name); mean difference/absolute difference (CI/SD/P	reactions (n): Day 1 D1: 24
		Value): Remission (DAS28-	D2: 31 D3: 42 Day 15
		ESR<2.6) Wk 24 D1: 4 D2: 16 (<i>P</i> <0.01)	D1: 14 D2: 12 D3: 10
		D3: 16 (P<0.01)	

 Wk 48	
D1: NR D2:15 (<i>P</i> =NR) D3: 19 (<i>P</i> =NR)	Any other AEs: Reported AEs only up to 24 wks

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
Author, yr: Feltelius et al., 2005 ⁵³ Country, Setting: Sweden, Swedish Society of Rheumatology database Funding: Wyeth Research Research Objective: To describe a nationwide system for postmarketing follow up of new antirheumatic drugs; to analyze safety and effectiveness in an ETA-treated cohort Study Design: Case series Overall N: 1,073 Study Duration: >2 yrs	Inclusion Criteria: Previous use of DMARDs: previous treatment with > 1 DMARD in addition to MTX Active RA as evaluated by the attending physician Exclusion Criteria: NR Interventions: D1: ETA Etanercept: 25mg twice weekly N: D1: 1073 Mean age (yrs): D1: 52 Sex, % female: D1: 76.6 Race, % white: NR	Mean disease duration, yrs: NR TJC, mean: NR SJC, mean: NR DMARD use, %: D1: 56.3 Corticosteroid use, %: D1: 95.2 MTX naive, %: NR Treatment resistant %: NR Patients with Early RA (≤3 yrs): NR Baseline DAS, mean: D1: 5.9 D1: MTX use: 40.1	In 294 pts (27%), at least 1 adverse drug reaction (ADR) was reported (421 reports; mean 1.5 report per patient; median 1; rand 1 to 6) 80 ADR reports (19%) were serious and 331 (79%) were non-serious 76 pts (7%) experienced at least one serious event and 114 (11%) had events exclusively classified as nonserious Incidence of adverse events remained constant over time	D1: 22 (% of all AE diagnoses) Serious Infections: D1: 5.4 (% of all AE diagnoses)	Overall Attrition Rate, %: NA ITT Analysis: Not applicable (Why not?) Quality Rating: Fair

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
Author, year, study	Inclusion Criteria	Interventions, dose	Mean disease duration,	ACR mean difference/	Attrition/withdrawal
name, if applicable Fernandez-Nebro et al., 2007 ⁵⁴	Treatment resistantNo response to	D1: IFX: Varied D2: ETN: Varied D3: ADA: Varied	years (SD) D1: 9.6 (7.9) D2: 9.9 (7.9)	absolute difference NR HAQ (SD)	Withdrawals due to adverse events, n: Overall: 8.1% (n: 13)
Country and setting Spain, tertiary care center Source of funding	at least 2 DMARDs, including MTX • Required biological	Number in group D1: 60 D2: 79 D3: 22 Overall: 161	D3: 9.5 (8.3) Overall: NR Patients with early RA, three years or less, % NR	D1: -0.32 (0.37) (n: 60) D2: -0.46 (0.63) (n: 78) D3: NR Overall: -0.35 (0.54), (<i>P</i> = 0.0001)	Primary efficacy endpoint of this study was time to treatment failure defined as definitive withdrawal of anti-
Research objective Evaluate effectiveness and safety of anti-TNF therapies and to identify factors involved in this response Study design Dynamic Prospective Cohort Study Overall N 161 Duration of study 6 years (secondary outcomes [DAS28, HAQ, EULAR response] measured at 6 mos) Quality rating Fair	therapy inopinion of a physician. No formal level of disease activity was required. No restriction ofuse of DMARD, steroids and NSAIDs Exclusion Criteria NR	Mean age, years (SD) D1: 54.0 (11.6) D2: 54.0 (12.4) D3: 54.0 (11.2) Overall: 54.0 (12) Sex, % female D1: 88 D2: 76 D3: 82 Overall: 81 Race, % white NR Race, % black NR Ethnicity, Latino NR	Treatment resistant, % D1: 100 D2: 100 D3: 100 Overall: 100 Tender Joint Count, mean (SD) D1: 16.6 (8.3) D2: 13.6 (7.9) D3: 13.3 (6.2) Overall: NR Swollen Joint Count, mean (SD) D1: 11.1 (7.3) D2: 9.7 (6.7) D3: 9.5 (7.8) Overall: NR Corticosteroid use, % D1: 65 D2: 67 D3: 48 Overall: NR DMARD use, % D1: 92 D2: 54 D3: 73 Overall: 70	DAS D1: -1.3 (1.2) D2: -1.7 (1.5) D3: NR Overall: -1.5 (1.4) (P = 0.0001) SF-36 NR Radiographic measures NR Quality of life scales, mean difference/absolute difference NR EULAR at 6 mo (%) IFX: Good 11% Moderate 49% No response 40% ETN Good 25% Moderate 43% No response 32% Overall: (P = 0.218) MCID HAQ at 6 mo: IFX: 58%	TNF for any reason, or substitution or addition of concomitant DMARD to maintainefficacy ofanti-TNF. Overall adverse events reported, n: D1: 112 D2: 84 D3: 19 Overall: 215 Serious adverse events Death, n: D1: 1 D2: 1 D3: 0 Overall: 2 Cardiovascular events (specify), n: D1: 1 D2: 4 D3: 0 Overall: • Total cardiovascular problems: 9% (n: 15) • Arterial hypertension/ decompensation: 10 • Cardiac rhythm disorder: 2 • Acute myocardial inforcation: 1
			MTX naïve, %	• ETN: 57%	infarction: 1Deep vein thrombosis: 1

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
			NR	• <i>P</i> = 0.951	 Cardiac insufficiency: 1
			Baseline DAS score D1: 6.2 (1.3) D2: 5.9 (1.4) D3: 6.2 (0.9) Overall: NR	6 yr results: Time to failure (patient-years) IFX: 105.7 ETN: 145.5 ADA: 23.1	Increased transaminases, n. D1: 9 D2: 2 D3: 0 Overall: 11
			Required treatment for latent TB years (98 NR • IFX: 40 • ETN: • ADA: Time to	Failure-Rate per 100 Patient- years (95% CI): • IFX: 40.7 (28.5-52.8)	Lymphoma or leukemia, n: D1: 0
				ETN: 25.4 (17.2-33.6)ADA: 39.0 (13.5-64.4)	D2: 0 D3: 0 Overall: 0
				Time to treatment failure: • Multivariate Hazard Ratio ETN (Ref: IFX): 0.34 (95% CI 0.18-0.61)	Skin cancer (basal cell or squamous cell), n: D1: 0
			LEF use: D1: 8 D2: 3 D3: 9	 Patients receiving ETN V IFX over first 24 mo remained for longer without treatment failure (P 	D2: basocellular carcinoma ofnasal dorsum: 1 D3: cutaneous basocellular carcinoma: 1 Overall: 2
			SSZ: D1: 0 D2: 0 D3: 5	= 0.032) and had a lower failure rate through follow-up (rate ratio: 0.6 95% CI 0.4-0.9)	Other cancer (specify), n: D1: pulmonary carcinoid tumor: 1 D2: pancreatic carcinoma: 1
			Hydroxcholoquine (HCQ): D1: 0 D2: 0 D3: 5		monoclonal lymphoproliferation of B cells: 2; IgG-kappa monoclonal
			MTX + HCQ D1: 0 D2: 0		gammopathy: 1 D3: 0 Overall: 5
			D3: 5 Overall: NR		Respiratory events Tuberculosis: NR
					Pneumonia, n: D1: 0 D2: 0 D3: 1 Overall: 1

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
					Other infections Urological sepsis, n: D1: 1 D2: 1 D3: 0 Overall: 1
					Other infections, n: Brucellosis: 1 Septic arthritis: 1
					Soft tissue: D1: 3 D2: 3 D3: 1
					Herpes zoster: D1: 0 D2: 2 D3: 1 Overall: 12
					GI NR
					Other Infusion/injection site reactions, n: D1: 7 D2: 2 D3: 1 Overall: 10
					Skin rash, n: D1: 7 D2: 5 D3: 1 Overall: 13
					Demyelenation or multiple sclerosis, n: D1: 0 D2: 0 D3: 0

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
					Overall: 0
					Worsening of ocular and ora dryness, n: D1: 0 D2: 7 D3: 0 Overall: 7
					Total infections, n: D1: 30 D2: 24 D3: 8 Overall: 62
					Herpes zoster, n: D1: 0 D2: 2 D3: 1 Overall: 3
					Dryness worsening, n: D1: 0 D2: 7 D3: 0 Overall: 7
					Onset of worsening high blood pressure: D1: 6 D2: 3 D3: 1

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
Author, year, study name, if applicable Finckh et al., 2007 ⁵⁵ (SCQM cohort) Country and setting Switzerland, university hospitals Source of funding Geneva University Research objective Compare effectiveness of RTX with alternative anti-TNF agents in managing pts who had inadequate response to anti-TNF therapy Study design Prospective Cohort Overall N 116 Duration of study January 1998 to end of September 2006 Quality rating Fair	Inclusion Criteria Treatment resistant at least one anti-TNF agent Initiation of second or third alternative anti-TNF agent or RTX Baseline assessment of DAS28 at time of treatment switch At least 1 f/u assessment within first 12 mos Diagnosis of RA by rheumatologist Inadequate response to at least 1 anti-TNF agent Exclusion Criteria A treatment switch because of personal preferences (i.e., in absence of an inadequate response to previous anti-TNF agent) and RTX therapy for lymphoma.	D2: • ETN: 50 mg subcutaneously weekly • IFX: 3mg/kg intravenously • ADA: 40 mg every two weeks Number in group D1: 50 D2: 66 Overall: NR Mean age, median D1: 55 D2: 54	Disease duration mean, median D1: 10 D2: 9 Disease duration mean, IQR D1: 6-18 D2: 5-16 $P = 39$ Patients with early RA, three years or less, % NR Treatment resistant, % At least 1 anti-TNF agent: D1: 100 D2: 100 Overall: NR TJC, mean D1: 11 D2: 10 $P = 0.44$ SJC, mean D1: 10 D2: 8 $P = 0.17$ Corticosteroid use, % D1: 58 D2: 55 $P = 0.71$ DMARD use, % MTX: D1: 52 D2: 39 $P = 0.18$ LEF: D1: 16	ACR NR HAQ NR DAS At 6 mos: D1: -1.6 mean decrease	Attrition/withdrawal There were 209 patients in SCQM databank who received RTX or a 2nd or 3rd anti-TNF agent. Of these, 60 (29%) were excluded from this study b/c of missing follow up assessments, 22 (11%) were excluded b/c they switched to an alternative biologic therapy b/c of personal preferences and not as a result of inadequate response to anti- TNF therapy, 8 (4%) were excluded b/c of missing baseline assessment, and 3 (1%) b/c RTX was administered to treat concomitant lymphoma rather than RA Respiratory events Tuberculosis: NR Upper respiratory infection, n: NR Other infections NR GI NR Other Infusion/injection site reactions, n: D1: 1 D2: 9 P = 0.03 Allergic complications, n: D1: 3

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
	 Any observations 		D2: 14 P = .72		D2: 0 P = 0.04
	after interruption of anti-TNF treatment or re- treatment with RTX were		Other DMARD: D1: 10 D2: 9 P = 0.87		
	censored.		None D1: 28 D2: 39 P = 0.20		
			MTX na ïve NR		
			Baseline DAS score mean (CI) D1: 5.43 (4.99-5.87) D2: 5.01 (4.70-5.32) P = 0.11		
			No. of previous anti-TNF agents (SD) D1: 1.96 - 0.7 () D2: 1.53 - 0.6 P = 0.001		

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
Author, year, study name, if applicable Finckh et al., 2009 ⁵⁶ (SCQM cohort) Country and setting Switzerland, multicenter Source of funding Sanofi-Aventis, Geneva University, SCQM Foundation, Swiss National Science Foundation Research objective Compare retention rates, effectiveness and safety ofrapeutic regimen associating anti- TNF agents and LEF, MTX or other conventional DMARDs in a large population based RA cohort. Study design Population-based Cohort Overall N 1218 Duration of study March 1996- December 2006, mean patient follow up 17 mos Quality rating Fair	Inclusion Criteria Diagnosis of RA by rheumatologist and treatment with INF, ETN, or ADA Exclusion Criteria Absence of concomitant DMARDrapy, and simultaneous prescription of LEF and MTX in combination with anti-TNF agents.	Interventions, Dose D1: MTX: 15mg/week (median dose at baseline) Other: this D was anti-TNF agents (all combined) + MTX D2: LEF: 20mg/day (median dose at baseline) Other: anti-TNF agents (combined) + LEF D3: Sulfasalazine, Hydroxychlorquine, Anti-TNF agents (combined) + any oral DMARD that was not MTX or LEF (minocycline, azathioprine, cyclosporine A, D-penicillamine, oral or intramuscular gold salts) Number in group D1: 842 D2: 260 D3: 116 Overall: 1218 Mean age (years) D1: 53 D2: 53 D3: 55 P = 0.23 Sex, % female	Mean disease duration, median D1: 8.4 D2: 8.9 D3: 9.9 Overall: Mean disease duration, IQR D1: 3.7-14.9 D2: 3.3-14.2 D3: 4.4-15.8 P = 0.14 Patients with early RA, three years or less, % NR Treatment resistant, % Anti-TNF failure: D1: 33 D2: 41 D3: 28 P = 0.06 TJC, mean NR SJC, mean NR Corticosteroid use, % Concomitant steroid use ever: D1: 48 D2: 51 D3: 67 P = .001 Previous DMARD use, median, n D1: 1 D2: 2 D3: 2	ACR NR HAQ, mean improvement after 1 year (CI) D1: 0.12 (0.08-0.15) D2: 0.14 (0.07-0.20) D3: 0.13 (0.03-0.23) P = 0.09 DAS, mean improvement after 1 year (CI) D1: 0.74 (0.63-0.84) D2: 0.63 (0.45-0.82) D3: 0.86 (0.60-1.12 P = 0.33 SF-36, mean difference/absolute difference NR Radiographic damage progression measures (CI) D1: 0.91% (0.54-1.27) D2: 0.74% (0.21-1.27) D3: 0.71% (-0.02-1.44) P = 0.77 Quality of life scales NR	Overall adverse events reported, n: 178; P = 0.13 Serious adverse events NR Malignancies NR Other infections NR GI Allergic complications, n (CI): D1: 0.45 0.20-0.98) D2: NR D3: NR P = 0.04 Any other AEs: • A total of 178 combinationrapies were interrupted because of adverse events (28%). most common adverse events leading to treatment interruption were: allergic reactions (28%), infections (19%), skin reactions (19%), skin reactions (19%), and gastrointestinal side effects (12%). • Hepatotoxicity (2%) and malignancies (6%) were rare causes of treatment interruption in this cohort.

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
		D1: 76 D2: 79 D3: 78 P = 0.57 Race, % white NR	Previous DMARD use, IQR D1: 0-2 D2: 1-3 D3: 1-3 P = 0.001		
		Race, % black NR Ethnicity, Latino NR	MTX naïve, % NR Baseline DAS28 score, mean (SD) D1: 4.1 (1.5) D2: 4.5 (1.4) D3: 4.6 (1.4) P = 0.31		
			Required treatment for latent TB NR		
			HAQ, mean (SD) D1: 1.24 (0.71) D2: 1.34 (0.67) D3: 1.33 (0.72)		

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
Author, yr: Fleischmann et al., 2003; ⁵⁷ ; Tesser et al., 2004 ⁵⁸ ; Schiff et al., 2006 ⁵⁹ ; Fleischmann et al., 2006 ⁶⁰ Country, Setting: Multinational, multicenter Funding: Amgen Research Objective: Long term safety of AKA in a large population of pts with RA Study Design: RCT Overall N: 1414 (1399) enrolled (open label 1103) Study Duration: 6 mos (up to 30 mos open label for a total of 3 yrs)	 Age: 18+ Diagnosed according to ACR criteria; duration 3+ mos Stable doses of NSAIDs and Cs 	Interventions, dose: D1: AKA (100mg/d) D2: placebo N: D1: 1116 D2: 283 Mean age, yrs: D1: 54.6 D2: 55.7 Sex, % female: D1: 74.7 D2: 74.6 Race, % white: D1: 87.8 D2: 90.1	Mean disease duration, yrs: D1: 10.2 (9.6) D2: 10.7 (9.5) TJC, mean: D1: 22.6 (14.7) D2: 22.6 (14.5) SJC, mean: D1: 18.8 (11.9) D2: 18.3 (11.7) DMARD use excluding MTX, and TNF inhibitors %: D1: 47.7 D2: 47.7 Corticosteroid use, %: D1: 57 D2: 60.8 MTX naive, %: NR Txt resistant %: NR Pts with Early RA (≤3 yrs): NR Baseline DAS, mean: NR MTX use: D1: 51.9 D2: 59.4	6 mos-injection site reactions, AKA vs. placebo. (72.6% v. 32.9%) <i>P</i> -value NR 13.4% AKA withdrew due to AE vs, 9.2% placebo (<i>P</i> = 0.057); overall discontinuation rates (21.6% vs. 18.7%) Serious infections AKA vs. placebo (2.1% v. 0.4%), may be clinically significant. (<i>P</i> = 0.068) Comorbid conditions, serious infectious events (2.5% vs. 0.0%; <i>P</i> = NR). Trend towards increased risk of serious infectious events with AKA in pts with pulmonary comorbidities vs. placebo (3.4% v. 1.6%), <i>P</i> = NS From 0-3 yrs rates per 100 yrs of patient exposure ISRs (122.26 events), Rheumatoid arthritis progression (67.80 events) URTIs(26.09 events) Concomitant use of corticosteroids vs. not serious infection (7.13 events/100 PY v 2.87 events/100 PY) pneumonia (1.5 events/100 PY) Cellulitis (1.2 events/100 PY)	Overall: D1: 92 D2: 92.2 D3: 96 SAEs: D1: 7.7 D2: 7.8 D3: 27 Infections: D1: 41.2 D2: 43.5 Serious Infections: D1: 2.1 D2: 0.4 D3: 8 Infusion or injection reaction: D1: 72.6 D2: 32.9 URTI: D1: 13.3 D2: 18.4 UTI: D1: 4.6 D2: 5.3 Adherence: AKA vs. placebo: 100% adherent with use of study drug: 43.8% vs. 47.8; <70% adherent: 0.8% vs. 1.7%>40% missed no injections and >90% received at least 90% of intended doses	Overall Attrition Rate, %: 21 ITT Analysis: Yes Quality Rating: Fair

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
				v 0.21 events/100 PY)		

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
Author, year, study name, if applicable Fleischmann et al., 2009 ⁶¹ ,FAST4WARD	Inclusion Criteria • Treatment resistant Failed ≥ 1DMARD • Aged 18-75 yrs	Interventions, dose D1: Certolizumab: 400mg every 4 weeks D2: Placebo: Every 4	Mean disease duration, years D1: 8.7 yrs ± 8.2 D2: 10.4 ± 9.6 Patients with early RA,	ACR mean difference/ absolute difference (%) ACR 20: D1: 45.5 D2: 9.3	Attrition/withdrawal (%) Overall, n: D1: 35 (31.5) D2: 81 (74.3) Overall: 116 (52.7)
Country and setting 36 sites in Austria,Czech Republic andUSA between June 2003	 Adult onset RA (defined byACR criteria) for ≥ 6 mos Failed ≥ 1 previous 	weeks Number in group D1: 111 D2: 109 Mean age, years (SD)	three years or less, % NR Treatment resistant, % Failed ≥ 1 previous DMARD D1: 100	P = 0.001 ACR 50: D1: 22.7 D2: 3.7 P = 0.001	Withdrawals due to adverse events, n: D1: 5 (4.5) D2: 2 (1.8) Overall: 7 (3.2)
and July 2004. Setting NR Source of funding UCB Research objective	DMARD due to lack of efficacy or intolerance Active disease at screening	D1: 52.7 ± 12.7 D2: 54.9 ± 11.6 Sex, % female D1: 78.4% D2: 89.0%	D1: 100 D2: 100 Tender Joint Count, mean D1: 29.6 ±13.7 D2: 28.3 ± 12.5	ACR 70: D1: 5.5 D2: 0 P =: 0.05 HAQ-DI, clinically	Withdrawals due to lack of efficacy, n: D1: 24 (21.6) D2: 75 (68.8) Overall: 99 (45.0)
Examine efficacy and safety of CZP 400 mg monotherapy in pts who had failed at least one prior	and baseline (defined by ≥ 9 tender joints, ≥ 9 swollen joints, ≥ 1 offollowing:	Race, % white NR Race, % black NR	Swollen Joint Count, mean D1: 21.2 ± 10.1 D2: 19.9 ± 9.3 Corticosteroid use, % D1: 55.9	meaningful improvement in physical function at week 24 (%) D1: 49 D2: 12	Overall adverse events reported, n (%): D1: 84/111 (75.7) D2: 63/109 (57.8)
DMARD Study design Controlled Trials	≥ 45 min morning stiffness, ESR ≥ 28 mm/h, or CRP > 10mg/l)	Ethnicity, Latino NR	D1: 33.9 D2: 58.7 DMARD use, % # of prior DMARDS: D1: 2 ± 1.19	P = 0.001 DAS28(ESR)3 (least square mean change at wk 24 from baseline)	D2: 0
Overall N 220 Duration of study 24 weeks	 DMARDs discontinued ≥ 28-d or 5 half lives of drug 		D2: 2 ± 1.25 MTX naïve, % D1: 18.0	D1: -1.5 D2: -0.6 P = 0.001	Malignancies Lymphoma or leukemia, n: D1: 0 D2: 0
Quality rating Fair	prior to administration of first study dose (exception being		D2: 18.3 DAS28 (ESR) 3 D1: 6.3 ± 1.1 D2: 6.3 ± 0.9	D1: Data not shown D2: Data not shown P = 0.001	Skin cancer (basal cell or squamous cell), n: D1: 0 D2: 0
	LEF, which was eliminated using cholestyramine administration		Required treatment for latent TB NR	Radiographic measures NR Quality of life scales D1: HRQoL	Other cancer (specify), n: D1: 0 D2: 0
	followed by a further 28-d		HAQ-DI (mean/SD) D1: 1.4 ± 0.63	Others, (please name)	Respiratory events Tuberculosis: NR

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
Characteristics	washout) Exclusion Criteria Inflammatory arthritis other than RA A history of chronic, serious or life- threatening infection Any current infection History of or chest x ray suggesting TB or a positive (defined by local practice) purified protein derivative (PPD) skin test (Patients positive for PPD who had received Bacille Calmette-Gue & acute Rin (BCG) vaccination and had a negative chest x ray and no clinical symptoms of TB could be enrolled) Received biological therapies for RA within 6 mos		D2: 1.6 ± 0.65	 Swollen joint count (least square mean change at wk 24 from baseline) CZP: -11.6, Placebo: -6.3 (P = 0.001) (reduced by approximately 38% for CZP compared with 16% for placebo) Tender joint count (least square mean change at wk 24 from baseline): CZP: -16.0, placebo: -7.3 (P = 0.001) (reduced by approximately 40% for CZP compared with 14% for placebo) Patient's global assessment of arthritis (least square mean change at wk 24 from baseline): CZP: -0.7, Placebo: 0.0 (P = 0.001) Patient's assessment of arthritis pain (clinically meaningful reductions in arthritis pain at wk 24): CZP: 47%, Placebo: 17% (P <0.001) Experienced minimally clinically important differences in Physical Component Summary: CZP: 46%, Placebo: 16% (P = 0.001) Experienced minimally clinically important differences in Mental Component Summary: CZP: 34%, Placebo: 7% (P = 0.001) 	Pneumonitis, n: D1: 0 D2: 1 Other infections Serious infections, n: D1: 2 (1.8%) D2: 0

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
	 Prior treatment 			clinically important	Ischaemic stroke n: 1
	with TNFα inhibitors Intra-articular, periarticular, intramuscular and intravenous corticosteroids (PRED equivalent 10 mg/day, stable for >4 weeks prior to enrollment and during study, non-steroidal anti-inflammatory drugs and analgesics were			improvemtns in fatigue: CZP: 46%, Placebo: 17% (P = 0.001)	SAE Placebo: • Vomiting: 1 • Pneumonitis: 1 • Chronic renal failure: 1

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %				
Author, yr: Flendrie et al., 2003 ⁶²	Inclusion Criteria: • Age: adult	Interventions: D1: ADA D2: INF	About 70% of pts were still receiving TNF blocking agents after the	Overall: D1: 12 D2: 30	Overall Attrition Rate, %: 17				
Country, Setting: Netherlands. University medical centre (Nijmegen)	Diagnosed with RA according to ACR criteria1) started treatment with ADA, INF, or ETA prior to January 1 2003 at department of rheumatology of University Medical Centre Nijmegen. 2) pts receiving ADA had been treated in phase	according to ACR criteria1) started treatment with ADA, INF, or ETA prior to	D3: ETA N: D1: 94 D2: 120	first yr. One yr. drug survival percentages (percentage of pts still taking the drug) were 73% for ADA, 66% for	D3: 7 Serious AEs: NR	ITT Analysis: NA Quality Rating:			
Funding: Not reported		D3: 16 Mean age (yrs):	INF, and 74% for ETA group.	Infections: D1: 2 D2: 6	Fair				
Research Objective: To determine the drug		University Medical Centre Nijmegen. 2) pts receiving ADA had been treated in phase	University Medical Centre Nijmegen. 2) pts receiving ADA had been treated in phase	University Medical D1: 55.2 Centre Nijmegen. 2) D2: 56.4 pts receiving ADA had D3: 50.6 been treated in phase : 55.5	2) D2: 56.4		D3: 0		
survival during treatment of RA pts with TNF blocking agents					: 55.5	between groups	Serious Infections: D1: 6.4		
Study Design: Retrospective cohort study	trials. ADA was given in different dosages subcutaneously or	Sex, % female: D1: 63 D2: 72 D3: 63		D2: 7.2 D3: 0 Infusion or injection					
Overall N: 230	intravenously. The pts then entered an open label extension study.	then entered an open label extension study.	then entered an open label extension study.	then entered an open label extension study.	then entered an open Rabel extension study.	Race, % white: NR		reaction: D1: 3 D2: 14	
Study Duration: About 6 yrs. (maximum follow up times for 3 groups were 69, 35, and 30 mos)	3) INF and ETA pts were treated in daily clinical practice and fulfilled the Dutch criteria for TNF blocking therapy; had moderate to high Wean disease dura yrs: D1: 11.4 D2: 11.9 D3: 10.1 TJC, mean:			D3: 0 Malignancies: D1: 2 D2: 0 D3: 0					
	disease activity, and high dosage MTX and at least one other DMARD had failed	NR SJC, mean: NR							
	Exclusion Criteria: NR	DMARD use, %: D1: previous DMARD use, mean 4.5 D2: 4.1 D3: 3.3							
		Corticosteroid use, %:							

D1: 51
D2: 24
D3: 19

MTX naive, %:
NR

Treatment resistant %:
NR

Patients with Early RA
(≤3 yrs):
NR

Baseline DAS, mean:
D1: 6.4
D2: 5.9
D3: 5.8

RF positive:
D1: 93%
D2: 82%

D3: 88%

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
Author, yr: Flendrie et al., 2005 63 Country, Setting: Netherlands, Hospital rheumatology clinic Funding: NR Research Objective: Whether dermatological conditions after TNF-alpha- blocking therapy are a significant and clinically important problem in RA pts receiving TNF- alpha -blocking therapy. Study Design: Prospective cohort study with historic control Overall N: 578 Study Duration: 911PY	Inclusion Criteria: Previous use of DMARDs: failure or intolerability of at least 2 DMARDS, including MTX, in adequate dosage regimens Control pts selected from Nijmegen inception cohort Pts required to meet Dutch guidelines for biological therapies: a moderate to high DAS score (DAS28 > 3.2) Besides therapy with registrated TNF-alphablocking agents -INF, ETA, and ADA -some pts were treated in clinical trials with lenercept Exclusion Criteria: NR	Interventions, dose: D1: TNF-apha blockers D2: Control N: NR Mean age at diagnosis, yrs: D1: 44.5 D2: 54.6 Sex, % female: D1: 69 D2: 62 Race, % white: NR	Median disease duration, yrs: D1: 9.2 D2: 6.2 TJC, mean: NR SJC, mean: NR DMARD use, %: NR PNL at baseline (%) D1: 39 D2: 7 MTX naive, %: NR Txt resistant %: NR Pts with Early RA (≤3 yrs): NR Baseline DAS, mean: D1: 5.9 D2: 3.6	Dermatological events recorded in 72/289 (25%) of RA pts receiving TNF- alpha-blocking therapy and in 37 (13%) of control group OR of TNF-alpha- blocking therapy for dermatological referral was 2.26 (95% CI,1.46 to 3.50, P < 0.0005) 128 dermatological events were recorded during follow-up in RA pts on TNF-alpha-blocking therapy (0.14 event per PY)	Overall: D1: 25 D2: 13 Infections (skin): D1: 9.3	Overall Attrition Rate, %: NR ITT Analysis: NA Quality Rating: Fair

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	
Author, year, study name, if applicable Fuerst et al., 2006 ⁶⁴	 RA or PsA, 3+ 	 RA or PsA, 3+ 	Interventions, Dose D1:	Mean disease duration, years (SD)	ACR ACR 20: No measures of efficacy or QOL were	Overall NA
Country and setting	months of continuous therapy with	MTX: 5-25 mgOther: Corticosteroids: dose:	D2: 14.3 yrs re	reported for this article	Overall adverse events reported, n:	
Germany, hospital Source of funding	one of study drugs (MTX,	2-10 mg D2:	Patients with early RA, three years or less, %	ACR 50: NR ACR 70: NR	SEE ADDITIONAL COMMENTS	
Not reported Research objective	LEF, ETA, INF, ADA, or ANA) • Undergoing elective orthopedic	LEF: 10-30 mgOther:	NR Treatment resistant, %	HAQ NR	Serious adverse events NR	
Assess whether tx with MTX or LEF		Corticosteroids: 2.5-8 mg	NR Tender Joint Count, mean	DAS NR	Malignancies NR	
increases risk of wound healing after		Number in group D1: 59	Number in group (SD) D1: 59 NR SF-36 NR	Respiratory events NR		
elective orthopedic surgery		Criteria Overall: 201	Swollen Joint Count, mean (SD)	Radiographic measures	Other infections	
Study design Prospective Cohort Study		Mean age (years) D1: 62.9 D2: 62.3	NR Corticosteroid use, % D1: 100%	Quality of life scales NR	GI NR	
Overall N 201				Overall: 62 Sex, % female	D2: 12.5% DMARD use, %	Others, (please name); mean difference/absolute
Duration of study 6 weeks+		D1: 72.9 D2: 78.1 Overall: 84.6	D1: 0 D2: 0	difference (CI/SD/P Value) NR	increased risk for wound healing complications compared to MTX+Cs	
Quality rating Fair		Race, % white NR Race, % black ND Race, % black ND Race, % black ND (SD)	*		(40.6% vs. 13.6%, P = 0.01).	
			Baseline DAS score, mean (SD) NR		 ETA and INF did not appear to increase risk of complications but N's were 	
	Ethnicity, Latino NR	Required treatment for			small (ETA: N = 16, 18.8% with complications • INF: N = 4, 1pt report complications-they were	
			Other population characteristics, %, NR		 taking INF+LEF+Cs). Logistic regression (wound complications, OR compared to those not receiving drug) MTX 0.99 (0.36-2.70), Corticosteroid 	

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
					1.15 (0.51-2.59), LEF 3.48
					(1.31-9.24), ETA 1.45 (0.35-5.93), INF 1.42
					(0.35-5.92)

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
Author, yr: Furst, 2003 ⁶⁵ STAR Trial Country, Setting: US and Canada, multicenter (69 sites) Funding: Abbott Laboratories, Abbott Park II Research Objective: To evaluate the safety and efficacy of ADA when given with standard anti- rheumatic therapy in pts with active RA not adequately responding to standard therapies Study Design: RCT Overall N: 636 Study Duration: 24 wks	Inclusion Criteria: Age: 18+ Diagnosed with RA (ACR criteria) Continued txt with standard antirheumatic therapy which included traditional DMARD, Cs, NSAID, or analgesics Exclusion Criteria: Prior txt with Anti-CD4 therapy or biologic DMARD Participated in other trials biolgic DMARD in RA History of active: inflammatory arthritide other than RA or active listeriosis or mycobacterial infection Major infection requiring hospitalization Txt with IV antibiotics within 30 ds Oral antibiotics within 14 ds Any uncontrolled medical condition	D2: placebo N: D1: 318 D2: 318	Mean disease duration, yrs: D1: 9.3 D2: 11.5 TJC, mean: D1: 27.3 D2: 27.6 SJC, mean: D1: 20.9 D2: 21.3 DMARD use, %: NR Corticosteroid use, %: D1: 50.9 D2: 54.4 MTX naive, %: D1: 20.9 (11) D2: 21.3 (11.2) Txt resistant %: NR Pts with Early RA (≤3 yrs): D1: 50.9 D2: 54.4 Baseline patient DAS (mean): D1: 53.9 D2: 52.9 Baseline physician DAS (mean): D1: 59.9 D2: 59.6	Health Outcome Measures: • At endpoint, significantly more ADA (28.9%) pts achieved an ACR50 response than placebo pts (11.3%) (<i>P</i> < 0.001) • At endpoint, significantly more ADA (14.8%) pts achieved an ACR70 response than placebo pts (3.5%) (<i>P</i> < 0.001) Intermediate Outcome Measures: • At endpoint, significantly more ADA (52.8%) pts achieved an ACR20 response than placebo pts (34.9%) (<i>P</i> < 0.001)	Overall: D1: 86.5 D2: 82.7 SAEs: D1: 5.3 D2: 6.9 Infections: D1: 52.2 D2: 49.4 Serious Infections: D1: 1.3 D2: 1.9 Rash: D1: 10.7 D2: 6.0 Infusion or injection reaction: D1: 19.5 D2: 11.6 URTI: D1: 19.8 D2: 15.1 UTI: D1: 9.1 D2: 5.7 Back pain: D1: 5.3 D2: 1.6	Overall Attrition Rate, %: 9.1 ITT Analysis: Yes Quality Rating: Fair

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
Author, year, study name, if	Inclusion Criteria	Comparisons (dosage and	Mean disease duration, years	ACR mean difference/ absolute	Overall NR	Quality rating for efficacy/effectiveness?
applicable Galloway JB et al., 2011 ⁶⁶ British Society for Rheumatogy Biologics	 Active RA Enrolled in BSRBR Had to have at least 1 returned 	frequency) D1: Non-biologic DMARDs: Dosage and frequency NR D2: All anti-TNF:	Median (IQR) D1: 6 (1-15) D2: 11 (6-19) D3: 12 (6-19) D4: 12 (6-19) D5: 10 (5-18)	difference (CI/SD/P Value): NR HAQ, mean difference/ absolute	Serious adverse events: Death (n): D1: 47 D2: 110	Quality rating for observational studies Fair
Register (BSRBR)	consultant follow up	Dosage and frequency NR D3: ETN: Dosage	TJC, mean NR	difference (CI/SD/P Value): NR	Malignancies: NR	
Country and setting UK, multicenter	questionnaire before 31 December	and frequency NR	SJC, mean NR	DAS, mean difference/absolute	Respiratory events: NR	
Source of funding University of Manchester	2008 Exclusion Criteria • NA	D4: INF:Dosage and frequency NR D5: ADA: Dosage and frequency NR	Corticosteroid use, % D1: 23 D2: 44 D3: 48	difference (CI/SD/P Value): NR SF-36, mean	Other infections: Other infections (specify) (n): D1: 296 D2: 1512	
Research objective To evaluate the		Number in group D1: 3598 D2: 11798	D4: 46 D5: 39 DMARD use, %: D1: 100	difference/absolute difference (CI/SD/P Value): NR	D3: 609 D4: 441 D5: 462	
risk of serious infections (SIs) in patients with RA		D3: 4129 D4: 3467 D5: 4202	MTX naïve, %:	Radiographic measures, mean difference/absolute	GI: NR Other:	
treated with anti- TNF therapy with emphasis on the risk across different ages.		Mean age (years) D1: 60 D2: 56 D3: 56 D4: 56	Treatment resistant, %: NR Patients with early RA,	difference (CI/SD/P Value): NR Quality of life scales,	Patients experienced at least one serious infection (SI), Rate/1000 pyrs (95% CI)	
Study design Observational		D5: 57 Sex, % female	three years or less, %:	mean difference/absolute difference (CI/SD/P	D1: 32 (28-36) D2: 42 (40-44) D3: 38 (35-42)	
Overall N 15,396 (11,798 in anti-TNF		D1: 2982 D2: 8777 D3: 3182	Baseline DAS score D1: 5.1 D2: 6.6	Value): NR	D4: 46 (42-50) D5: 43 (39-47)	
cohort and 3,596 in non-biologic		D4: 2620 D5: 3149	D3: 6.6 D4: 6.6 D5: 6.5	Others, (please name); mean difference/absolute	Unadjusted HR D1: Ref D2: 15 (1.3-1.7)	
DMARD cohort) Duration of		Race, % white NR	Required treatment for	difference (CI/SD/P Value):	D3: 1.4 (1.2-1.6) D4: 1.6 (1.4-1.9) D5: 1.4 (1.2-1.7)	

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
study Median duration of folow-up anti- THF cohort: 3.9 yrs (IQR, 2.4- 4.9) Non-biologic DMARD cohort: 2.6 yrs (IQR, 1.4- 3.8)		Race, % black NR Ethnicity, Latino NR	latent TB NR Other population characteristics, %, (CI/SD/P value): Diabetes, n D1: 234 D2: 675 D3: 254 D4: 165 D5: 252 COPD, n D1: 300 D2: 565 D3: 222 D4: 165 D5: 178		AdjHR (95% CI) (adjusted for age, gender, COPD, DM, smoking, disease duration, DAS, HAQ, entry yr, steroid use and MTX use) D1: Ref D2: 1.2 (1.1-1.5) D3: 1.2 (1.0-1.4) D4: 1.3 (1.1-1.6) D5: 1.3 (1.1-1.5) 30-day mortality rate D1: 16% (n=47) D2: 7% (n=110) P<0.001; adjusted OR, 05 (95% CI, 0.3-0.8)	

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
Author, yr: Geborek, 2002 ⁶⁷ Country, Setting: Sweden, primary care clinics, unversity clinic Funding: NR Research Objective: To assess efficacy and safety of ETA, INF, and LEF in a population- based setting Study Design: Nonrandomized open-label trial Overall N: 369 (33 pts tried 2 different txts and 1 tried all 3; 404 txts) Study Duration: 12 mos	Inclusion Criteria: Age: 18+ Previous use of DMARDs: required to have failed to respond to or not tolerated at least 2 DMARDs, including MTX Diagnosis of RA according to clinical judgment of treating doctor All pts included were required to have failed to respond to or not tolerated at least 2 DMARDs, including MTX Pts were selected on basis of current disease activity and/or unacceptable steroid requirement as judged by treating doctor, but had different backgrounds concerning previous txt, concomitant diseases, and functional impairment and disability Other meds allowed	D1: 166 D2: 135 D3: 103 Mean age, yrs: D1: 54 D2: 55.4 D3: 61.3 Sex, % female: D1: 78 D2: 79 D3: 82 Race, % white: NR	Mean disease duration, yrs: D1: 14.9 D2: 14.1 D3: 14.9 TJC, mean: NR SJC, mean: NR DMARD use, %: D1: 100 D2: 100 D3: 100 Corticosteroid use, %: D1: 83 D2: 81 D3: 73 MTX naive, %: D1: 0 D2: 0 D3: 0 Txt resistant, %: D1: 100 D2: 100 D2: 100 D3: 100 Pts with Early RA (≤3 yrs): NR Baseline DAS, mean: D1: 5.8 D2: 5.6 D3: 5.4	At 3 months ACR20/50: INF significantly higher than LEF (data NR; <i>P</i> < 0.01) ETA higher ACR 20 response rate than INF (data NR; <i>P</i> < 0.02) ETA had a significantly higher ACR50 response rate than INF (data NR; <i>P</i> < 0.05) At 6 months ACR 20/50: ETA better than LEF (data NR; <i>P</i> < 0.01) ETA higher ACR 20 response rate than INF (data NR; <i>P</i> < 0.02) At 12 months No significant difference between ETA and INF ETA and INF led to significant reduction in prednisolone use starting at 2 wks No reduction in prednisolone use for LEF		Overall Attrition Rate, %: N/A ITT Analysis: No Quality Rating: Fair

Exclusion Criteria: NR •	D1: 1.55 D2: 1.47 D3: 1.46	
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Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
Author, yr: Geborek et al., 2005 ⁶⁸ Country, Setting: Sweden, rheumatology centers Funding: Österlund and Kock Foundations, King Gustav V, and Reumatiker-förbundet Research Objective: To determine whether TNF blockers increase tumour risk in pts with RA Study Design: Retrospective cohort study Overall N: 1557 Study Duration: Median duration of anti-TNF txt was 1.7 yrs (5,571 PY)	 Pts with RA treated with ETA or INF from South Swedish Arthritis Txt Group (SSATG), which includes pts from 8 rheumatologic centers For comparison group, pts with RA not treated with anti-TNF drugs from a community based cohort in Malmo, a city from the SSATG catchment area. Controls recruited from Malmo University outpatient rheumatology clinic and from 4 rheumatologists in private 	Interventions, dose: D1: Anti-TNF txt D2: Comparison ETA: varied INF: varied N: D1: 757 D2: 800 Median age, yrs: D1: 56 D2: 64 Sex, % female: D1: 76 D2: 73 Race, % white: NR	Mean disease duration, yrs: D1: 12 D2: 11 TJC, mean: NR SJC, mean: NR DMARD use, %: NR Corticosteroid use, %: NR MTX naive, %: NR Txt resistant %: NR Pts with Early RA (≤3 yrs): NR Baseline DAS, mean: NR % with HAQ quartile >: 3: D1: 61 D2: 41 Median number of previous DMARDS: D1: 3 D2: 1	 Anti-TNF vs. Control: All tumors: SIR 1.1 (95% CI, 0.6-1.8) vs. 1.4 (95% CI, 1.1-1.8) Lymphomas: SIR 11.5 (95% CI, 3.7 to 26.9) vs. 1.3 (95% CI, 0.2 to 4.5) All tumors excluding lymphomas: SIR 0.79 (95% CI, 0.4-1.42) vs. 1.39 (95% CI, 1.08-1.76) Hazard ratio indicates a higher risk of lymphoma for anti-TNF drugs than for controls (RR: 4.9; 95% CI, 0.9-26.1) 	NA	Overall Attrition Rate, %: NA ITT Analysis: NA Quality Rating: Fair

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
Author, yr: Genovese, 2004 ⁶⁹ Country, Setting: US, multicenter, specialty clinic Funding: Amgen, Inc., Thousand Oaks, CA Research Objective: To determine potential for additive or synergistic effects of combination therapy with selective anti-TNF-alpha agent ETA and anti-IL1 agent AKA Study Design: RCT Overall N: 242 Study Duration: 24 wks	medications, such as corticosteroids Exclusion Criteria: • Any DMARD other than MTX within past 4 wks • Txt with AKA or	D1: 82.5 D2: 71.6 D3: 77.8 Race, % white: D1: 86.3 D2: 77.8 D3: 75.3	Mean disease duration, yrs: D1: 9.7 D2: 9.5 D3: 10.6 TJC, mean: D1: 31 D2: 31 D3: 35.9 SJC, mean: D1: 21.4 D2: 19.8 D3: 23.4 DMARD use, %: NR Corticosteroid use, % D1: 48.8 D2: 54.3 D3: 44.4 MTX naive, %: Overall: 0 Txt resistant, %: Overall: 100 Pts with Early RA (≤3 yrs): NR Baseline DAS, mean: NR MTX use, %: Overall: 100 HAQ: D1: 1.5	At week 24 ACR20, %: D1: 68 D2: 51 D3: 62 D1 vs. D2 (<i>P</i> = 0.037) All others NS ACR50, %: D1: 41 D2: 39 D3: 31(<i>P</i> = 0.914) OR (ETA + AKA vs. ETA alone) 0.64 (90% CI, 0.37-1.09); sensitivity analysis yielded similar results ACR70, %: D1: 21 D2: 24 D3: 14 (<i>P</i> = NR) Sustained ACR20 response: Between 43% and 54% of subjects in each group (specifics NR) EULAR response, %: D1: 79 D2: 66 D3: 73 (<i>P</i> = NR) Mean % reduction in DAS: D1: 39 D2: 41 D3: 40 (<i>P</i> = NR)	Overall: D1: 90 D2: 95.1 D3: 93.8 SAEs: D1: 2.5 D2: 4.9 D3: 14.8 Infections: D1: 40 D2: 37 D3: 46.9 Serious Infections: D1: 0 D2: 3.7 D3: 7.4 Infusion or injection reaction: D1: 40 D2: 67.9 D3: 70.4 URTI: D1: 20 D2: 11.1 D3: 13.6	Overall Attrition Rate, %: 15.7 ITT Analysis: Yes Quality Rating: Fair

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
	past 4 wks • Recent history of significant infection or other important concurrent illness		D2: 1.5 D3: 1.6			

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
Author, year, study name, if applicable Genovese et al., 2008 ⁷⁰ , TOWARD Country and setting	 Inclusion Criteria 18 years or older Moderate-to-severe RA of at 	Interventions, dose D1: • Tocilizumab: 8 mg/kg, 60-min infusion every 4 wks	Mean disease duration, years D1: 9.8 (8.8) D2: 9.8 (9.1) Patients with early RA,	ACR ACR 20: D1: 60.8 D2: 24.5 P = 0.0001	Overall Overall attrition/withdrawal, n: D1: 53 D2: 43 Overall: 96
International (18 countries, half ofstudy sites US-based), multi-center	least 6 mos' duration • Diagnosed according toACR 1987	 Background of stable DMARD therapy D2: Placebo: 60-min infusion every 4 wks 	three years or less, % Disease Duration = 2 yrs: D1: 19 D2: 20	ACR 50: D1: 37.6 D2: 9.0 P = 0.0001	Withdrawals due to adverse events, n: D1: 32 D2: 8 Overall: 40
Source of funding F. Hoffmann-L Roche	revised criteria for classification of RA • SJC of ≥ 6	Background of stable DMARD therapy Number in group	Treatment resistant, % NR Tender Joint Count, mean	ACR 70: D1: 20.5 D2: 2.9 P = 0.0001	Adherent/compliant, n: D1: 751 D2: 370
Research objective Examine efficacy and safety of tocilizumab	 TJC of ≥ 8 CRP level of ≥ 1 mg/dl or an 	D1: 803 D2: 413 Overall: 1216	D1: 30.1 (16) D2: 29.1 (14.8) Swollen Joint Count, mean	HAQ, HAQ-DI D1: -0.5	Overall: 1121 Overall adverse events reported, n:
combined with conventional DMARDs in pts with	ESR of ≥ 28 mm/hour received stable doses of	Mean age, years (SD) D1: 53 D2: 54	D1: 19.7 (11.6) D2: 18.7 (10.8) Corticosteroid use, %	D2: -0.2 P = 0.0001 DAS28	D1: 584 D2: 253 Overall: 837
active RA Study design Controlled Trials	permitted DMARDs (MTX, chloroquine,	Sex, % female D1: 81 D2: 84	D1: 51.2 D2: 54.6 DMARD use, %	D1: -3.17 D2: -1.16 Overall: , <i>P</i> = 0.0001	Serious adverse events Death, n: D1: 2 D2: 2
Overall N 1220 Duration of study	HCQ, parenteral gold, SSZ, azathioprine, and LEF) for at	D1: 72 D2: 72	D1: 100 D2: 100 Overall: 100	DAS28 = 2.6 (%) D1: 30 D2: 3	Overall: 4 Malignancies
24 wks Quality rating	least 8 weeks prior to study entry.	Race, % black D1: 4 D2: 7	MTX naïve, % NR Baseline DAS score	P = 0.0001 SF-36 NR	NR Respiratory events Tuberculosis: NR
Fair	Exclusion Criteria • Unsuccessfully	Ethnicity Asian D1: 9	D1: 6.7 D2: 6.6	Radiographic measures NR	Pneumonia, n: D1: 3
	treated with an anti-TNF agent	D2: 10 American Indian	Required treatment for latent TB NR	Quality of life scales NR	D2: 2 Overall: 5 Upper respiratory infection, n:
	previously treated with any cell-depleting therapy were	D1: 10 D2: 8 Other		Others, (please name) SJC, mean change from baseline:	D1: 9% D2: 7% Overall: NR

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
	excluded	D1: 3 D2: 3		 Tocilizumab = -10.3 Placebo = -4.9 P = 0.0001 	Other infections NR
				TJC, mean change from baseline: • Tocilizumab = -15.7 • Placebo = -8.5 • P = 0.0001 Good or Moderate Eular Response: • Tocilizumab = 80% • P = 0.0001 FACIT-F, mean change from baseline: • Tocilizumab = 8.0	GI Nausea or vomiting, n: D1: 4% D2: 3% Overall: NR
					Abdominal pain, n: D1: 3% D2: 1% Overall: NR
					Mouth ulceration, n (%): D1: 2 D2: 1 Overall: NR
				Placebo = 3.6P = 0.0001	Stomatitis, %: D1: 1 D2: 0
					Upper gastrointestinal tract events suggestive of gastric inflammation, gastritis, and ulcer, % D1: 3 D2: 1
					Other Headache, n: D1: 6% D2: 4% Overall: NR
					Hypertension, %: D1: 5 D2: 3 Overall: NR
					Elevations in alanine amino- transferase level, from normal at baseline to > 3-

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
					foldupper limit of normal, %: D1: 4 D2: 1
					Elevated total cholesterol levels, %: D1: 23 D2: 6 Overall: NR
					Grade 3 neutropenia, %: D1: 3.7 D2: 0 Overall: NR
					Any other AEs: Cellulitis: Tocilizumab: 5 Placebo: 0, Overall: 5 Herpes Zoster: Tocilizumab: 3 Placebo: 0 Overall: 3
					Adverse events occurring in ≥ 5% of patients, Tocilizumab, Placebo, Overall: • Infections and infestations = 300, 131, 431 • Gastrointestinal disorders = 167, 61, 228; • Musculoskeletal and connective tissue disorders = 104, 74, 178 • Skin and subcutaneous tissue disorders = 133, 29 162 • Nervous system disorders = 93, 36, 129 • Laboratory investigations = 94, 11,

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
					 105 General disorders and administration-site conditions = 66, 30, 96 Injury, poisoning, and procedural complications = 63, 29, 92 Respiratory, thoracic, and mediastinal disorders = 69, 21,90 Vascular disorders = 54; 21; 75
					Serious adverse events occurring in ≥ 3 patients, Tocilizumab, Placebo, Overall: • Infections and infestations = 22, 8, 30; • Musculoskeletal disorders = 2, 3, 5; • Gastrointestinal disorders = 9, 1, 10; • Nervous system disorders = 6, 2, 8; • Cardiac disorders = 3, 1, 4; • Injuries, poisoning = 7, 0, 7; • Renal and urinary disorders = 3, 0, 3;

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
Author, year, study	Inclusion	Interventions, dose	Mean disease duration,	ACR mean difference/	Attrition/withdrawal
name, if applicable Goekoop-Ruiterman, 2005 ⁷¹ ; Allaart et al., 2006 ⁷² ; Goekoop- Ruiterman, 2007 ⁷³ ; van der Kooij, 2009 ⁷⁴ ; van der Kooij, 2009 ⁷⁵ BeST Study Country and setting The Netherlands 18 peripheral and 2 university hospitals Source of funding Schering-Plough and Centocor. Dutch College of Health Insurances Research objective Evaluate whether initial clinical and radiographic efficacy of combination therapies could be maintaned after 2 ⁷³ and 4 yrs ⁷⁵ Study design RCT Overall N 508 Duration of study 2- and 4-year follow up data Quality rating Good	Criteria: Age > 18 yrs RA according to ACR criteria Duration of condition: 2 yrs Active disease with at least 6 of 66 swollen joints At least 6 of 68 tender joints ESR > 28 mm/hr OR global health score greater than or equal to 20mm on 0 to 100 VAS Concomittant NSAIDS and intraarticular steroids Exclusion Criteria: Pregnant Prior txt with: DMARDS other than antimalarials Impaired renal or hepatic system	D1: Sequential monotherapy D2: Step-up combination therapy D3: Initial combination therapy with PRED D4: Initial combination therapy with IFX Number in group D1: 126 D2: 121 D3: 133 D4: 128 Overall: 508 Mean age, years (SD) D2: 54 D3: 55 D4: 54 Overall: 54 Sex, % female D1: 86 D2: 86 D3: 86 D4: 85 Overall: 86 Race, % NR	years D1: 23 wks D2: 26 wks D3: 23 wks D4: 23 wks Patients with early RA, three years or less Overall: 100% Treatment resistant, % NR Tender Joint Count, mean NR Swollen Joint Count, mean NR Corticosteroid use, % NR DMARD use, % NR MTX naïve, % Overall: 100 Baseline DAS score, mean D1: 4.5 +/- 0.9 D2: 4.5 +/- 0.8 D3: 4.4 +/- 0.9 D4: 4.3 +/- 0.9 Required treatment for latent TB NR	absolute difference NR HAQ (mean \pm SD) At 3 months: D1: 0.4 ± 0.6 D2: 0.3 ± 0.6 D3: 0.8 ± 0.7 D4: 0.7 ± 0.6 $P = 0.050$ for D1/D2 vs. D3/D4 At 6 months: D1: 0.5 ± 0.7 D2: 0.5 ± 0.7 D3: 0.9 ± 0.7 D4: 0.8 ± 0.6 $P = 0.050$ for D1/D2 vs. D3/D4 At 9 months: D1: 0.6 ± 0.7 D2: 0.6 ± 0.7 D2: 0.6 ± 0.7 D3: 0.8 ± 0.7 D4: 0.8 ± 0.6 $P = 0.050$ for D1/D2 vs. D3/D4 At 12 months: D1: 0.7 ± 0.7 D2: 0.7 ± 0.7 D2: 0.7 ± 0.7 D2: 0.7 ± 0.7 D3: 0.9 ± 0.7 D4: 0.9 ± 0.7 D4: 0.9 ± 0.7 D7: 0.9 ± 0.7 D8: 0.9 ± 0.7 D9: 0.8 ± 0.7 D1: 0.7 ± 0.7 D2: 0.8 ± 0.7 D3: 0.7 ± 0.8 D4: 0.9 ± 0.7 D7: 0.8 ± 0.7 D8: 0.9 ± 0.7 D9: $0.8 \pm$	Withdrawals through 4 years of followup, n: D1: 11 D2: 20 D3: 14 D4: 9 Overall: 54 (11%) Over time, 27 (5%) patients who were equally distributed across treatment groups (<i>P</i> = 0.474) were lost to follow-up: 12 withdrew consent (7 declined follow-up, 4 discontinued all medications despite having no adverse events, and 1 moved from area), 7 had a revised diagnosis, 1 discontinued treatment because of an adverse event, 4 died, and 3 were lost to follow-up for other reasons (2 were admitted to a nursing home and 1 wanted to become pregnant) (Figure 1). Noncompliant but included in ITT, n (%): D1: 12 (10) D2: 11 (9) D3: 14 (11) D4: 6 (5) Deviated from study protocol, n: D1: 19 D2: 15 D3: 36 D4: 11

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
				At 18 months:	(P = 0.343)
				D1: 0.7 ± 0.7 D2: 0.8 ± 0.7	Overall adverse events reported, n
				D3: 0.8 ± 0.8	• 210 (41%) of patients had
				D4: 0.9 ± 0.7	an adverse event in year 1
				P = NS	• 193 (38%) of patients had
				A + O 4	an adverse event in year 2
				At 21 months:	 Mean number of adverse
				D1: 0.7 ± 0.7 D2: 0.8 ± 0.7	events per patient was 1.9
				D3: 0.8 ± 0.7	(SD, 1.2) in first year and
				D4: 0.9 ± 0.7	1.8 (SD, 1.2) in the second
				P = NS	year.
					 56 serious adverse events
				At 24 months:	were reported in the
				D1: 0.7 ± 0.7	second year (16 events [13
				D2: 0.8 ± 0.7	patients] in group 1, 10
				D3: 0.9 ± 0.7	events [10 patients] in
				D4: 0.9 ± 0.7	group 2, 17 events [11
				At 36 months:	patients] in group 3, and 13 events [8 patients] in
				D1: 0.8 ± 0.7	group 4)
				D2: 0.7 ± 0.7	• ,
				D3: 0.8 ± 0.8	Serious adverse events
				D4: 0.9 ± 0.7	D1: NR
				P = 0.66	D2: Cerebrovascular event:
				At 48 months:	D3: Malignant ovarian
				D1: 0.8 ± 0.6	cancer: 1
				D2: 0.7 ± 0.8	D4: Mycardial infarction: 1, disseminated TB: 1
				D3: 0.8 ± 0.8	uisseiiiiilaleu ID. I
				D4: 0.8 ± 0.8	Cardiovascular events, n:
				P = 0.64	D1: Atrial fibrillation: 1,
				DAS44 goal of 2.4 reached,	myocardial infarction: 1,
				%	coronary artery bypass: 1
				D1: 75	D2: NR
				D2: 81	D3: NR
				D3: 78	D4: Myocardial infarction: 1,
				D4: 82	unstable angina pectoris:
				P = NS	ı
				Overall: 79	Hepatotoxicity/elevated liver
				P = 0.554	enzymes, n: NR

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
				Sustain DAS44 of less than or: 2.4. After 1 yr: D1: 53% D2: 64% D3: 71% D4: 74%	Malignancies Basal cell carcinoma, n: D1: 1 D2: NR D3: NR D4: NR
				P = 0.004 for 1 vs. 3 P = 0.001 for 1 vs. 4 P = NS and NR for others SF-36 D1: SF-36 PCS (values are mean change from baseline, except baseline values): Baseline 32.9, 3 mos 5.8, 6 mos 8.0, 12 mos 8.9, 24 mos 11.9, SF-36 MCS at baseline, 3 months, 6 months, 12 months, and 24 mos (values are mean change from baseline values): Baseline 47.5; 3 mos 2.1; 6 mos 3.1; 12 mos 4.3; 24 mos 4.3 D2: Baseline 32.9, 3 mos 3.9, 6 mos 8.5; 12 mos 11.2; 24 mos 12.3; SF-36 MCS at baseline, 3 mos, 6 mos, 12 mos, and 24 mos (values are mean change from baseline, except baseline values): Baseline 46.3; 3 mos 2.5; 6 mos 3.5; 12 mos 4.4; 24 mos 4.6 D3: Baseline 32.8, 3 mos	Other cancer (specify), n: D1: Renal cell carcinoma: 1 D2: Malignant prostate cancer: 1 D3: Malignant ovarian cancer: 1 D4: Basal cell carcinoma: 1 Respiratory events Tuberculosis: NR Pneumonia, n: D1: 1, D2: 1 D3: NR D4: NR Pleural effusion, n: D1: 1 D2: NR D3: NR D4: NR Other infections Urinary tract infection, n: D1: pyelonephritis, n: 1 D2: NR D3: NR D3: NR D4: NR
				11.2, 6 mos 12.5; 12 mos 11.9; 24 mos 12.3; SF-36	D4: septic arthritis, n: 1

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
				MCS at baseline, 3 mos, 6 mos, 12 mos, and 24 mos (values are mean change from baseline, except baseline values): Baseline 47.6; 3 mos 0.4; 6 mos 1.2; 12 mos 3.2; 24 mos 4.6 D4: Baseline 33.4, 3 mos 9.6, 6 mos 12.4; 12 mos 12.0; 24 mos 12.7; SF-36 MCS at baseline, 3 mos, 6 mos, 12 mos, and 24 mos (values are mean change from baseline, except baseline values): Baseline 47.6; 3 mos 3.1; 6 mos 4.1; 12 mos 4.3;	GI bleed or ulcer, n: D1: NR D2: NR D3: NR D4: GI bleed, n: 1 Other Perforated gastric ulcer, n: D1: 1 D2: NR D3: NR D4: NR Complicated calcaneous fractures, n: D1: NR D2: 1 D3: NR D4: NR
				24 mos 4.0 Overall: At 3 and 6 mos, P=0.05 for SF-36 PCS comparing groups 1 and 2 to groups 3 and 4. Others were NS (For PCS: P = 0.93 at baseline, 0.10 at 12 months, 0.95 at 24 months; For MCS at each timepoint: 0.73, 0.22, 0.17, 0.83, 0.97)	disease: 1 • Surgery for carpal tunne
				Radiographic measures, mean difference (SD) Progression of SHS at 12 mos: D1: 2.0 D2: 2.5 D3: 1.0 D4: 0.5 (P = 0.003 for group 1 vs. group 3; P = 0.001 for 1 vs.	syndrome: 1 Uterus extirpation: 1 Placement of total hip prostheses: 2 D3: Placement of total hip prostheses: 2 implantation of intracardidevice: 1 syncope due to aortic

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
				4; <i>P</i> = 0.007 for 2 vs. 3; <i>P</i> = 0.001 for 2 vs. 4)	valve dysfunction: 1 • limb amputation due to
				Progression of SHS at 24 months, mean (SD): Total Sharp Score D1: 9.0 ± 17.9 D2: 5.2 ± 8.1 D3: 2.6 ± 4.5 D4: 2.5 ± 4.6 Sharp van der Heijde median Increase at 12 mos: D1: 2.0 D2: 2.5 D3: 1.0 D4: 0.5 $P = 0.001$	occlusion of the femoral artery: 1 retinal hemorrhage: 1 scleroderma: 1 active RA: 1 D4: Active RA: 1 cholecystectomy: 1 placement of total knee prostheses: 1 placement of elbow protheses: 1 one patient had 4 episode of disseminated TB
				Total Sharp Score, median (IQR): D1: 2.0 (0.0 - 8.6) D2: 2.0 (0.3 - 7.0) D3: 1.0 (0.0 - 2.5) D4: 1.0 (0.0 - 3.0)	
				Narrowing-score: D1: 4.3 ± 9.8 D2: 2.1 ± 3.8 D3: 1.5 ± 3.2 D4: 1.2 ± 2.9 P = 0.072	
				Relative risk for SHS- progression, at 24 months: D1: 1.0 D2: 0.91 (0.73, 1.12) D3: .74 (0.61, 0.89) D4: .73 (0.61, 0.88)	
				Progression of SHS at 48 months, mean (SD): D1: 11.7 ± 17.3 D2: 9.7 (12.8)	

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
				D3: 6.7 (9.6) D4: 5.4 (9.2) P = 0.002 D1 vs. D4	
				SHS median (IQR) D1: 50 (1.0 - 15.8) D2: 5.5 (1.0 - 13.8) D3: 3.0 (1.0 - 7.5) D4: 2.5 (0.5 - 6.5)	
				Narrowing-score at 48 months, mean (SD): D1: 5.7 (10) D2: 4.0 (7.0) D3: 3.7 (6.7) D4: 2.4 (4.6)	
				Narrowing-score median (IQR): D1: 1.8 (0.0 - 7.0) D2: 1.0 (0.0 - 4.5) D3: 1.0 (0.0 - 3.9) D4: 1.0 (0.0 - 2.5) P = 0.17	
				Quality of life scales NR	
				Others (CI/SD/P Value) Baseline: D1: 47.5 D2: 47.1 D3: 47.3 D4: 47.0	
				At 3 months: D1: 10.6 D2: 9.5 D3: 16.7 D4: 17.3	
				At 6 months: D1: 12.6 D2: 15.4	

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
				D3: 16.4 D4: 19.1	
				12 months: D1: 15.2 D2: 16.3 D3: 16.9 D4: 19.3	
				P = 0.001 for 3 for D1 and 2 compared to D3 and 4, $P = 0.001$ for D1 and 2 compared to D4 and D1 vs. D3	

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
Author, yr: Gomez-Reino, 2003 ⁷⁶ Country, Setting: Spain 71 Centers Funding: Agencia Española del Medicamento (Ministerio de Sanidad y Consumo) Research Objective: Long-term safety of INF and ETA, in rheumatic diseases based on a national active-surveillance Study Design: Retrospective cohort study Overall N: 1,540 (1578 txts) Study Duration: Mean 1.1 yrs	Inclusion Criteria: • Pts with rheumatic diseases being treated with biologic response modifiers registered in BIOBADASER Exclusion Criteria: NA	Interventions, dose: D1: INF/ETA ETA: varies INF: varies N: D1: 1540 (1578 txts) Mean age, yrs: D1: 51 Sex, % female: D1: 72 Race, % white: NR	Mean disease duration, yrs: NR TJC, mean: NR SJC, mean: NR DMARD use, %: NR Corticosteroid use, %: NR MTX naive, %: NR Txt resistant %: NR Pts with Early RA (≤3 yrs): NR Baseline DAS, mean: NR PsA: D1: 5.8 AS: D1: 4.9	Background TB incidence in Spain in 2000 was 21/100,000 1,893 cases of TB per 100,000 pts in yr 2001 and 1,113 cases per 100,000 pts in yr 2001 in pts treated with TNF RR of TNF pts compared general population 90.1 (95% CI,58.8-146.0) in yr 2000 and 53.0 (95% CI,34.5-89.0) in yr 2001 Estimated annual incidence of TB among RA pts not exposed to TNF inhibitors was 95/100,000 RR in RA pts who did not receive TNF of TB (adjusted for age and sex) was 4.13 (95% CI,2.59-6.83) relative to background rate RR of TB in INF-treated RA pts vs. RA pts not exposed to this therapy was 19.9 (95% CI,16.2-24.8) in yr 2000 and 11.7 (95% CI,9.5-14.6) in yr 2001 15 pts with TB were diagnosed as having RA, and 2 additional pts with TB had PsA; all pts with active TB were being treated with INF; 59% were diagnosed with TB within 3 mos of txt initiation	Infections: D1: 7.7 Infusion or injection reaction: D1: 2 (INF) URTI: D1: 9 UTI: D1: 11	Overall Attrition Rate, %: NA ITT Analysis: NA Quality Rating: Fair

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
					·	
Author, year,	Inclusion	Comparisons	Mean disease	ACR mean difference/	Overall	Quality rating for
study name, if	Criteria	(dosage and	duration, years	absolute	Overall adverse events	efficacy/effectiveness?
applicable	 Patients with 	frequency)	D1: 9.5 (9.8)	difference (CI/SD/P	reported (n):	NR
Greenberg JD et	RA	D1: MTX: dosage	D2: 11.4 (9.6)	Value):	D1: 1714	Quality rating for
al., 2010 ⁷⁷	 Participants in 	and frequency	D3: 11.1 (9.6)	NR	D2: 890	observational studies
Consortium of	CORRONA	NR	D4: 10.1 (9.8)	HAQ, mean difference/	D3: 1514	Fair
Rheumatology	rheumatology	D2: Anti-TNF:	TIC maan		D4: 447	raii
Researchers of	practices	dosage and	TJC, mean	absolute	0.1	
North American	enrolled from	frequency NR	D1: 4.2	difference (CI/SD/P	Serious adverse	
(CORRONA)	Oct 1, 2001-	D3: MTX: dosage	D2: 4.8	Value):	events:	
registry	Sept 2006	and frequency	D3: 4.7	NR	NR	
-	At least 1	NR	D4: 3.6	DAS, mean	Malignancies:	
Country and	follow-up visit	Anti-TNF: dosage	SJC, mean	difference/absolute	NR	
setting	ioliow-up visit	and frequency	•		INIX	
US	Exclusion	NR	D1: 5.4	difference (CI/SD/P	Respiratory events:	
0	Criteria	D4: Other DMARDs:	D2: 5.1	Value):	Pneumonia (n):	
Source of	• NA		50.0.0	NR	Non-pyogenic	
funding	- 14/1	dosage and	D4: 4.1	SF-36, mean	D1: 51	
National Institute		frequency NR	Corticosteroid use, %	difference/absolute	D2: 40	
of Arthritis and		Number in group	D1: 39.3	difference (CI/SD/P	D3: 61	
Musculoskeletal		D1: 4206	D1: 39.3 D2: 40.9	Value):	D4: 16	
and Skin		D2: 1804	D3: 38.3	NR	D4. 10	
Disease; Arthritis		D3: 2855		INIX	Pyogenic	
Foundation		D4: 1274	D4: 36.6	Radiographic	D1: 49	
B		D4. 1274	DMARD use, %:	measures, mean	D2: 22	
Research		Mean age (years)	D1: 100	difference/absolute	D3: 46	
objective		D1: 59.7	D2: 0	difference (CI/SD/P	D4: 22	
To examine the		D2: 56.8	D3: 100	Value):	D4. 22	
association of		D3: 57.9	D4: 100	NR	Upper respiratory	
MTX (MTX) and		D4: 60.1	D4. 100	INIX	infection (n):	
tumour necrosis			MTX naïve, %:	Quality of life scales,	D1: 660	
factor (TNF)		Sex, % female	NR	mean	D2: 303	
antagonists with		D1: 73.8		difference/absolute	D3: 522	
the risk of		D2: 76.0	Treatment resistant,	difference (CI/SD/P	D4: 148	
infectious		D3: 77.7	%:	Value):		
outcomes		D4: 74.1	NR	NR	Other infections:	
including			Detients with souls DA	INIX	Urinary tract	
opportunistic		Race, % white	Patients with early RA,	Others, (please name);	infection (n):	
infections		D1: 86.8	three years or less, %:	mean	D1: 157	
		D2: 86.7	NR	difference/absolute	D2: 81	
inpatients with		D3: 86.2	Baseline DAS score	difference (CI/SD/P	D3: 111	
rheumatoid		D4: 88.2		Value):	D4: 32	
arthritis (RA).		= ••. -	NR	· u.ucj.	D-7. UZ	

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating	
Study design Observational Overall N		Race, % black NR Ethnicity, Latino	Required treatment for latent TB NR	NR	Cellulitis: D1: 59 D2: 49 D3: 71		
7971 Duration of		NR	Other population characteristics, %, (CI/SD/P value): NR	characteristics,	characteristics,	D4: 18	
study October 1, 2001					GI: NR		
to September 30, 2006					Other: Bursitis D1: 9 D2: 5 D3: 7 D4: 3		
				Sinusitis D1: 370 D2: 166 D3: 331 D4: 71			
					Infectious arthritis D1: 9 D2: 5 D3: 5 D4: 2		
					Septicaemia D1: 8 D2: 8 D3: 10 D4: 4		
					Other Site of Infection D1: 342 D2: 211 D3: 350 D4: 131		
					All Types of Infections, Unadjusted rate/100 pys- D1: 33.3		

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
					D2: 41.8 D3: 37.6 D4: 26.9	
					Rate of Infection, Adjusted rate/100 pys (95% CI) D1: 30.9 (29.2-32.7) D2: 40.1 (37.0-43.4) D3: (34.9-39.3) D4: 24.5 (21.8-27.5)	
					IRR (95% CI) D1: 1.30 (1.12-1.50); P<0.001 D2: 1.52 (1.30-1.78); P<0.001 vs. D3 (ref group)	
					PRED use>10 mg daily independently associated with risk of infection: IRR (95% CI), 1.30 (1.11-1.53); P<0.001	

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
Author, year, study name, if applicable Grijalva et al., 2007 ⁷⁸ Country and setting US - Tennessee Medicaid data Source of funding AHRQ Research objective Evaluate adherence and persistence during new episodes of traditional and biologic DMARD use Study design Retrospective Cohort Study Overall N 6018pts with 10,574 episodes of new DMARD use. Duration of study Cohort members were followed from date when selection criteria were met to end of study (December 31, 2004), date of death, date of diagnosis of a serious medical condition, or loss of enrollment from TennCare, whichever came earliest.	enrollees with RA • Filled 1 prescription during screening period Exclusion Criteria • <365 days of continuous enrollment prior to study entrance • Established serious medical	Interventions, Dose D1: MTX: varied D2: Hydroxychlorquine: varied D3: SSZ: varied D4: LEF: varied D5: MethylPNL: varied Hydroxychlorquine: varied 7 other groups (all dose varied): INX, ETA, ADA, MTX+INX, MTX+ETA, MTX + ADA, AKA and AKA+MTX Number in group *N of new tx episodes*: D1: 3859 D2: 3174 D3: 944 D4: 558 D5: 904 D6: 75 D7: 374 D8: 120 D9: 98 D10: 262 D11: 107 D12: 72 Mean age (years) D1: 54 D2: 51 D3: 51 D4: 55 D5: 52 D6: 53 D7: 51 D8: 58 D9: 56	Mean disease duration, years (SD) NR Patients with early RA, three years or less, % NR Treatment resistant, % NR Tender Joint Count, mean (SD) NR Swollen Joint Count, mean (SD) NR Corticosteroid use, % NR DMARD use, % NR MTX naïve, % NR Baseline DAS score, mean (SD) NR Required treatment for latent TB NR Other population characteristics, %, (CI/SD/P value)	ACR ACR 20: No efficacy ACR 50: NR ACR 70: NR HAQ NR DAS NR SF-36 NR Radiographic measures NR Quality of life scales NR Others, (please name); mean difference/absolute difference NR	 Median Persistence in days, Cox Regression Model Adjusted* HR (95%CI): MTX 150, 1.0 (ref); HCQ 121, 1.03 (0.98-1.08); SSZ 53, 1.59 (1.47-1.72); LEF 136, 1.02 (0.93-1.11); MTX + HCQ 125, 1.05 (0.97-1.14); INX 85, 1.37 (1.09-1.73); ETA 175, 0.82 (0.73-0.92); ADA 134, 0.85 (0.67-1.08); MTX+IFX 155, 0.91 (0.73-1.15); MTX+ETA 147, 1.01 (0.87-1.17); MTX+ADA 219, 0.63 (0.48-0.84); ANK OR ANK+MTX 156, 0.94 (0.75-1.18). Mean Medication Possession Ratio, linear regression Adjusted* coefficient (95%CI): 0.80, 1.0 (ref); HCQ 0.79, 0.00 (-0.01 to 0.001); SSZ 0.77, -0.02 (-0.04 to 0); LEF 0.85, 0.05 (0.04 to 0.07); MTX+HCQ 0.66, -0.11 (-0.13 to -0.09); IFX 0.90, 0.11 (0.06 to 0.16); ETN 0.83, 0.04 (0.02 to 0.06); ADA 0.85, 0.04 (0.001 to 0.08); MTX+IFX 0.66, -0.12 (-0.17 to-0.07); MTX+ETN 0.64, -0.11 (-0.14 to-0.08); MTX+ADA 0.72, -0.07 (-0.11 to -0.03); ANA or ANA+MTX 0.71, -0.08 (-0.13 to -0.02) *Adjusted for age, sex, race,

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
Quality rating Fair: Not controls for Disease		D10: 53 D11: 58 D12: 53 Sex, % female			calendar year, residential location, disability, residence in nursing home, and risk score
Activity or Severity (would assume patients with higher severity/activity		D1: 78.1 D2: 82.7 D3: 71.2			Overall adverse events reported, n: NR
would be more likely to adhere), limited to a poor population in		D4: 79.4 D5: 84.2 D6: 74.7			Serious adverse events NR
which access is likely to be an issue.	,	D7: 77.5 D8: 80.8			Malignancies NR
Predetermined inclusion criteria of having fi		D9: 76.5 D10: 83.6 D11: 79.4			Respiratory events NR
		D12: 72.2 Race, % white			Other infections NR
		D1: 72.4 D2: 71.2 D3: 76.5			GI NR
		D3: 76.5 D4: 72 D5: 69.9 D6: 66.7 D7: 70.9 D8: 64.2 D9: 72.4 D10: 64.9 D11: 61.7 D12: 63.9			Other NR
		Race, % black			
		Ethnicity, Latino NR			

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
Characteristics Author, year, study name, if applicable Grijalva et al., 2010 ⁷⁹ Country and setting USA; Tennessee Medicaidenrolled patients Source of funding Vanderbilt Multidisciplinary Clinical Research Center (NIH/NIAMS Grant P60 AR056116) Research objective To compare serious infections following initiation of different RA regimens Study design Observational	Inclusion Criteria Inclusion Criteria RA patients with new episodes of DMARD use Exclusion	and Interventions Comparisons (dosage and frequency) D1: TNF-α	Treatment Characteristics Mean disease duration, years NR TJC, mean NR SJC, mean NR Corticosteroid use, % 100 DMARD use, %: 0 MTX naïve, %: NR Treatment resistant, %: NR Patients with early RA, three years or less, %: NR Required treatment for latent TB NR Other population characteristics, %, (CI/SD/P value):	ACR mean difference/absolute difference (CI/SD/P Value): NR HAQ, mean difference/absolute difference (CI/SD/P Value): NR DAS, mean difference/absolute difference (CI/SD/P Value): NR SF-36, mean difference/absolute difference (CI/SD/P Value): NR RAdiographic measures, mean difference/absolute difference (CI/SD/P Value): NR Radiographic measures, mean difference/absolute difference (CI/SD/P Value): NR Quality of life scales, mean difference/absolute difference/absolute difference (CI/SD/P	Overall NR Serious adverse events: NR Malignancies: NR Respiratory events: Pneumonia (n): Crude HR (95% CI) D1: 1.17 (0.67, 2.05) D2: 1.64 (0.79, 3.39) D3: 0.47 (0.14, 1.53) D4: 1.11 (0.67, 1.85) D5: 1.00 (reference) D6: 2.00 (1.1, 3.64) D7: 2.08 (1.31, 3.3) D8: 3.91 (2.31, 6.62) Age/gender adjusted HR (aHR) (95% CI) D1: 1.28 (0.73, 2.24) D2: 1.64 (0.79, 3.39) D3: 0.51 (0.16, 1.68) D4: 1.20 (0.72, 2) D5: 1.00 (reference) D6: 1.71 (0.94, 3.1) D7: 1.92 (1.22, 3.01) D8: 3.67 (2.19, 6.15) Propensity Scoreadjusted HR (95% CI)	
Overall N 21981 Duration of study 180 days of exposure during 2002-2005		D5: 55 D6: 57 D7: 55 D8: 55 Sex, % female D1: 74.86 D2: 77.03	NR	Value): NR Others, (please name); mean difference/absolute difference (CI/SD/P Value):	D1: 1.61 (0.85, 3.03) D2: 1.65 (0.77, 3.54) D3: 0.60 (0.19, 1.97) D4: 1.24 (0.73, 2.08) D5: 1.00 (reference) D6: 2.30 (1.2, 4.41) D7: 2.36 (1.44, 3.87) D8: 4.33 (2.49, 7.54)	

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
		D3: 68.04 D4: 81.11 D5: 76.21 D6: 77.75 D7: 76.38 D8: 75.60 Race, % white D1: 83.90 D2: 84.32 D3: 84.88 D4: 79.64 D5: 80.60 D6: 80.47 D7: 84.72 D8: 84.44 Race, % black D1: 12.73 D2: 13.49 D3: 12.70 D4: 18.01 D5: 16.67 D6: 17.15 D7: 13.28 D8: 13.30	Characteristics	NR	Adverse Events, % Other infections: Any infection Crude HR (95% CI) D1: 1.04 (0.66, 1.64) D2: 1.39 (0.78, 2.48) D3: 0.82 (0.4, 1.66) D4: 1.06 (0.71, 1.56) D5: 1.00 (reference) D6: 1.46 (0.88, 2.43) D7: 2.12 (1.47, 3.05) D8: 3.37 (2.19, 5.19) Age/gender adjusted HR D1: 1.12 (0.71, 1.77) D2: 1.39 (0.78, 2.48) D3: 0.89 (0.44, 1.8) D4: 1.13 (0.76, 1.67) D5: 1.00 (reference) D6: 1.28 (0.77, 2.13) D7: 1.98 (1.38, 2.83) D8: 3.21 (2.1, 4.9) Propensity Scoreadjusted HR (95% CI) D1: 1.31 (0.78, 2.19) D2: 1.48 (0.81, 2.69)	-
		Ethnicity, Latino NR			D2: 1.48 (0.81, 2.69) D3: 1.03 (0.51, 2.1) D4: 1.20 (0.81, 1.79) D5: 1.00 (reference) D6: 1.62 (0.94, 2.78) D7: 2.39 (1.63, 3.51) D8: 3.72 (2.37, 5.84)	
					GI: NR	
					Other: NR	

Study Characteristic s	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
AB Research Objective: Compare efficacy and safety of SSZ, MTX, and	positive and/or HLA DR1 positive • Functional class of: DAS ≥ 3.0 • Duration of condition: < 12 mos • Analgesica and NSAIDS allowed Exclusion Criteria:	mg/wk) + SSZ (1 g/day; max 3 g/day) N: D1: 34 D2: 35 D3: 36 Mean age, yrs: D1: 56.8 D2: 54.9 D3: 57.0 Sex, % female: D1: 61.8 D2: 65.7 D3: 66.7 Race, % white: NR	Mean disease duration, yrs: D1: 3.1 mos D2: 3.0 mos D3: 2.6 mos TJC, mean: D1: 20.8 D2: 20.6 D3: 24.8 SJC, mean: D1: 17.0 D2: 19.9 D3: 20.8 DMARD use, %: Overall: 0 Corticosteroid use, % Overall: 0 MTX naive, %: NR Txt resistant, %: NR Pts with Early RA (≤3 yrs): Overall: 100 Baseline DAS, mean: D1: 4.6 D2: 4.7 D3: 5.0	No significant differences in efficacy between combination (MTX, SSZ) and single therapy (MTX or SSZ), only a trend favoring combination therapy, MTX and SSZ were comparable At 52 weeks DAS mean change: D1: -1.6 (95% CI, -2.0 to -1.2) D2: -1.7 (95% CI, -2.0 to -1.4) D3: -1.9 (95% CI, -2.2 to -2.3) Ritchie mean change: D1: -8.6 (95% CI, -10.7 to -6.5) D2: -8.2 (95% CI, -10.1 to -6.4) D3: -9.4 (95% CI, -11.1 to -7.7) Swollen joints mean change: D1: SSZ -7.9 (95% CI, -11.1 to -7.7) Swollen joints mean change: D1: SSZ -7.9 (95% CI, -10.1 to -5.7) D2: -10.2 (95% CI, -12.5 to -8.0) D3: -11.3 (95% CI, -13.5 to -9.2)	D1: 88.2 D2: 77.1 D3: 88.9 SAEs: D1: 8.8 D2: 0 D3: 0 Abdominal Pain: D1: 26.5 D2: 20 D3: 36 Cardiovascular Events (Dyspnea): D1: 5.9 D2: 0 D3: 5.6 Dizziness: D1: 17.6 D2: 8.6 D3: 27.8 Headache: D1: 17.6 D2: 11.4 D3: 11.1 Nausea: D1: 29.4 D2: 25.7 D3: 63.9 URTI	Overall Attrition Rate, %: 19 ITT Analysis: Yes Quality Rating: Fair
			HAQ:	HAQ change from	D1: 17.6	

Study Characteristic s	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
			D1: 0.97 D2: 0.92 D3: 1.20	baseline: D1: -0.32 (95% CI, -0.53 to -0.10) D2: -0.46 (95% CI, -0.68 to -0.25) D3: -0.51 (95% CI, -0.76 to -0.26)	D2: 20.0 D3: 27.8	
				Number of pts with a response according to ACR criteria at end of study: D1: 25 D2: 25 D3: 28		
				Number of pts with good response according to EULAR definition: D1: 14 D2: 15 D3: 14		

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
Author, yr: Harley, 2003 ⁸¹ Country, Setting: US, Health Plan Data Funding: Centocor Research Objective: To examine txt compliance and dosage administration with MTX, ETC and INF therapy for RA Study Design: Observational- retrospective data analysis Overall N: 2662 Study Duration: 30 mos	Inclusion Criteria: Commercial or Medicare enrollees Exclusion Criteria: MTX, ETA or INF within 182 days of index date	Interventions: D1: INF D2: ETA D3: INF N: D1: 141 D2: 853 D3: 1668 Mean age (yrs): D1: 56.3 D2: 47.4 D3: 53.3 Sex, % female: D1: 27 D2: 26.3 D3: 26.9 Race, % white: NR	Mean disease duration, yrs: NR TJC, mean: NR SJC, mean: NR DMARD use, %: D1: 34 D2: 41 D3: 37.9 Corticosteroid use, %: NR MTX naive, %: NR Treatment resistant %: NR Patients with Early RA (≤3 yrs): NR Baseline DAS, mean: NR	Compliance with at least 80% of expected dosages: • ETA: 68.4; OR 0.462; 95 CI, 0.290-0736 • MTX: 63.7; OR 0.385; 95 CI, 0.245-0604 • INF: 80.9 • OR:Reference • P < 0.05 Dosage Increases: • MTX: 61.6% • INF: 37.4% • ETA: 7.4%	NR	Overall Attrition Rate, %: NA ITT Analysis: Not applicable Quality Rating: Fair

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
Author, year, study name, if applicable Harrison, 2009 et al., British Society for Rheumatology Biologics Register (BSRBR) ⁸² Country and setting UK, hospitals/general practice Source of funding Financial support to BSRBR comes indirectly from following UK companies marketing biologic agents in UK: Schering Plough, Wyeth Laboratories, Abbott Laboratories, and Amgen. The resources used to fund BSRBR are received under contract Research	Inclusion Criteria • Treatment cohort (all anti-TNFa): first 4000 patients with RA starting each anti-TNFa therapy were required by National Institute for Health and Clinical Excellence to be registered with BSRBR and followed up for information on drug use, disease activity and adverse events. • All patients with a doctor diagnosis of RA who were receiving ETN, IFX or ADA as their first anti-TNFα therapy comprise anti-TNFα cohort	Interventions, Dose D1: Other: NR (traditional DMARDs) D2: ETN: dosage and frequency NR IFX: dosage and frequency NR ADA: dosage and frequency NR Number in group D1: 2880 D2: 9826 Overall: 12,706 Mean age (years) D1: 60 D2: 56.2 Sex, % female D1: 72 D2: 76 Race, % white NR Race, % black NR Ethnicity, Latino NR	Mean disease duration, years (SD) D1: 7 yrs (IQR: 1 - 15) D2: 11 yrs (IQR: 6 - 19) Patients with early RA, three years or less, % NR Treatment resistant, % NR Tender Joint Count, mean (SD) NR Swollen Joint Count, mean (SD) NR Corticosteroid use, % NR DMARD use, % D1: 100 D2: 100 Overall: 100 MTX naïve, % NR Baseline DAS score, mean (SD) D1: 5.0 D2: 6.6 Required treatment for latent TB NR Other population	ACR NR HAQ, NR DAS NR SF-36 NR Radiographic measures NR Quality of life scales NR Others, (please name); mean difference/absolute difference (CI/SD/P Value) NR	Overall Withdrawals due to adverse events, n: D1: NA D2: 8 Overall adverse events reported, n: NR Serious adverse events NR Malignancies NR Respiratory events NR Other infections NR GI NR Other Psoriasis, n: D1: 0; Rate of psoriasis/1000 person years (95% CI): 0 (upper 97.5% CI O.71) D2: 25; Rate of psoriasis/1000 person years (95% CI): 1.04 (0.67 - 1.54) Overall: Psoriasis, n: 25 Subanalysis: Patients treated with ADA had a significantly increased risk
objective	TIVI G COHOIT		Other population		significantly increased risk

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
To compare incidence rates of psoriasis in RA patients treated with anti-TNFa therapy and traditional DMARDs Study design Prospective Cohort Study	for this study. Comparison cohort: biological naive, doctordiagnosed RA, active disease (guideline DAS28 > 4.2), current treatment with a DMARD		characteristics, %, (CI/SD/P value) D1: Current Smoker: 24% Former Smoker: 40% Never smoked: 36% HAQ, median: 1.6 D2: Current Smoker: 22% Former Smoker: 38% Never smoked: 40% HAQ, median: 2.1		of psoriasis compared to thosetreated with ETN (IRR 4.6, 95% CI 1.7 to 12.1) and IFX (IRR 3.5, 95% CI 1.3 to 9.3) adjusted for age, sex, smoking status and calendar year of registration
Overall N 12,706	Exclusion Criteria				
Duration of study Approximately 1 to 2 years (current analysis based on early BSRBR data - follow up will continue for at least 5 years)	 Comparison cohort: No previous exposure to any anti-TNFa drug 				
Quality rating Fair					

Study Characteristic s	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
Author, year, study name, if applicable Hetland et al., 2010 ⁸³ Country and setting Denmark; natioal registry Source of funding Unrestricted grants to DANBIO from Abbott,Wyeth, and Schering-Plough (since 2004), Bristol-Myers Squibb, and Roche (since 2006), and UCB-Nordic (since 2007). The Danish Regions provided financial support for the activities related to quality improvement of biologic treatment.	Inclusion Criteria RA, as diagnosed by the treating rheumatologist Treated with 1 or more oral DMARD, but treatment failed to such an extent that therapy with either ADA, ETN, or INF Exclusion Criteria NR	Comparisons (dosage and frequency) D1: • MTX: 70%, mean of 20 mg/week • ADA: 40 mg every 2 wks D2: • MTX: 61%, mean of 15 mg/week • ETN: 45 mg every week D3: • MTX: 87%, mean of 15 mg/week • INF: 25 mg every 7 wks Number in group D1: 544 D2: 425 D3: 908 *Note that the #s here did not include the full 2326, it excludes those who withdrew (19%) Mean age	Mean disease duration, years D1: mean (range) 9	ACR mean difference/ absolute difference (CI/SD/P Value): ACR 20: NR ACR 50: 6 mos D1: 8.7 D2: 10.4 D3: 3.6 12 mos D1: 12.4 D2: 12.4 D3: 5.8 ACR 70: 6 mos D1: 4.6 D2: 5.5 D3: 1.6 12 mos D1: 7.0 D2: 7.8 D3: 2.6 HAQ, mean difference/ absolute difference (CI/SD/P Value): NR DAS, mean difference (CI/SD/P Value): DAS28 remission/	Overall Overall attrition/withdrawal (n): • ADA vs ETA 1.47 (1.20-1.80) • INF vs. ETA 1.98 (1.63-2.40) • INF vs ADA 1.35 (1.15-1.58) Withdrawals due to adverse events (n): • ADA vs ETA 1.50 (1.04-2.16) • INF vs. ETA 2.65 (1.88-3.73) • INF vs ADA 1.77 (1.34 - 2.34) Withdrawals due to lack of efficacy (n): • ADA vs ETA 1.47 (1.15-1.87) • INF vs. ETA 1.70 (1.35- 2.15 • INF vs ADA 1.16 (0.95-1.41) Serious adverse events: NR Malignancies: NR Respiratory events: NR Other infections:	Quality rating for efficacy/effectivenes s? NR Quality rating for observational studies Fair

Study Characteristic s	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
Research objective To compare TNF inhibitors directly regarding the rates of treatment response, remission, and the drug		(years) D1: 56 D2: 58 D3: 57 Sex, % female D1: 75 D2: 72 D3: 73 Race, % white NR	Required treatment for latent TB NR Other population characteristics, %, (CI/SD/P value): NR	Lundex corrected (n) 6 mos D1: 32/26 (536) D2: 26/21 (414) D3: 21/17 (889) DAS28 remission/ Lundex corrected (n) 12 mos D1: 39/27 (444) D2: 33/24 (377) D3: 27/16 (/690)	NR GI: NR Other: NR	
survival rate in patients with RA and to identify clinical prognostic factors for		Race, % black NR Ethnicity, Latino NR		SF-36, mean difference/absolute difference (CI/SD/P Value): NR		
response. Study design Observational				Radiographic measures, mean difference/absolute difference (CI/SD/P		
Overall N 2326				Value): NR		
Duration of study 1 year				Quality of life scales, mean difference/absolute difference (CI/SD/P Value): NR		
				Others, (please name); mean difference/absolute difference (CI/SD/P Value): Adjusted ORs for		

Study Characteristic s	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
				ACR70 response		
				 ADA vs INF: 2.05 		
				(1.52 to 2.76)		
				• ETN vs. INF: 1.78		
				(1.28 to 2.5)		
				• ADA vs. ETN: 1.15		
				(0.82		

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
Author, year, study name, if applicable Hjardem et al., 2007 ⁸⁴ Country and setting Danish, multicenter Source of funding Abbott, Wyeth, Schering-Plough Research objective Investigate efficacy of switching to a second biologic drug in RA Study design Population — based Dynamic Cohort Study Overall N 235 (switchers	Inclusion Criteria RA pt who had received 2+ biologics (IFX, ETN, or ADA only) Exclusion Criteria Incomplete baseline data (DAS)	D2: ETN: varied, dose NR D3: ADA: varied, dose NR Number in group D1: 178 D2: 18 D3: 39 Mean age (years) D1: 55 D2: 54 D3: 52 Sex, % female D1: 77 D2: 61 D3: 74 Race, % white NR Race, % black NR Ethnicity, Latino	Mean disease duration, years (SD) D1: mean (range): 9 yrs (4-17) D2: 11 (3-23) D3: 7 (3-17) Patients with early RA, three years or less, % NR Treatment resistant, % NR Tender Joint Count, mean (SD) NR Swollen Joint Count, mean (SD) NR Corticosteroid use, % NR DMARD use, % D1: current MTX: 82 D2: 42 D3: 62 MTX naïve, %	ACR NR HAQ NR DAS D1: Efficacy outcomes stratified by 1st & 2nd drug and cannot be combined. SF-36 NR Radiographic measures NR Quality of life scales NR Others, (please name); mean difference/absolute difference NR	Overall All pts included in study withdrew from their tx, reasoning as follows (% withdrew for :Lack of Efficacy/Adverse Event/Other): IFX 45/34/21, ETN 44/22/34, ADA 54/21/26 Overall adverse events reported, n: NR Serious adverse events NR Malignancies NR Respiratory events NR Other infections NR Other
only) Duration of study		NR	NR Baseline DAS score,		
Varied, NR Quality rating Fair: No controls for confounding, baseline difference in current mtx use			mean (SD) D1: 5.8 (5.0-6.5) D2: 5.9 (5.4-6.5) D3: 5.6 (5.0-6.7) Required treatment for latent TB		

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics NR	Health Outcomes	Adverse Events, %
			Other population characteristics, %, (CI/SD/P value)		

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
Author, year, study name, if applicable Hoff, M. et al., 2009 ⁸⁵ PREMIER Country and setting Norway, multicenter	Inclusion Criteria • MTX Naïve • Early RA • Aggressive RA: ≥ 8 swollen joints, ESR ≥ 28 or CRP ≥ 1.5 mg/dl, erosions or	Interventions, dose D1: MTX: weekly by mouth (rapidly increased to 20 mg/week) ADA: 40 mg subcutaneously every other week D2: ADA: 40 mg	Mean disease duration, years (SD) D1: 0.7 (0.8) D2: 0.7 (0.8) D3: 0.8 (0.9) Patients with early RA, three years or less, % D1: 100 D2: 100 D3: 100	ACR NR HAQ (SD) D1: 1.5 (0.6) D2: 1.6 (0.6) D3: 1.5 (0.7) DAS NR SF-36 NR	Attrition/withdrawal Overall, n: D1: 65 D2: 104 D3: 88 Overall: 257 Adherent/compliant, n: D1: 203 D2: 167 D3: 169 Overall: 539
Source of funding Abbott Laboratories Research objective Examine effect of ADA on hand osteoporosis and relation to	rheumatoid factor positive. No prior treatment with cyclophosphamide, cyclosporine, azathioprine or more than 2 other DMARDs.	subcutaneously every other week • Placebo D3: • MTX: weekly by mouth • Placebo Number in group D1: 261 D2: 261	Treatment resistant, % NR TJC, mean (SD) D1: 31.1 (14.1) D2: 31.7 (13.5) D3: 32.2 (14.3) SJC, mean D1: 21.2 (42.4) D2: 21.7 (10.2) D3: 21.6 (11.3)	Radiographic measures (SD) Modified TSS change from baseline: Median at 26 weeks, n: D1: 0 (0.5) D2: 1.0 (3.4) D3: 0.5 (2.2) Median at 52 weeks:	Overall adverse events reported, n: NR NR Serious adverse events NR Malignancies NR Respiratory events
radiographic joint damage in 3 tx arms: ADA + MTX, ADA, and MTX to identify predictors of hand bone loss	Exclusion	D3: 246 Overall: 768 Mean age, years (SD) D1: 52.2 (13.8) D2: 51.9 (13.7)	Corticosteroid use, % D1: 35.2 D2: 36 D3: 34.6 DMARD use, %	D1: 0 (0.9) D2: 2.0 (5.1) D3: 0.5 (3.3) Median at 104 weeks: D1: 0 (1.0) D2: 2.0 (6.4)	Tuberculosis: NR Other infections NR GI NR
Study design Controlled Trials Overall N 768 Duration of study 2 yrs Quality rating		D3: 51.9 (13.3) Sex, % female D1: 71.6 D2: 78.5 D3: 73.6 Race, % white NR	D1: 32.2 D2: 33.3 D3: 31.7 MTX naïve, % D1: 100 D2: 100 D3: 100	D3: 1.0 (4.8) Quality of life scales NR	

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
Fair		Race, % black NR Ethnicity, Latino	Baseline DAS score (SD) D1: 6.3 (0.9) D2: 6.4 (0.9)		
		NR	D3: 6.3 (0.9) Required treatment for latent TB NR		
			Median Modified TSS (SD) D1: 12.8 (60.24) D2: 13.5(5.1-25.5) D3: 15.5 (7.5-28.5)		
			Mean D1: 18.1 (20.3) D2: 18.4 (18.2) D3: 21.5 (21.8)		

Author, yr: Inclusion Interventions, dose: Mean disease duration, yrs: At 6 months Adherence: Hyrich et al., 2007 ⁸⁶ - Age > 16 yrs D1: ETA (25 mg 2x D1: 16 D2: 15 D3 vs. D1: (OR 1.98, 95% CI, 1.45-2.71) D2: ETA + DMARD D3: 13 D2 vs. D1 (OR 1.20, 95% D3: ETA + MTX D4: 16 CI, 0.89-1.61) D2 vs. D1 (OR 1.20, 95% D3: ETA subgroups D4: INF (3 mg/kg) D5: 14 ETA subgroups D3 vs. D2: (OR 1.66, 05% CI, 0.89-1.61) ETA subgroups D3 vs. D2: (OR 1.66, 05% CI, 0.89-1.61) ETA subgroups D3 vs. D3: (OR 1.20, 95% CI, 0.89-1.61) ETA subgroups D3 vs. D3: (OR 1.20, 95% CI, 0.89-1.61) ETA subgroups D3 vs. D3: (OR 1.20, 95% CI, 0.89-1.61) ETA subgroups D3 vs. D3: (OR 1.20, 95% CI, 0.89-1.61) ETA subgroups D3 vs. D3: (OR 1.20, 95% CI, 0.89-1.61) ETA subgroups D3 vs. D3: (OR 1.20, 95% CI, 0.89-1.61) ETA subgroups D3 vs. D3: (OR 1.20, 95% CI, 0.89-1.61) ETA subgroups D3 vs. D3: (OR 1.20, 95% CI, 0.89-1.61) ETA subgroups D3 vs. D3: (OR 1.20, 95% CI, 0.89-1.61) ETA subgroups D3 vs. D3: (OR 1.20, 95% CI, 0.89-1.61) ETA subgroups CI vs. D3: (OR 1.20, 95% CI, 0.89-1.61) ETA subgroups CI vs. D3: (OR 1.20, 95% CI, 0.89-1.61) ETA subgroups CI vs. D3: (OR 1.20, 95% CI, 0.89-1.61) ETA subgroups CI vs. D3: (OR 1.20, 95% CI, 0.89-1.61) ETA subgroups CI vs. D3: (OR 1.20, 95% CI, 0.89-1.61) ETA subgroups CI vs. D3: (OR 1.20, 95% CI, 0.89-1.61) ETA subgroups CI vs. D3: (OR 1.20, 95% CI, 0.89-1.61) ETA subgroups CI vs. D3: (OR 1.20, 95% CI, 0.89-1.61) ETA subgroups CI vs. D3: (OR 1.20, 95% CI,	Overall Attrition Rate, %: 21 ITT Analysis: N/A
## About Amgen British Society For Rheumatology Biologics Register	

Study Characteristic s	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
		Daga (/ white	mean:			
		Race, % white:	D1: 6.8			
		NR	D2: 6.6			
			D3: 6.6			
			D4: 6.8			
			D5: 6.8			
			D6: 6.7			

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
Author, year, study name, if applicable Hyrich et al., 2006, 87 BSRBR Country and setting UK, hospitals/general practice Source of funding BSRBR receives financial support from following UK companies: Schering Plough, Wheth Laboratories, Abbott Laboratories and Amgen. Aforementioned resources are used by BSR to provide research grants to University of Manchester. Research objective	Inclusion Criteria Patients registered with BSRBR who had fulfilled1987 ACR criteria for RA Started therapy with either ETN or IFX within 6 mos of registration Only patients who had reached 6 mos of follow-up prior to 10/1/04 were considered for study. Exclusion Criteria NR	Interventions, dose D1: ETN: 25 mg, twice/wk Both study arms included participants who were concurrently using NSAIDs, corticosteroids, other DMARDs, or MTX (see patient characteristics for specifics) D2: IFX: 3 mg/kg at weeks 0, 2, 6, and 8 weekly thereafter Both study arms included participants who were concurrently using NSAIDs, corticosteroids, other DMARDs, or MTX (see patient characteristics for specifics) Number in group D1: 1267 D2: 1612 Overall: 2879	Mean disease duration, years D1: 14 D2: 14 Overall: 14 Patients with early RA, three years or less, % NR Treatment resistant, % NR TJC, mean (SD) D1: 16 (7) D2: 16 (7) Overall: 16 SJC, mean (SD) D1: 12 (6) D2: 12 (6) Corticosteroid use, % D1: 50 D2: 49 Overall: 49.3 DMARD use, % D1: 100 D2: 100 Overall: 100 MTX naïve, % D1: NR D2: NR Overall: 2%	ACR mean difference/ absolute difference (CI/SD/P Value) ACR 20: NR ACR 50: NR ACR 70: NR HAQ, mean difference/ absolute difference NR DAS, mean difference/absolute difference (CI/SD/P Value) D1: NR D2: NR Overall: -2.1 SF-36, mean difference/absolute difference NR Radiographic measures, mean difference/absolute difference/absolute difference/nR Quality of life scales, mean difference/absolute difference/absolute difference/absolute difference NR	Attrition/withdrawal Overall, n: D1: 146 D2: 198 Withdrawals due to adverse events, n: D1: 129 D2: 166 Adherent/compliant, n: D1: 1149 D2: 1460 Overall adverse events reported, n: D1: 129 D2: 166
Identify clinical factors present at start of anti-TNF-alpha therapy		Mean age, years (SD) D1: 55	Baseline DAS score D1: 6.7 D2: 6.7	Others, (please name), mean difference/absolute	

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
associated with response at 6 mos		D2: 55 Overall: 55	Overall: 6.7	difference (CI/SD/P Value)	
			Overall: 6.7 Required treatment for latent TB NR Other population characteristics, % Concurrent NSAIDs: D1: 65 D2: 67 Concurrent corticosteroids: D1: 50 D2: 49 Concurrent DMARDs: D1: 48 D2: 94 Concurrent MTX: D1: 28	Value) Good EULAR response, n (%): • ETN: 245 (17.3) • IFX: 339 (18.70, Overall: 584 (18.1) • Concurrent MTX + ETN: 101 (41) • Concurrent steroids + ETN: 113 (46) • Concurrent NSAIDs + ETN: 117 (72) • Concurrent MTX + IFX: 300 (89) • Concurrent steroids + IFX: 155 (46) • Concurrent NSAIDs + IFX: 255 (75)	
			D2: 86 Overall: NR	Moderate EULAR response, n (%): ETN: 727 (51.5) IFX: 875 (48.3), Overall: 1602 (49.7) Concurrent MTX + ETN: 200 (27) Concurrent steroids + ETN: 352 (48) Concurrent NSAIDs + ETN: 472 (65) Concurrent MTX + IFX: 756 (86) Concurrent steroids + IFX: 442 (51) Concurrent NSAIDs +	

Study	Inclusion and Exclusion	Characteristics and	Baseline Disease and Treatment		
Characteristics	Criteria	Interventions	Characteristics	Health Outcomes	Adverse Events, %
				IFX: 575 (66)	
				No EULAR response, n (%): • ETN: 441 (31.2) • IFX: 596 (32.9), Overall: 1037 (32.2) • Concurrent MTX + ETN: 55 (18) • Concurrent steroids + ETN: 163 (55) • Concurrent NSAIDs + ETN: 176 (59) • Concurrent MTX + IFX: 326 (82) • Concurrent steroids + IFX: 195 (49) • Concurrent NSAIDs + IFX: 248 (62)	
				Remission, n (%): • ETN: 120 (8.0) • IFX: 172 (9.0), Overall: 292 (8.6)	
				Predictors of remission at 6 mos, OR (95% CI): • Concurrent MTX + ETN: 1.80 (1.14 - 2.85) • Concurrent steroid + ETN: 0.81 (0.52 - 1.25) • Concurrent NSAIDs + ETN: 1.79 (1.07 - 2.99) • Concurrent MTX + IFX: 1.24 (0.68 - 2.27) • Concurrent steroids + IFX: 1.10 (0.76 - 1.59)	

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
				 Concurrent NSAIDs + 	
				IFX: 1.93 (1.23 - 3.03)	

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
Author, year, study name, if applicable Hyrich et al., 2007 ⁸⁸ Country and setting UK, hospitals/general practice Source of funding Schering Plough, Wyeth, Abbott, Amgen, British	Inclusion Criteria • Patients registered with BSRBR with a diagnosis of RA (as determined by treating rheumatologist) who had reached a minimum of 6 months of followup by end of April	twice/wk D3: IFX: 3 mg/kg, administered at weeks 0, 2, 6, and 8 and every 8	Mean disease duration, years (SD) Overall: 14 yrs (9) Patients with early RA, three years or less, % NR	ACR NR HAQ NR DAS NR SF-36 NR Radiographic measures NR Quality of life scales NR Others, (please name);	Overall Overall attrition/withdrawal, n: D1: 265 D2: 822 D3: 1273 Overall: 2360 Withdrawals due to adverse events, n: D1: 98 D2: 405 D3: 520 Overall: 1023 Withdrawals due to lack of efficacy, n:
Society for Rheumatology Register Research objective	2005. Exclusion Criteria • NR	2005. 55 Exclusion Sex, % female 77 NR Race, % white	Corticosteroid use, % 49 DMARD use, % 100	mean difference/absolute difference (CI/SD/P Value)	D1: 109 D2: 277 D3: 455 Overall: 841 Adherent/compliant, n:
Compare drug continuation rates between 1st and 2nd course of anti- TNF therapy		NR Race, % black NR Ethnicity, Latino	MTX naïve, % 0 Baseline DAS score, mean (SD)		D1: 611 D2: 2004 D3: 1764 Overall: 4379 Overall adverse events
Study design Prospective Cohort Study		NR	6.6 Required treatment for latent TB		reported, n: NR
Overall N 6739			NR Other population characteristics,		Serious adverse events NR Malignancies
Duration of study Mean length of followup per			%, (CI/SD/P value) Overall: HAQ: 2.1		NR Respiratory events NR

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
patient was 15 months (maximum 61 months). Due to difference in availability of 3 agents, mean followup of patients starting IFX (18 months) was longer than that of patients starting either ADA (11 months) or ET			 Receiving concomittant DMARDS, All: 69% ETN group: 48, IFX group: 92 ADA group: 58 Receiving concomitant MTX All: 56% ETN group: 30% IFX group: 85% ADA group: 40% 		Other infections NR GI NR Other NR
Quality rating Fair					

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
Author, yr: Jacobsson et al., 2005 ⁸⁹ Country, Setting: Sweden, population- based (2 Swedish registers) Funding: NR Research Objective: Risk of cardiovascular disease (CVD) in pts with RA treated with TNF inhibitors, compared to a standard RA population Study Design: Retrospective cohort study Overall N: 983 (combined cohort) Study Duration: NR	Inclusion Criteria: Age-: 20 -79 yrs Diagnosed according to 1987 ACR criteria Case cohort South Swedish Arthritis Txt Group (SSATG): pts with RA treated with anti-TNF agents and included in SSATG register between 2/1/99 and 12/31/01 Exclusion Criteria: Previous hospital discharge due to CVD	Interventions, dose: D1: Anti-TNF exposed D2: Not Anti-TNF exposed N: D1: 531 D2: 452 Median age, yrs: D1: 55 D2: 61 Sex, % female: D1: 78 D2: 75 Race, % white: NR	Median disease duration, yrs: D1: 12 D2: 11 TJC, mean: NR SJC, mean: NR Median # of previous DMARDs used (IQR): D1: 4 (2-5) D2: 2 (1-4) PNL use, %: D1: 75 D2: 22 MTX naive, %: NR Txt resistant %: NR Pts with Early RA (≤3 yrs): NR Baseline DAS, mean: NR Median HAQ: D1: 1.50 D2: 1.13 VAS patient global	Decreased incidence and RR for the development of first-time CVD event when controlling for disease severity in pts with RA treated with TNF blocking therapy Controlling for disability (HAQ), age-sex adjusted rate ratio was 0.46 (95% CI,0.25 - 0.85; P = 0.013) in anti-TNF treated vs. not treated Anti-TNF group, 13 CVD events (in 656 PY at risk); age-adjusted incidence rate: 14 events/1000 PY Unexposed comparison group, 85 CVD events (in 2056 PY at risk); age-adjusted incidence rate: 35.4 events/1000 PY Relative risk: 0.62 (95% CI, 0.34 to 1.12; P = 0.111) SMR revealed increased risk of new onset CVD in those not treated with TNF blockers in relation to	ruptured aortic	Overall Attrition Rate, %: NA ITT Analysis: NA Quality Rating: Fair

assessment	background population
median:	of Malmo (SMR: 228,
D1: 69	95% CI,179 to 277)
D2: 48	TNF blockers, risk of
	new onset CVD was
	lower, with CIs
	enclosing unity with
	background population
	(SMR: 157, 95% CI,72
	-242)

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
Author, year, study name, if applicable Karanikolas et al., 2008 Country and setting Greece, multicenter	Inclusion Criteria Treatment resistant defined as an inadequate response to non-biologic DMARD 18 years or older	Interventions, dose D1: • MTX: Continued at 25mg/wk or maximum tolerated dose • ANK: 100mg/daily D2: • LEF: Continued at 20mg/wk or maximum tolerated	D2: 6.8 (4.3) D3: 7.1 (4.7) Patients with early RA,: 2 years or less, % D1: 27 D2: 25 D3: 23	ACR ACR 20: D1: 65 D2: 81 D3: 74 (Comparison: $P = 0.218$) ACR 50: D1: 38 D2: 64 D3: 47 (Comparison: $P = 0.039$)	Attrition/withdrawal Overall, n: D1: 9 D2: 3 D3: 5 Withdrawals due to adverse events, n: D1: 3* D2: 2* D3: 2 (*includes 1 death)
funding NR Research objective Understand if adding ANK totx regime will improve response of pts with suboptimal response to LEF, MTX, or CSA	• Active RA (defined as 9+ TJC, 6 SJC, and one offollowing: ESR ≤ 28mm/1st hr, ≥ 20mg/l and morning stiffness ≥ 45minutes), stable dose of non-biologic	dose ANK: 100mg/daily D3: ANK: 100mg/daily CSA: 3.5mg or maximum tolerated dose Number in group D1: 48 D2: 42 D3: 38	Treatment resistant, % D1: 100 D2: 100 D3: 100 Overall: 100 Tender Joint Count, mean NR Swollen Joint Count, mean NR	ACR 70: D1: 15 D2: 36 D3: 21 (Comparison: $P = 0.057$) HAQ NR for groups DAS NR, Reported in graph only	Withdrawals due to lack of efficacy, n: D1: 2 D2: 1 D3: 3 Adherent/compliant, n: NR Overall adverse events reported, n: D1: 34 D2: 30 D3: 20
monotherapy Study design Open-label comparison Overall N 128 Duration of study 48wks Quality rating Fair	DMARD (LEF MTX or CSA), NSAIDS, & oral corticosteroids Exclusion Criteria Treatment with TNF-antagonist or intra-articular or systemic	Mean age, years (SD) D1: 48.1 D2: 47.2 D3: 47.6 Sex, % female D1: 68 D2: 69 D3: 70 Race, % white NR	Corticosteroid use, % D1: 60 D2: 62 D3: 63 DMARD use, % D1: 100 D2: 100 D3: 100 MTX naïve, % D1: 0 D2: NR D3: NR	SF-36 NR Radiographic measures Comparisons: • SJC P = NS • TJC P = NS • HAQ P = NS Quality of life scales NR	Serious adverse events Death, n: D1: 1 D2: 1 Arterial hypertension, n: D1: 0 D2: 4 D3: 2 Thrombocytopenia, n: D1: 1 D2: 0

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
	corticosteroids within 8 wks	Race, % black NR	Baseline DAS score D1: 6.55		D3: 0 Hepatotoxicity/elevated
		Ethnicity, Latino NR	D2: 6.93 D3: 6.97		liver enzymes, n: D1: 0 D2: 0
			Required treatment for latent TB		D3: 0
			NR		Malignancies Ovarian cancer, n: D1: 1 D2: 0 D3: 0
					Respiratory events Tuberculosis: NR
					Upper respiratory infection, n: D1: 4 D2: 4 D3: 0
					Other infections Urinary tract infection, n: D1: 1 D2: 2 D3: 0
					Ocular infection, n: D1: 0 D2: 1 D3: 0
					GI GI bleed or ulcer, n: D1: 0 D2: 0 D3: 1
					Other

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
					Infusion/injection site reactions, n: D1: 20 D2: 10 D3: 7
					Skin rash, n: D1: 0 D2: 0 D3: 0
					Headache, n: D1: 0 D2: 4 D3: 1

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
Author, year, study name, if	Inclusion Criteria:	Interventions, dose D1:	Mean disease duration, years	ACR At week 12	Overall NR
applicable Kavanaugh et al., 2008, 91 TEMPO	Age > 18Diagnosed according to	 MTX: 7.5mg/wk escalated to 20mg/wk over 8wks 	D1: NR D2: NR Overall: 6.8 yrs	ACR 20: D1: 75.8 D2: 66.4	Serious adverse events NR
Country and setting Multinational,	ACR criteria • Functional class	• ETN: 25mg, 2/wk D2: ETN: 25mg, 2/wk D3: MTX 7.5mg/wk	Patients with early RA, three years or less, % NR	D3: 61.0 ACR 50: D1: 41.6	Malignancies NR Respiratory events
multicenter Source of	I-III • Less than satisfactory	escalated to 20mg/wk over 8 wks	Treatment resistant, %	D2: 32.7 D3: 25.9	Tuberculosis: NR Other infections
funding Immunex Corporation &	response to at least 1 DMARD other	Number in group D1: 231 D2: 223	TJC, mean NR	ACR 70: D1: 22.1 D2: 9.4	NR GI NR
Wyeth Pharmaceuticals Research	than MTX • Duration 6 mos to 20 yrs	D3: 228 Overall: 682	SJC, mean NR Corticosteroid use, %	D3: 5.7 At week 24	Other NR
objective Evaluate clinical	 RA defined as 10 swollen and > 12 	Mean age, years (SD) D1: see TEMPO ⁹² for	NR DMARD use, %	ACR 20: D1: 84.8 D2: 77.1	
response between 12 and 24 wks in subjects with RA	painful joints and at least	baseline characteristics by arm	NR MTX naïve, %	D3: 77.2 ACR 50:	
from TEMPO trial Study design Controlled Trials	one of: ESR > 28 mm/h, CRP >	Overall: 52.5 Sex, % female	NR Baseline DAS score	D1: 57.6 D2: 44.4 D3: 41.7	
Overall N 682	20 mg/L, or morning stiffness for >	NR Race, % white	NR Required treatment for latent TB	ACR 70: D1: 32.0	
Duration of study 52 weeks (TEMPO	45 minutesFolic acid 5 mg twice per	NR Race, % black NR	NR Other population	D2: 14.8 D3: 14.0 HAQ	
trial), 12 & 24 weeks outcomes reported here	wk • NSAIDs	Ethnicity, Latino	characteristics, %, (CI/SD/P value) NR	NR DAS	
Quality rating Fair	Exclusion Criteria:			D1: NR (different stratification for	

• TNF antagonist, any immunosuppressive drugs w/in 6 mos

Any

investigational drug or

biologic agent within 3 mos DMARD or corticosteroid injection within

4 mos

Relevant comorbidity, Previous txt with MTX if pt experienced clinically toxic side effects or had no response

analysis)

D2: NR D3: NR Overall: NR

SF-36 NR

Radiographic measures

D1: NR (different stratification for analysis) D2: NR

D3: NR Overall: NR

Quality of life scales

NR

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
Author, year, study name, if applicable Kay et al., 2008 ⁹³	Inclusion Criteria • Active RA for 3+ mos (TJC and SJC ≥ 6	Interventions, dose D1: MTX: continued 10mg/wk Placebo ALL ARMS:	Mean disease duration, median (IQR) D1: 5.6 (1.4, 10.9) D2: 8.2 (4.1, 14.3) D3: 8.2 (2.9, 12.8)	ACR ACR 20: D1: 37.1 D2: 60.0 D3: 50.0	Attrition/withdrawal Overall, n: D1: 6 D2: 4 D3: 6
Country and setting Multlinational, multienter	and 2 of following 3: CRP ≥ 1.5mg/dl, ESR	continued (stable dose for > 4wks) corticosteroids	D4: 6.3 (3.4, 14.1) D5: 9.0 (4.1, 14.1) Overall: 7.8 (3.0, 13.3)	D4: 55.9 D5: 79.4* Overall: ALL - compared to Placebo 61.3 *P =	D4: 5 D5: 2 Overall: 23
Source of funding Centocor	≥ 28mm, morning stiffness ≥ 30 minutes), Age	PRED/day) and NSAIDs D2: MTX: continued 10mg/wk	Patients with early RA, three years or less, % NR Treatment resistant, %	0.010 ACR 50: D1: 5.7	Withdrawals due to adverse events, n: D1: 3 D2: 2
Research objective Asssess efficacy, safety and pharmacology of	≥ 18 Exclusion Criteria • Abnormal lab	GOL: 50mg/4wks D3: MTX: continued 10mg/wk GOL: 50mg/2wks D4: MTX: continued	NR Tender Joint Count, median D1: 22	D2: 37.1* D3: 23.5* D4: 29.4* D5: 32.4* Overall: 30.7 *P = 0.003	D3: 3 D4: 2 D5: 1 Overall: 11 Withdrawals due to lack of
subcutaneous GOL in pts with active RA despite tx with MTX	results • Latent or active TB • Planning pregnancy or	10mg/wk GOL: 100mg/4wks D5: MTX: continued 10mg/wk GOL: 100mg/2wks	D4: 32 D5: 22	ACR 70: D1: 0 D2: 8.6 D3: 14.7* D4: 17.6*	efficacy, n: D1: 3 D2: 2 D3: 1 D4: 3
Study design Controlled Trials Overall N	inadequate birth control • Other	Number in group D1: 35	Swollen Joint Count, median D1: 13	D5: 8.8 Overall: 12.4 *P = 0.028	D5: 1 Overall: 10
Duration of study 16 wks (efficacy), 20 wks (AEs) after week 20- drug and dosing schedules were adjusted and	inflammatory disease • DMARD use w/in 4wks of study start • Failed 3+ DMARDS	D2: 35 D3: 34 D4: 34 D5: 34 Overall: 172 Mean age, median D1: 52.0	D2: 14 D3: 14 D4: 20 D5: 14 Overall: 15	HAQ NR DAS28-CRP mean (SD) D1: -0.9 (1.0) D2: -1.9 (1.3) D3: -1.4 (1.3) D4: -1.9 (1.5)	Overall adverse events reported, n: Pts reporting 1+ AE: D1: 29 D2: 34 D3: 24 D4: 29
patients were followed for efficacy & AEs -AE	 Previous treatment with TNF-alpha 	D2: 57.0	NR DMARD use, % NR	D5: -1.9(1.1) Overall: -1.8 (1.3) DAS28-ESR mean (SD)	D5: 31 Serious adverse events Congestive cardiac failure,

	Inclusion and		Baseline Disease and		
Study	Exclusion	Characteristics and	Treatment		
Characteristics	Criteria	Interventions	Characteristics	Health Outcomes	Adverse Events, %
data reported (thru week 52) were not included inabstraction to prevent confusion. Quality rating Fair	antagonist (more reported online in journal suppl materials)	D5: 53.5	MTX naïve, % D1: 0 D2: 0 D3: 0 D4: 0 D5: 0 Overall: 0 Baseline DAS28/CRP score D1: 5.3 D2: 5.3 D3: 4.8 D4: 5.4 D5: 5.1 Overall: 5.2 DAS28/ESR - median D1: 6.3 D2: 6.4 D3: 6.4 D4: 6.7 D5: 6.2 Overall: 6.4 Required treatment for latent TB D1: 0 (exluded) HAQ disability index - median D1: 1.3 D2: 1.7 D3: 1.6 D4: 1.8 D5: 1.3	D1: -1.0 (1.1) D2: -2.1 (1.4) D3: -1.9 (1.5) D4: -2.1(1.7) D5: -2.3(1.2) Overall: -2.1 (1.4) SF-36 NR Radiographic measures NR Quality of life scales NR Others, (please name) mean difference/absolute difference (CI/SD/P Value) ACR-N mean (SD): D1: -2.4 (50) D2: 22.7 (46.8) D3: 16.2 (57.4) D4: 24.8 (41.7) D4: 30.4 (42.3) D2 vs. D1: P = 0.006, D3 vs. D1 P = 0.095, D4 vs. D1: P = 0.01, D5 vs. D1: P < 0.01	n: D1: 0 D2: 1 D3: 0 D4: 0 D5: 0 Cardia tamponade, n: D1: 0 D2: 0 D3: 0 D4: 0 D5: 1 Malignancies Lung adenocarcinoma, n: D1: 0 D2: 0 D3: 1 D4: 0 D5: 0 Respiratory events Tuberculosis: NR Pneumonia, n: D1: 0 D2: 1 D3: 1 D4: 1 D5: 0 Other infections 1+ infection, n: D1: 13 D2: 12 D3: 6
			Overall: 1.6		D4: 9 D5: 9

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
					GI Nausea, n: D1: 1 D2: 2 D3: 7 D4: 6 D5: 8
					Other 1+ injection site disorder thru 20wk, n: D1: 4 D2: 5 D3: 2 D4: 5 D5: 13
					Headache, n: D1: 7 D2: 6 D3: 5 D4: 7 D5: 3
					Any other AEs: All AEs reported thru 20 weeks. Only those in ≥ 10% of all GOL groups combined or SAEs. Additional surveillance for AEs continued thru wk 52 however, treatment and dosing schedule was adjusted for 3/5 arms.

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
Author, yr: Keane, 2001 ⁹⁴ Country, Setting: Multinational, NA NA Funding: National Heart, Lung and Blood Institute; Massachusetts Thoracic Society; American Lung Association of Massachusetts Research Objective: To explore relationship between INF and tuberculosis based on data from MedWatch Study Design: Database analysis; AERS Overall N: 70 cases 47 Crohn's: 18 Other: 5	Inclusion Criteria: If during or after txt with INF, patient received diagnosis of TB on basis of clinical, radiologic, and laboratory findings Exclusion Criteria: NR	Interventions, dose: D1: TB pts INF: varies N: D1: 57 Median age, yrs: D1: 57 Sex, % female: D1: 64 Race, % white: D1: NR	Mean disease duration, yrs: NR TJC, mean: NR SJC, mean: NR DMARD use, %: NR Corticosteroid use, %: D1: 20 MTX naive, %: NR Txt resistant %: NR Pts with Early RA (≤3 yrs): NR Baseline DAS, mean: NR	Estimated incidence for pts with RA who have been treated with INF during previous is 24.4 cases per 100.000 per yr (95% CI,0.6 to 34.0); background incidence in US for pts with RA not exposed to TIM therapy: 6.2 cases per 100,000 per yr • Median interval from start of INF txt until development of TB: 12 wks; 68.6% developed TB after 3 or fewer INF infusions; reported frequency of TB in association with INF was much higher than reported frequency of other opportunistic infections associated with this drug	NR	Overall Attrition Rate, %: NA ITT Analysis: NA Quality Rating: Fair

Study Duration: 1-52 wks

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
Author, year, study name, if applicable Keystone, E. et al., 2008 ⁹⁵ RAPID 1 trial Country and setting Multinational, multicenter Source of funding UCB Inc. Research objective Evaluate efficacy and safety of 2 dosage regimens of CZP as adjunctive therapy to MTX in RA pts with an inadequate response to MTX Study design Controlled Trials Overall N 982 Duration of study	Inclusion Criteria • ≥ 18 years of age • Diagnosis of RA as defined byACR 1987 criteria for ≥ 6 mos prior to screening but for < 15 years • Active disease was defined as ≥ 9 tender and 9 swollen joints at screening and at baseline, with either an ESR ≥ 30 mm//hr or a CRP level > 15 mg/liter. • Pts were required to have received MTX for ≥ 6 onths prior to baseline. Exclusion	Interventions, dose D1: MTX Placebo D2: MTX Certolizumab: 400 mg at weeks 0, 2, and 4 followed by 200 mg every 2 weeks D3: MTX Certolizumab: 400 mg at weeks 0, 2, and 4 followed by 400 mg every 2 weeks Number in group D1: 199 D2: 393 D3: 390 Overall: 982 Mean age, years (SD) D1: 52.2 (11.2) D2: 51.4 (11.6) D3: 52.4 (11.7) Sex, % female D1: 83.9 D2: 82.4 D3: 83.6	Patients with early RA, three years or less, % NR Treatment resistant, % NR TJC, mean D1: 29.8 (13.0) D2: 30.8 (12.4) D3: 31.1 (13.3) SJC, mean D1: 21.2 (9.7) D2: 21.7 (9.9) D3: 21.5 (9.8) Corticosteroid use, % NR Previous DMARD use (except MTX), n (SD) D1: 1.4 (1.4) D2: 1.3 (1.3) D3: 1.3 (1.3) MTX naïve, % NR	ACR ACR 20: Week 1: D1: 5.6 D2: 22.9 D3: 22.3 Overall:: D1 vs. D2 $P < 0.001$, D1 vs. D3 $P < 0.001$ Week 24: D1: 13.6 D2: 58.8 D3: 60.8 Overall: D1 vs. D2 $P < 0.001$, D1 vs. D3 $P < 0.001$ ACR 50: D1: In Figure, NR D2: In Figure, NR D3: In Figure, NR Overall: by week 2, ACR50 responses in certolizumab Dwere significanlty higher thanplacebo D($P \le 0.01$ for each comparison); difference remained ($P \le 0.001$ for weeks 4-52)	Attrition/withdrawal Withdrawals due to adverse events, n: D1: 3 D2: 17 D3: 22 12 patients discontinued due to infection (6 from each CZP arm). Overall adverse events reported, n: D1: 125.9 D2: 96.6 D3: 94.5 Serious adverse events Death, n: D1: 1 (myocardial infarction) D2: 2 (hepatic neoplasm, cardiac arrest) D3: 4 (stroke, myocardial necrosis, cardiac arrest, atrial fibrillation) Malignancies Malignancy, incidence rate per 100 person years: D1: 1.1 D2: 2.3 D3: 1.3
52 weeks Quality rating Fair	Diagnoses of any other inflammatory arthritis or	Race, % white NR Race, % black NR	Baseline DAS score, median (range) D1: 7.0 (4.9-8.7) D2: 6.9 (4.3-8.9) D3: 6.9 (4.8-9.1)	ACR 70: D1: In Figure, NR D2: In Figure, NR D3: In Figure, NR Overall: by week 4,	Respiratory events Upper respiratory infection, incidence rate per 100 person years: D1: 5.5

	Inclusion and		Baseline Disease and		
Study	Exclusion	Characteristics and	Treatment		
Characteristics	Criteria	Interventions	Characteristics	Health Outcomes	Adverse Events, %
	secondary noninflammato	Ethnicity, Latino	Required treatment for latent TB	ACR70 responses in certolizumab 200	D2: 7.9 D3: 6.7
	ry arthritis that could have interfered with		NA Other population	Dwas significanlty higher thanplacebo $D(P \le 0.05)$; and by	Other infections Urinary tract infection,
	their evaluation ofeffects of certolizumab		characteristics, %, (CI/SD/P value) HAQ DI: D1: 1.7 (0.6	week 6, forcertolizumab 400 $D(P \le 0.05)$; differences remained	incidence rate per 100 person years: D1: 14.2 D2: 7.6
	pegol on RA • History of TB		D2: 1.7 (0.6 D3: 1.7 (0.6	$(P \le 0.001 \text{ for weeks} $ 10-52)	D3: 10.5 Other infections (specify),
	or chest radiograph showing active or latent TB • High risk of			% Change Baseline to week 1: D1: -2.4 D2: -13.5 D3: -10.9	incidence rate per 100 person years: Nasopharyngitis: D1: 3.3 D2: 6.9
	infectionHistory of malignancy, demyelinating disease, blood			Overall: D1 vs. D2 <i>P</i> < 0.001, D1 vs. D3 <i>P</i> < 0.001 Baseline to week 4:	D3: 9.5 Lung/lower respiratory tract, incidence rate per 100 person years: D1: 0
	dyscrasias, or severe, progressive,			D1: -5.4 D2: -21.5 D3: -21.9	D2: 1.0 D3: 1.3
	and/or uncontrolled renal, hepatic,			Overall: D1 vs. D2 <i>P</i> < 0.001, D1 vs. D3 <i>P</i> < 0.001	Herpes viral, incidence rate per 100 person years: D1: 0
	hematologic, GI, endocrine,			Baseline to week 12: D1: -8.2	D2: 0.3 D3: 0.3
	pulmonary, cardiac, neurologic, or cerebral disease			D2: -30.4 D3: -27.6 Overall: D1 vs. D2 <i>P</i> < 0.001, D1 vs. D3 <i>P</i> < 0.001	Bacterial peritonitis, incidence rate per 100 person years: D1: 0 D2: 0.3
	 Those having received any biologic 			Mean change, baseline to week 52 (SD)	D3: 0 Opportunistic infection,

	Inclusion and		Baseline Disease and		
Study	Exclusion	Characteristics and	Treatment		
Characteristics	Criteria	Interventions	Characteristics	Health Outcomes	Adverse Events, %
	therapy within			D1: -2.4 (1.3)	incidence rate per 100
	6 mos (OR,			D2: -3.3 (1.3)	person years:
	had received			D3: -3.4 (1.4)	D1: 0
	ETN and/or			Overall:	D2: 0
	ANK within 3			Baseline to week 52:	D3: 0
	mos) of			D1 vs. D2 $P < 0.001$,	
	baseline			D1 vs. D3 <i>P</i> < 0.001	GI
	and/or any			SF-36	Gastroenteritis, incidence
	privous			NR	rate per 100 person years:
	biologic				D1: 1.1
	therapy			Radiographic measures	D2: 0.0
	resulted in a			Sharp Baseline to week	D3: 0.0
	severe			52:	Any other AEs:
	hypersensitivit			D1: 2.8	Headache, incidence rate
	y or			D2: 0.4	per 100 person years:
	anaphylactic			D3: 0.2	D1: 12.0
	reaction			Overall: D1 vs. D2 P <	D2: 7.3
	 Those who 			0.001, D1 vs. D3 P <	D3: 5.7
	had previously			0.001	
	failed to			Quality of life scales	Hypertension, incidence
	respond to			NR	rate per 100 person years:
	treatment with				D1: 2.2
	an anti-TNF			% ChangeSJC	D2: 8.2
	agent.			Baseline to week 1:	D3: 10.2
				D1: 4.5	Back pain, incidence rate
				D2: -18.2	per 100 person years:
				D3: -18.8	D1: 2.2
				Overall: D1 vs. D2 P <	D2: 5.6
				0.001, D1 vs. D3 P <	D3: 6.4
				0.001	DO. 0. 1
				Baseline to week 4:	Injection site pain and
				D1: -10.3	injection site reaction
				D1: -10.3 D2: -37.3	200mg
				D2: -37.3 D3: -40.4	(2% and 2.3%) or 400mg
				Overall: D1 vs. D2 <i>P</i> <	(1.3% and 0.8%), none in
				0.001, D1 vs. D3 P <	placebo group.
				0.001, D1 VS. D3 P <	piaceno group.

Study	Inclusion and Exclusion	Characteristics and	Baseline Disease and Treatment	Haalth Outsamas	Advance Front - 0/
Characteristics	Criteria	Interventions	Characteristics	Health Outcomes 0.001	Adverse Events, %
				Baseline to Week 12: D1: -10.7 D2: -56.7 D3: -61.5 Overall: D1 vs. D2 <i>P</i> < 0.001, D1 vs. D3 <i>P</i> < 0.001	
				TJC: Baseline to week1: D1: -6.7 D2: -18.9 D3: -19.1 Overall: D1 vs. D2 P < 0.001, D1 vs. D3 P < 0.001	
				Baseline to week 4: D1: -11.4 D2: -36.2 D3: -37.0 D1 vs. D2 <i>P</i> < 0.001, D1 vs. D3 <i>P</i> < 0.001	
				Baseline to Week 12: D1: -10.8 D2: -52.6 D3: -56.8 D1 vs. D2 <i>P</i> < 0.001, D1 vs. D3 <i>P</i> < 0.001	
				Patient's global assessment: Baseline to week1: D1: -2.9 D2: -12.9 D3: -16.1	

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
<u> </u>	•·········			Overall: D1 vs. D2 <i>P</i> < 0.001, D1 vs. D3 <i>P</i> < 0.001	7. d. c.
				Baseline to week 4: D1: -6.5 D2: -10.4 D3: -27.9 D1 vs. D2 <i>P</i> < 0.001, D1 vs. D3 <i>P</i> < 0.001	
				Baseline to Week 12: D1: -4.9 D2: -38.3 D3: -39.2 D1 vs. D2 <i>P</i> < 0.001, D1 vs. D3 <i>P</i> < 0.001	
				Patient's assessment of arthritis pain: Baseline to week1: D1: -1.0, D2: -20.6, D3: -19.0 D1 vs. D2 <i>P</i> < 0.001, D1 vs. D3 <i>P</i> < 0.001	
				Baseline to week 4: D1: -5.0, D2: -26.6, D3: -28.8 D1 vs. D2 <i>P</i> < 0.001, D1 vs. D3 <i>P</i> < 0.001	
				Baseline to Week 12: D1: -4.8, D2: -38.2, D3: -39.6 D1 vs. D2 <i>P</i> < 0.001, D1	

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
<u> </u>	Gilloria	into vontiono	Gildiagionoliga	vs. D3 <i>P</i> < 0.001	ravolos Evolito, 70
				ESR (ratio): Baseline to week1: D1: 0.96, D2: 0.73, D3: 0.70 D1 vs. D2 <i>P</i> < 0.001, D1 vs. D3 <i>P</i> < 0.001 Baseline to week 4: D1: 0.90, D2: 0.59,	
				D3: 0.54 D1 vs. D2 <i>P</i> < 0.001, D1 vs. D3 <i>P</i> < 0.001	
				Baseline to Week 12: D1: 0.84, D2: 0.53, D3: 0.52 D1 vs. D2 <i>P</i> < 0.001, D1 vs. D3 <i>P</i> < 0.001	

than MTX; Research Moderate RA was defined post hoc as DAS28 > 3.2 and radiographic responses to MTX, ETA, and ETA + MTX in pts with moderate vs. severe RA in early and late disease Study design Moderate RA was defined post hoc as DAS28 > 3.2 and ≤5.1; severe 211 Severe 211 Severe 211 Severe 214 Moderate Shwbe weakly to 12 1	Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
hoc analysis Exclusion Criteria Moderate 32 NR ERA: NR ERA NR Moderate 32	Author, year, study name, if applicable Keystone, E. et al.; 2009; FEMPO and ERA Country and setting See original abstractions for TEMPO and ERA Source of funding Immunex Corporation, a wholly owned subsidiary of Amgen Inc., and by Wyeth Research Objective Examine clinical and radiographic responses to MTX, ETA, and ETA + MTX in pts with moderate vs. severe RA in early and late disease Study design Pooled data – post	Inclusion Criteria • MTX Naive • ERA sample only: early RA, pts who had had RA for no more than 3 years and had not been previously been treated with MTX. • TEMPO sample only: active RA not adequately responding to DMARD other than MTX; • Moderate RA was defined post hoc as DAS28 > 3.2 and ≤5.1; severe was > 5.1. • See original abstractions of TEMPO and ERA studies for further details Exclusion	Interventions, Dose D1: • MTX: TEMPO: twice weekly for 12 mos • ERA: 10 mg for 12 mos D2: • ETN: TEMPO & ERA: 25 mg twice weekly for 12 mos D3: • MTX: TEMPO: twice weekly for 12 mos • ETN: TEMPO: 25 mg twice weekly for 12 mos Number in group D1: • TEMPO: Moderate 16 Severe 211 • ERA: Moderate 33 Severe 178 D2: • TEMPO: Moderate 8 Severe 214 • ERA:	Mean disease duration, years (years) TEMPO Moderate: D1: 3.2 D2: 5.1 D3: 6.1 Severe: D1: 7.1 D2: 6.4 D3: 6.8 Overall: 6.6 ERA Moderate: D1: NR D2: NR D3:NR Severe: 1 Patients with early RA, three years or less, % TEMPO NR ERA D1: 100 D2: 100 D3: NR Overall: 100 Treatment resistant, % NR TJC, mean (SD)	ACR mean difference/absolute difference (%) TEMPO ACR 20: Moderate D1: 75 D2: 75 D3: 82 Severe: D1: 75 D2: 76 D3: 85 ERA Moderate D1: 55 D2: 66 Severe: D1: 65 D2: 70 Overall: P NS ACR 50: TEMPO Moderate D1: 31 D2: 25 D3: 71 Severe: D1: 43 D2: 50 D3: 69 Overall: P NS	Overall Adherent/compliant, n: D1: TEMPO: 227; ERA: 211 D2: TEMPO: 222; ERA: 203 D3: TEMPO: 228 Overall: TEMPO: 677; ERA: 414; COMBO: 1091 see original abstractions for TEMPO and ERA for attrition and withdrawal information Overall adverse events reported, n: NR Serious adverse events NR Malignancies NR Respiratory events NR Other infections NR

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %		
				D1: 39	Adverse Events, %		
1091 Duration of study	 See original abstractions for TEMPO 	D3: • TEMPO: Moderate 17	NR Corticosteroid use, %	D2: 53			
12 mos Quality rating Fair	and ERA	and ERA Severe 211 Overall:	NR DMARD use, % MTX:	Severe: D1: 40 D2: 47			
		ERA: 414COMBO: 1091	TEMPO: 43 ERA: 0	ACR 70: TEMPO			
		Mean age (years) TEMPO: 53; ERA: 50	MTX naïve, % TEMPO NR	Moderate D1: 13 D2: 13 D3: 65			
	Sex, % female NR Race, % white NR Race, % black NR Ethnicity, Latino NR	NR	ERA D1: 100 D2: 100	Severe: D1: 19			
			Overall: 100	D2: 25 D3: 40			
		Race, % black NR Ethnicity, Latino	Race, % black	Baseline DAS score, mean (SD) NR	Overall: TEMPO D3 <i>P</i> <0.05		
				Required treatment for latent TB NR	ERA Moderate D1: 18 D2: 22		
						Other population characteristics, %, (CI/SD/P value) D1:	D3: Severe: D1: 21 D2: 24
		HAQ: TEMPO: Moderate 0.92, SD 0.67 Severe 1.77, SD 0.66 D2: NR D3: NR	HAQ score, HAQ score TEMPO (SD) Moderate: D1: 0.6 (0.1) D2: 0.6 (0.2) D3: 0.4 (0.2)				
				Severe:			

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
				D1: 1.1 (0.1) D2: 1.0 (0.1) D3: 0.8 (0.0)	
				ERA Moderate: D1: 0.6 (0.1) D2: 0.4 (0.1)	
				Severe: D1: 0.8 (0.0) D2: 0.8 (0.1)	
				HAQ less than or equal to 0.5 (%): TEMPO Moderate: D1: 50 D2: 50 D3: 82	
				Severe: D1: 33 D2: 34 D3: 41	
				ERA Moderate: D1: 58 D2: 75	
				Severe: D1: 44 D2: 42	
				HAQ mean change from baseline to 12 mos (SD): TEMPO Moderate: D1: 0.29 (0.12)	

Cturder	Inclusion and	Ob anastanistica and	Baseline Disease and		
Study Characteristics	Exclusion Criteria	Characteristics and Interventions	Treatment Characteristics	Health Outcomes	Adverse Events, %
GHAI AGUSTISTICS	Ontona	interventions	- Characteristics	D2: 0.42 0.21) D3: 0.74 (0.18)	Adverse Events, 76
				Severe: D1: 0.68 (0.05) D2: 0.74 (0.05) D3: 1.00 (0.05)	
				ERA Moderate: D1: 0.44 (0.09) D2: 0.45 (0.09)	
				Severe: D1: 0.77 (0.05) D2: 0.75 (0.05)	
				Overall: HAQ score: • TEMPO D1 P <0.05 • ERA D2 P <0.05 • TEMPO D3 P <0.05 • HAQ less than or equal to 0.5: ERA D2 P <0.001 TEMPO D3 P <0.001 • HAQ change in mean scores: TEMPO D1 P <0.05 ERA D1 P <0.05 ERA D2 P <0.05	
				DAS (%) DAS28 remission (%): TEMPO Moderate: D1: 44 D2: 38 D3: 77	

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
				Severe: D1: 15 D2: 17 D3: 35	
				ERA: Moderate: D1: 33 D2: 47 D3:	
				Severe: D1: 15 D2: 14 D3:	
				DS28 low disease activity (%): TEMPO Moderate: D1: 56 D2: 63 D3: 82	
				Severe: D1: 28 D2: 31 D3: 50	
				ERA Moderate: D1: 55 D2: 56	
				Severe: D1: 28 D2: 26	
				DAS28 mean change from baseline to 12 mos (SD):	

	Inclusion and		Baseline Disease and		
Study	Exclusion	Characteristics and	Treatment		
Characteristics	Criteria	Interventions	Characteristics	Health Outcomes	Adverse Events, %
				TEMPO	
				Moderate:	
				D1: 1.6 (0.3)	
				D2: 1.5 (0.4)	
				D3: 2.5 (0.3)	
				Severe:	
				D1: 2.6 (0.1)	
				D2: 2.7 (0.1)	
				D3: 3.5 (0.1)	
				ERA Madagata	
				Moderate	
				D1: 1.2 (0.2) D2: 1.7 (0.2)	
				D2: 1.7 (0.2) D3:	
				Severe	
				D1: 2.4 (0.1)	
				D2: 2.4 (0.1)	
				D3:	
				Overall:	
				 DAS28 remission: 	
				TEMPO D1 P < 0.05	
				ERA D1 <i>P</i> <0.05	
				ERA D2 <i>P</i> <0.001	
				TEMPO D3 <i>P</i> <0.001	
				DAS28 low disease	
				activity:	
				TEMPO D1 <i>P</i> <0.05 ERA D1 <i>P</i> <0.05	
				ERA DT P <0.05 ERA D2 P <0.001	
				TEMPO D3 <i>P</i> <0.05	
				DAS28 change in mean	
				scores:	
				TEMPO D1 <i>P</i> <0.05	
				ERA D1 <i>P</i> <0.001	
				TEMPO D2 <i>P</i> <0.05	

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
				ERA D2 <i>P</i> <0.05 TEMPO D3 <i>P</i> <0.05	·
				SF-36 NR	
				Radiographic measures (SD) TSS Progression: Moderate: D1: 0.62 (1.94) D2: -0.51 (1.04) D3:	
				Severe: D1: 2.95 (13.08) D2: 0.55 (4.70) D3: -0.53 (3.64)	
				ERA: Moderate: D1: 2.15 (6.27) D2: -0.04 (1.36)	
				Severe: D1: 1.71 (3.99) D2: 0.89 (2.70)	
				No radiographic progression (%): TEMPO Moderate D1: 44 D2: 75 D3: NR	
				Severe D1: 51 D2: 59 D3: NR	

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
				ERA: Moderate D1: 47 D2: 69 D382	
				Severe: D1: 49 D2: 65 D3: 71 Overall: NR	
				Quality of life scales	

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
Author, year, study name, if applicable Keystone et al., 2009 ⁹⁷ Country and setting	Inclusion Criteria 18 years of age or older Diagnosis of RA for at least mos before	Interventions, dose D1: MTX: dosage NR but stable throughout 24 week study period. Patients with less than	Mean disease duration, median (IQR) D1: 6.5 (3.1-11.9) D2: 5.9 (2.4-12.2) D3: 4.5 (2.1-9.7) D4: 6.7 (2.4-14.3) Patients with early RA,	ACR ACR 20: At 14 weeks: D1: 33.1 D2: 44.4%, P = 0.059 D3: 55.1, P = 0.001 D4: 56.2, P = 0.001	Attrition/withdrawal Overall, n: D1: 10 D2: 9 D3: 2 D4: 7 Overall: 28
Multinational Source of funding Centocor Research and	 Screening On a stable MTX dose of 15 mg/week or greater but 25 mg/week or 	GOL/4wks forremainder	three years or less, % NR Treatment resistant, % NR Tender Joint Count,	At 24 weeks: D1: 27.8 D2: 35.3, P = 0.187 D3: 59.6, P = 0.001 D4: 59.6%, P = 0.001	Withdrawals due to adverse events, n: D1: 6 D2: 6 D3: 2 D4: 5
Research objective Evaluate efficacy and safety of GOL	less during4- week period immediately preceding screening • Patients were	ofstudy Placebo D2: GOL: 100mg every 4 weeks Placebo: Patients with = 20%	median (IQR) D1: 21.0 (14.0-34.0) D2: 22.0 (14.0-32.0) D3: 26.0 (16.0-39.0) D4: 23.0 (15.0-33.0)	ACR 50: At 14 weeks: D1: 9.8 D2: 20.3, P = 0.016 D3: 34.8, P = 0.001 D4: 29.2, P = 0.001	Overall: 19 Withdrawals due to lack of efficacy, n: D1: 2 D2: 1
intx of patients with active RA despite MTX therapy Study design Controlled Trials	to have tolerated 15 mg/ week or greater of MTX for at	improvement in SJC and TJC and TJC at week 16 began receiving active MTX	Swollen Joint Count, median (OQR) D1: 12.0 (8.0-19.0) D2: 11.0 (8.0-17.0) D3: 13.0 (8.0-22.0)	At 24 weeks: D1: 13.5 D2: 19.5, <i>P</i> = 0.187 D3:, 37.1, <i>P</i> = 0.001 D4: 32.6, <i>P</i> = 0.001	D3: NR D4: NR Overall: 3 Adherent/compliant, n: D1: 123
Overall N 444 Duration of study 24 weeks	least 3 mos before screening and to have active RA.	forremainder ofstudy D3: MTX: stable dose, NR (looks likely to be 15mg/wk not	D4: 12.0 (8.0-18.0) Corticosteroid use, % D1: 65.4 D2: 67.7 D3: 75.3	ACR 70: At 14 weeks: D1: 3.8 D2: 7.5, <i>P</i> = 0.184 D3: 13.5, <i>P</i> = 0.008	D2: 125 D3: 87 D4: 82 Overall: 417
Quality rating Good	 Patients who were using NSAIDs or other analgesics for RA had to be taking stable 	explicit in methods) GOL: 50mg every 4 weeks. Patients with <20% improvement in	D4: 69.7 DMARD use, other than MTX % D1: 70.7 D2: 75.9 D3: 78.7	D4: 9.0, <i>P</i> = 0.104 At 24 weeks: D1: 5.3 D2: 11.3, <i>P</i> = 0.075 D3: 20.2, <i>P</i> = 0.001 D4: 14.6, <i>P</i> = 0.017	D1: 1 lost to follow-up, 1 "other" D2: 1 discontinued oral study agent D3: NR D4: 1 lost to follow-up, 1 discontinued oral study

	Inclusion and		Baseline Disease and		
Study	Exclusion	Characteristics and	Treatment		
Characteristics	Criteria	Interventions	Characteristics	Health Outcomes	Adverse Events, %
	dose for at	SJC and TJC at	D4: 75.3	Improvement from	agent
	least 2 wks before first dose of study	week 16 began receiving 100mg of GOL/4 wks	MTX naïve, % NR	baseline in HAQ-DI at 24 weeks: (CI/SD/P Value) D1: -0.13 (-0.38-0.13)	Overall adverse events reported, n: D1: 89
	agent.Patients who were taking	forremainder ofstudy D4: MTX: Stable dose	Baseline DAS score, n (CI)	D1: -0.13 (-0.36-0.13) D2: -0.13 (-0.63-0.25), P = 0.240 D3: -0.38 (-0.750.13),	D2: 98 D3: 87 D4: 78
	oral		D1: DAS28 using CRP:	P = 0.001	Overall: 352
	corticosteroids had to have been receiving a stable dose	GOL: 100mg/4wks Number in group D1: 133 D2: 133	4.860 (4.194-5.480); DAS28 using ESR: 6.111 (5.260-6.574) D2: DAS28 using CRP:	D4: -0.50 (-0.75 0.13), P = 0.001	Serious adverse events Death, n: D1: NR
	equivalent to 10 mg/day or less of PRED for at least 2	D2: 133 D3: 89 D4: 89 Mean age, years	4.803 (4.151-5.558); DAS28 using ESR: 6.013 (5.198-6.800) D3: DAS28 using CRP:	D1: DAS28 (ESR) remission: 14 weeks: 1.5%, 24 weeks: 6.0%, DAS28 (ESR)	D2: 1 D3: NR D4: NR Overall: 1
	wks before first dose of study agent.	(SD) D1: 52 (42-58) D2: 51 (42-59)	5.100 (4.060-5.651); DAS28 using ESR: 6.105 (5.366-6.940)	sustained remission: 24 weeks: 0.8%, EULAR responders	Malignancies Lymphoma or leukemia, n: NR
	Exclusion Criteria • Known	D3: 52 (43-57) D4: 50 (45-56) Sex, % female	D4: DAS28 using CRP: 4.902 (4.320-5.521); DAS28 using ESR:	(DAS28 calculated using ESR): 14 weeks: 44.4%, 24 weeks:	Skin cancer (basal cell or squamous cell), n:
	hypersensitivit y to human immunoglobuli n proteins or	D1: 82 D2: 105	5.905 (5.292-6.805) Required treatment for latent TB (%) D1: 23.3	42.1% D2: DAS28 (ESR) remission: 14 weeks: 8.3%, P = 0.010, 24 weeks: 12.0%, P=	D1: 1 D2: 2 D3: NR D4: NR Overall: 3
	other components of GOL	Race, % white NR	D2: 19.5 D3: 20.2 D4: 19.1	0.087; DAS28 (ESR) sustained remission: 24 weeks: 6.3%, P=	Other cancer (specify), n: D1: NR
	Any previous use of any anti TNE	Race, % black NR		0.018; EULAR responders (DAS28	D2: NR D3: NR D4: Breast: 1
	anti-TNF agent, RIT, RIT or	Ethnicity, Latino NR		calculated using ESR): 14 weeks: 59.4%, P=	Overall: 1
	cytotoxic agents			0.014; 24 weeks: 51.9%, P= 0.110 D3: DAS28 (ESR)	Respiratory events Tuberculosis: NR Pneumonia, n: NR

Study	Inclusion and Exclusion	Characteristics and	Baseline Disease and Treatment		
Characteristics	Pts should not have received ANK DMARDs other than MTX or intravenous, intramuscular, or intraarticular corticosteroids within 4 weeks beforefirst dose of study agent or alefacept or efalizumab within 3 mos beforefirst dose ofstudy agent.	Interventions	Characteristics	remission: 14 weeks: 15.7%, P<0.001; 24 weeks: 20.2%, P= 0.001; DAS28 (ESR) sustained remission: 24 weeks: 10.2%, P= 0.001; EULAR responders (DAS28 calculated using ESR): 14 weeks: 70.8%, P<0.001; 24 weeks: 71.9%, P<0.001 D4: DAS28 (ESR) remission: 14 weeks: 18.0%, P<0.001; 24 weeks: 18.0%, P<0.001; 24 weeks: 18.0%, P<0.001; DAS28 (ESR) remission: 14 weeks: 18.0%, P<0.001; DAS28 (ESR) sustained remission: 24 weeks: 11.9%, P<0.001; EULAR responders (DAS28 calculated using ESR): 14 weeks: 75.3%, P<0.001; 76.4%, P<0.001	Adverse Events, % Upper respiratory infection, n: NR Other infections Urinary tract infection, n: D1: 1 D2: NR D3: NR D4: 2 Overall: 3 Other infections (specify) n: D1: NR D2: Sepsis: 2 D3: Cellulitis: 1 D4: Cellulitis: 1, Sepsis: 2, lower RTI: 1, Overall: 7 Other GI symptoms, n: D1: 0 D2: Colitis: 1, Diarrhoea: D3: 0 D4: 0 Overall: 2
				SF-36 NR	Other
				Radiographic measures NR	Infusion/injection site reactions, n: D1: 4
				Quality of life scales NR	D2: 10 D3: 5
				Others, mean difference/absolute difference ACR90 (14 weeks):	D4: 5 Overall: 24 Infective arthritis, n: D1: 0

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events. %
Study Characteristics	Exclusion Criteria	Characteristics and Interventions	Treatment Characteristics	Health Outcomes D1: 0.8 D2: 0.8 , $P = 1.000$ D3: 2.2 , $P = 0.344$ D4: 0.0 , $P = 0.412$ ACRIO (24 weeks): D1: 0.8 D2: 2.3 , $P = 0.314$ D3: 5.6 , $P = 0.028$ D4: 2.2 , $P = 0.344$ ACR-N (14 weeks): D1: 0.00 (-28-25.50) D2: 10.50 (-11.80-42.60), $P = 0.042$ D3: 28.20 (0.00 -60.00), $P = 0.001$ D4: 25.00 (0.00 -54.50), $P = 0.001$ ACR-N (24 weeks):	Adverse Events, % D2: 1 D3: 0 D4: 0 Overall: 1 Bacterial arthritis, n: D1: 0 D2: 0 D3: 0 D4: 1 Overall: 1 Subcutaneous abscess, n D1: 0 D2: 0 D3: 1 D4: 0 Overall: 1 Skin laceration, n: D1: 0
				D1: 0.00 (-25.00-22.20) D2: 0.00 (-25.40-37.10), P = 0.151 D3: 36.60 (0.00-60.40), P = 0.001 D4: 28.60 (0.00-55.30), P = 0.001	D2: 1 D3: 0 D4: 0 Overall: 1

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
Author, year, study name, if applicable Keystone et al., 2009 and 2010, Go-Forward ^{97,98}	Inclusion Criteria 18 years of age or older Diagnosis of RA for at least 3 mos before	Interventions, dose D1: MTX: dosage NR but stable throughout 24 week study period. Patients with less than	D1: 6.5 (3.1-11.9) D2: 5.9 (2.4-12.2) D3: 4.5 (2.1-9.7) D4: 6.7 (2.4-14.3)	ACR ACR 20: At 14 weeks: D1: 33.1 D2: 44.4%, P = 0.059 D3: 55.1, P = 0.001 D4: 56.2, P = 0.001	Attrition/withdrawal Overall, n: D1: 10 D2: 9 D3: 2 D4: 7 Overall: 28
Country and setting Multinational Source of funding Centocor Research and development Research objective Evaluate efficacy and safety of GOL intx of patients with active RA despite MTX therapy Study design Controlled Trials Overall N 444 Duration of study 24 weeks with open label extension up to 52 weeks	screening Stable MTX dose of 15 mg/week or greater but 25 mg/week or less during 4- week period immediately preceding screening Tolerated 15 mg/ week or greater of MTX for at least 3 mos before screening and have active RA. Patients taking NSAIDs or other analgesics for RA had to be taking stable	20% improvement in SJC and TJC by week 16 began receiving 50mg GOL/4wks for remainder ofstudy Placebo D2: GOL: 100mg every 4 weeks Placebo: Patients with = 20% improvement in SJC and TJC and TJC at week 16 began receiving active MTX forremainder ofstudy D3: MTX: stable dose, NR (looks likely to be 15mg/wk not explicit in methods) GOL: 50mg every 4 weeks. Patients with <20%	Patients with early RA, three years or less, % NR Treatment resistant, % NR Tender Joint Count, median (IQR) D1: 21.0 (14.0-34.0) D2: 22.0 (14.0-32.0) D3: 26.0 (16.0-39.0) D4: 23.0 (15.0-33.0) Swollen Joint Count, median (OQR) D1: 12.0 (8.0-19.0) D2: 11.0 (8.0-17.0) D3: 13.0 (8.0-22.0) D4: 12.0 (8.0-18.0) Corticosteroid use, % D1: 65.4 D2: 67.7 D3: 75.3 D4: 69.7 DMARD use, other than MTX % D1: 70.7	ACR 50: At 14 weeks: D1: 9.8 D2: 20.3, $P = 0.016$ D3: 34.8, $P = 0.001$ D4: 29.2, $P = 0.001$ ACR 70: At 14 weeks: D1: 3.8 D2: 7.5, $P = 0.184$ D3: 13.5, $P = 0.008$ D4: 9.0, $P = 0.104$ DAS D1: DAS28 (ESR) remission: 14 weeks: 1.5%, 24 weeks: 6.0%, EULAR responders (DAS28 calculated using ESR): 14 weeks: 44.4%, 24 weeks: 42.1% D2: DAS28 (ESR) remission: 14 weeks: 43.3%, $P = 0.010$, EULAR responders	Withdrawals due to adverse events, n: D1: 6 D2: 6 D3: 2 D4: 5 Overall: 19 Withdrawals due to lack of efficacy, n: D1: 2 D2: 1 D3: NR D4: NR Overall: 3 Adherent/compliant, n: D1: 123 D2: 125 D3: 87 D4: 82 Overall: 417 D1: 1 lost to follow-up, 1 "other" D2: 1 discontinued oral study agent
Quality rating Good	dose for at least 2 wks before first	with <20% improvement in SJC and TJC at	D1: 70.7 D2: 75.9 D3: 78.7	(DAS28 calculated using ESR): 14 weeks: 59.4%, P= 0.014; D3:	D3: NR

	sion and		Baseline Disease and		
Study Exclu	sion (Characteristics and	Treatment		
Characteristics Criter	ia I	Interventions	Characteristics	Health Outcomes	Adverse Events, %
dos	e of study	week 16 began	D4: 75.3	DAS28 (ESR)	agent
oral cort had bee a st	entstaking icosteroids to have In receiving able dose	receiving 100mg of GOL/4 wks forremainder ofstudy D4: MTX: Stable dose and frequency NR GOL: 100mg/4wks	D1: DAS28 using CRP:	remission: 14 weeks: 15.7%, P<0.001; EULAR responders (DAS28 calculated using ESR): 14 weeks: 70.8%, P<0.001; D4: DAS28 (ESR)	Overall adverse events reported, n: D1: 89 D2: 98 D3: 87 D4: 78 Overall: 352
10 r less for a wks first stud Exclu Criter • Kno hype y to imm n prothe com GOI • Prio any age cyto age • Prio ANM • DM/ othe MTX	ang/day or of of PRED at least 2 before dose of an	Number in group D1: 133 D2: 133 D3: 89 D4: 89 Mean age, years (SD) D1: 52 (42-58) D2: 51 (42-59) D3: 52 (43-57) D4: 50 (45-56) Sex, % female D1: 82 D2: 105 D3: 72 D4: 72 Race, % white NR Race, % black NR Ethnicity, Latino NR	4.860 (4.194-5.480); DAS28 using ESR: 6.111 (5.260-6.574) D2: DAS28 using CRP: 4.803 (4.151-5.558); DAS28 using ESR: 6.013 (5.198-6.800) D3: DAS28 using CRP: 5.100 (4.060-5.651); DAS28 using ESR: 6.105 (5.366-6.940) D4: DAS28 using CRP: 4.902 (4.320-5.521); DAS28 using ESR: 5.905 (5.292-6.805) Required treatment for latent TB (%) D1: 23.3 D2: 19.5 D3: 20.2 D4: 19.1	remission: 14 weeks: 18.0%, P<0.001; EULAR responders (DAS28 calculated using ESR): 14 weeks: 75.3%, P<0.001; SF-36 NR Radiographic measures NR Quality of life scales NR Others, mean difference/absolute difference ACR90 (14 weeks): D1: 0.8 D2: 0.8, P = 1.000 D3: 2.2, P = 0.344 D4: 0.0, P = 0.412 ACR-N (14 weeks): D1: 0.00 (-28-25.50) D2: 10.50 (-11.80-42.60), P = 0.042 D3: 28.20 (0.00-60.00), P = 0.001	Serious adverse events Death, n: D1: NR

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
Characteristics	intramuscular, or intra-	interventions	Characteristics	D4: 25.00 (0.00-54.50), P = 0.001	Upper respiratory infection, n: NR
	articular corticosteroids within 4 weeks before first dose of study agent or alefacept or efalizumab				Other infections Urinary tract infection, n: D1: 1 D2: NR D3: NR D4: 2 Overall: 3
	within 3 mos beforefirst dose of study agent.				Other infections (specify), n: D1: NR D2: Sepsis: 2 D3: Cellulitis: 1 D4: Cellulitis: 1, Sepsis: 2, lower RTI: 1, Overall: 7
					Other GI symptoms, n: D1: 0 D2: Colitis: 1, Diarrhoea: 7 D3: 0 D4: 0 Overall: 2
					Other
					Infusion/injection site reactions, n: D1: 4 D2: 10 D3: 5 D4: 5 Overall: 24
					Infective arthritis, n: D1: 0 D2: 1 D3: 0 D4: 0 Overall: 1

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
					Bacterial arthritis, n: D1: 0 D2: 0 D3: 0 D4: 1 Overall: 1
					Subcutaneous abscess, n: D1: 0 D2: 0 D3: 1 D4: 0 Overall: 1
					Skin laceration, n: D1: 0 D2: 1 D3: 0 D4: 0 Overall: 1
					Adverse events at 52 weeks- N (%) and Events per 100 patient yrs Any adverse event D1:98 (73.7) 546 (486 to 612) D2: 108 (81.2) 514 (471 to 560) D3: 167 (78.8) 459 (425 to 495) D4:122 (85.9) 595 (552 to 641) Serious adverse events D1: 6 (4.5) 15 (6 to 29) D2: 16 (12.0) 28 (19 to 40) D3: 17 (8.0) 14 (9 to 22) D4: 26 (18.3) 34 (24 to 46) Any infection D1:42 (31.6) 132 (104 to 167) D2: 69 (51.9) 133 (112 to

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
					158)
					D3:98 (46.2) 114 (98 to
					133)
					D4:75 (52.8) 156 (135 to
					181)
					Serious infections
					D1:1 (0.8) 2 (0 to 10)
					D2:5 (3.8) 8 (3 to 15)
					D3:4 (1.9) 3 (1 to 8)
					D410 (7.0) 10 (5 to 18)

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
		Interventions Interventions, dose D1: • ADA Patients starting with ADA and ETN did so at registered dose in		ACR NR HAQ, mean (SD) Absolute difference in HAQ from baseline at 3, 6, 9, and 12 mos: At 3 mos, decrease: D1: -0.35 (0.5) D2: -0.33 (0.5) D3: -0.19 (0.5) At 6 mos, decrease: D1: -0.42 (0.5) D2: -0.35 (0.5) D3: -0.23 (0.5) At 9 mos, decrease: D1: -0.4 (0.5) D2: -0.36 (0.6) D3: -0.26 (0.5) At 12 mos, decrease: D1: -0.42 (0.6) D2: -0.35 (0.6)	Overall Overall attrition/withdrawal, n (%): D1: 22 D2: 21 D3: 31 Overall: IFX compared to ADA, P = 0.049 IFX compared to ETN, P = 0.024 Overall: occurrence of adverse events was reason for discontinuation in 48% of patients Overall: 33%reason was a lack of efficacy Adherent/compliant, n: After discontinuation ofinitial anti-TNFa treatment, 42% of ADA
content of this manuscript. Funding from Dutch National Health Insurance Board	(DAS28) > 3.2 and failed on at least 2 DMARDs including MTX (MTX) at an	cases, respectively. • Within 12 mos, 7.1% and 4.8% of ADA and ETN patients had a dose increase.	NR Baseline DAS score D1: 5.3 D2: 5.5 D3: 5.2 Required treatment for	D3: -0.26 (0.5) D1: Missing HAQ values, all groups combined(%): baseline 9.9 • 3 mos 9.2 • 6 mos 12.2	and ETN users switched to another anti-TNFa treatment, and 67% of IFX switched.same anti-TNFa treatment was rechallenged in 8%, 15% and in 2%,
Research objective Evaluate effects of ADA, ETN and IFX on disease activity, functional ability, QOL and		 Median of12- month averaged dose was 50 mg per week for ETN. D3: IFX patients started in 80% of cases 	Iatent TB NR Other population characteristics, %, (CI/SD/P value) Number of previous	 9 mos 15.6 12 mos 16.3. P value for ADA compared to IFX: P = 0.05 for all time points	respectively. • Another option was to start with one ofconventional DMARD therapies, which occurred in 27% ofADA

	Inclusion and		Baseline Disease and		
Study	Exclusion	Characteristics and	Treatment		
Characteristics	Criteria	Interventions	Characteristics	Health Outcomes	Adverse Events, %
medication costs Study design Prospective cohort comparison Overall N N: 707 Between February 2003 and August 2007, 916 patients were included. In total, 707 patients had at least 1-year follow-up and fully accessible data at time of analysis (August 2007). Duration of study One year Quality rating Fair		with an average dose of 3 mg/kg per 8 weeks, in 18% of cases with an average dose of 4 mg/kg per 8 weeks and 2% started with higher dosages. • All patients who started with average dose of 4 mg/kg dose did Number in group D1: 267 D2: 289 D3: 151 Mean age, years (SD) D1: 55.1 D2: 54.6 D3: 57.8 Sex, % female D1: 70.0 D2: 68.9 D3: 70.2 Race, % white NR Race, % black NR Ethnicity, Latino NR	D2: 3 D3: 3 HAQ	 P value for ETN compared to IFX: P = 0.05 only at 3 mos DAS D1: Absolute difference in DAS28 from baseline at 3, 6, 9, and 12 mos (values are means with SD): 3 mos, decrease - 1.6 (1.3) EULAR response 76%*, 6 mos, decrease -1.8 (1.4) EULAR response 78%*, 9 mos, decrease -1.8 (1.4) EULAR response 79%*, 12 mos, SF-36 NR Radiographic measures NR Quality of life scales NR Others Mean score and 95% CI, at each follow up for DAS28, SF-36, and HAQ were presented in graphs, so numbers are NR. Repeated measures analyses (linear mixed model) showed 	they remained on their

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
				significant differences in DAS28 course over 12 mos between IFX and both ADA and ETN patients (<i>P</i> = 0.001) and between ADA and ETN patients (<i>P</i> = 0.031). • Figures for HAQ and EQ-5D show same trend: functionality and QoL was best for ADA patients. However,repeated measures analyses did not show any significant differences.	, , , , , , , , , , , , , , , , , , ,

Study Characteristic s	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
Author, year, study name, if applicable Kim et al., 2007 ¹⁰⁰ Country and setting Korea; multicenter Source of funding Abbott Laboratories Research objective To investigate the efficacy and safety of 40 mg ADA with MTX versus placebo with MTX in Korean RA patients with an insufficient responses to MTX Study design Controlled Trials Overall N 128 Duration of	Inclusion Criteria Treatment resistant ≥18 yrs old Met ACR criteria for diagnosis of active RA ≥6 swollen joints and ≥9 tender joints at both screening and baseline visits Received at least 1 prior DMARD other than MTX but could have had efficacy failures to no more than 4 standard DMARDs other than MTX Been treated with MTX for at least 6 mos Been receiving stable	Comparisons (dosage and frequency) D1: • MTX: dose NR • ADA: 40 mg, every other week D2: • MTX: NR • Placebo Number in group D1: 65 D2: 63 Overall: 128 Mean age (years) D1: 48.5 D2: 49.8 Overall: NR Sex, % female D1: 95.4 D2: 85.7 Overall: 90.6 Race, % white NR Race, % black NR Ethnicity, Latino NR	Mean disease duration, years D1: 6.8 (4.2) D2: 6.9 (4.5) Overall: NR TJC, mean D1: mean (SD): 19.2 (9.2) D2: mean (SD): 20.3 (8.6) Overall: NR SJC, mean D1: mean (SD): 12.2 (5.6) D2: mean (SD): 12.8 (5.8) Overall: NR Corticosteroid use, % NR DMARD use, %: D1: 100 D2: 100 Overall: 100 MTX naïve, %: D1: 0 D2: 0 Overall: 0 Treatment resistant, %: D1: 100 D2: 100 Overall: 100	ACR mean difference/ absolute difference (CI/SD/P Value): ACR 20: D1: 61.5 D2: 36.5 Overall: P<0.01 ACR 50: D1: 43.1 D2: 14.3 Overall: P<0.001 ACR 70: D1: 21.5 D2: 7.9 Overall: P<0.05 HAQ, mean difference/ absolute difference (CI/SD/P Value): Disability Index of the KHAQ, mean (SD) D1: -0.5 (0.55) D2: -0.2 (0.50) Overall: P=0.002 DAS, mean difference/absolute difference (CI/SD/P Value): NR SF-36, mean difference/absolute difference/absolute difference (CI/SD/P Value):	Overall Overall attrition/withdrawal (n): D1: 6 D2: 4 Overall: 10 Withdrawals due to adverse events (n): D1: 4 D2: 4 Overall: 8 Adherent/compliant (n): D1: 59 D2: 59 Overall: 118 Overall adverse events reported (n): D1: 84.6% D2: 82.5% Overall: NR Serious adverse events: Death (n): D1: 1 D2: NR Malignancies: Lymphoma or leukemia (n): D1: 0 D2: 0 Overall: 0 Skin cancer (basal	Quality rating for efficacy/effectiveness? Fair Quality rating for observational studies NR

Study Characteristic s	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
study 24 wks	dosage for at least 4 wks prior to screening		Patients with early RA, three years or less, %:	NR Radiographic measures, mean difference/absolute	cell or squamous cell) (n): D1: 0 D2: 0 Overall: 0	
	Exclusion Criteria • Patients with acute inflammatory joint		Baseline DAS score NR Required treatment for latent TB NR	difference (CI/SD/P Value): NR Quality of life scales, mean	Other cancer (specify) (n): D1: 0 D2: 0 Overall: 0	
	diseases other than RA • Active Listeria or tuberculosis		Other population characteristics, %, (CI/SD/P value):	difference/absolute difference (CI/SD/P Value): Duration of morning stiffness, mean (SD) D1: -116.7 (165.3)	Respiratory events: Pneumonia (n): D1: 2 D2: NR Overall: NR	
	infection • Positive serology for human immuno-			D2: -16.7 (166.5) Overall: NR Others, (please name); mean difference/absolute	Upper respiratory infection (n): D1: 18 D2: 18 Overall: 36	
	deficiency virus antibody, hepatitis B surface antigen, or			difference (CI/SD/P Value): TJC, mean (SD): D1: -9.5 (9.61) D2: -3.4 (11.50) Overall: P=0.002	Other infections: NR GI: NR Other:	
	hepatitis C antibody • Calcified granuloma and/or			SJC mean (SD): D1: -7.9 (6.78) D2: -2.0 (7.17) Overall: <i>P</i> <0.001	Infusion/injection site reactions (n): Injection site pain: D1: 2 D2: 5	
	pleural			CRP, mg/L, mean (SD): D1: -1.4 (3.23) D2: -0.4 (1.94) Overall: <i>P</i> =0.001	Overall: 7 Headache (n): D1: 4	

Study Characteristic s	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
				Physician's Global Assessment of	D2: 3 Overall: 7	
				Disease Activity, mm VAS, mean (SD): D1: -29.2 (27.48) D2: -9.6 (26.47) Overall: P < 0.001 Patient's Global	Vasovagal attack: D1: 1 D2: NR Overall: NR Acute respiratory distress syndrome:	
				Assessment of Disease Activity, mm VAS, mean (SD): D1: -23.7 (26.54) D2: -10.7 (24.85) Overall: P = 0.004	D1: 1 D2: NR Overall: NR Cough: D1: 7 D2: 2	
				Patient's Global Assessment of Pain, mm VAS, mean (SD): D1: -23.7 (22.86) D2: -7.3 (27.50) Overall: P < 0.001	Overall: 9 Rhinorrhea: D1: 6 D2: 1 Overall: 7	
					Fatigue (n): D1: 5 D2: 3	
					Pruritus (n): D1: 4 D2: 1	
					Alanine aminotransferase increased (n): D1: 4 D2: 0	
					Aspartate aminotransferase increased (n):	

Study Characteristic s	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
					D1: 4	
					D2: 1	
					Hypercholesterolemia	
					(n):	
					D1: 4	
					D2: 0	
					RA flare-up (n):	
					D1: 0	
					D2: 4	

Study Characteristic s	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
Author, yr: Kirwan et al., 2004 ¹⁰¹ Country, Setting: Belgium, Sweden, and United Kingdom, multicenter (16) Funding: Astra-Zeneca Research Objective: To compare BUD, a locally acting glucocorticoid with minimal systemic exposure, with conventional glucocorticoid txt and placebo in RA Study Design: RCT Overall N: 143 Study	 Diagnosed according to ACR criteria Functional class I-III Stable doses of NSAIDs (30 ds) and/or DMARDs (90 ds) Exclusion Criteria: Pregnant or lactating Glucocorticoids by any route for at least 30 ds Systemic lupus erythematosus Polymyalgia rheumatica Psoriatic arthropathy Spondylo-arthropathy 	Interventions, dose: D1: BUD (3 mg/d) D2: BUD (9 mg/d) D3: PNL (7.5 mg/d) D4: Placebo N: D1: 37 D2: 36 D3: 39 D4: 31 Mean age, yrs: D1: 54.2 D2: 57.8 D3: 53.4 D4: 54.7 Sex, % female: D1: 70 D2: 77 D3: 62 D4: 77 Race, % white: NR	Mean disease duration, yrs: D1: 13.1 D2: 8.5 D3: 7.0 D4: 7.2 TJC, mean: D1: 14.2 D2: 11.8 D3: 12.3 D4: 12.6 SJC, mean: D1: 12.9 D2: 9.8 D3: 11.6 D4: 11.8 DMARD use, %: D1: 76 D2: 69 D3: 67 D4: 65 Corticosteroid use, % NR MTX naive, %: NR Txt resistant, %: NR Pts with Early RA (≤3 yrs): NR	Functional capacity and health related quality of life are secondary outcomes for this study ACR20, %: D1: 22 D2: 42 D3: 56 D4: 25 D2 vs D3, P = 0.11 TJC: D1: 2.23 (-0.63 to 5.1) D2: 3.65 (0.75 to 6.54) (P < 0.05) D3: 4.83 (2.01 to 7.65) (P < 0.001) SJC: D1: 1.53 (0.92 to 3.98) D2: 3.81 (1.3 to 6.52) (P < 0.01) D3: 3.67 (1.25 to 6.09) (P < 0.01) Pain: D1: 6.6 (-5.8 to 18.9) D2: 11.4 (-1.3 to 24) D3: 22.3 (10 to 34.6) (P < 0.001) DAS, patient: D1: 7.9 (-4.7 to 20.5) D2: 16.4 (3.6 to 29.3) (P < 0.05) D3: 24.5 (12.1 to 37) (P <	Overall: D1: 89 D2: 94 D3: 85 D4: 90 SAEs: D1: 5 D2: 0 D3: 5 D4: 6 Abdominal Pain: D1: 11 D2: 8 D3: 10 D4: 6 Headache: D1: 11 D2: 14 D3: 15 D4: 3 URTI: D1: 19 D2: 11 D3: 15 D4: 3	Overall Attrition Rate, %: 16 ITT Analysis: Yes Quality Rating: Fair

Study Characteristic s	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
Duration: 12 wks	Local or systemic infection Allergy to BUD or other glucocorticoids; txt w/ live viruses (i.e., polio) or live bacteria (i.e., tubercle bacilli) during previous 90 days Undergone resection of stomach or more than 100 cm of small bowel		Baseline DAS, mean: NR HAQ: D1: 1.61 D2: 1.57 D3: 1.51 D4: 1.52	0.001) DAS, physician: D1: 0.25 (-0.12 to 0.62) D2: 0.45* (0.07 to 0.82) (P < 0.05) D3: 0.66 (0.3 to 1.03) (P < 0.001) HAQ: D1: 0.009 (-0.19 to 0.21) D2: 0.107 (-0.31 to 0.09) D3: 0.383 (0.188 to 0.578) (P < 0.001) Difference: D3 vs. D1: 0.393; P < 0.001 D3 vs. D2: 0.276; P < 0.01 SF-36: D1: 2 (-2 to 6) D2: 3.7 (-0.4 to 7.8) D3: 7.4 (3.5 to 11.4) (P < 0.001) SF-36 Mental Subscale D1: 4.8 (-0.8 to 10.4) D2: 6.0 (0.4 to 11.7) (D3 vs D1; P < 0.05) D3: 7.2 (1.7 to 12.8) (D3 vs D2; P < 0.001)		

Study Characteristic s	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
Author, yr: Klareskog, 2004 ⁹² ; van der Heijde, 2005 ¹⁰² , van der Heijde, 2006 ¹⁰³ , van der Heijde, 2006 ¹⁰⁴	 Inclusion Criteria: Age ≥ 18 Diagnosed according to ACR criteria Functional class I-III Less than satisfactory 	Interventions, dose: D1: MTX (20 mg/wk) D2: ETA (25 mg 2x wkly) D3: ETA (25 mg 2x wkly) + MTX (7.5 titrated to 20 mg/wk) N:	Mean disease duration, yrs: D1: 6.8 D2: 6.3 D3: 6.8 TJC, mean: D1: 33.1 D2: 35 D3: 34.2	At 24 weeks AUC of ACR-N, %-yrs: D1: 12.2 D2: 14.7 D3: 18.3 (<i>P</i> < 0.0001) ACR20, %: D1: 75 D2: 76	Overall: D1: 81 (87) D2: 86 (92) D3: 81 (86) Infections: D1: 64 (75) D2: 59 (71) D3: 67 (76)	Overall Attrition Rate, %: 52 wks: 23.5 2 Yrs: 38.4 ITT Analysis: Yes Quality
Country, Setting: Multinational (Europe), multicenter Funding: Wyeth Research	response to at least 1 DMARD other than MTX Duration 6 mos to 20 yrs RA defined as > 10 swollen and > 12 painful joints and at least one of:	D1: 228 (152) D2: 223 (163) D3: 231 (188) Overall (at 2yrs): 503 Mean age, yrs: D1: 53 D2: 53.2 D3: 52.5	SJC, mean: D1: 22.6 D2: 23 D3: 22.1 DMARD use, %: NR Corticosteroid use, %	D3: 85 (<i>P</i> = 0.0151) ACR50, %: D1: 43 D2: 48 D3: 69 (<i>P</i> < 0.0001) ACR70, %: D1: 19 D2: 24 D3: 43 (<i>P</i> < 0.0001)	Serious Infections: D1: 4 (7) D2: 4 (6) D3: 4 (6) Infusion or injection reaction: D1: 2 (2) D2: 21 (21) D3: 10 (11)	Rating: Fair
Research Objective: To compare safety and efficacy of combination of ETA and MTX with	ESR > 28 mm/h, CRP > 20 mg/L, or morning stiffness for > 45 minutes • Folic acid 5 mg twice per wk • NSAIDs	Overall (at 2yrs): 52.1 Sex, % female: D1: 79 D2: 77 D3: 74 Overall (at 2yrs): 76 Race, % white:	D1: 64 D2: 57 D3: 62 MTX naive, %: D1: 58 D2: 58 D3: 56 Txt resistant, %:	At 52 weeks DAS < 1.6 remission, %: D1: 13 D2: 16 D3: 35 (D3 vs. D2: P < 0.0001; D2 vs. D1: P = 0.5031)	Abdominal Pain: D1: 18 D2: 12 D3: 18 Hypertension: D1: 5 D2: 13 D3: 9	
monotherapies in pts with RA who had failed previous DMARD txt Study Design: RCT	Exclusion Criteria: TNF antagonist, any immuno- suppressive drugs w/in 6 mos Any	D1: 98 D2: 99 D3: 98 Overall (at 2yrs): 99	Overall: 100 Pts with Early RA (≤3 yrs): NR Baseline DAS, mean:	HAQ, decline: D1: 0.65 D2: 0.7 D3: 1.0 (<i>P</i> < 0.05) D3 therapy significantly more likely to attain HAQ DI similar to population	Headache: D1: 14 D2: 15 D3: 15 Nausea: D1: 32 (39) D2: 10 (13)	

Study Characteristic s	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
Overall N: 686 (2 yr	investigational drug or biologic		D1: 5.5 D2: 5.7 D3: 5.5	norms (< 0.5) than monotherapy	D3: 24 (29)	
results: 503) Study	agent w/in 3 mos DMARD or css injection w/in 4	with	Sharp: D1: 26.8 D2: 21.8 D3: 21.8 JSN: D1: 13.3	Radiograhic outcomes Total Sharp Score		
Duration: 52 wks (2 yrs, 100 wks)	mos • Previous txt with			change: D1: 0.28 D2: 0.52		
roo waa	MTX if pt experienced clinically toxic			D3: -0.54; D3 vs D2; $P = 0.0006$ D2 vs D1; $P = 0.047$		
	side effects or had no response		D3: 10.3	Erosion score change: D1: 1.68 D2: 0.21 D3: -0.30; D3 vs D2; P = 0.0001 D2 vs D1; P = 0.008		
				JSN score change: D2: 0.32 D3: -0.23; <i>P</i> = 0.0007		
				At 2 years		
				Total Sharp score change: D1: 1.12 D2: 1.10 D3: -0.56; P = 0.05 D3 vs D2; P = 0.05 D2 vs D1; P = NR		
				Erosion score change D2: 0.36 D3: -0.76 P < 0.05		
				JSN score change		

Study Characteristic s	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
				D2: 0.74 D3: 0.20; <i>P</i> = NS, NR		

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
Author, yr: Kremer, 2002 ¹⁰⁵ Country, Setting: US and Canada, multicenter (20 outpatient practice centers) Funding: Aventis Pharmaceutical s Research Objective: To evaluate efficacy and safety of LEF vs. Placebo when added to ongoing stable dose MTX therapy in pts with persistently active RA Study Design: RCT Overall N: 263 Study Duration:	Inclusion Criteria: Age: 18 or 75 Diagnosed with RA according to ACR criteria: Active:>9 tender joints, >6 sollen joints, >45 mornign stiffness Previous use of DMARDs: Failed in 11 pts Other (Please include concomitant drugs that are allowed)? MTX (15-20mg/wk or 10-15mg/wk if max tolerated dose) for at least 6 mos, AND stable dosing for at least 8 wks Exclusion Criteria: Pregnant or lactating Prior txt with: prohibited DMARDs in past 30 ds Impaired renal or hepatic system: Hep B or C, 3 or more elevations of AST or ALT,	Interventions, dose: D1: MTX + LEF D2: MTX + Placebo Methotrexate: 15 -20 mg/wk or 10 -15 mg/wk if toleration problems Leflunomide: 100 mg 2 ds then 10mg/d or 10mg/every other d if adverse effects Placebo: Folate 1 mg/d for ALL N: D1: 130 D2: 133 Mean age, yrs: D1: 55.6 D2: 56.6 Sex, % female: D1: 76.2 D2: 80.5 Race, % white: D1: 90.8 D2: 87.2	Mean disease duration, yrs: D1: 10.5 D2: 12.7 TJC, mean: D1: 26.9 D2: 26.4 SJC, mean: D1: 17.3 D2: 18.7 DMARD use, %: NR Corticosteroid use, %: NR MTX naive, %: NR Txt resistant %: NR Patients with Early RA (≤3 yrs): NR Baseline DAS, mean: NR HAQDI: D1: 1.6 D2: 1.5	ACR20: • LEF 46.2%; Placebo 19.5% <i>P</i> < 0.001 HAQ: • LEF -0.42 • Placebo -0.09 <i>P</i> < 0.001 • SF-36: LEf + 6.8 Placebo + 0.3 <i>P</i> < 0.001	Overall: D1: 89.2 D2: 89.5 Infections: D1: 40.8 D2: 51.9 Dizziness: D1: 7.7 D2: 5.3 Headache: D1: 10 D2: 8.3 Nausea: D1: 16.2 D2: 11.3 URTI: D1: 22.3 D2: 24.1 Adherence: Overall, 98% adherent Mean adherence Adherence: Rates 80 120% Lef 87.7% Placebo 90.2%	Overall Attrition Rate, %: Discontinuatio n Rates: LEF 23.1 Placebo 24.8% ITT Analysis: Yes Quality Rating: Fair

24 wks	elevated SrCR	
	Psoriatic Arthritis	
	or other acute	
	inflammatory joint	
	disease not RA	

Study Characteristic s	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
Author, year, study name, if applicable Kremer et al., 2010 ¹⁰⁶ LITHE Study; Venkiteshwara n et al., 2009 CDER Statistical Review Application Number 125276 Country and setting Multinational and multicenter Source of funding Roche Research objective Efficacy and safety of TCZ plus MTX vs. MTX alone in preventing structural joint damage and improving physical function and disease activity in patients with	Inclusion Criteria Treatment resistant Inadequate response to MTX RA diagnosis according to ACR criteria Moderate to severe in the investigator's opinion and lasted for ≥ 6 mos 1 adiographically confirmed joint erosion despite having received MTX for at least 12 wks before baseline (stable at 10-25 mg/wk for ≥ 8 wks) Exclusion Criteria Serious concomitant	(Rescue at 16 wks) D4: D5: Number in group D1: 398 D2: 399 D3: 393 Mean age (years) D1: 53.4 D2: 51.4 D3: 51.3 Sex, % female D1: 82 D2: 84 D3: 83 Race, % white D1: NR D2: NR	Mean disease duration, years D1: 9.3 (0.6-48.8) D2: 9.4 (0.5-43.2) D3: 9.0 (0.5-44.3) TJC, mean D1: 29.3 D2: 27.9 D3: 27.9 SJC, mean D1: 17.3 D2: 17.0 D3: 16.6 Corticosteroid use, % D1: 62 D2: 69 D3: 70 DMARD use, %: D1: Past use 75.4 D2: 784 D3: 71.2 MTX naïve, %: D1: 0 D2: 0 D3: 0 Treatment resistant, %: D1: 100 D2: 100 D3: 100 Patients with early RA, three years or	ACR mean difference/ absolute difference (CI/SD/P Value): ACR 20: Week 24 D1: 56% D2: 51% D3: 27% Week 52 NR ACR 50: Week 24 D1: 32% D2: 25% D3: 10% Week 52 NR ACR 70: Week 24 D1: 13% D2: 11% D3: 2% Week 52 NR HAQ, mean difference/ absolute difference (CI/SD/P Value): AUC HAQ-DI change from baseline to week 52 (LOCF) D1: -144.1 units, P<0.0001 vs.	Overall Overall attrition/withdrawal (n): NR Overall: 167 Withdrawals due to adverse events (n): D1: 33 (8%) D2: 28 (7%) D3: 11 (3%) Withdrawals due to lack of efficacy (n): D1: 2 D2: 4 D3: 12 Overall adverse events reported (n): Per 100 PY D1: 325.4 D2: 324.0 D3: 279.6 Serious adverse events: Death (n): D1: 4 D2: 0 D3: 2 Malignancies: Skin cancer (basal cell or squamous cell) (n): NR Overall: 5	Quality rating for efficacy/effectiveness? Fair Quality rating for observational studies NR

Study Characteristic s	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
moderate to severe RA and inadequate responses to MTX. Study design RCT Overall N 1196 Duration of study One year RCT (with 16 week escape) then open label	diseases Significant systemic involvement of RA Functional class IV RA Other inflammatory joint diseases Current/ recurrent infections Abnormal ALT or AST (>1.5X ULN), total bilirubin (>ULN), hemoglobin (<8.5 g/dL), or triglycerid		less, %: NR Baseline DAS score D1: 6.6 D2: 6.5 D3: 6.5 Required treatment for latent TB NR Other population characteristics, %, (CI/SD/P value): NR	placebo D2: -128.4 units,	nonmelanoma skin cancers and 1 unclassified skin cancer Other cancer (specify) (n): D1: 1 (uterine) D2: 5 (lung, cervical, breast, 2 prostate) D3: 1 (breast) Respiratory events: Pneumonia (n): Pnuemonia/bronchitis, n (%) D1: 2 (0.5) D2: 3 (0.8) D3: 2 (0.5) Other infections: Serious infections per 100 PY D1: 4.0 D2: 3.7 D3: 2.3 GI: NR Other: Infusion/injection site reactions (n): D1/D2: 6 (4 were serious anaphylactic reaction/shock events) D3: NR	

Study Characteristic s	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
				NR		
				Radiographic measures, mean difference/absolute difference (CI/SD/P Value): Reduction in structural damage at 52 wks (extrapolated) D1: 74%, P<0.0001 compared with placebo D2: 70%, P<0.0001 compared with placebo		
				Quality of life scales, mean difference/absolute difference (CI/SD/P Value): NR		
				Others, (please name); mean difference/absolute difference (CI/SD/P Value): Change in total Genant modified Sharp score ≤0 from baseline to week 52 D1: 84% D2: 81% D3: 67% P≤0.0001, linear extrapolation,		

Study	Inclusion and	Characteristics	Baseline Disease			
Characteristic	Exclusion	and	and Treatment			Analysis and Quality
s	Criteria	Interventions	Characteristics	Health Outcomes	Adverse Events, %	Rating
				exploratory analysis		

Study Characteristic s	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
Author, yr: Kristensen et al., 2006 ¹⁰⁷	Inclusion Criteria: • Unsuccessful txt with 2 DMARDS including MTX	Interventions, dose: D1: ETA (25 mg s.c. twice wkly)	Mean disease duration, yrs: D1: 14.7 D2: 12.7	At 3 months D1: 63 D2: 45 (P < 0.001)	NR	Overall Attrition Rate, %: NR
Country, Setting: Sweden, multicenter	 Pts diagnosed with RA according to clinical judgment of treating physician Treated at 8 centers in Southern Sweden during March 1999 through January 2004 Meds allowed, NR Exclusion Criteria: 	with RA D2: INF (≥3 mg/kg nical at 0, 2, 6, and 12 wks and then every 8 wks)	TJC, mean: NR	At 6 months D1: 61 D2: 47 (P = NS)		ITT Analysis: N/A
Funding:			SJC, mean: NR	At 12 months		Quality
Osterlund and Kock Founda- tions, 80-yr		D1: 309 D2: 640	DMARD use, %: NR	LUNDEX values (index of drug efficacy in clinical practice): D1: ~55% (~ 4 0% at 3 yrs) D2: ~45% (~ 30% at 3 yrs) ACR20, %: D1: 69 D2: 53 (P = 0.001)		Rating: Fair
Fund of King Gustav V, and Reumat-		Meds allowed, NR D1: 55.1 Exclusion Criteria: D2: 56.2	Corticosteroid use, % NR			
ikerfor-bundet Research	therapy	Prior txt with biologic herapy Sex, % female: D1: 82 D2: 75 Race, % white:	MTX naive, %: NR			
Objective: LUNDEX index			Txt resistant, %: Overall: 100			
to compare long-term		NR	Pts with Early RA (≤3 yrs): NR At 2 ACR D1:	At 24 months		
efficacy and tolerability of				ACR20, %: D1: 65		
biologic therapies in			Baseline DAS, mean:	D2: 56 (<i>P</i> = NS) At 36 months		
RA pts treated in clinical practice		D1: 5.9 D2: 5.6 MTX use, %: D1: 31	ACR20, %: D1: 63			
Study Design: Prospective			D1: 31	D2: 61 (P = NS)		
cohort study			D2: 73 HAQ:	ACR50, %: D1: 39		
Overall N: 949				D2: $39 (P = NS)$		
			D2: 1.4	ACR 70, %:		

Study Characteristic s	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
Study Duration:				D1: 16 D2: 18 (<i>P</i> = NS)		
Varied (results reported for 3 yrs)				EULAR (moderate), %: D1: 46 D2: 29 (P = NS)		
				EULAR (good), %: D1: 36 D2: 45 (<i>P</i> = NS)		
				Intermediate Outcome Measures: INF had significantly lower adherence compared to ETA (P < 0.001)		

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
	Inclusion Criteria Inclusion Criteria Diagnonsis of RA according to clinical judgment of treating physician (98% fullfilled ACR classification) Biologic naïve, no formal level of disease activity Pts should have received at least 2 DMARDs, including MTX prior to inclusion without		Treatment Characteristics Mean disease duration, mos D1: 185.3 (121.4) D2: 192.9 (132.4) D3: 132.8 (107.3) D4: 133.5 (113.8) D5: 180.1 (115.1) D6: 165.4 (118.5) Patients with early RA, three years or less, % NR Treatment resistant, % Inadequate response to previous DMARD including MTX (%) D1: 100 D2: 100 D3: 100 D4: 100 D5: 100	ACR mean difference/ absolute difference (CI/SD/P Value) ACR 20: NR ACR 50: NR ACR 70: NR HAQ, mean difference/ absolute difference NR DAS, mean difference/absolute difference/nR SF-36, mean difference/absolute difference/nR Radiographic measures, mean difference/absolute difference/absolute	Adverse Events, % Attrition/withdrawal Adherent/compliant, %: At 1 year: D1: 74 D2: 47 D3: 89 D4: 69 D5: 85 D6: Unadjusted At 4 years: D1: 53 D2: 18 D3: 75 D4: 38 D5: 71 D6:NR At 5 years D1: NR D2: NR D3: 65 D4: 36 D5: NR
TNF-blocking treatment course and to identify potential predictors for tx termination andimpact of concomitant MTX	satisfactory response Exclusion Criteria • Having received biologic	2x per week D4: MTX: 14.3 mg/wk IFX: 3 mg/kg at 0, 2, and 6 weeks and then every 8th week	NR SJC, mean NR Corticosteroid use, % NR	NR Quality of life scales, mean difference/absolute difference NR	D5: NR D6: NR For treatment failure withdrawal, IFX had sig more withdrawals than ETN only for subarm of patients receiving MTX
on other DMARDs Study design Observational Overall N 1,161	therapy prior to inclusion in study.	depending on primary or secondary failure IFX could be increased in increments of 100	DMARD use, % D1: 0 D2: 0 D3: 100 D4: 100 D5: 100	Others, (please name) mean difference/absolute difference (CI/SD/P Value) There were no differences	(P = 0.026) and Monotherapy (P = 0.002) Patients receiving concomitant MTX compared to monotherapy

	Inclusion and		Baseline Disease and		
Study	Exclusion	Characteristics and	Treatment		
Characteristics	Criteria	Interventions	Characteristics	Health Outcomes	Adverse Events, %
Duration of study March 1999 to		mg to max of 500 mg administered	D6: 100 MTX naïve, %	in DAS28 at treatment termination between	had fewer dropouts due to AE (<i>P</i> < 0.001)
December 2004 clinical data collected at 0, 3, 6, and 12 mos and subsequently every 3 to 6 mos.		at 4 to 8 week intervals D5: LEF: NR SSZ: NR Hydroxychlorquin e: NR Azathioprine	D1: 0 D2: 0 D3: 0 D4: 0 D5: 0 D6: 0	patients terminating because of failure in IFX D(DAS28= 5.1 95% CI, 4.9-5.4) compared with ETN D (DAS28= 5.1 95% CI, 4.8-5.4)	Adjusted HR for terminating treatment: IFX V ETN: 2.92 (95% CI, 2.32-3.69) Monotherapy V MTX: 1.82 (95% CI, 1.45-2.29) Other DMARDs V MTX:
Quality rating Fair		ETN: 25 mg subcutaneously 2x per week D6: LEF: NR SSZ: NR	Baseline DAS score (SD) D1: 5.9 (1.1) D2: 5.7 (1.2) D3: 5.5 (1.0) D4: 5.5 (1.2)		1.45 (9% CI 1.12-1.87) Monotherapy V other DMARDS: 1.22 (95% CI, 1.22 (95% CI, 0.94-1.61)
		Hydroxychlorquin e: NR	D5: 5.8 (1.2) D6: 5.8 (1.1)		Adjusted HR for terminating treatment (all
		Azathioprine: NR IFX: 3 mg/kg at 0, 2, and 6 weeks and then every	Required treatment for latent TB NR		reasons, time-dependent cox regression analysis): IFX V ETN: 2.83 (95% CI, 2.27-3.54)
		8th week depending on primary or secondary failure	Other population characteristics, %, (SD) HAQ: D1: 1.60 (0.65)		Monotherapy V MTX: 1.48 (95% CI, 1.19-1.85) Other DMARDs V MTX: 1.33 (95% CI, 1.08-1.55)
		Number in group D1: 193 D2: 104	D2: 1.69 (0.58) D3: 1.30 (0.61) D4: 1.34 (0.62)		Monotherapy V other DMARD: 1.10 (95%CI 0.86-1.40)
		D3: 179 D4: 501 D5: 68	D5: 1.61 (0.58) D6: 1.57 (0.58) VAS global (mm):		Adjusted HR for terminating treatment (AE):
		D6: 116	D1:): 66 (21) D2: 67 (22)		(AE). Monotherapy V MTX: 2.14 (95% CI, 1.61-2.84)
		Mean age, years (SD) D1: 57.7 D2: 61.0 D3: 53.4	D3: 60 (22) D4: 60 (22) D5: 71 (17) D6: 70 (18)		Other DMARD V MTX: 1.75 (95% CI, 1.28-2.04) Monotherapy V other DMARD: 1.23 (95% CI,

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
		D4: 55.0 D5: 54.0 D6: 57.4	VAS pain (mm): D1: 65 (22) D2: 64 (24)		0.88-1.71) Adjusted HR for terminating treatment
		Sex, % female D1: 84 D2: 78 D3: 78 D4: 74	D3: 60 (22) D4: 60 (23) D5: 66 (19) D6: 70 (17)		(Treatment Failure): Monotherapy V MTX: 1. (95% CI, 0.86-1.99) Other DMARD V MTX: 1.07 (95% CI, 0.66-1.73
		D5: 84 D6: 75 Race, % white	EVAL global (mm): D1: 60 (24) D2: 58 (23) D3: 56 (24)		Monotherapy V other DMARD: 1.22 (95% CI, 0.72-2.06)
		NR Race, % black NR	D4: 57 (23) D5: 56 (21) D6: 57 (22)		
		Ethnicity, Latino NR			

Study Characteristics, Quality Rating	Study Information	Study Characteristics	Results	Adverse Events
Author, Year: Kristensen et al., 2007 ¹⁰⁹ Country and setting: NR Funding: The Oak	Study design: Systematic Review Number of Patients: 1,126 Studies Included: N = 3	Characteristics of Included Studies: Double-blind RCTs with a minimum of 2 arms comparing ADA, ETN, or INF and concomitant use of MTX compared to MTX alone; explicit data on the ACR50 response after at least 12 months of follow-up was collected in all included studies.	Study Results: NNT (control event-adjusted; among randomized) INF 3mg/8 wks: 8 (4-66) INF 3mg/4 wks: 4 (3-11) ETN 2 x 25 mg/wk: 4 (3-6) ADA 40 mg/2 wks: 4 (3-6) NNT (unadjusted; among	Adverse Events: NR
Foundation, Osterlund and Kock Foundations, Reumatikerforbundet, and the King Gustav V 80-year fund.		Characteristics of Included Populations RA patients with an average disease duration of at least 5 years	randomized) INF 3mg/8 wks: 8 (5-38) INF 3mg/4 wks: 4 (3-7) ETN 2 x 25 mg/wk: 4 (3-6) ADA 40 mg/2 wks: 4 (3-5)	
Aims of Review: To compare NNTs based on the 3 different types of NNT calculations for ADA, ETN, and INF combined with MTX, from the published double-blind, 12-month RCTs in established RA.		Characteristics of Interventions: 1 INF trial (doses: 3 mg/8 wks, 3 mg/4 wks, or placebo) 1 ETN trial (doses: 2 x 25 mg/wk or placebo) 1 ADA trial (doses: 40 mg/2 wks or placebo)	NNT (unadjusted; 1-year completers) INF 3mg/8 wks: 8 (4-35) INF 3mg/4 wks: 4 (3-9) ETN 2 x 25 mg/wk: 5 (4-9) ADA 40 mg/2 wks: 3 (2-4)	
Quality Rating: Fair				

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
2006 ¹⁰⁷ Country, Setting: Sweden, multicenter Funding: Osterlund and Kock Founda-		Interventions, dose: D1: ETA (25 mg s.c. twice wkly) D2: INF (≥3 mg/kg at 0, 2, 6, and 12 wks and then every 8 wks) N: D1: 309 D2: 640 Mean age, yrs: D1: 55.1 D2: 56.2 Sex, % female: D1: 82 D2: 75 Race, % white: NR	Mean disease duration, yrs: D1: 14.7 D2: 12.7 TJC, mean: NR SJC, mean: NR DMARD use, %: NR Corticosteroid use, %: NR MTX naive, %: NR Txt resistant, %: Overall: 100 Pts with Early RA (≤3 yrs): NR Baseline DAS, mean: D1: 5.9 D2: 5.6 MTX use, %: D1: 31 D2: 73 HAQ: D1: 1.6 D2: 1.4	At 3 months D1: 63 D2: 45 (P < 0.001) At 6 months D1: 61 D2: 47 (P = NS) At 12 months LUNDEX values (index of drug efficacy in clinical practice): D1: ~55% (~4 0% at 3 yrs) D2: ~45% (~30% at 3 yrs) ACR20, %: D1: 69 D2: 53 (P = 0.001) At 24 months ACR20, %: D1: 65 D2: 56 (P = NS) At 36 months ACR20, %: D1: 63 D2: 61 (P = NS) ACR50, %: D1: 39 D2: 39 (P = NS) ACR 70, %: D1: 16 D2: 18 (P = NS) EULAR (moderate), %: D1: 46 D2: 29 (P = NS)	NR	Overall Attrition Rate, %: NR ITT Analysis: N/A Quality Rating: Fair

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
				EULAR (good), %: D1: 36 D2: 45 (<i>P</i> = NS)		
				Intermediate Outcome Measures: INF had significantly lower adherence compared to ETA (P < 0.001)		

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
Author, year, study name, if applicable Lacaille, 2008 ¹¹⁰	Inclusion Criteria RA diagnosis At least 2	D1: MTX: dosage NR D2: LEF: dosage NR	Mean disease duration, years (SD) D1: NR	ACR NA HAQ,	Overall Overall attrition/withdrawal, n: NA
Country and setting Province of BC, Canada,	physician visits more than 2 months apart with an RA ICD-	D3: DMARD and corticosteroid (CS): dosage NR D4: DMARD alone	D2: NR D3: NR D4: NR D5: NR	NA DAS NA	Overall adverse events reported, n:
administrative data Source of funding	9 RA diagnostic code	D5: Corticosteroid alone: 10.4 mg PRED other CS NR	Overall: 5 years or less: 36%; more than 5 years: 17%	SF-36 NA	Serious adverse events NR
Bristol-Myers Squibb, Canadian Arthritis Network,	Exclusion Criteria • At least 2 visits	Number in group D1: NR	Patients with early RA, three years or less, % NR	Radiographic measures NA	Malignancies NR
Arthritis Society of Canda	subsequent to second RA visit	D2: NR D3: NR	Treatment resistant, %	Quality of life scales	Respiratory events NR
Research objective Determine effect of	with diagnoses of other	D4: NR D5: NR	Tender Joint Count, mean	Others, (please name);	Other infections
nonbiologic DMARDs on infection risk in RA	inflammatory arthritides (systemic lupus	Overall: 27,710 Mean age (years) D1: NR	(SD) NR Swollen Joint Count, mean	mean difference/absolute difference (CI/SD/P Value)	Unadjusted rate of infection per person yr of follow-up, n: D1: 1.28 (95% CI 1.25-1.32)
Study design Retrospective longitudinal cohort study	erythematosus, other connective tissue diseases,	D2: NR D3: NR D4: NR D5: NR	(SD) NR Corticosteroid use, %		D2: 1.67 (95% CI 1.41-1.97) D3: 1.12 (95% CI 1.08-1.16) P = 0.0001; Serious infections: 1.63 (95% CI
Overall N 27,710	PsA, ankylosing spondylitis, and other	Overall: 57 ±17 Sex, % female	D1: NR D2: NR D3: NR		1.5-1.77) <i>P</i> = 0.0001 D4: 0.9 (95% CI 0.88-0.93) <i>P</i> = 0.0001; Serious infections: 0.92 (95% CI
Duration of study 7 years (162,720 person	spondylarthritides) Those with a	D1: NR D2: NR D3: NR D4: NR	D4: NR D5: NR Overall: 44		0.85-1.0) <i>P</i> = 0.0502 D5: 1.15 (95% CI 1.11-1.19) <i>P</i> = 0.0001; Serious
years of follow-up)	diagnosis of RA not confirmed by a	D5: NR Overall: 67	DMARD use, % D1: NR		infections: 1.9 (95% CI 1.75-2.05) <i>P</i> = 0.0001
Quality rating Fair: analysis did not adjust for all	rheumatologist	Race, % white	D2: NR D3: NR D4: NR		Overall: NR GI
confounders, such as baseline disease activity or severity		Race, % black NR	D5: NR Overall: 45		NR Other
(however it did adjust for RA duration); Use of administrative		Ethnicity, Latino NR	MTX naïve, % NR		NR

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
billing data.			Baseline DAS score, mean (SD) NR		
			Required treatment for latent TB NR		
			Other population characteristics, %, NR		

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
Author, yr : Langer, 2003 ¹¹¹	Inclusion Criteria:	Interventions: D1: AKA, all pts	Pts responded well to AKA therapy; 67.5%	See adverse	Overall: D1: 41.2	Overall Attrition Rate, %:
Country, Setting: Germany, multiple sites,	 Age: adult Patients who fell within approved indication for 	ients who blocker naive moderate (46.4) within D3: AKA, TNF- broved blocker pretreated for Anakinra moderate (46.4) EULAR responsion of them because the provided for the provid	blocker naive moderate (46.5%) Serious AES:	ocker naive moderate (46.5%)	Serious AEs: D1: 4.2	NR ITT Analysis:
daily clinical practice Funding:			6 mos. of therapyDAS decreased by		Infections: D1: 6.6	NA Quality Rating:
Amgen Research Objective: To assess the response	anakinraPts with RA who had been ineffectively	N: D1: 166 D2: 105	44% for all ptsTender joint count decreased by 53%, swollen joint count by		Serious Infections: D1: 1.5	Fair
rate, time to response, efficacy and safety of anakinra during 52 wks of therapy after launch in daily clinical practice in	treated with at least 2 DMARDs including MTX	D3: 61 Mean age (yrs): D1: 53.7 D2: 54.7	49%, pain by 31%, and global health by 28%Response to AKA was rapid, within 1 mo;		Infusion or injection reaction: D1: 20.7	
Germany and to gain knowledge of the routine	Exclusion Criteria:	D3: 51.9	shown in figuresData suggest AKA is effective in pts who		Abdominal Pain: NR	
application of anakinra in RA pts under special conditions (RA pts who failed TNF-blocking	NR	Sex, % female: D1: 78.9 D2: 78.1	have failed anti-TNF therapy with comparable results to anti-TNF naive pts • 69.4% of TNF-blocker pretreated pts had a good or moderate EULAR response at 6	have failed anti-TNF therapy with comparable results to	Cardiovascular Events: NR	
drugs)		D3: 80.3			Dizziness: NR	
Study Design: Case series; postmarketing		Race, % white: NR			Headache:	
surveillance		Mean disease duration, yrs:	mos. compared to		D1: 2	
Overall N: 454	D1: 12.3 D2: 12.0 D3: 12.8 TJC, mean: D1: 12.8 D2: 12.4	D1: 1	D1: 12.3 naive pts		Hepatotoxicity: NR	
Study Duration: 52 wks		47% respectively	decreased by 39% and	Malignancies: NR		
		 Pain decreased by 35% and 29% respectively 		Nausea: NR		
		D3: 13.4 SJC, mean:	 Tender joint count by 49% vs. 55% 		URTI: NR	
		D1: 10.5 D2: 10.4	Swollen joint count 44% vs. 52%		•	

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
		D3: 10.8	Global health by 33% vs.			
		DMARD use, %: D1: on MTX: 66.3 D2: 72.4 D3: 55.7	26%			
		Corticosteroid use, %: D1: 84.9 D2: 81.9 D3: 90.1				
		MTX naive, %: NR				
		Treatment resistant %: NR				
		Patients with Early RA (≤3 yrs): NR				
		Baseline DAS, mean: D1: 5.8 D2: 5.6 D3: 6.1				
		D1: morning stiffness (minutes) 112.5 D2: 104.1 D3: 126.6				
		D1: # of previous DMARDs: 3.6 D2: 3.0 D3: 4.4				

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
Author, yr: Lebwohl, 2005 ¹¹² Country, Setting: US, clinical trial participants receiving ETA from private and institutional practices Funding: Amgen Inc. Research Objective: Incidence of cutaneous SCC in pts with rheumatoid arthritis receiving ETA for up to 5 yrs Study Design: Postmarketing database review Overall N: 1,442 (4257 PY) Study Duration: Mean 3.7 yrs	 Participant in 1 of various studies* of ETA in pts with rheumatoid arthritis Pts had active RA; and, received 10 to 50 mg ETA subcutaneously twice weekly for majority of time they received study drug 	D1: 1442 Mean age, yrs: D1: 49.9 Sex, % female: D1: 76.5 Race, % white:	Mean disease duration, yrs: D1: 7.1 TJC, mean: NR SJC, mean: NR DMARD use, %: NR Corticosteroid use, %: NR MTX naive, %: NR Txt resistant %: NR Pts with Early RA (≤3 yrs): NR Baseline DAS, mean: NR	Health Outcome Measures: Total # of cases of SCC reported from postmarketing database population: 4 cases Age and sex-matched expected incident cases based on: From Arizona general population-based incidence study: 13.1 cases From Minnesota general population-based incidence study: 5.9 cases Number of cases of SCC per PY of exposure to ETA In clinical trial population: 0.9/1000 PY From post-marketing surveillance data: .01/1000 PY Summary Statement: The incidence of SCC among pts taking ETA is likely no different from that of the general population.	NR	Overall Attrition Rate, %: NA ITT Analysis: NA Quality Rating: Fair:

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
Author, yr: Lee, 2002 ¹¹³ Country, Setting: US, clinics Funding: NR Research Objective: To identify post- licensure cases of opportunistic histoplasmosis in pts treated with INF and ETA Study Design: Database analysis; AERS Overall N: 10 cases (from FDA passive surveillance database for monitoring postlicensure AEs) Study Duration: varied	Any report of histoplasmosis in a patient receiving ETA or INF had been received by AERS by July 2001 Exclusion	Interventions, dose: D1: ETA D2: INF D3: Overall ETA: varied INF: varied N: D1: 9 D2: 1 D3: 10 Mean age, yrs: D1: 11-78 (range) D3: median: 43.5 Sex, % female: D1: 4/9 (44.4%) D2: 0/1 (0%) D3: 40 Race, % white: NR	Mean disease duration, yrs: NR TJC, mean: NR SJC, mean: NR DMARD use, %: NR Corticosteroid use, %: NR MTX naive, %: NR Txt resistant %: NR Pts with Early RA (≤3 yrs): NR Baseline DAS, mean: NR Concomitant immunosuppressive : D1: 100 D2: 100	Cases of histoplasmosis reported to the AERS by July 2001 • 9 cases among pts receiving INF • 1 case among pts receiving ETA Through August 2001, number of pts treated • With INF: ~150,000 • With ETA: ~96,500 Histoplasmosis case rates per 100,000 pts receiving drug • INF: ~6/100,000 • ETA: ~1/100,000 Deaths due to histoplasmosis • INF: 1/10 • ETA 0/1 Summary: More cases of histoplasmosis were reported to AERS by July 2001 among pts receiving INF than those receiving ETA. When accounting for actual number of pts taking each of drug, histoplasmosis case rate was ~6 times higher among pts receiving INF than among those receiving ETA	NR	Overall Attrition Rate, %: NA ITT Analysis: NA Quality Rating: Fair

Study Characteristics, Quality Rating	Study Information	Study Characteristics	Results	Adverse Events
Author, Year: Lee et al., 2007 ¹¹⁴ Country and setting: NR Funding: NR Aims of Review: To examine whether combination therapy with the TNF blockers and MTX is effective compared to MTX mono-therapy and if ADA, ETN, and INF have the same effect in patients suffering from active RA Quality Rating: fair	Study design: Systematic Review and Meta- analysis Number of Patients: 1, 040 Studies Included: N = 3	Characteristics of Included Studies: A study was included in the analysis if: (1) it was published before February 2006; (2) it was original data; (3) it was a double blind, RCT that completed 50- 55 weeks of trials and (4) it compared TNF inhibitors plus MTX with MTX alone in patients with a Characteristics of Included Populations Patients with active RA despite treatment with DMARDs Characteristics of Interventions: 1 ETN trial: 25 mg twice weekly 1 INF trial: 3 mg/kg intravenously every 8 wks 1 ADA trial: 40 mg subcutaneously every 2 wks	Meta-analysis results: TNF blockers + MTX vs. MTX monotherapy ACR20: RR, 1.89 (95% CI, 0.89- 4.00) ACR50: RR, 2.61 (95% CI, 1.20- 5.66) ACR70: RR, 3.43 (95% CI, 1.74- 6.75) Adjusted indirect comparisons of the anti-TNF inhibitors: ETN vs. INF ACR20: RR, 0.45 (95% CI, 0.27-0.73): P = 0.001	Adverse Events: Meta-analysis results: TNF blockers + MTX vs. MTX monotherapy Withdrawals due to lack of efficacy: RR, 0.38 (95% CO 0.22-0.64) Withdrawals due to adverse events: RR, 1.05 (95% CI, 0.52-2.09) Adjusted indirect comparisons of the anti-TNF inhibitors: ETN vs. INF Withdrawals due to lack of efficacy: RR, 0.52 (95% 0.19-1.42); P = 0.20 Withdrawals due to adverse events: RR, (95% 1.01 0.30-3.42); P = 0.98 ETN vs. ADA Withdrawals due to lack of efficacy: RR, 1.12 (95% 0.32-3.94); P = 0.86 Withdrawals due to adverse events: RR, 0.38 (95% 0.17-0.86); P = 0.02 INF vs. ADA Withdrawals due to lack of efficacy: RR, 2.16 (95% 0.77-6.07); P = 0.14 Withdrawals due to adverse events: RR, 0.37 (95% 0.11-1.36); P = 0.14

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
Author, year, study name, if applicable Li et al., 2008, AIM Trial 115,116 Country and setting multinational, multicenter Source of funding NR Research objective Examine relationship between external help home use and clinical/ patient-reported outcomes and whether ABA + MTX tx reduces need for external home help Study design Controlled Trials Overall N Duration of study 12 mos Quality rating Fair	Inclusion Criteria NR, see #3475 Exclusion Criteria NR, see #3475	Interventions, Dose D1: • MTX: dosage and frequency NR, see #3475 • Placebo D2: • MTX: dosage and frequency NR, see #3475 • Abatacept patients 60 kg or less: 500 mg • Patients 60-100 kg: 750 mg • Patients greater than 100 kg: 1000 mg • Dosing schedule: 30 minute IV infusion given at baseline, days 15 and 30, and monthly thereafter Number in group D1: 219 D2: 433 Overall: 590 Mean age (years) D1: NR, see #3475 D2: NR Overall: 51.0 Sex, % female Overall: 80 Race, % white Overall: 87 Race, % black Overall: 2.4 Ethnicity, Latino NR	Mean disease duration, years (SD) NR Overall: 8.7 yrs (7.3) Patients with early RA, three years or less, % NR Treatment resistant, % NR TJC, mean (SD) Overall: 31.8 (13.3) SJC, mean (SD) Overall: 21.8 (8.8) Corticosteroid use, % NR DMARD use, % NR MTX naïve, % NR Baseline DAS score, mean (SD) NR Overall: 6.8 (0.9) Required treatment for latent TB NR Other population characteristics, n (%) EHH use: D1: 75 (38) D2: 157 (40) Mean number of days of EHH: D1: 16 D2: 15 Overall: 15.6 (11.3)	ACR NR HAQ NR DAS NR SF-36 NR Radiographic measures NR Quality of life scales NR Others, (please name) • FOR PLACEBO GROUP: EHH use at 12 mos (among those who reported no EHH use at baseline): 21 (17%) • No EHH use at 12 mos: 42.5% • Needing full help at 12 mos: 12.3%. • FOR ABA group: 22 (9%), 53.2% 9.0% • Mean improvements from baseline in EHH at 12 mos were greater in ABA Gthan placebo G (AUC 361.8 (P = 0.001). • After 12 mos, proportions of patients who were shifted to lesser help categories were similar between 2 groups, with fewer patients requiring full help of > 2 weeks of help.	Overall Overall attrition/withdrawal, n: D1: 43 D2: 19 Withdrawals due to adverse events, n: D1: 4 D2: 18 Withdrawals due to lack of efficacy, n: D1: 40 D2: 13 Adherent/compliant, n: D1: 3 D2: 1 Overall adverse events reported, n: NR Serious adverse events NR Malignancies NR Respiratory events NR Other infections NR Other NR

	Inclusion and				
Study	Exclusion	Characteristics and	Baseline Disease and		
Characteristics	Criteria	Interventions	Treatment Characteristics	Health Outcomes	Adverse Events, %

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
Author, year, study name, if applicable Li et al., 2010 ¹¹⁷ Country and setting United States; Medicaid patients Source of funding Abbott Labs Research objective To examine adherence, discontinuation, and switching of RA biologics over a 1-year period after initiation of the biologic treatment in Medicaid patients with RA Study design Observational Overall N 2638 Duration of study 12 mos	Inclusion Criteria Treatment resistant Continuous eligibility under fee-for- service Medicaid in the 12-month pre-index and 12-month post-index dates At least 1 inpatient or 2 outpatient diagnoses of RA across Medicaid or Medicare claims in the 12-month pre- index date Exclusion Criteria Previous use of any RA biologic in the 12-month pre- index date	Comparisons (dosage and frequency) D1: ETN: 25 mg twice a week D2: ANK: 100 mg daily D3: INF: NR Number in group D1: 1359 D2: 267 D3: 1012 Mean age (years) D1: 54.9 D2: 55.9 D3: 63.3 Sex, % female D1: 88.4 D2: 91.8 D3: 87.6 Race, % white D1: 45.8 D2: 47.9 D3: 49.6 Race, % black D1: 12.6 D2: 14.6 D3: 13.0 Ethnicity, Latino D1: 18.3 D2: 20.2 D3: 13.9	Mean disease duration, years NR TJC, mean NR SJC, mean NR Corticosteroid use, % D1: 76.5 D2: 77.9 D3: 71.2 DMARD use, %: D1: 83.4 D2: 82.0 D3: 85.5 MTX naïve, %: NR Treatment resistant, %: NR Patients with early RA, three years or less, %: NR Baseline DAS score NR Required treatment for latent TB NR Other population characteristics, %, (CI/SD/P value): NR	ACR mean difference/absolute difference (CI/SD/P Value): NR HAQ, mean difference/absolute difference (CI/SD/P Value): NR DAS, mean difference/absolute difference/absolute difference (CI/SD/P Value): NR SF-36, mean difference/absolute difference (CI/SD/P Value): NR Radiographic measures, mean difference/absolute difference (CI/SD/P Value): NR Quality of life scales, mean difference (CI/SD/P Value): NR Quality of life scales, mean difference (CI/SD/P Value): NR Others, (please name); mean difference/absolute difference (CI/SD/P Value):	Overall Adherent/compliant (n): D1: 435 (32%) D2: 28 (10.5%) D3: 435 (43%) P<0.05 for ANK compared to the other arms Adherence defined as PDC of 0.80 or greater. Serious adverse events: NR Malignancies: NR Respiratory events: NR Other infections: NR GI: NR	Quality rating for efficacy/effectiveness? NR Quality rating for observational studies Fair

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
				Mean PDC over 12 mos D1: (ref group): 0.57 D2: 0.36 (P<0.05) D3: 0.64 (P<0.05)		
				Discontinuation with continuous gap of 120 days or more D1: 34.5% D2: 70.0% (P<0.05) D3: 33.6%		
				Continuous gap of 90 days or more D1: 40.7% D2: 76.0% (p<0.05) D3: 40.		

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
Author, yr: Listing et al., 2005 118 Country, Setting: Germany, population-based Funding: Joint grant from Essex, Wyeth, Amgen, and Abbott Research Objective: Incidence rates of serious and nonserious infections in pts with RA who start txt with a biologic agent, and to compare these rates with those in pts with RA who receive conventional txt Study Design: Prospective cohort study Overall N: 1529 Study Duration: Up to 12 mos	 Age: 18 to 75 Diagnosed according to ACR criteria new txt with ETA, INF, or AKA Controls: pts started on DMARD therapy after failure of > 1 other DMARD, or with additional DMARD added to existing DMARD 	Interventions, dose: D1: ETA D2: INF D3: AKA D4: DMARDS (control) N: D1: 512 D2: 346 D3: 70 D4: 601 Mean age, yrs: D1: 53.7 D2: 53.6 D3: 54.3 D4: 56.5 Sex, % female: D1: 78.1 D2: 70.8 D3: 77.1 D4: 82.7 Race, % white: NR	Mean disease duration, yrs: D1: 9 D2: 8 D3: 13 D4: 6 TJC, mean: D1: 13.3 D2: 12.7 D3: 12.6 D4: 10 SJC, mean: D1: 10.5 D2: 10.8 D3: 10.2 D4: 7.7 DMARD use, %: D1: 51.6 D2: 89.6 D3: 71.4 D4: 0 Glucocorticoids use, %: D1: 87.4 D2: 85.2 D3: 87 D4: 77.2 MTX naive, %: NR Txt resistant %: NR Pts with Early RA (≤3 yrs): NR Baseline DAS, mean: D1: 6.1	See AEs	Overall: D1: 22.6 per 100 PY D2: 28.3 per 100 PY D3: 17.5 per 100 PY (95% CI,8.8-31.2) D4: 6.8 per 100 PY SAEs: D1: 6.4 per 100 PY D2: 6.2 per 100 PY (95% CI,0.4-11.5) D4: 2.3 per 100 PY Infections: D1: 15 D2: 21 D4: 6 Serious Infections: D1: 6.4 per 100 PY D2: 6.2 per 100 PY URTI: D1: 7.0 D2: 11.4 D3: 1.8	Overall Attrition Rate, %: 11.1 ITT Analysis: Yes Quality Rating: Fair

D2: 6.0
D3: 6.1
D4: 5.4

MTX use:
D1: 33
D2: 64.5
D3: 61.4
D4: 20.1

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
Author, yr: Listing et al., 2006 ¹¹⁹ Country, Setting: Germany Registry Data Funding: Pharmas: Essex, Wyeth, A mgen, Abbott Research Objective: To investigate frequency of remission and improved functional status in pts with 2 or more DMARD failures who have received new txt with biologics Study Design: Prospective cohort study Overall N: 1,083 Study Duration: 1 yr	 No failure of MTX Rec'd new txt ≥ 1 days before study entry DAS < 3.2 at baseline 	Interventions, dose: D1: Biologics (ADA, ANA, ETN, INF) (dose NR) D2: DMARDs as a class (dose NR) N: D1: 818 D2: 265 Mean age, yrs: D1: 53.7 D2: 57.4 Sex, % female: D1: 76.6 D2: 83.8 Race, % white: NR	Mean disease duration, yrs: D1: 10 D2: 9 TJC, mean: D1: 12.9 D2: 10.5 SJC, mean: D1: 10.5 D2: 8.2 DMARD use, %: 100 Corticosteroid use, % NR MTX naive, %: NR Txt resistant, %: NR Pts with Early RA (≤3 yrs): NR Baseline DAS, mean: D1: 6.1 D2: 5.5 # previous DMARDs: D1: 4.0 D2: 2.8	Biologics had double chance of remission compared to conventional DMARD therapies, via multivariate regression (OR: 1.95; 95% CI, 1.20-3.19) Severely disabled pts (≤ 50% of full function) in D1 (biologics) significantly more likely to achieve physical independence (≥ 67% of full function) than D2 (DMARDs/controls) (OR 3.88, 95% CI, 1.7-8.8) Functional remission (≥ 83% of full function) more often achieved in D1 (biologics)than in D2 (DMARDs/controls) (OR 2.18 95% CI, 1.04-4.6) At 12 months DAS28 remission, %: D1: 24.9 D2: 12.4 (P < 0.004) ARA remission, %: D1: 16.1 D2: 8.3 (P < 0.036) Pts in remission by DAS Criteria, %: D1: 16.3 D2: 15.3 Pts in ARA Remission, %: D1: 13.2 D2: 10.2 Approximately half of pts in remission at 6 mos relapsed	NR	Overall Attrition Rate, %: 14% ITT Analysis: No Quality Rating: Fair

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
				until 12 mos, %: D1: 55 D2: 58		
				Patients with moderate disease acitvity (DAS28, 3.2-5.1) at start of treatment, had high remission rates in biologics group: DAS 30.6 ARA 16.9%		
				Sustained remission at 6 and 12 months achieved in <10 % of patients		

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
Author, year, study name, if applicable Listing et al., 2008 ¹²⁰ Country and setting Germany Source of funding Unconditional, joint grants from Essex and Wyeth since 2001, from Essex, Wyeth, and Amgen since January 2003, and from Essex, Wyeth, Amgen, and Abbott since September 2003 Research objective Determine hazard risk of developing or worsening heart failure in RA pts treated with tumor necrosis factor inhibitors. Study design Cross Sectional Cohort Study Overall N 4,248 Duration of study 5 years Quality rating Good	Treated with ADA, ETN, IFX, or conventional.	Interventions, Dose D1: ETN: dose NR IFX: dose NR ADA: dose NR D2: Conventional DMARDs: dose NR Number in group D1: 2,757 D2: 1,491 Mean age (years) D1: 53.7 D2: 56.1 P = 0.00001 Sex, % female D1: 78.1 D2: 78.9 Race, % white NR Race, % black NR Ethnicity, Latino NR	Mean disease duration, years (SD) D1: median duration 9 years D2: median duration 6 years P = 0.00001 Patients with early RA, three years or less, % NR Treatment resistant, % NR Tender Joint Count, mean (SD) NR Swollen Joint Count, mean (SD) D1: mean 9.3 D2: mean 6.8 P = 0.00001 Corticosteroid use, % D1: 83.9 D2: 76.1 D 3P = 0.00001 DMARD use, % NR MTX naïve, % NR Baseline DAS score, mean (SD) D1: mean 5.8 D2: mean 5.1 D 3P = 0.00001 Required treatment for latent TB NR Other population	ACR NR HAQ NR DAS NR SF-36 NR Radiographic measures NR Quality of life scales NR Others, (please name); mean difference/absolute difference (CI/SD/P Value) NR	Overall • At followup, 101 pts (2.4%) had died, 14 due to heart failure. Four hundred twelve patients (9.7%) dropped out, and 168 (4.0%) had not attended last 2 or 3 followup visits. annual loss-to-followup rate (with loss-to-followup defined as dropping out or failure to attend last 2 or 3 visits) was 5.1%. annual dropout rate was 3.9% on average, and total dropout rate at 48 months was 15.5% (Kaplan-Meier estimate). Patients who dropped out did not differ significantly from those who completed study with regard to age, sex, treatment with TNFα inhibitors, or cardiovascular disease status, but they did have slightly more active disease at start of treatment (mean ± SD DAS28 score 5.7 ± 1.3 versus 5.5 ± 1.3). Overall adverse events reported, n: NR Serious adverse events NR Malignancies

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics Health Outcomes	Adverse Events, %
			characteristics, %, (CI/SD/P value) D1: Comorbidiities: Heart	Respiratory events NR
			failure 75 (2.7%); Coronary heart disease	Other infections NR
			149 (5.4%); cardiovascular disease total 1,026 (37.3%);	GI NR
			Diabetes 226 (8.2%); Chronic lung disease 201 (7.3%); Rhuematoid factor positive 2,219 (80.5%). D2: Comorbidiities: Heart failure 23 (1.5%), $P = 0.014$; Coronary heart disease 105 (7.0%), $P = 0.033$; cardiovascular disease total 569 (38.2%), $P = 0.566$; Diabetes 128 (8.6%), $P = 0.673$; Chronic lung disease 95 (6.4%), $P = 0.256$; Rhuematoid factor positive 1,069 (71.7%), $P = 0.00001$.	 Other Adjusted hazard ratios (HR) for developing heart failure de novo: Anti-TNF vs. conventional DMARDs (multivariate analysis final model): adjusted HR: 1.66 95% CI: 0.67, 4.10; P = 0.28 Adjusted HR for heart failure: Anti-TNF vs. conventional DMARDs (multivariate analysis final model): adjusted HR: 1.49 95% CI 0.70, 3.18; P = 0.31 Adjusted HR for heart failure in 98 patients with prevalent heart failure Anti TNF vs. conventionals 1.18 95% CI 0.30-4.733.90 P = 0.81. Patients with heart failure prior to study entry compared to patients without CVD at study entry had an adjusted HR of 23.88 (95% CI 8.04, 70.90 P = 0.0001. In a multivariate analysis adjusted HR was 15.99 (95% Ci 5.40, 47.36), P = 0.0001.

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
					 And in a simplified model to offset efficacy of anti-TNF treatment, adjusted HR was 18.06 (95% Ci 6.10, 53.49) P = 0.0001. When incident heart failure cases were compared to matched controls, controls had a significantly lower mean DAS28 score at follow up compared to cases (4.4 vs. 5.1, P = 0.03). Adverse events were not systematically reported; there were 101 deaths, 14 of which were result of heart failure. Twenty five patients experienced heart failure for first time during study period. A worsening of severity of prevalent heart failure was observed in 12 of 98 patients.

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
Author, yr: Maini et al. 2004 ¹⁸ Country, Setting: Multinational Multicenter Funding: Centocor Research Objective: Efficacy and safety of repeated administration of infliximab plus MTX over a 2-yr period in pts with RA Study Design: RCT plus extension Overall N: 428 (259 in extension) Study Duration: 54 wks plus additional yr of follow-up	Inclusion Criteria: • Age 18-75 • Active RA despite MTX Exclusion Criteria: • NR	Interventions, dose: D1: INF D2: Placebo Mean age, yrs: Overall: 54 Sex, % female: Overall: 78 Race, % white: NR	Mean disease duration, yrs: D1: TJC, mean: Overall: 31 SJC, mean: Overall: 20 DMARD use, %: NR Corticosteroid use, %: NR MTX naïve, %: NR DMARD Txt resistant, %: NR Patients with Early RA (≤ 3 yrs): NR	The incidence of serious adverse events remained constant over time	Serious adverse events were reported by similar proportions of pts who received MTX only (33%) and infliximab plus MTX (29%) • Number of observed cancer cases vs. number expected Placebo 0 vs. 1.02 INF 5 vs. 5.15	Overall Attrition Rate, %: • At 52 wks 27% • At 2 yrs 17% of those that continued into extension ITT Analysis: Yes Quality Rating: Fair

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
Author, year, study	Inclusion Criteria	Interventions, dose	Mean disease duration,	ACR	Attrition/withdrawal
name, if applicable	 Treatment 	D1:	mos	ACR 20:	Overall, n:
Maini et al., 2006, 121	resistant	 Tocilizumab: 2 mg/kg 	D1: 9.19	D1: 31	D1: 12
CHARISMA	 Patients must 	every 4 weeks	D2: 9.79	D2: 61	D2: 11
Country and setting	have shown an	 Placebo MTX 	D3: 9.21	D3: 63	D3: 8
Rheumatology	inadequate	placebo: once/week	D4: 9.33	D4: 64	D4: 6
Centers, Europe	response to	D2:	D5: 7.82	D5: 63	D5: 7
•	MTX or a	 Tocilizumab: 4 mg/kg 	D6: 10.62	D6: 74	D6: 7
Source of funding	disease flare	every 4 weeks	D7: 11.24	D7: 41	D7: 9
Chugai	while receiving	 Placebo MTX 	Patients with early RA,		Withdrawals due to
Pharmaceuticals (a	MTX (at a	placebo: once/week	three years or less, %	 4 mg/kg and 8 mg/kg of 	adverse events, n:
member ofRoche	dosage of 10-25		NR	tocilizumab vs. placebo	AE and Possible Drug-
Group)	mg weekly)	 Tocilizumab: 8 mg/kg 		plus MTX (<i>P</i> < 0.05)	Related Toxicity:
Research objective	during a	every 4 wks	Treatment resistant, %	 2 mg/kg of tocilizumab vs. 	D1: 4
Establish safety and	minimum of 6	 Placebo MTX 	D1: 100	placebo plus MTX (NS)	D2: 6
efficacy of repeat	mos of therapy.	placebo: once/week	D2: 100	 Tocilizumab (2 mg/kg, 4 	D3: 5
infusions of	 Inadequate 	D4:	D3: 100	mg/kg, and 8 mg/kg) plus	D4: 3
tocilizumab alone	response was	 MTX: once/week 	D4: 100	MTX vs.	D5: 6
and in combination	defined as	 Tocilizumab: 2 mg/kg 	D5: 100	ACR 50:	D6: 6
with MTX	presence of	every 4 weeks	D6: 100	D1: 6	D7: 4
	active disease,	D5:	D7: 100	D2: 28	AACO I I I I I I I I I
Study design	as described	 MTX: once/week 	Overall: 100	D3: 41	Withdrawals due to lack of
Controlled Trials	above, despite	 Tocilizumab: 4 mg/kg 	TJC, mean	D4: 32	efficacy, n:
Overall N	MTX therapy	every 4 wks	D1: 15	D5: 37	D1: 6
359	Dagnosis of RA	D6: Tocilizumab: 8	D2: 15	D6: 53	D2: 5
	according to	mg/kg every 4 wks +		D7: 29	D3: 2
Duration of study	ACR revised	MTX once/week	D4: 15	8 mg/kg of tocilizumab plus	D4: 1
16 wks (20 wks for	criteria	D7: MTX: once/wk +	D5: 13	MTX vs. placebo plus	D5: 1 D6: 1
Safety)	Disease	placebo infusions	D6: 15	MTX (<i>P</i> < 0.05). All	D6. 1 D7: 6
Quality rating	duration of at	every 4 wks	D7: 16	others NS.	D7. 0
Fair	least 6 mos	Number in group	Overall: 15	4.00.70	Adherent/compliant, n:
ı uli	Active disease	D1: 53	C.I.C	ACR 70:	D1: 41
	(defined as ≥ 6	D1. 53 D2: 54	SJC, mean	D1: 2	D2: 43
	tender joints	D2: 54 D3: 52	D1: 11	D2: 6	D3: 44
	and 6 swollen	D3: 52 D4: 52	D2: 11	D3: 16	D4: 46
	joints, based on	D4: 52 D5: 49	D3: 12	D4: 14	D5: 42
	a 28-joint count)	D6: 50	D4: 11	D5: 12	D6: 43
	• ESR of ≥ 28	D7: 49	D5: 11	D6: 37	D7: 40
	mm/hour, and/or	Overall: 359	D6: 11	D7: 16	Overall adverse events
	a CRP level ≥	Overall. 339	D7: 12	8 mg/kg of tocilizumab plus	Overall adverse events

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
	Exclusion Criteria 1.0 mg/dl. If patients required concomitant treatment with nonsteroidal antiinflammatory drugs and/or oral steroids, dose must have been stable for at least 4 weeks prior to study entry and during course ofstudy (for steroids, ≥ 10 mg PNL or equivalent). Exclusion Criteria Leukopenia and/or thrombocytopen ia, any hepatic dysfunction as shown by aspartate transaminase and alanine transaminase	Interventions Mean age, years D1: 52.2 D2: 49.3 D3: 50.1 D4: 49.2 D5: 50.2 D6: 50.1 D7: 50.9 Overall: 50.3 Sex, % female D1: 83 D2: 76		Health Outcomes MTX vs. placebo plus MTX (P < 0.05). All others NS. HAQ NR DAS D1: NR (in figure only) D2: NR (in figure only) D3: NR (in figure only) D5: NR (in figure only) D6: -3.57 D7: NR (in figure only) monotherapy with 2 mg/kg of tocilizumab vs. placebo + MTX (P = NS) SF-36 NR Radiographic measures NR Quality of life scales NR • Mean difference/absolute difference (CI/SD/P Value): • Rate of Remission According toDAS: 8 mg/kg of tocilizumab + MTX: 34%, Monotherapy with 8	reported, n: Patients with 1 or more treatment-emergent AE: D1: 30 D2: 27 D3: 31 Treatment-related AE: D1: 13 D2: 14 D3: 15 Serious adverse events NR Malignancies NR Respiratory events Tuberculosis: NR Other infections Limb abscess D1: 1 All else NR Osteomyelitis: D1: 1 All else NR Respiratory infection: D1: 2 All else NR
	levels > 1.5-fold upper limit of normal or significant renal impairment (serum creatinine level > 1.5-fold upper limit of normal) • Patients who received		Required treatment for latent TB NR	mg/kg tocilizumab: 17%, Placebo + MTX: 8%, other arms and overall: NR • Mean Reduction in SJCs Monotherapy with 8 mg/kg of tocilizumab vs. placebo + MTX (<i>P</i> < 0.01), 8 mg/kg of tocilizumab + MTX vs. placebo + MTX (<i>P</i> < 0.001), other drugs:	Infective arthritis: D3: 1 All else NR Sepsis D3: 1 All else NR Anaphylactic shock/reaction and hypersensitivity: D1: 3

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
	DMARDs (excluding MTX) within 4 weeks prior tostart ofstudy • Patients who received anti- TNF agents within 12 weeks or LEF within 6 mos of infusion of study medication.			NR • Mean Reduction inTJC: 8 mg/kg of tocilizumab plus MTX vs. placebo + MTX (<i>P</i> < 0.009), other drugs: NR • CRP/ESR: NR for all drugs (in figure only)	D6: 0

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
Author, year, study name, if applicable Malysheva et al., 2008 122 Country and setting Germany Source of funding Not reported Research objective Assess incidence and severity of DMARD-induced AEs in pts taking/not taking glucocorticoids and whether glucocorticoids can prolong survival time of DMARD in pts receiving combination therapy Study design Retrospective Cohort Study Overall N 154 Duration of study 2-62 months Quality rating Fair	 Previous history of active gastrointestinal problems 	Interventions, Dose D1: MTX: 7.5-20 mg/week D2: MTX: 7.5-20 mg/week Other: 7.5 mg/day or less glucocorticoids D3: Hydroxychlorquine: 200-400 mg/day D4: Hydroxychlorquine: 200-400 mg/day Other: 7.5 mg/day or less glucocorticoids D5: SSZ: 1-2 g/day Other: with and without 7.5mg/day glucocorticoid Number in group D1: 74 D2: 51 D3: 69 D4: 22 D5: 28 // 19 Overall: 154 Mean age (years) NR Overall: 47.2 Sex, % female NR Overall: 84 Race, % white NR Race, % black NR Ethnicity, Latino NR	Mean disease duration, years (SD) Overall: 17.8 yrs (3.9) Patients with early RA, three years or less, % NR Treatment resistant, % NR Tender Joint Count, mean (SD) NR Swollen Joint Count, mean (SD) NR Corticosteroid use, % NR DMARD use, % NR MTX naïve, % NR Baseline DAS score, mean (SD) NR Required treatment for latent TB NR Other population characteristics, %, NR	ACR NR HAQ NR DAS NR SF-36 NR Radiographic measures NR Quality of life scales NR Others, (please name); mean difference/absolute difference (CI/SD/P Value) • Time in months until withdrawal of DMARD due to AD (mean + SD)- MTX: 21.8 (2.9) • MTX + GC: 43.3 (2.7) • SSZ: 10.4 (2.3) • SSZ + GC: 22.5 (1.9) • Time in months until occurence of AE: MTX: 3.0 (0.6) • MTX + GC: 18.8 (1.3) • HCQ: 34.5 (4.6) • HCQ + GC: 54.4 (5.1) • Time to cessation due to loss of efficacy: SSZ: 16.8 (1.2); SSZ + GC: 31.3 (2.9)	Overall Use of GC significantly increased time until withdrawal of DMARD therapy due to AE (18.6 \pm 2.3 vs. 12.5 \pm 1.4 mo; P = 0.05). However, timing of withdrawal of DMARD due to loss of efficacy was not different between RA patients taking GC and GC-naïve patients, probably due to higher level of disease activity in RA patients with GC comedication. Stratifying for DMARD revealed that comedication with GC significantly increased duration of therapy with SSZ from 10.4 \pm 2.3 to 22.5 \pm 1.9 months (SSZ + GC; P = 0.05) and for MTX from 21.8 \pm 2.9 to 43.3 \pm 2.7 months (MTX + GC; P = 0.01). GC comedication significantly increased time until occurrence of AE for MTX (3.0 \pm 0.6 vs. 18.8 \pm 1.3 mo; P = 0.05), HCQ (34.5 \pm 4.6 vs. 54.4 \pm 5.1 mo; P = 0.05). Patients taking SSZ, time to cessation due to loss of efficacy increased significantly under GC comedication, from 16.8 \pm 1.2 to 31.3 \pm 2.9 months (P = 0.05). Overall adverse events reported, n: D1: 9

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
					D2: 17 D3: 19 D4: 12 D5: 4//5 Overall: 64
					Serious adverse events NR
					Malignancies Other cancer (specify), n: NR Overall: unspecified: 5
					Respiratory events NR
					Other infections NR
					GI NR
					Other Grade 1 AE (mild, not requiring treatment), n: D1: 3 D2: 7 D3: 1 D4: 1 D5: 2//1
					Grade 2 AE (moderate, resolved with treatment), n: D1: 4 D2: 5 D3: 17 D4: 9 D5: 1//2
					Grade 3 AE (severe, result in inability to carry on normal activities and requiring professional medical attention), n: D1: 2

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
					D2: 4 D3: 4 D4: 1 D5: 4//1 Overall: nephrectomy: 1 Osteoporosis (DMARD monotherapy versus DMARD + GC): 16 vs. 22 Diabetes mellitus: 4 vs. 10 Malignancy: 6 vs. 3
					 Thyroid dysfunction: 5 vs. 5 Infections: 2 vs. 3 Gastrointestinal Complications: 11 vs. 6 Mucocutaneous complications: 5 vs. 7 Intolerance: 6 vs. 5

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
study name, if applicable Marchesoni et al., 2009 ¹²³ LOHREN registry Country and setting Italy, Lombary Source of funding NR Research objective To evaluate survival of INF, ETN, and ADA in	Inclusion Criteria Patients with RA according to ACR with at least one dose of anti-TNF treatment Exclusion Criteria Active infection History of malignancy Pre-malignant condition Class 3/4 congestive heart failure Demyelinating disorders	Comparisons (dosage and frequency) D1: INF: dose NR D2: ADA: dose NR D3: ETN: dose NR Number in group D1: 519 D2: 303 D3: 242 Overall: 1064 Mean age (years) D1: 55.72 D2: 56.07 D3: 55.81 Overall: 55.84 Sex, % female D1: 81.5 D2: 85.1 D3: 84.3 Overall: 83.2 Race, % white NR Race, % black NR Ethnicity, Latino NR	Mean disease duration, years D1: 9.28 (7) D2: 9.56 (7.9) D3: 9.63 (7.11) Overall: 9.44 (7.29) TJC, mean NR SJC, mean NR Corticosteroid use, % D1: 80.7 D2: 76.9 D3: 84.3 Overall: 84.2 DMARD use, %: NR MTX naïve, %: NR Treatment resistant, %: NR Patients with early RA, three years or less, %: NR Baseline DAS score D1: 6.01 (0.94) D2: 5.68 (0.96) D3: 5.93 (1.02) Overall: 5.90 (0.97) Required treatment for latent TB NR Other population characteristics,	ACR mean difference/absolute difference (CI/SD/P Value): NR HAQ, mean difference/absolute difference (CI/SD/P Value): NR DAS, mean difference/absolute difference (CI/SD/P Value): NR SF-36, mean difference/absolute difference (CI/SD/P Value): NR Radiographic measures, mean difference/absolute difference (CI/SD/P Value): NR Quality of life scales, mean difference/absolute difference (CI/SD/P Value): NR Quality of life scales, mean difference/absolute difference (CI/SD/P Value): NR Others, (please name); mean difference/absolute difference (CI/SD/P Value):	Overall Overall attrition/withdrawal (n): D1: 226 D2: 111 D3: 68 Overall: 405 Withdrawals due to adverse events (n): D1: 106 D2: 60 D3: 28 Overall: 194 Withdrawals due to lack of efficacy (n): D1: 104 D2: 45 D3: 31 Overall: 180 Long-term survival rate at 36 mos (INF vs. ADA vs. ETN): 49.1% vs. 53.6% vs. 62.5% RR of discontinuation due to all causes compared to ETN • ADA: 1.45 (1.05 to 2.00, P=0.024) • INF: 1.50 (1.10 to 2.05; P=0.011) RR of discontinuation due to loss of effica Serious adverse events: Death (n): D1: 3 D2: 5	Quality rating for efficacy/effectiveness? NR Quality rating for observational studies Fair

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
			%, (CI/SD/P value):	NR	D3: 5 Overall: 13	
					Malignancies: Malignancies: D1: 6 D2: 8 D3: 4 Overall: 18	
					Respiratory events: NR	
					Other infections: Serious infections (specify) (n): D1: 42 D2: 20 D3: 11 Overall: 73	
					GI : NR	
					Other: Infusion/injection site reactions (n): D1: 48 D2: 8 D3: 2 Overall: 58	

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
Author, year, study name, if applicable	Inclusion Criteria • Ad Veterans	Interventions, Dose D1:	Mean disease duration, years (SD)	ACR NR	Overall NA
McDonald, J.R. et al., 2009 ¹²⁴	who had an ICD-9-CM code	SSZ: dose NRHCQ: dose NR	NR Patients with early RA,	HAQ NR	Overall adverse events reported, n: NA
Country and setting United States; Veterans	during study period and who,	 Auronofin, injectable gold, penicillamine: NR 	three years or less, % NR	DAS NR	Serious adverse events NA
hospital Source of funding	after a ≥ 4 month history of receiving	11171. 0000 1111	Treatment resistant, %	SF-36 NR	Malignancies NA
US Department of Veterans Affairs,	medications from VA during	 LEF: dose NR ANK: dose NR Azathioprine,	Tender Joint Count, mean (SD) NR	Radiographic measures NR	Respiratory events NA
Veterans Health Administration, and National Institutes of	study period, subsequently received a first	cyclophosphamid, cyclosporine: dose NR	Swollen Joint Count, mean (SD)	Quality of life scales NR	Other infections NA
Health Research objective	prescription for a DMARD.	D3: • ETN: dose NR	NR	Others, (please name); mean difference/absolute	GI NA
Examine HZ risk, risk factors, treatments	Exclusion Criteria	IFX: dose NRADA: dose NR	Corticosteroid use, % D1: PRED: 34.5 D2: PRED: 62.7	difference (CI/SD/P Value) Antiviral Treatment:	Other NA
and outcomes with a focus on contribution	at any time prior	Number in group D1: 9673	D3: PRED: 55.0 DMARD use, %	 Oral: D1 65.4, D2 65.5, D3 69.8, D2 vs. D1: P > 0.5, D3 vs. D1: P > 0.1; 	
of different classes of immunosuppressive medications to risk of	DMARD or who did not have ≥ 2	D2: 12888 D3: 3661 Overall: 20357	D1: HCQ: 72.8; SSZ: 39.7; MTX: 0; LEF: 0; CSA: 0; CYC: 0; ANK: 0; ETN: 0;	• Intravenous: D1 1.0, D2 6.8, D3 3.1, D2 vs. D1: <i>P</i> =	
HZ Study design	separate outpatient or inpatient clinical	Mean age (years) D1: 61.9, SD 12.8	IFX: 0; ADA: 0 D2: HCQ: 28.7; SSZ: 17.3;	0.001, D3 vs. D1: P > 0.1;HZ complication: HZ Meningitis: D1 0.5, D2 0.5,	
Retrospective Cohort Study	encounters during study	D2: 63.7, SD 12.0 D3: 59.3, SD 11.6	MTX: 83.7; LEF: 19.8; CSA: 2.7; CYC: 2.7;	D3 0, D2 vs. D1: P > 0.1, D3 vs. D1: P > 0.5;	
Overall N 20,357	period.	Sex, % female D1: 10.9	ANK: 0.5; ETN: 0; IFX: 0; ADA: 0	 Other HZ nervous system complication: D1 20.7, D2 	
Duration of study October 1998 to		D2: 8.7 D3: 9.0	D3: HCQ: 22.0; SSZ: 17.0; MTX: 51.5; LEF: 19.8; CSA: 1.3; CYC: 0.6;	18.6, D3 17.7, D2 vs. D1: P > 0.5, D3 vs. D1: P > 0.5:	
June 2005 Quality rating		Race, % white D1: 65.2	ANK: 1.5; ETN: 68.9; IFX: 22.0; ADA: 32.4	 Ophthalmic HZ: D1 7.2, D2 6.8, D3 5.2, D2 vs. D1: P> 	
Fair		D2: 67.5 D3: 70.1	MTX naïve, % D1: 100	0.5, D3 vs. D1: <i>P</i> > 0.1; • Other HZ complication: D1	
		Race, % black	D2: NR D3: NR	6.3, D2 6.8, D3 4.2, D2 vs. D1: P > 0.5, D3 vs. D1: P >	

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
		D1: 13.6 D2: 10.1 D3: 8.9	Baseline DAS score, mean (SD) NR	0.1; • Hospitalization for HZ: D1 2.9, D2 6.1, D3 4.2, D2 vs.	
		Ethnicity, Latino NR	Required treatment for latent TB	D1: <i>P</i> > 0.5, D3 vs. D1: <i>P</i> > 0.1;	
			Other population characteristics, %, (CI/SD/P value) D1: Episodes of HZ (%): 2.2; Episodes of HZ per 1000 patient-years: 8.00 D2: Episodes of HZ (%): 3.2; Episodes of HZ (%): 3.2; Episodes of HZ per 1000 patient-years: 11.18 D3: Episodes of HZ (%): 2.6; Episodes of HZ per 1000 patient-years: 10.60 Overall: Episodes of HZ per 1000 patient-years: D2 vs. D1 P = 0.001; D3 vs. D1 P = 0.001		

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
Author, year, study name, if applicable Mease et al., 2008, DANCER trial 46,125 Country and setting United States multicenter Source of funding Genentech, Inc. Research objective Evaluate effect of RIT treatment on HRQOL Study design Controlled Trials Overall N 367 Duration of study 24 weeks Quality rating Fair	Inclusion Criteria Treatment resistant failed to respond to treatment with at least 1 but not more than 5 DMARD or biologic agents SJC of 8 or more TJC of 8 or more CRP serum levels of 1.5 mg/dl or more or erythrocyte sedimentation rate of 28 mm/h or more despite ongoing MTX treatment of more than 12 weeks See ⁴⁶ for more details Exclusion Criteria See ⁴⁶	Interventions, Dose D1: MTX: 10-25 mg/week PlacebolV infusion on days 1 and 15 D2: MTX: 10-25 mg/week RIT: 500 mg IV infusion on days 1 and 15 D3: MTX: 10-25 mg/week RIT: 500 mg IV infusion on days 1 and 15 MTX: 10-25 mg/week RIT: 1000 mg IV infusion on days 1 and 15 Number in group D1: 122 D2: 123 D3: 122 Overall: 367 Mean age (years) D1: 50.8 D2: 51.4 D3: 52.1 Overall: 51.0 Sex, % female D1: 79.5 D2: 83.7 D3: 76.2 Overall: 80.0 Race, % white D1: 77.9 D2: 76.4 D3: 82.8 Overall: 79.0 Race, % black NR	Mean disease duration, years (SD) D1: 9.6 yrs (7.7) D2: 11.2 (8.5) D3: 11.3 (8.5) Overall: 11.0 (NR) Patients with early RA, three years or less, % NR Treatment resistant, % D1: 100 D2: 100 D3: 100 Overall: 100 TJC, mean (SD) D1: 35 D2: 33 D3: 32 SJC, mean (SD) D1: 21 D2: 22 D3: 22 Corticosteroid use, % NR DMARD use, % D1: 27 D2: 39 D3: 31.1 Overall: 32.4 MTX naïve, % D1: 0 D2: 0 D3: 0 Overall: 0 Baseline DAS score, mean (SD)	ACR NR HAQ, D1: NR, in figure only D2: NR, in figure only D3: NR, in figure only D3: NR, in figure Overall: • Significant differences were seen for 1000mg Gps. placebo after 8 weeks (P = 0.05) and were maintained over 24 weeks. • For 500mg group, significant differences vs. placebo were seen by 12 weeks (P NR). • At week 24, 34.4% vs. 62.6% vs. 67.2% achieved prespecified MCID of 0.22 points (P = 0.05 for both groups vs. placebo) DAS NR SF-36 (SD) Mean changes from baseline to 24 weeks: physical component summary (PCS): D1: 2.36 (0.78) D2: 7.08 (0.77) D3: 7.40 (0.78) Mental component summary: D1: 1.88 (1.00) D2: 4.49 (1.22) D3: 3.03 (1.11) Physical function: D1: 2.18 (0.83) D2: 6.44 (0.90) D3: 5.79 (0.88)	Overall Overall attrition/withdrawal, n: D1: see below D2: see below O3: see below Overall: 33-53 Withdrawals due to adverse events, n: NR Withdrawals due to lack of efficacy, n: NR Adherent/compliant, n: NR Missing outcome data (% without baseline and endpoint scores): • For SF-36, 26% vs. 9% vs. 4% • For HAQ, 27% (placebo) vs. 2% (combined RIT groups) • For FACIT-Fatigue, 27% vs. 1%. Overall adverse events reported, n: NR

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
		Ethnicity, Latino NR	D1: 6.85 (0.74) D2: 6.84 (0.79) D3: 6.67 (0.82) Overall: 6.79 (NR)	Role-physical: D1: 0.64 (1.25) D2: 7.19 (0.98) D3: 5.51 (1.22)	
			Required treatment for latent TB NR Other population	Bodily pain: D1: 4.16 (0.89) D2: 8.96 (0.97) D3: 8.51 (0.85)	
			characteristics, %, (CI/SD/P value) NA	General health: D1: 2.15 (0.89) D2: 3.94 (0.80) D3: 4.52 (0.87)	
				Vitality: D1: 2.69 (0.95) D2: 6.71 (0.96) D3: 6.02 (0.98)	
				Social function: D1: 2.68 (1.11) D2: 6.97 (1.22) D3: 5.93 (0.98)	
				Role-emotional: D1: 0.95 (1.39) D2: 5.54 (1.57) D3: 3.27 (1.57)	
				Mental health: D1: 2.34 (1.03) D2: 3.96 (1.04) D3: 2.83 (1.01) Overall: • For 500 mg vs. placebo and 1000 mg vs. placebo respectively: PCS, P = 0.001 for both comparisons),
				 MCS, P = 0.087, P = 0.10 Proportion of patients achieving an MCID 	67

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
				(minimal clinically important difference) of 5 points on PCS: 23.8% vs. 55.3% vs. 52.5%, significantly higher (P = 0.05) for both groups vs. placebo • MCS scores were not significantly different (data NR)	
				Radiographic measures NR	
				Quality of life scales D1: FACIT-Fatigue, change from baseline: 3.91 D2: 7.63 D3: 8.20 P = 0.009 placebo vs. 500 mg group P = 0.001 for 1000 mg vs. placebo	

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
Author, year, study name, if applicable	 NDB 	Interventions, Dose	Mean disease duration, years (SD)	ACR NR	Overall NR
Michaud, K. et al.; 2006 ¹²⁶ Country and setting	participants who completed a questionnaire in	MTX: NR LEF: NR	NR Patients with early RA, three years or less, %	HAQ, D1: 1.03, CI 1.07 - 1.25, SD 0.72, <i>P</i> = 0.05	Overall adverse events reported, n: NR
United States; doctors offices	December 2003 that included questions	Hydroxychlorquine: NR	NR Treatment resistant, %	DAS NR	Serious adverse events NR
Source of funding National Database for Rheumatic	related to sinus problems. Exclusion	NR • ETN: NR • IFX: NR • ADA: NR	NR Tender Joint Count, mean (SD)	SF-36 NR	Malignancies NR
Diseases Research objective	Criteria • NR	Number in group D1: 7243	NR	Radiographic measures NR	Respiratory events NR
Determine sinus disease rates are increased in pts with		Swollen Joint Count, mean (SD)	Quality of life scales NR	Other infections NR	
RA and whether tx alters risk of sinus disease.		Sex, % female D1: 78.5	Corticosteroid use, % D1: PRED: 34.1	Others, (please name); mean difference/absolute difference (CI/SD/P Value)	GI NR
Study design Cohort Study		Race, % white D1: 92.7	D1: HCO: 19 0: MTX: 57 5: problems: OR (95% CI): VIX	OR (95% CI) for visits to physician for sinus problems:	
Overall N 7,243 patients with		Race, % black NR	ETN: 14.5; ADA: 3.0; SSZ: 5.8	unnamed): 4.2, CI 1.05 - 1.09, SD 2.87, <i>P</i> = 0.05;	MTX: 1.06 (0.93, 1.20) 0.371PRED: 0.98 (0.86, 1.11) 0.776
RA Duration of study		Ethnicity, Latino NR	MTX naïve, % NR	 Pain (0-10 scale, unnamed): 3.5, CI 1.03 - 1.07, SD 2.68, P = 0.05 	IFX: 1.00 (0.88, 1.15) 0.973HCQ: 1.08 (0.93, 1.25) 0.313
longitudinal (length not specified); questionnaire			Baseline DAS score, mean (SD) NR		 LEF: 0.84 (0.70, 0.99) 0.041 ETN: 1.21 (1.02, 1.42) 0.025 ADA: 1.09 (0.79, 1.51) 0.600
completion December 2003 Quality rating			Required treatment for latent TB NR		• SSZ: 0.68 (0.51, 0.90) 0.007
Fair			Other population characteristics, %, NR		

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
Author, year, study name, if applicable Migliore et al. 2009 127 Country and setting Italy, Multicenter Source of funding NR Research objective To determine the safety profiles for ETN, INF and ADA in patients of 65+ yrs, undergoing anti-TNF treatment for an active inflammatory disease such as rheumatoid arthritis Study design Observational Overall N 138 Duration of study Duration of treatment with anti-TNF: 39 mos (SD 14)	Inclusion Criteria • Age 65 or more with RA Exclusion Criteria • Treated for other conditions, or with other anti-TNFs or different doses	Number in group	Mean disease duration, years NR Overall: 11.6 (7.8) TJC, mean NR SJC, mean NR Corticosteroid use, % NR DMARD use, %: 100 MTX naïve, %: NR Treatment resistant, %: NR Patients with early RA, three years or less, %: NR Baseline DAS score NR Required treatment for latent TB NR Other population characteristics, %, (CI/SD/P value): NR	ACR mean difference/absolute difference (CI/SD/P Value): NR HAQ, mean difference/absolute difference (CI/SD/P Value): NR DAS, mean difference/absolute difference (CI/SD/P Value): NR SF-36, mean difference/absolute difference (CI/SD/P Value): NR Radiographic measures, mean difference/absolute difference (CI/SD/P Value): NR Radiographic measures, mean difference/absolute difference (CI/SD/P Value): NR Quality of life scales, mean difference/absolute difference (CI/SD/P Value): NR Others, (please name); mean difference/absolute difference (CI/SD/P Value):	Overall NR Serious adverse events: NR Malignancies: NR Respiratory events: Tuberculosis (n): NR Pneumonia (n): NR Upper respiratory infection (n): NR Other infections: Urinary tract infection (n): NR Other infections (specify) (n): Infections (total, not stratified by age) Total D1: 10 D2: 10 D3: 10 Mild D1: 2 D2: 8 D3: 5 Moderate D1: 2 D2: 8 D3: 5 Moderate D1: 2 D2: 0 D3: 1 Severe D1: 0 D2: 0 D3: 1	Quality rating for efficacy/effectiveness? NR Quality rating for observational studies Fair

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
		Overall: 79% Race, % white NR		NR	Total D1: 4 D2: 4 D3: 3	
		Race, % black NR Ethnicity, Latino NR			Mild D1: 4 D2: 4 D3: 3	
					Moderate D1: 0 D2: 0 D3: 0	
					Severe D1: 0 D2: 0 D3: 0	
					Infections, age 71-75 Total D1: 1 D2: 1	
					Mild D1: 0 D2: 0	
					Moderate D1: 0 D2: 0	
					Severe D1: 0 D2: 0	
					Infections, age 76+ Total D1: 5 D2: 3 D3: 3	
					Mild D1: 4	

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
					D3: 3 Moderate D1: 1 D2: 3 D3: 1	
					Severe D1: 0, D2: 0 D3: 1	
					GI: NR	
					Other: Allergic reactions (total, not stratified by age) Total D1: 4 D2: 2 D3: 5	
					Mild D1: 2 D2: 1 D3: 2	
					Moderate D1: 2 D2: 1 D3: 2	
					Severe D1: 0 D2: 0 D3: 1	
					Allergic reactions, age 65-70 Total D1: 2 D2: 4 D3: 1	

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
					Mild D1: 1 D2: 2 D3: 1	
					Moderate D1: 1 D2: 2 D3: 0	
					Severe D1: 0 D2: 0, D3: 0	
					Allergic reactions, age 71-75 Total D1: 1 D2: 1 D3: NR	
					Mild D1: 1 D2: 0 D3: NR	
					Moderate D1: 0 D2: 1 D3: 0	
					Severe D1: 0 D2: 0 D3: 1	
					Allergic reactions, age 76+ Total D1: 1 D2: 0 D3: 0	

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
					Mild	
					D1: 0	
					D2: 0	
					D3: 0	
					Moderate	
					D1: 1	
					D2: 0	
					D3: 0	
					Severe	
					D1: 0	
					D2: 0	
					D3: 0	

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
Author, year, study name, if applicable Miyasaka, 2008, CHANGE study 128 Country and setting Japan, Multicenter Source of funding Abbott Japan Co., Ltd. and Eisai Co. Research objective Compare effects of 3 doses of ADA vs. placebo in Japanese RA pts Study design Controlled Trials	Inclusion Criteria 20 years or older Met ACR criteria for active RA Failed 1 DMARD 10 or more swollen joints and 12 or more tender joints (excluding distal interphalangeal joints) and a CRP concentration 2 mg/dL or more Exclusion Criteria	Interventions, dose D1: ADA: 20 mg every other week D2: ADA: 40 mg every other week D3: ADA: 80 mg every other week D4: Placebo Number in group D1: 87 D2: 91 D3: 87 D4: 87 Overall: 352 Mean age, years (SD) D1: 54.8 D2: 56.9 D3: 54.3 D4: 53.4	Mean disease duration, mean years (SD) D1: 10 (7.7) D2: 9.9 (7.9) D3: 9.5 (8.3) D4: 8.4 (8.2) Overall: 9.5 Patients with early RA, three years or less, % NR Treatment resistant, % NR Tender Joint Count, mean D1: 24.6 D2: 24.4 D3: 24.9 D4: 23.7 Overall: 24.4	ACR mean difference/ absolute difference (%) ACR 20: Week 12, n: D1: 39 (44.8) D2: 39 (49.2) D3: 47 (54) D4: 11 (12.6) Overall: Placebo vs. ADA 20, ADA 40, ADA 80: P < 0.05, P < 0.05, P < 0.05 Week 24, n: D1: 25 (28.7) D2: 40 (44) D3: 44 (50.6) D4: 12 (13.8) Overall: Placebo vs. ADA 20, ADA 40, ADA 80: P < 0.05, P < 0.0001, P < 0.0001	D1: 5 D2: 12 D3: 3 D4: 4 Overall: 24 Other reasons for discontinuation included withdrawal of consent,
Overall N 352 Duration of study 24 weeks Quality rating Fair	 Acute inflammatory joint diseases other than RA Active Listeria or TB, lymphoma, or leukemia, or any malignancy except for successfully treated nonmetastatic basal-cell carcinoma ofskin, HIV, hepatitis B virus surface antigen, or anti-hepatitis C virus antibody Ongoing or 	Overall: 54.9 Sex, % female D1: 79.3 D2: 79.1 D3: 82.8 D4: 77 Overall: 79.5 Race, % white NR Race, % black NR Ethnicity, Latino NR	Swollen Joint Count, mean D1: 19.2 D2: 19.1 D3: 20.8 D4: 19.3 Overall: 19.6 Corticosteroid use, % NR DMARD use, % NR MTX naïve, % NR Baseline DAS score NR Required treatment for latent TB NR	ACR 50: Week 12, n D1: 16 (18.4) D2: 19 (20.9) D3: 23 (26.4) D4: 3 (3.3) Overall: Placebo vs. ADA 20,	107 patients received rescue medication after 8+ weeks of double-blind study treatment (45, 26, 17, and 19 in placebo and ADA 20, 40, and 80 mg groups, respectively) 3 discontinuations that

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
	active infection Advanced or poorly controlled diabetes CNS demyelinating disorders		Mean Subject's global assessment of disease activity VAS (mm): D1: 73.1 D2: 71.2 D3: 75.7	Week 12, n: D1: 6 (6.9) D2: 15 (16.5) D3: 10 (11.5) D4: 1 (1.1) Overall: Placebo vs. ADA 20,	Serious adverse events Death, n: D1: 0 D2: 1 D3: 1 D4: 0
	Pregnancy		D4: 64.6 Overall: NR	ADA 40, ADA 80: <i>P</i> = NS, <i>P</i> = 0.05, <i>P</i> = 0.05	Malignancies NR
			Mean Subject's assessment of pain VAS (mm): D1: 69	Week 24, n (%) D1: 9 (10.3) D2: 11 (12.1)	Respiratory events Tuberculosis, n: 2,747
			D2: 68.1 D3: 70.4 D4: 62.7 Overall: NR	D3: 13 (14.9) D4: 1 (1.1 Overall: Placebo vs. ADA 20, ADA 40, ADA 80: P =	Placebo 2.3%
			Mean HAQ DI score: D1: 1.57	0.05, P = 0.05, P = 0.05 HAQ ,	Other infections NR
			D2: 1.64 D3: 1.77 D4: 1.39	12 week, mean difference (SD): D1: 0.2 (0.5)	GI NR
			Overall: NR Mean Duration of morning stiffness (min): D1: 216.7 D2: 193.3 D3: 202.3 D4: 195.5 Overall: NR	D2: -0.3 (0.6) D3: -0.4 (0.5) D4: -0.1 (0.6) Overall: Placebo vs. ADA 20, ADA 40, ADA 80: P = 0.05, P = NS, P = 0.05 24 week, mean difference (SD):	Other Fractures, n: Infusion/injection site reactions, n: D1: 27 D2: 28 D3: 29 D4: 2
			Any morning stiffness (%): D1: 81.4 D2: 76.9 D3: 88.4 D4: 86.2 Overall: NR	D1: -0.2 (0.5) D2: -0.2 (0.6) D3: -0.4 (0.6) D4: -0.1 (0.6) Overall: Placebo vs. ADA 20, ADA 40, ADA 80: P = NS, P = NS, P = NS	Serious AE, n: D1: 10 D2: 17 D3: 8 D4: 8 Overall: 43
				DAS NR	Severe AE, n: D1: 3 D2: 4
				SF-36	D3: 5

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
				NR Radiographic measures	D4: 5 Overall: 17
				NR Quality of life scales NR	Infectious AE, n: D1: 30 D2: 41 D3: 37
				Others TJC week 12:	D4: 32 Overall: 140
				D1: -8.3 D2: -11.2 D3: -10.1 D4: -0.6 Overall: Placebo vs. 20, 40, 80: P = 0.05, P = 0.05, P = 0.05	Serious Infectious AE, n: D1: 4 D2: 6 D3: 3 D4: 1 Overall: 14
				TJC week 24: D1: -6.6 D2: -10.7 D3: -10.0 D4: -0.5 Overall: Placebo vs. 20, 40, 80: P = NS, P = 0.05, P	Immunologic reaction: • ADA 20: 4 • ADA 40: 2 • ADA 80: 0 • Placebo: 0 • Overall: 6 Malignancies:
				= 0.05 SJC week 12: D1: -6.8 D2: -8.1 D3: -8.7 D4: -1.6 Overall: Placebo vs. 20, 40, 80: P = 0.05, P = 0.05,	 ADA 20: 0 ADA 40: 0 ADA 80: 0 Placebo: 2 Overall: 2 Opportunistic infection including TB:
				SJC week 24: D1: -5.9 D2: -8.2 D3: -8.7 D4: -1.8 Overall: Placebo vs. 20, 40, 80: $P = 0.05$, $P = 0.05$,	ADA 20: 0 ADA 40: 0 ADA 80: 0 Placebo: 0 Overall: 0

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
				Patient's global assessment of disease activity week 12: D1: -19.9 D2: -19.1 D3: -25.9 D4: -2.1 Overall: Patient's global assessment of disease activity week 12 vs. 20, 40, 80: $P = 0.05$, $P = 0.05$, $P = 0.05$	
				Patient's global assessment of disease activity week 24: D1: -16.6 D2: -19.9 D3: -25.8 D4: -2.6 Overall: Placebo vs. 20, 40, 80: <i>P</i> = NS, <i>P</i> = 0.05, <i>P</i> = 0.05	
				Patient's assessment of pain 12 week: D1: -17.3 D2: -17.2 D3: -20.5 D4: -2.3 Overall: Placebo vs. 20, 40, 80: $P = NS$, $P = 0.05$, $P = 0.05$	
				Patient's assessment of pain 24 week: D1: -12.8 D2: -17.4 D3: -20.3 D4: -3.5 Overall: Placebo vs. 20, 40, 80: $P = NS$, $P = 0.05$, $P = NS$	

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
Author, yr: Mohan et al, 2001 ¹²⁹ Country, Setting:	Inclusion Criteria: • Pts with refractory RA who developed	Interventions, dose: NR N:	duration, yrs: NR TJC, mean:	In addition to 1 case reported of suspected demyelination, 17 cases of demyelination after ETA and 2 cases after INF txt were	NR	Overall Attrition Rate, %: NA
US, NA Medwatch, AERS Funding:	confusion and difficulty walking Other meds allowed: MTX.	NR Mean age, yrs: NR	NR SJC, mean: NR	detected in MedWatch		ITT Analysis: NA
NR prednisone, amlodipine,	prednisone,	Sex, % female: NR	DMARD use, %: NR			Quality Rating: Fair
Objective: To review occurrence of	zolpidem, dexamethasone, a;prasolam,	Race, % white: NR	Corticosteroid use, %: NR			- -
neurologic events suggestive of demylenation during anti TNF	hydrocodone, naproxen sodium,		MTX naive, %: NR			
alpha therapy for inflammatory arthritides	acyclovir, metronidazole, ceftriaxone,		Txt resistant %: NR			
Study Design: Database	ranitidine, atenolol, fluoxetine,		Pts with Early RA (≤3 yrs): NR			
analysis; AERS Overall N: 20 cases	piroxicam Exclusion Criteria: NA		Baseline DAS, mean: NR			
Study Duration: 4 mos			NR			

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
Author, yr: Mohan et al., 2004 130 Country, Setting: Multinational, population-based Funding: NR Research Objective: To summarize all cases of TB following use of ETA reported to AERS from November 1998 through March 2002 Study Design: Database analysis; AERS Overall N: 25 cases Study Duration: NA	All pts receiving ETA and reported to have	Interventions, dose: D1: ETA N: D1: 25 cases Mean age at diagnosis, yrs: D1: 59 Sex, % female: D1: 72 Race, % white: NR	Mean disease duration, yrs: NR TJC, mean: NR SJC, mean: NR DMARD use, %: NR Corticosteroid use, %: NR MTX naive, %: NR Txt resistant %: NR Pts with Early RA (≤3 yrs): NR Baseline DAS, mean: NR	As of April 2002, a total of 25 reports of TB associated with ETA therapy reported to FDA from 11/1998 through 3/2002 17 cases (68%) were reported from US, 7 (28%) from Europe, and 1 (4%) from India 46% of 24 pts with a reported clinical manifestation had pulmonary TB 2 deaths occurred among 25 pts 17 US cases of TB have been reported to the FDA According to ETA manufacturer, 113,238 pts treated with ETA in US between 11/1998 and 5/2002, with estimated 172,212 PY of exposure; thus reporting rate of TB among pts in US receiving ETA is ~10 cases / 100,000 PY of exposure	NR	Overall Attrition Rate, %: NA ITT Analysis: NA Quality Rating: Fair

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
Author, yr: Mottonen, 1999 ¹³¹ ; Korpela, 2004 ¹³² ; Puolakka, 2004 ¹³³ FIN-RACo Study Country, Setting: Finland, NR Funding: Finnish Society for Rheumatology and Medical Research Foundation of Turku University Central Hospital Research Objective: Efficacy and tolerability of combo of DMARDs vs. a single DMARD Study Design: RCT Overall N: 199 randomized 187 completed 2 yrs, 160 at 5 yrs Study Duration: 24 mos (5 yr	condition: < 2 yrs Exclusion Criteria: Previous use of DMARDs Underwent glucocorticoid glucocorticoid therapy within the previous weeks serious comorbidity suspected inability to comply with the protocol hypersensitivity to any study medication history of cancer pregnant women women of childbearing age who were not using reliable methods of contraception	Interventions, dose: D1: Combo: MTX + HCQ + SSZ + PNL D2: Single DMARD (SSZ could be changed to MTX or 3 rd DMARD) + PNL PNL: 5 to 10 mg/day MTX: 7.5 to 10 mg/wk SSZ: 2 g/day Combo: 500 mg/2xd Single: 1000 mg 2xd w/ or w/out PNL HCQ: 300 mg/d Combo: if patient reaches remission in first year, patietn could be tapered and PNL could be discontinued at 9 and 18 months N: D1: 97 D2: 98 Mean age, yrs: D1: 45 D2: 46 Sex, % female: D1: 58 D2: 66 Race, % white: NR	SJC, mean: D1: 14	At 2 years Eroded joints, number: D1: 2 D2: $3 (P = 0.006)$ btw groups Progression of radiological joint damage lower in combination versus monotherapy Larsen Erosion Score improvement: D1: 2 D2: $10 (P = 0.002)$ Median increase in Larsen Score: D1: 1.5 D2: $2.0 (P < 0.001)$ Clinical remission, %: D1: 37.9 D2: $18.4 (P = 0.011)$ ACR50, %: D1: 71 D2: $58 (P = 0.058)$ Median work disability per pt-observation yr, days: D1: 12.4 D2: $32.2 (P = 0.008)$ At 5 years Eroded joints, number: D1: 3 D2: 6 Larsen Erosion Score: D1: 11 D2: $24 (P = 0.001)$	Overall: D1: 70 D2: 71 SAEs: D1: 3 D2: 5 Cardiovascular Events: D1: 1 MI D2: 2 MIs Malignancies: 1 prostate cancer; 1 multiple myeloma URTI: 1 pneumonia	Overall Attrition Rate, %: 195 started txt (97/98) 178 completed 2 yrs (87/91); 160 at 5 yrs (78/82) ITT Analysis: Yes Quality Rating: Fair

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
				Score: D1: 1.5 D2: 2.0 (<i>P</i> < 0.001)		
				5 year Remiission D1: 28 D2: 22 (<i>P</i> = NS)		
				Increase in Larsen score D1: lower than (P = 0.004)		

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
Author, yr: Mottonen, 1999 ¹³¹ ; Mottonen, 2002 ¹³⁴ ; Korpela, 2004 ¹³² ; Puolakka, 2004 ¹³³ FIN-RACo Study Country, Setting: Finland, NR Funding: Finnish Society for Rheumatology and Medical Research Foundation of Turku University Central Hospital Research Objective: Efficacy and tolerability of combo of DMARDs vs. a single DMARD Study Design: RCT Overall N: 199 randomized, 187 completed 2 yrs, 160 at 5 yrs	Exclusion Criteria: Previous use of DMARDs Underwent glucocorticoid therapy within the previous 2 weeks serious comorbidity suspected inability to comply with the protocol hypersensitivity to any study medication history of cancer pregnant women women of childbearing age who were not using reliable methods of contraception	Interventions, dose: D1: Combo: MTX + HCQ + SSZ + PNL D2: Single DMARD (SSZ could be changed to MTX or 3 rd DMARD) + PNL PNL: 5 to 10 mg/day MTX: 7.5 to 10 mg/wk SSZ: 2 g/day Combo: 500 mg/2xd Single: 1000 mg 2xd w/ or w/out PNL HCQ: 300 mg/d Combo: if patient reaches remission in first year, patietn could be tapered and PNL could be discontinued at 9 and 18 mos N: D1: 97 D2: 98 Mean age, yrs: D1: 45 D2: 46 Sex, % female: D1: 58 D2: 66 Race, % white: NR	SJC, mean: D1: 14	At 2 years Eroded joints, number: D1: 2 D2: $3 (P = 0.006)$ btw groups Progression of radiological joint damage lower in combination versus monotherapy Larsen Erosion Score improvement: D1: 2 D2: $10 (P = 0.002)$ Median increase in Larsen Score: D1: 1.5 D2: $2.0 (P < 0.001)$ Clinical remission, %: D1: 37.9 D2: $18.4 (P = 0.011)$ ACR50, %: D1: 71 D2: $58 (P = 0.058)$ Median work disability per pt-observation yr, days: D1: 12.4 D2: $32.2 (P = 0.008)$ At 5 years Eroded joints, number: D1: 3 D2: 6	Overall: D1: 70 D2: 71 SAEs: D1: 3 D2: 5 Cardiovascular Events: D1: 1 MI D2: 2 MIs Malignancies: 1 prostate cancer; 1 multiple myeloma URTI: 1 pneumonia	Overall Attrition Rate, %: 195 started txt (97/98) 178 completed 2 yrs (87/91); 160 at 5 yrs (78/82) ITT Analysis: Yes Quality Rating: Fair

24 mos (5 yr followup)

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
Characteristics Author, year, study name, if applicable Nadareishvili et al., 2008 ¹³⁵ Country and setting US, multicenter Source of funding Centocor, Sanofi-Aventis, Bristol Myers Squibb, Abbott, Amgen, Wyeth-Australia, Merck, Pfizer	Criteria Inclusion Criteria RA, Ischemic stroke Exclusion	Interventions Interventions, Dose D1: Other: Patients grouped by Case vs. Control; included txts relevant to this review: PRED, LEF, SSZ, HCQ, MTX, and anti-TNF (combined ETA, INF, and ADA) dosing not reported Number in group D1: 41 D2: 791	Treatment Characteristics Mean disease duration, years (SD)	ACR ACR 20: No measures of efficacy or QOL were reported for this article, go to AEs ACR 50: NR ACR 70: NR HAQ, NR DAS NR SF-36 NR	Overall NR Overall adverse events reported, n: NR Serious adverse events NR Malignancies NR Respiratory events NR Other infections
Research objective To determine risk of stroke in patients with RA and risk factors associated with stroke Study design Nested Case / Control, Prospective Cohort Study			n age (years) It stoke: 69.8 9.9 It stoke: 69.8 It	Radiographic measures NR Quality of life scales NR Others, (please name); mean difference/absolute difference (CI/SD/P Value) NR	NR GI NR Other Results of multivariate analysis of association of RA therapy (within a 6mo window prior to event) and ischemic stroke in RA: PRED OR: 1.75, P =
Overall N 269 Duration of study varied (prospective cohort) Quality rating Fair: Possibility that					 0.114 [95%CI 0.87-3.53]; MTX OR: 0.63 P = 0.191 [CI: 0.32-1.26]; Anti-TNF OR: 0.79, P = 0.584 [CI: 0.34-1.82]. A significant increased risk was found for Rofecoxib (not included in this
databank has a higher proportion of moderate-serverly ill RA pts decreases generalizability. Use of covariates in statistical analyses			NR		review). • An analysis assessing length of treatment exposure was associated with stroke; a univariate but not multivariate effect

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
decreases potential for bias. Recall bias avoided by a review of medical records of pts reporting strokes.					 was seen for PRED OR: 1.19, P = 0.039 [CI: 1.00- 1.40]; no other drug effects seen. Further analysis suggested a possible dose effect for PRED.
					NOTE: A second set of analyses were conducted using only drug pts were on at baseline. I did not think this was as comprehensive as this analysis so I did not include it - SWL

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
Author, year, study name, if applicable Naranjo et al., 2008 ¹³⁶ Country and setting Multinational, multicenter Source of funding Abbott Laboratories Research objective Assess prevalence of CV morbidity in RA patients and its association with traditional risk factors, clinical features, and DMARD use Study design Cross – Sectional Cohort Study Overall N 4363 Duration of study varied (prospective cohort) Quality rating Fair	Inclusion Criteria RA diagnosis Exclusion Criteria NR	Interventions, Dose D1: MTX D2: Glucocorticoids D3: Antimalarials D4: SSZ D5: Gold D6: LEF D7: TNF-alpha blockers Dosing not reported Number in group Overall: 4364 Mean age (years) Overall: 57 Sex, % female Overall: 78 Race, % white Overall: 90 Race, % black NR Ethnicity, Latino NR	Mean disease duration, years (SD) Overall: 11 yrs (9) Patients with early RA, three years or less, % NR Treatment resistant, % NR Tender Joint Count, mean (SD) NR Swollen Joint Count, mean (SD) NR Corticosteroid use, % NR DMARD use, % NR MTX naïve, % NR Baseline DAS score, mean (SD) NR Required treatment for latent TB NR Other population characteristics, %, NR	ACR NR HAQ NR DAS NR SF-36 NR Radiographic measures NR Quality of life scales NR Others, (please name); mean difference/absolute difference NR	Overall NR Overall adverse events reported, n: NR Serious adverse events NR Malignancies NR Respiratory events NR Other infections NR GI NR Other • All results adjusted for age, gender, disease activity/severity, rheumatoid arthritic characteristics (e.g. RF+), and traditional cardiovascular risk factors (e.g. hypertension). • CV All/Ml/Stroke: MTX 0.85(0.81-0.89)/0.82 (0.74-0.91)/0.89 (0.82-0.98), Glucocorticoids: 0.95 (0.92-0.98)/ 0.96(0.91-1.0)/0.98(0.93-1.03), SSZ 0.92 (0.87-0.98)/ 0.90 (0.79-1.03) • LEF 0.59 (0.43-0.79)/0.52(0.26-1.06)/0.91

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
					 TNF-alpha 0.64 (0.49- 0.83)/0.42 (0.21-0.81)/ 0.64 (0.39-105)

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
Author, year, study name, if applicable Nishimoto et al, 2009, SATORI ¹³⁷	 Inclusion Criteria Ages 20 to 75 years old Active RA as define byACR 	Interventions, dose D1: MTX: 8 mg/wk (control) Placebo toculizumab placebo	Mean disease duration, years D1: 8.7 yrs ± 7.1 D2: 8.5 ± 8.4	ACR ACR 20 (% at week 24): D1: 25 D2: 80.3 P = 0.001	Attrition/withdrawal Overall, n (%): D1: 33 (50) D2: 7 (11) Overall: 40 (31.5)
Country and setting 25 sites in Japan, setting NR Source of funding Chugai Pharmaceutical	 RA > 6 mos MTX 8 mg/week for at least 8 weeks prior to enrollment 	D2: Tocilizumab: 8 mg/kg every 4 wks Placebo MTX placebo Number in group	Patients with early RA, three years or less, % NR Treatment resistant, % NR	ACR 50 (% at last observation): D1: 10.9 D2: 49.2 ACR 70 (% at last	Withdrawals due to adverse events, n (%): D1: 3 (4.6) D2: 2 (3.28) Overall: 5 (3.94)
Research objective Investigate efficacy and safety of	At least 6 tender joints (of 49 evaluated)At least 6	D1: 66 D2: 61 Overall: 127	Tender Joint Count, mean D1: 14.2 ± 8.6 D2: 13.8 ±7.5	observation): D1: 6.3 D2: 29.5	Withdrawals due to lack of efficacy, n (%): D1: 20 (30.3)
tocilizumab monotherapy in pts with inadequate	swollen joints (of 46 evaluated)	Mean age, years (SD) D1: 50.8 ± 12.2 D2: 52.6 ± 10.6	Swollen Joint Count, mean D1: 12.7 ± 7.5 D2: 12.4 ± 5.9	HAQ (%) Decrease of at least 0.22 units in HAQ at last OBS	D2: 1 (1.64) Overall: 21 (16.6) Note: In control (MTX) group,
response to MTX Study design Controlled Trials	• ESR of at least 30 mm/h or CRP of at least	Sex, % female D1: 75.0 D2: 90.2	Corticosteroid use, %	D1: 34 D2: 67 P = 0.001	2 patients withdrew before treatment but after randomization, these are
Overall N 127	10 mg/l at enrollment • Inadequate response to	Overall: 81.1 Race, % white NR	# failed DMARD use, (mean/range) D1: 3.6 (1-8) D2: 3.3 (1-8)	DAS28 at last OBS (%) Good D1: 3.2	included in attrition count Overall adverse events reported, n (%):
Duration of study 24 wks	MTX defined aspresence of active disease	Race, % black NR	MTX naïve, % D1: 0	D2: 65.5 Good or Moderate D1: 39.7	D1: 104 AE in 46/64 patients (71.9) D2: 211 AE in 56/61 patients
Quality rating Fair	 White blood cell counts at least 3.5 x 109/l 	Ethnicity, Latino NR	D2: 0 Overall: 0 Baseline DAS28 score	D2: 96.6 P = 0.001	(91.8) Overall: 315 AE in 102/125 patients (81.6)
	 Lymphocyte counts at least 0.5 x 109/l 		D1: 6.2 ± 0.9 D2: 6.1 ± 0.9	SF-36 NR	Serious adverse events NR
	Platelet count of at least lower		Required treatment for latent TB NR	Radiographic measures NR	Hepatotoxicity/elevated liver enzymes, n:
	limit of normal as defined by respective local		Other population characteristics, %, (CI/SD/P	Quality of life scales NR	D1: 0 D2: 0 Overall: 0
	laboratory used • Sexually active		value) D1:	Others Remission at last OBS	Malignancies NR

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
	premenopausal women were required to have		 Functional class I/II/III/IV: 7:50:7:0 RA stage I/II/III/IV: 	(defined as DAS28: 2.6): • MTX arm: 1.6 • TOC arm: 43.1%	Respiratory events Tuberculosis: NR
	a negative urine pregnancy test at entry to study and to use		3:18:17:26 D2: • Functional class I/II/III/IV: 2:49:10:0	• P = 0.001	Pneumonia, n (%): D1: 1 (1.56) D2: 1 (1.64) Overall: 2 (1.6)
	effective contraception during study period.		• RA stage I/II/III/IV: 1:20:22:18		Upper respiratory infection, (%): D1: "upper respiratory tract Inflammation" 4 (6.3)
	Exclusion Criteria				D2: Inflammation 3 (4.9) Overall: 7 (5.6%)
	 Treatment with anti-TNF agents or LEF (within 12 weeks prior tofirst dose) Plasma 				Other infections Stomatitis, n (%): D1: 0 D2: 7 (11.5) Overall: 7 (5.6)
	exchange therapy or surgical treatments (within 4 weeks prior to first				GI NR Diarrhea (%) D1: 1 (1.6) D2: 4 (6.6) Overall: 5 (4)
	dose) • DMARDs other than MTX or immuno-suppressants (within 2 weeks prior to first dose)				Other Fractures, n: D1: 2 (3.13%) (spinal compression fracture an femoral neck fracture) D2: NR Overall: 2 (1.6%)
	 Functional class IV using Steinbrocker's criteria Aspartate transaminase 				Infusion/injection site reactions, n (%): D1: NR D2: 7 (8 events 7 patients) (11.5) Overall: 7 (5.6)
	(AST), Alanine				Skin rash, n (%):

Otrodes	Inclusion and	Observations	Decelled Discount		
Study Characteristics	Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
Characteristics	transaminase	interventions	Treatment Characteristics	Health Outcomes	D1: 2 (3.1)
	(ALT) and				D2: 4 (6.6)
	serum				Overall: 6 (4.8)
	creatinine at				` ,
	least 1.5-fold				Headache, n (%):
	upper limit of				D1: 2 (3.1)
	normal, were				D2: 4 (6.6)
	HBs antigen				Overall: 6 (4.8)
	and/ or HCV				Nasopharyngitis, n (%):
	antibody				D1: 7 (10.9)
	positive, had				D2: 11 (18.0)
	pulmonary				Overall: 18 (14.4)
	fibrosis or active				Serious AE (pneumonia,
	pulmonary				spinal compression fracture
	disease				femoral neck fracture), n (%
	 History of 				D1: 3/64 (4.7)
	serious adverse				D2: 4/61 (6.6)
	drug reaction to				Llumpulinido maio un (0/)
	MTX,				Hyperlipidemia, n (%): D1: 1 (1.6)
	concomitant				D2: 4 (6.6)
	pleural effusion,				Overall: 5 (4)
	ascites, varicella				Overall. 5 (4)
	infection				Lab test abnormalities, n (%
	Excessive users				D1: 15 (23)
	of alcohol on a				D2: 34 (56)
	regular basis.				Overall: 49 (39.2)
	Patients were				
	also excluded if				
	they had				
	significant				
	cardiac, blood, respiratory				
	system,				
	neurologic,				
	endocrine,				
	renal, hepatic,				
	or				
	gastrointestinal				
	disease, or had				
	an active				
	infection				

requiring medication within 4 weeks before first dose or medical history of a serious allergic reaction. Sexually active premenopausal women were required to have negative urine pregnancy test at entry to study and to use effective contraception during study period. Oral corticosteroids (PNL, less than or equal to 10	
within 4 weeks before first dose or medical history of a serious allergic reaction. Sexually active premenopausal women were required to have negative urine pregnancy test at entry to study and to use effective contraception during study period. Oral corticosteroids (PNL, less than	
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Oral corticosteroids (PNL, less than)	
corticosteroids (PNL, less than	
(PNL, less than	
or equal to 10	
mg/day) were	
allowed	
ifdosage had	
not been	
changed within 2 weeks.	

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
Author, yr: Nuki et al. 2002 ¹³⁸ Country, Setting: Multinational multicenter Funding: Amgen	 Inclusion Criteria: ACR criteria Disease duration of ≥ 12 mos < 8.5 yrs Exclusion Criteria: NR is this article 	Interventions, dose: D1: Anakinra D2: Placebo N: D1: 351 D2: 121 Mean age, yrs: D1: 53.4 D2: 52.2	Mean disease duration, yrs: D1: 4.1 D2: 3.7 TJC, mean: D1: 34.8 D2: 32.8 SJC, mean: D1: 26.3	See AEs	Number of occurrences per subject-yr of exposure n for safety: D1: 427 D2: 121 ISRs: D1: 2.00	Overall Attrition Rate, %: At 24 wks 27% At 76 wks 32% of those that continued
Research Objective: Long-term efficacy of anakinra, in pts with RA		Sex, % female: D1: 76.6 D2: 70.2 Race, % white: NR	D1: 20.3 D2: 25.6 DMARD use, %: D1: 73.5 D2: 80.0 Corticosteroid use, %		D2: 0.82 Frequency of injection site reactions (ISRs) was 0.82 per patient-yr of exposure in placebo group (first 24 wks) and 1.01, 2.43, and 3.73 for 30-mg, 75-mg,	into extension ITT Analysis: Yes Quality Rating:
Study Design: RCT plus extension			D1: 43.6 D2: 39.7 MTX naïve, %:		and 150-mg doses over 72 wks	Fair
Overall N: 472 (309 enrolled in 54 wk extension)			NR DMARD Txt resistant, %: NR			
Study Duration: 76 wks			Patients with Early RA (≤ 3 yrs): NR			

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events (%)	Analysis and Quality Rating
Author, year: O'Dell et al., 1996 ¹³⁹ Country, Setting: US, multicenter (Rheumatology clinics) Funding: Lederle, Sanofi, Winthrop, and Pharmacia provided study drugs Research Objective: To determine whether DMARDs were effective as combination therapy for RA and whether combinations studied had better efficacy than MTX alone Study Design: RCT Overall N 102 Study Duration: 2 yrs	mos • Poor response to at least 1 DMARD • At least 3 of: ESR ≥ 28 mm/hr, morning stiffness ≥ 45 mins, ≥ 8 tender joints, ≥ 3 swollen joints; stable therapy w/ Css ≤ 10 mg/day; • NSAIDs allowed Exclusion Criteria: • Pregnant or lactating	D1: MTX (7.5 to 17.5 mg/week) D2: SSZ (1 g/day) + HCQ (400 mg/day) D3: MTX + SSZ+HCQ N D1: 36 D2: 35 D3: 31 Mean age, yrs:	Mean disease duration, yrs: D1: 10 D2: 6 D3: 10 TJC, mean: D1: 31 D2: 32 D3: 29 SJC, mean: D1: 31 D2: 31 D3: 27 DMARD use, %: All groups: 100 Current Corticosteroid use, %) D1: 53% D2: 46% D3: 52% MTX naive, %: D1: 92 D2: 89 D3: 87 Treatment resistant, %: All 100 Pts with Early RA (≤3 yrs): All groups: 0 Baseline DAS, mean: NR Duration of morning	Outcome improved by at least 50%, as determined by whether 3 following requirements had been fulfilled (modified Paulus composite criteria): morning stiffness of less than 30 minutes' duration, decreased by 50%; joint tenderness decreased by 50%; joint swelling decreased by 50%; joint swelling decreased by 50%; ESR < 30 mm per hour in women and < 20 mm per hour in men Comparison between MTX + SSZ+HCQ and each of other groups with respect to good responses was statistically significant (<i>P</i> = 0.003 by log-rank test) At 2 years Maintenance of at least 50% improvement at 9 mos to end of 2-year treatment period (total n=50): D1: 33%, 12/36 pts D2: 40%, 14/35 pts D3: 77%, 24/31 pts (D3 vs D2, <i>P</i> = 0.003 and D3 vs. D1, <i>P</i> < 0.001 for respective comparisons between D3 (3-drug group) and D2; D3 vs D1)	Similar withdrawal rates due to Adverse Events across groups Treatment with all 3 drugs did not produce more toxic effects than did MTX alone D1: discontinued treatment because of toxic effects: • 2 w/ pneumonia; • 1 each had stomatitis, diarrhea, nausea, and vertigo; • 1 pt had sepsis and died. D2: 3 discontinued due to pneumonia, diarrhea, and Crohn's disease; D3: 3 in 3-drug group discontinued due to nausea, cervical cancer, and weight gain. No pt had serum aspartate aminotransferase values more than twice upper limit of normal D3: higher serum creatinine values than D2 or D1 at nine mos (P = 0.03)	

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events (%)	Analysis and Quality Rating
	Retinal disease Macular degeneration Active peptic ulcer disease		stiffness (minutes): D1: 190 D2: 156 D3: 135 RF: D1: 89% D2: 85% D3: 84%			

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
Author, yr: O'Dell et al., 2002 ¹⁴⁰ Country, Setting: US, multicenter (7) Funding: Pharmacia & Upjohn, Mylan,Sanofi- Winthrop- meds. Albert G. and Bernice F. Hansen Foundation Research	Inclusion Criteria: • Age: 19-80 yrs • Diagnosed with RA according to ACR criteria • Duration of condition: > 6 mos • Active disease with at least 3 of 4 following features: ESR > 28 mm/hour, duration of morning stiffness ≥ 45 minutes, ≥ 8 tender joints, and ≥ 3 swollen joints Exclusion Criteria:	Interventions, dose: D1: MTX and HCQ D2: MTX and SSZ D3: MTX, HCQ, and SSZ: All pts MTX: accelerated from 7.5 mg/wk to 17.5 mg/wk in all pts not in remission SSZ: escalated from 500 mg twice daily to 1gram twice daily in pts not in remission HCQ: 200 mg twice daily N: D1: 58	Mean disease duration, yrs: D1: 7.9 +/- 10 D2: 5.8 +/- 5.9 D3: 6.9 +/- 8.4 TJC (mean +/- SD): D1: 15.7 +/- 8.2 D2: 15.6 +/- 7.4 D3: 19.7 +/- 9.2 SJC, mean: D1: 21.1 +/- 8.3 D2: 19.1 +/- 7.9 D3: 24.0 +/- 8.8 DMARD use, %: NR Corticosteroid use, %	At 2 years ACR 20, %: D1: 60, 35/58 pts D2: 49 27/55 pts D3: 78, 45/58 pts (D3 vs D2; P = 0.002) (D3 vs. D1; (P = 0.05) ACR 50, %: D1: 40 D2: 29 D3: 55 (D3 vs D2; P = 0.005) (D3 vs. D1, P = 0.10) ACR 70, %: D1: 26 D2: 18 D3: 16	Overall: D1: 8.6 D2: 9.1 D3: 6.9 Infections: D2: 1.8 Serious Infections: D1: 1.7 Cardiovascular Events: D1: 1.7 (1 MI) Headache: D2: 1.8 Hepatotoxicity: D3: 1.7	Overall Attrition Rate, %: 14.6% (25/171 subjects) ITT Analysis: Yes Quality Rating: Good
Objective: Efficacy of combination therapy with MTX, HCQ, and SSZ to MTX + HCQ and to MTX + SSZ in txt of RA Study Design: RCT Overall N: 171 Study Duration: 2 yrs	 Previous combination therapy with any medications studied Significant liver or renal disease Stage IV disease Allergy to any study drugs women of childbearing age not using adequate contraception Significant hematologic, pulmonary, or CVD 	D2: 55 D3: 58 Overall: 171 Mean age, yrs: D1: 50.9 D2: 52.5 D3: 48.9 Overall: 50.9 Sex, % female: D1: 78 D2: 84 D3: 76 Overall: 79 Race, % white: NR	D1: 71 D2: 56 D3: 50 MTX naive, %: D1: 43.1 D2: 54.5 D3: 41.4 Txt resistant, %: NR Pts with Early RA (≤3 yrs): NR Baseline DAS, mean: NR % RF positive: D1: 88 D2: 88 D3: 89	(P = NS) Changes in values for ACR core set, improvement in triple therapy group was greater than either of other 2 txt groups. TJC differences were statistically significant, D3 vs D1 (P ≤ 0.005) Reduced morning stiffness, minutes: D1: -59.2 +/- 103.3 D2: -53.2 +/- 89.5 D3: -109.3 +/- 86.4 minutes (D3 vs. D1; P = 0.01) (D3 vs. D2; P = 0.006)	Malignancies: D3: 1.7 (1 non- Hodgkins lymphoma)	

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
			ESR:			
			D1: 28.5 +/- 20.3			
			D2: 34.1 +/- 26.5			
			D3: 30.1 +/- 21.0			

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
Author, yr: O'Dell et al., 2006 ¹⁴¹ Country, Setting: US, multicenter Funding: NR Research Objective: Determine safety and efficacy of ETA in combination with SSZ, hydroxychloro- quine, IM Gold over 48 wks Study Design: Observational Overall N: 119 Study Duration: 48 wks	Age: 19-75Diagnosed	Interventions, dose: D1: ETA (25mg sc twice weekly) + SSZ D2: ETA (25mg sc twice weekly) + HCQ D3: (Gold + ETA) N: D1: 50 D2: 50 D3: 19 Mean age, yrs: D1: 47 D2: 49.7 Sex, % female: D1: 78 D2: 76 Race, % white: D1: 88 D2: 92	Mean disease duration, yrs: D1: 8.1 D2: 8.7 TJC, mean: D1: 16.5 D2: 16.4 SJC, mean: D1: 17.7 D2: 17.1 DMARD use, %: NR Corticosteroid use, %: NR Txt resistant %: NR Pts with Early RA (≤3 yrs): NR Baseline DAS, mean: NR HAQ: D1: 1.32 D2: 1.33	Pts in each ETA combination showed significant improvement at 24 and 48 wks No significant differences for ACR20/50 BETWEEN combination groups at 24 or 48 wks (NR). At 24 and 48 wks, ETA/SSZ combo showed highest ACR70 response (NR) At 24 wks change in HAQ SSZ -0.56+/-0.77 HCQ -0.71+/-0.65 P = NR	NR	Overall Attrition Rate, %: 30% ITT Analysis: Yes Quality Rating: Fair

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
Author, year, study name, if applicable Pallavicini et al., 2010 ¹⁴³ Country and setting Italy, 4 tertiary centers and 2 general population cancer registries Source of funding NR Research objective To compare cancer risk in a RA cohort population treated with TNF antagonists, and identify the characteristics of the patients at higher risk Study design Observational Overall N 1064 Duration of study	Inclusion Criteria RA patients treated with anti-TNF agents Exclusion Criteria NA	Comparisons (dosage and frequency) D1: ETN: dosage and frequency NR INF: dosage and frequency NR ADA: dosage and frequency NR D2: General population Number in group D1: 1064 Mean age (years) D1: 55.84 Sex, % female D1: 83 Race, % white D1: NR Race, % black NR Ethnicity, Latino NR	Mean disease duration, years D1:<5 yrs=324; 5-10 yrs=338; >10 yrs=402 TJC, mean D1: 11.35 SJC, mean D1: 10.06 Corticosteroid use, % D1: NR DMARD use, %: D1: 100 MTX naïve, %: D1: NR Treatment resistant, %: D1: 100 Patients with early RA, three years or less, %: D1: NR Baseline DAS score D1: 5.90 Required treatment for latent TB D1: NR Other population characteristics, %, (CI/SD/P value): NR	mean difference/absolute difference (CI/SD/P Value): NR Others, (please name); mean	Overall NR Serious adverse events: NR Malignancies: Risk of cancer: ETN: reference group ADA: HR 1.66 (95% CI 0.50-5.52); P=0.407 INF: HR 0.59 (95% CI 0.17-2.09); P=0.412 Respiratory events: NR Other infections: NR GI: NR Other: NR	Quality rating for efficacy/effectiveness? NR Quality rating for observational studies Fair
1064 Duration of				Others, (please name);		

Inclusio Study Exclusio Characteristics Criteria		Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
Pan, S.M. et al.; 2009 ¹⁴⁴ Country and setting Switzerland; doctors offices, non-academic hospitals, academic centers Source of funding Swiss Clinical Quality Management Existe Swiss Qualit Manage Rheur Arthrit (SCQI) registr with a TNF a betwe Janua	Clinical frequency NR D2: ETN: dosage and frequency NR D3: ADA: dosage and frequency NR D3: ADA: dosage and frequency NR M-RA) by treated n anti-gent en cy 1997 ecember Mean age (years) D1: 53, SD 13 D2: 54, SD 14	D3: 10 yrs, SD 9	D3 0.67 (0.45-0.97), P = 0.02; Acute systemic reaction: : D2 0.40 (0.21-	Overall Overall attrition/withdrawal, n: D1: 209 D2: 237 D3: 213 Overall: 659 Withdrawals due to adverse events, n: D1: 154 D2: 172 D3: 149 Overall: 318; $P = 0.093$ Withdrawals due to lack of efficacy, n: D1: 90 D2: 125 D3: 112 Overall: 327; $P = 0.17$ Adherent/compliant, n: D1: 386 D2: 650 D3: 669 Overall: 1705 Overall adverse events reported, n: D1: 108 D2: 118 D3: 92 Overall: 318 Serious adverse events Death, n: D1: 2 D2: 0 D3: 2 Overall: 4; $P = 0.33$

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
			(SD) D1: 4.27, SD 1.52 D2: 4.23, SD 1.53 D3: 4.14, SD 1.42 P = 0.066	(0.55-1.19), D3 0.85 (0.58-1.25), $P = 0.55$; All nontoxic causes: D2 0.90 (0.64-1.26), D3 0.82 (0.58-1.18), $P = 0.38$; Ineffectiveness: D2	Malignancy), n: D1: 8 D2: 5 D3: 2 Overall: 15; <i>P</i> = 0.12
			Required treatment for latent TB NR	0.95 (0.71-1.26), D3 0.82 (0.61-1.11), <i>P</i> = 0.42; Remission: D2 0.85 (0.22-	Respiratory events
			Other population characteristics, %, (CI/SD/P value) D1: Glucocorticoids: 52%; Failure of previous anti-TNF agent: 23%; RADAI: 4.29, SD 2.14 D2: Glucocorticoids: 52%;; Failure of previous anti-TNF agent: 19%; RADAI: 4.31, SD 2.24 D3: Glucocorticoids: 49%; Failure of previous anti-TNF agent: 27%; RADAI: 4.16, SD 2.15 Overall: Glucocorticoids: P = 0.409; Failure of previous anti-TNF agent: P = 0.001; RADAI:	3.3), D3 1.10 (0.36-3.44), P = 0.91; Desire for	Other infections NR GI NR Other Infusion/injection site reactions, n: D1: 50 D2: 24 D3: 31 Overall: 105; $P = 0.001$ Infection, n: D1: 26 D2: 41 D3: 22 Overall: 89; $P = 0.088$ Dermatologic disease, n: D1: 16
			P = 0.37		D2: 20 D3: 29 Overall: 65; <i>P</i> = 0.09
					General (inc fatigue, headache, weight changes n: D1: 14 D2: 13 D3: 9 Overall: 36; $P = 0.46$

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
					D1: 15 D2: 13 D3: 21 Overall: 49; <i>P</i> = 0.22
					Any other AEs: Opthamologic: D1: 3 D2: 7 D3: 2 Overall: 12, $P = 0.29$ Ear nose throat: D1: 2 D2: 3 D3: 0 Overall: 5, $P = 0.29$ Cardiovacular: D1: 7 D2: 14 D3: 6 Overall: 27, $P = 0.23$ Pulmonary: D1: 3 D2: 10 D3: 5 Overall: 18, $P = 0.22$ Gastroenterological: D1: 11 D2: 17 D3: 16 Overall: 44, $P = 0.67$ Renal disease: D1: 4 D2: 7 D3: 0 Overall: 11, $P = 0.03$ Hematologic: D1: 2 D2: 4 D3: 2 Overall: 8, $P = 0.75$ Osteoarticular:

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
					D1: 6
					D2: 4
					D3: 4
					Overall: 14, $P = 0.63$

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
Author, year, study name, if applicable Russell et al., 2006 and 2007, AIM ¹⁴⁵ ; Kremer et al.,	Inclusion Criteria Diagnosis of RA according to ARA and classification	D1:MTX: 15 mg or more per weekAbatacept: fixed dose	Mean disease duration, years (SD) D1: 8.5 (7.3) D2: 8.9 (7.1) Overall: 8.6	ACR mean difference/ absolute difference (%) ACR 20: At 6 months: D1: 67.9 (N: 424)	Attrition/withdrawal Overall, n: D1: 48 D2: 57 Overall: 105
2006 ¹¹⁶ , AIM Country and setting NR Source of funding	within functional status I, II, or III according to revised criteria of ACR	of 10 mg/kg at days 1, 15, 29, and every 28 days thereafter for up to 1 year D2:	Patients with early RA, three years or less, % NR Treatment resistant, %	D2: 39.7 (N: 214) P = 0.001, difference 28 percentage points, 95% CI: 19.8 - 36.7 percentage points	Withdrawals due to adverse events, n: D1: 18 D2: 4
Bristol-Myers Squibb Research objective Examine impact of ABA tx on HRQOL in		 MTX: 15 mg or more per week Placebo: dose NR Number in group 	NR Tender Joint Count, mean (SD) NR	At 1 year: D1: 73.1 (N: 424) D2: 39.7 (N: 214) Overall: difference: 33.4 percentage points, 95%	Overall: 22 Withdrawals due to lack of efficacy, n: D1: 13 D2: 40
Study design Controlled Trials Overall N	MTX for at least 3 months, and at a stable dose for 28 days before	D1: 433 D2: 219 Overall: 652 Mean age (years) D1: 51.5	Swollen Joint Count, mean (SD) NR Corticosteroid use, % NR	CI: 25.1 - 41.7 ACR 50: At 6 months: D1: 39.9 (N: 424)	Overall: 53 Adherent/compliant, n: D1: 385 D2: 162 Overall: 547
Duration of study 12 mos Quality rating Fair	 treatment Washout of all DMARDs other than MTX at least 28 days before 	D2: 50.4 Overall: 51.5 Sex, % female D1: 77.8 D2: 81.7	DMARD use, % D1: 100 D2: 100 Overall: 100	D2: 16.8 (N: 214) Overall: Difference at 6 mos: 23 percentage points, 95% CI: 15 - 31.1 percentage points (P = 0.001)	Overall adverse events reported, n: D1: 378 D2: 184 Overall: NR
	treatment • Active disease • Characterized by > 10 swollen joints, > 12	Overall: 79.2 Race, % white D1: 87.5 D2: 88.1 Overall: 87.7	MTX naïve, % D1: 0 D2: 0 Overall: 0 Baseline DAS score, mean	At 1 year: D1: 48.3 (N: 424) D2: 18.2 (N: 214) Overall:Difference at 1 year: 30.1 percentage	Serious adverse events Death, n: D1: 1 D2: 1 Overall: NR
	tender joints, and CRP > 10 mg/l. Exclusion	Race, % black NR Ethnicity, Latino	(SD) D1: 6.4 D2: 6.4 Overall: NR	points, 95% CI: 21.8, 38.5 percentage points (P = 0.001) ACR 70:	Cardiac disorders, n: D1: 4 D2: 2
	Criteria NR	NR	Required treatment for latent TB NR Other population	At 6 months: D1: 19.8 (N: 424) D2: 6.5 (N: 214) Overall: Difference at 6	Hypertension: D1: 24 D2: 3 Overall: NR

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
			characteristics, %, (CI/SD/P value) MTX dose (mg/week):	mos: 13.3 percentage points, 95% CI: 7.0 - 19.5 percentage points (<i>P</i> =	Malignancies NR
			D1: 16.1 D2: 15.7	0.001)	Neoplasms, n: D1: 4
			Pain (VAS 100 mm) : D1: 63.3	At 1 year: D1: 28.8 (N: 424) D2: 6.1 (N: 214)	D2: 2 Overall: NR
			D2: 65.9 Patient global assessment of	Overall: Difference at 1 year: 22.7 percentage	Respiratory events NR
			disease activity (VAS 100 mm): D1: 62.7	points, 95% CI: 15.6 - 29.8 percentage points (P = 0.001) HAQ-DI (%)	Other infections, n Nasopharyngitis: D1: 66
			D2: 62.8 DAS28 (CRP): D1: 6.4 D2: 6.4	Significantly Improved D1: 63.70 D2: 39.30	D2: 25 Pharyngitis: D1: 26 D2: 10
			SF-36 Physical functioning (PF): D1: 28.7	Modified worst-case sensitivity analysis D1: 64 D2: 42	Sinusitis: D1: 18 D2: 15
			D2: 28.3 SF-36 Mental health (MH): D1: 39.4 D2: 39.7	Worst-case analysis D1: 64 D2: 64 Overall: [from #3475] <i>P</i> =	Bronchitis: D1: 18 D2: 12
			SF-36 Physical component summary (PCS): D1: 30.6	0.001, difference 24.4 (CI 15.9-32.9)	Serious Infections (not prespecified): D1: 17 D2: 5
			D2: 30.7 SF-36 Mental component summary (MCS): D1: 41.8	NR SF-36 D1: NR - reported in figure only	Bronchopneumonia: D1: 2 D2: 5
			D2: 40.8	D2: NR - reported in figure only	Cellulitis: D1: 1
			HAQ Disability Index (0-3): D1: 1.7 D2: 1.7	Overall: • PCS, abatacept vs. placebo, day 29: (P =	D2: 0 Sepsis:
			Fatigue (VAS 100 mm): D1: 63.2	0.01) • MCS, abatacept vs.	D1: 1 D2: 1

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
			D2: 66.2	placebo, 6 months: (P = 0.01) • Fatigue, abatacept vs. placebo, day 29: (P =	Abscess: D1: 1 D2: 0
				 0.01) Physical function, abatacept vs. placebo, day 57: (P = 0.05) 	Bacterial arthritis: D1: 1 D2: 0 Bronchopulmonary
				Radiographic measures D1: (Note: for radiographic data, N: 391 for abatacept group) mean	aspergillosis: D1: 1 D2: 0 Acute pyelonephritis:
				change from baseline for total score: 1.21 D2: (Note: for radiographic data, N: 195 for placebo group) mean change	D1: 1 D2: 0 Limb abscess: D1: 0
				from baseline • for total score: 2.32 Overall: NR	D2: 1 Overall: NR GI
				Quality of life scales NR	Nausea or vomiting, n: D1: 52 D2: 24
				Others, (please name) • Achieved normative PCS benchmark, 6 months:	Overall: NR
				abatacept: 47.1%, Placebo: 30.7, overall, Number Needed to Treat: 6	Abdominal pain, n: D1: 19 D2: 13 Overall: NR
				Achieved normative MCS benchmark, 6 months: abatacept: 60.4%, Placebo: 50.5%, overall,	Diarrhea, n: D1: 47 D2: 21
				Number Needed to Treat: 10 Percentage of patients	Dyspepsia, n: D1: 27 D2: 10
				who exhibited improved HRQOL scores by at least 0.5 SD over 12 month	Other Acute infusional adverse events, n:

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
				period of study: PCS (abatacept: 67.2%, Placebo: 51.1%, <i>P</i> = 0.001), HAQ (abatacept: 72.4%, Placebo: 55.2%, <i>P</i> = 0.001), Fatigue (abatacept: 64.9%, Placebo: 47.4%, <i>P</i> = 0.001)	D1:38 D2: 9 Per-Infusional adverse event n: D1: 106 D2: 37 Overall: NR Skin rash, n: NR Demyelenation or multiple
					sclerosis, n: NR Progressive multifocal leukoencephalopathy, n: D1: NR D2: NR Overall: NR
					Headache, n: D1: 76 D2: 26 Overall: NR
					Dizziness, n: D1: 40 D2: 16 Overall: NR
					Musculoskeletal and connective tissue disorders, n: D1: 20 D2: 10
					Cough, n: D1: 29 D2: 13
					Influenza, n: D1: 31 D2: 12

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
					Back pain, n: D1: 40 D2: 12

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
Author, yr: Saag et al., 1994 146 Country, Setting: US, multicenter Funding: General Clinical Research Program, NIH and Halifax Clinical Research Center Research Objective: To determine whether low dose steroids in txt of RA independently cause an increased incidence of steroid-associated SAEs Study Design: Observational Overall N: 224 Study Duration: At least one yr (4.9 +/-3.9 yrs of txt).	 Age > 16 Diagnosed according to ACR criteria On low-dose steroids ≥ 1 yr; matched for age, sex, race, and 	Interventions, dose: D1: Treated (with low dose long-term corticosteroids) D2: Untreated (with low dose long-term corticosteroids) Prednisone: corticosteroids, less than or equal to 15mg/d of PRE (or equivalent dose of an alternative steroid) N: D1: 112 D2: 112 Mean age, yrs: D1: 51.8 D2: 51.7 Sex, % female: D1: 75 D2: 75 Race, % white: D1: 98.2 D2: 98.2	Mean disease duration, yrs: D1: 4.9 +/-6.3 D2: 4.9 +/-6.7 TJC, mean: NR SJC, mean: NR Average no of SAARDs: D1: 0.47 +/-0.82 D2: 0.13 +/-0.37 Corticosteroid use, %: D1: 100 D2: NR MTX naive, %: NR Txt resistant %: NR Pts with Early RA (≤3 yrs): NR Baseline DAS, mean: NR RF: D1: 77.7 D2: 58.0 ESR: D1: 50 +/-29.7 D2: 36.4 +/-30.5 Extra-articular disease	n for Treated and Untreated groups respectively: Fracture 21 and 8; GI bleed or ulcer 11 and 4; cataracts 17 and 5; diabetic complications 8 and 3; herpes zoster 8 and 1; glaucoma 1 and 1; death 2 and 0. OR of 32.3 (95% CI,4.6, 220) (<i>P</i> = 0.0004) for pts treated with > 10 up to 15mg/d PRE equivalent; OR of 4.5 (95% CI,2.1, 9.6) (<i>P</i> = 0.0001) for pts treated with 5-10mg/d; Prednisone dose <5mg/d did not show a significant increase in risk of having an AE compared to the untreated group; *Although PRE average dose and cumulative dose had small but significant emsitmated relative risks (OR 1.21, 95%CI,1.0-1.5 for both), PRE use (yes/no) was most highly linked to infection (OR 8.0, 95% CI,1.0-64.0, <i>P</i> < 0.05) Fracture (OR 3.9, 95% CI,0.8-18.1, <i>P</i> < 0.09) First GI event: OR 3.3 (95% CI,0.9-12.1, <i>P</i> < 0.07)	Overall: D1: n:92 AEs D2: n:31 Serious Infections: D1: n:14 D2: n:4 Cardiovascular Events: D1: n:10 (4 myocardial infarctions, 6 strokes) D2: n:5 (4 myocardial infarction, 1 stroke)	Overall Attrition Rate, %: NA ITT Analysis: Yes Quality Rating: Fair

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
	 Bedridden status Referral 2nd to a steroid complication 		D1: 16.1% D2: 6.3%			

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
Author, yr: Salliot et al., 2006 ¹⁴⁷ Country, Setting: France, tertiary care Funding: NR Research Objective: To evaluate rate of infections in rheumatic pts treated with TNF-alpha blockers in daily practice and to determine potential risk factors of infections Study Design: Case series Overall N: 709 w/ follow-up	Exclusion Criteria	Interventions, dose: D1: Follow up D2: Follow up and	******	Health Outcomes 34.5% experienced infection during course of txt; Incidence rate: 48.2 per 100 PY • 6.2 percent experienced a serious infection; incidence rate: 10.4 per 100 PY • Infections by txt: • Any: INF 69.8 ETA 44.1 Adalimumab 37.3 per 100 PY • Serious: INF 10.2 ETA 12.3 Adalimumab 5.3 per 100 PY	Infections: D1: 50.5 D2: 34.2 D3: 15.3 URTI: D1: 13.4 D2: 9.4 D3: 9.9 UTI: D1: 5.1 D2: 1.1 D3: 1.6	•
at least once and 623 w/ with a control period Study Duration: NR			NR MTX use: D1: 43.7 D2: 43.6			

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating											
Author, yr: Schaible et al., 2000 ¹⁴⁸	Inclusion Criteria: 12 clinical trials Exclusion	Infliximab	duration, yrs:(headache, fever, chills,NRurticaria, chest pain:	(headache, fever, chills,	duration, yrs: (headache, fever, chills, A NR urticaria, chest pain: R TJC, mean: infliximab 17% versus NR placebo 7%; P = NR Infliximab nts had NR 0.5% of infliximab nts had	(headache, fever, chills, urticaria, chest pain:	(headache, fever, chills, urticaria, chest pain:	(headache, fever, chills,	(headache, fever, chills, urticaria, chest pain:	(headache, fever, chills,	(headache, fever, chills, urticaria, chest pain:	See outcomes	See outcomes	See outcomes	(headache, fever, chills,	See outcomes	Overall Attrition Rate, %:
Country, Setting: US; safety		Mean age, yrs: NR	TJC, mean: NR			ITT Analysis:											
database of efficacy trials	Sex, % female: SJC, mean: severe infusion reactions NR NR • Less than 2%		Not applicable														
Funding: Centocor		Race, % white:	DMARD use, %:	discontinued treatment because of infusion		Quality Rating:											
Research Objective: Long term safety of infliximab			Corticosteroid use, %: NR	reactions Infections: Infliximab 26% over 27 wks of follow-up versus		Fair											
Study Design: Observational			MTX naive, %: NR	placebo 16% over 20 wks of follow-up)													
Overall N: 963			Treatment resistant %: NR	 Incidence of serious infections per patient-yr infliximab 0.064 versus 													
Study Duration: Up to 3 yrs	y Duration: Patients with Early	placebo 0.114															
			Baseline DAS, mean: NR														

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
Author, yr: Schiff et al., 2006 ¹⁴⁹ Country, Setting: Mulitnational, multicenter Funding: Abbott Labs Research Objective: To assess safety of adalimumab in global clinical trials and postmarketing surveillance among pts with rheumatoid arthritis Study Design: Retrospective cohort study; postmarketing surveillance Overall N: 10,050 (12506 PY) Study Duration: Varied	 Pts from RCTs, open label extensions, and two phase IIIb 	Interventions, dose: NR N: 10,050 Mean age, yrs: NR Sex, % female: NR Race, % white: NR	Mean disease duration, yrs: NR TJC, mean: NR SJC, mean: NR DMARD use, %: NR Corticosteroid use, %: NR Txt resistant %: NR Txt resistant %: NR Pts with Early RA (≤3 yrs): NR Baseline DAS, mean: NR	Rates per 100 PY: TB: 0.27 Histoplasmosis: 0.03 Demyelinating diseases: 0.08 Lymphoma: 0.12 SLE/lupus-like syndrome: 0.10 Congestive heart failure: 0.28	NA .	Overall Attrition Rate, %: NA ITT Analysis: NA Quality Rating: Fair

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
Author, year, study name, if applicable Schiff et al., 2008, ATTEST ¹⁵⁰ Country and setting International, Multicenter Source of funding Bristol-Myers Squibb, Princeton, New Jersey, USA Research objective Evaluate change from baseline in DAS for ABA vs. placebo and reduction in DAS28 for IFX vs. placebo and ABA vs. IFX Study design Controlled Trials Overall N 431 Duration of study ABA vs. placebo and IFX vs. placebo: 197 days ABA vs. IFX: 365 days Quality rating Fair	Inclusion Criteria Treatment resistant ACR criteria for RA ≥ 18 years old RA ≥ 1 year, inadequate response to MTX, as demonstrated by ongoing active disease (at randomization SJC >10, TJC >12, and CRP >1 mg/dl All patients had received MTX >15 mg/week for >3 mos prior to randomization (stable for at least 28 days) and washed out all DMARDs (>28 days prior) except for MTX Anti-TNF-therapy naive Exclusion Criteria Positive screen for TB by purified protein derivative testing and	Interventions, dose D1: MTX: dosage and frequency NR Abatacept: 500-1000 mg, days 1, 15, 29, and every 28 days thereafter D2: MTX: dosage and frequency NR Placebo D3: MTX: dosage and frequency NR Flacebo D3: MTX: dosage and frequency NR IFX: 3 mg/kg, days 1, 15, 43, 85, and every 56 days thereafter Number in group D1: 156 D2: 110 D3: 165 Overall: 431 Mean age, years (SD) D1: 49.0 (12.5) D2: 49.4 (11.5) D3: 49.1 (12.0) Sex, % female D1: 83.3 D2: 87.3 D3: 82.4 Race, % white D1: 80.8 D2: 76.4 D3: 80.6 Race, % black NR	Mean disease duration, years (SD) D1: 7.9 (8.5) D2: 8.4 (8.6) D3: 7.3 (6.2) Patients with early RA, three years or less, % NR Treatment resistant, % NR Tender Joint Count, mean D1: 31.3 (13.9) D2: 30.3 (11.7) D3: 31.7 (14.5) Swollen Joint Count, mean D1: 21.3 (8.6) D2: 20.1 (7.0) D3: 20.3 (8.0) Corticosteroid use, % D1: 75.6 D2: 70 D3: 71.5 Overall: 72.6 DMARD use, % D1: 100 D2: 100 Overall: 100 MTX naïve, % D1: 0 D2: 0 D3: 0 Overall: 0 Baseline DAS score D1: 6.9 D2: 6.8 D3: 6.8	ACR ACR 20: Day 197 D1: 66.7 D2: 41.8 D3: 59.4 Overall: ABA vs. Placebo: (P = 0.001), IFX vs. Placebo: (P = 0.006) Day 365: D1: 72.4 D2: 41.8 D3: 55.8 Overall: ABA vs. IFX: estimate of difference of 16.7 (5.5, 27.8) ACR 50: Day 197: D1: 40.4 D2: 20 D3: 37 • Overall: ABA vs. Placebo: (P = 0.001), IFX vs. Placebo: (P = 0.004) Day 365: D1: 45.5 D2: 20 D3: 36.4 Overall: Overall: ABA vs. IFX: estimate of difference (95% CI): 9.1 (-2.2, 20.5) ACR 70: Day 197 D1: 20.5 D2: 9.1 D3: 24.2	Attrition/withdrawal Overall, n: D1: 17 D2: 6 D3: 24 Overall: 47 Withdrawals due to adverse events, n: D1: 4 D2: 1 D3: 12 Overall: 17 Withdrawals due to lack of efficacy, n: D1: 4 D2: 2 D3: 6 Overall: 12 Adherent/compliant, n: D1: 139 D2: 104 D3: 141 Overall: 384 Overall adverse events reported, n: Day 197 D1: 129 D2: 92 D3: 140 Overall: 361 Day 365 D1: 139 D2: 92 D3: 154 Overall: 293 Serious adverse events Death, n:
	chest x ray.		20. 0.0	Overall: ABA vs. Placebo: (P	·

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
		Ethnicity, Latino NR	Required treatment for latent TB	= 0.019), IFX vs. Placebo: (<i>P</i> = 0.002)	Day 197 D1: 1 D2: 0
		Other population characteristics, %, (CI/SD/P value) Erythrocyte sedimentation rate, mm/h (SD): D1: 49.4 (31.2) D2: 47.0 (32.6) D3: 47.8 (30.4) Overall: NR	Day 365: D1: 26.3 D2: 9.1 D3: 20.6 Overall: ABA vs. IFX): estimate of difference (95% CI): 5.7 (-4.2, 15.6) HAQ, mean difference/ absolute difference (CI/SD/P Value) D3: 1 Overall: 2 Day 365 D1: 1 D2: 0 D3: 2 Overall: 3 Overall: 3		
			HAQ-DI, 0-3 (SD): D1: 1.8 (0.6) D2: 1.8 (0.7) D3: 1.7 (0.7) Overall: NR	Proportion demonstrating improvement in physical function Day 197 D1: 61.5 D2: 40.9	Day 197: D1: 1 D2: 1 D3: 2 Overall: 4
			Total patients on concomitant medications, n (%): D1: 156 (100) D2: 110 (100) D3: 165 (100)	Overall: Proportion demonstrating improvement in physical function, ABA vs.	Day 365: D1: 1 D2: 1 D3: 2 Overall: 3
			Overall: 431 (100) MTX Dose, mg/week (SD):	Placebo: $(P = 0.001)$, IFX vs. Placebo: $(P = 0.005)$	Respiratory events Tuberculosis, n: 2863
			D1: 16.5 (3.7) D2: 16.6 (3.7) D3: 16.3 (3.6) Overall: NR	Day 365 D1: 57.7 D2: 40.9	Pneumonia, n: Day 197: D1:2 D2:0
			MTX Duration, months (SD): D1: 18.3 (20.0) D2: 23.7 (25.6) D3: 23.6 (26.8)	D3: 52.7 Overall: ABA vs. IFX: estimate of difference (95% CI): 5.0 (-6.5, 16.5)	D3:2 Overall: 4 Day 365:
			Overall: NR Corticosteroids, n (%): D1: 118 (75.6)	DAS Day 197 D1: 2.53 D2: 1.48	D1: 2 D2: 0 D3: 3 Overall: 5
			D2: 77 (70.0) D3: 118 (71.5)	D2: -1.48 D3: 2.25 Overall: ABA vs. Placebo: (<i>P</i>	Other infections Infections and Infestations

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
			Overall: 313 (72.6) NSAIDs, n (%): D1: 133 (85.3) D2: 93 (84.5) D3: 142 (86.1) Overall: 368 (85.4)	= 0.001), IFX vs. Placebo: (P = 0.001) Day 365 D1: -2.88 D2: -1.48 D3: -2.25 Overall: ABA vs. IFX: estimate of difference (95% CI): -0.62 (-0.96, - 0.29)	Day 197: D1: 2 D2:3 D3: 7 Overall: 12 Day 365: D1: 3 D2: 0 D3: 14 Overall: 17
				SF-36 NR Overall: Day 197, ABA vs. Placebo: PCS (<i>P</i> = 0.001) and MCS (<i>P</i> = 0.004) ofSF-36 IFX vs. Placebo: PCS (<i>P</i> = 0.002) and MCS (<i>P</i> = 0.027) of SF-36 ABA vs. IFX, PCS (difference of 1.93, 95% CI: 0.02, 3.84) MCS (difference of 1.92, 95% CI: -0.30, 4.15)	GI Nausea or vomiting, n: Day 197: D1: 2 D2: 1 D3: 6 Overall: 9 Day 365: D1: 3 D2: D3: 7 Overall: 10 Other
				Radiographic measures NR Quality of life scales NR Others, (please name) Day 197:	NR Headache, n: Day 197: D1: 2 D2: 2 D3: 7 Overall: 11
				 Proportion of patients achieving a good EULAR response, ABA: 20&, Placebo: 10.8%, IFX: 22.9% LDAS, ABA: 20.7%, 	Day 365: D1: 2 D2: D3: 7 Overall: 9

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
				 DAS28 (ESR)-defined remission, ABA: 11.3%, Placebo: 2.9%, IFX: 12.8% Day 365: Proportion of patients achieving a good EULAR response (ABA 32.0 vs. INF 18.5%, estimate of difference (95% CI): 13.5% (3.6, 23.3)) LDAS (ABA 35.3 vs. INF 22.4%, estimate of difference (95% CI): 12.9 (2.1, 23.7)) DAS28 (ESR)-defined remission (ABA 18.7 vs. INF 12.2%, estimate of difference (95% CI): 18.7 (-2.2, 15.2)) 	D1: 0 D2: D3: 2 Overall: 2 Day 365: D1: 1 D2: 0 D3: 4 Overall: 5 Autoimmune symptoms and disorders: Day 197: • ABA: 1 • Placebo: 1 • IFX: 1 Day 365:
					Hypotension Day 197: • ABA: 0 • Placebo: 0 • IFX: 7
					Day 365: • ABA: 0 • IFX: 8
					Flushing Day 197: • ABA: 1 • Placebo: 0 • IFX: 4
					Day 365 ABA: 1 IFX 5
					Dyspnea Day 197:

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
					ABA: 0Placebo: 0IFX: 4,
					Day 365: • ABA: 0 • IFX: 5;
					Urticaria Day 197: • ABA: 0 • Placebeo: 1 • IFX: 4
					Day 365: • ABA: 0 • IFX: 8;
					Pruritus Day 197: • ABA: 0 • Placebo: 0 • IFX: 2
					Day 365: • ABA: 0 • IFX: 5
					Sinusitis Day 197: • ABA: 1 • Placebo: 0 • IFX: 0
					Day 365: • ABA: 1 • IFX: 0
					Postoperative wound infection Day 197: • ABA: 0 • Placebo: 1

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
					IFX: 0Day 365:ABA: 0IFX: 1
					Soft tissue abscess Day 197: • ABA: 0 • Placebo: 1 • IFX: 0
					Day 365: • ABA: 0 • IFX: 0
					Infective bursitis Day 197: • ABA: 0 • Placebo: 1 • IFX: 0
					Day 365: • ABA: 0 • IFX: 0
					Bronchitis Day 197: • ABA: 0 • Placebo: 0 • IFX: 1
					Day 365: • ABA: 0 • IFX: 1
					Cellulitis Day 197: • ABA: 0 • Placebo: 0 • IFX: 1
					Day 365: ● ABA: 0

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
					 IFX: 1 Gastroenteritis Day 197: ABA: 0 Placebo: 0 IFX: 1
					Day 365: • ABA: 0 • IFX: 1
					Herpes zoster Day 197: • ABA: 0 • Placebo: 0 • IFX: 1
					Day 365: • ABA: 0 • IFX: 1
					Lung infection pseudomona Day 197: • ABA: 0 • Placebo: 0 • IFX: 1
					Day 365: • ABA: 0 • IFX: 1
					Pneumocystis jiroveci pneumonia Day 197: • ABA: 0 • Placebo: 0 • IFX: 1
					Day 365: • ABA: 0 • IFX: 1
					Infection skin ulcer

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
					Day 197: • ABA: 0 • Placebo: 0 • IFX: 0
					Day 365: • ABA: 1 • IFX: 0
					Encephalitis herpetic Day 197: • ABA: 0 • Placebo: 0 • IFX: 0
					Day 365: • ABA: 0 • IFX: 1
					Erysipelas, Day 197: • ABA: 0 • Placebo: 0 • IFX: 0
					Day 365: • ABA: 0 • IFX: 1
					Lobar pneumonia Day 197: • ABA: 0 • Placebo: 0 • IFX: 0
					Day 365: • ABA: 0 • IFX: 1
					Septic shock Day 197: • ABA: 0 • Placebo: 0

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
					• IFX: 0
					Day 365:
					 ABA: 0
					• IFX: 1

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
Author, year, study name, if applicable Schipper et al., 2009 ¹⁵¹ Nijmegen RA Inception Cohort Country and setting Netherlands Source of funding Wyeth Research objective To compare the efficacy of a swtich to MTX monotherapy with that of the addition of MTX to SSZ in RA patients who had failed SSZ monotherapy Study design Observational Overall N 230 Duration of study 52 wks	Inclusion Criteria • Early RA symptoms less than 1 year • Treatment resistant SSZ monotherapy • RA according to to 1987 ACR • ≥18 yrs old • No prior use of DMARDs Exclusion Criteria • Use of concomitant DMARD therapy other than MTX or SSZ at baseline	Comparisons (dosage and frequency) D1: MTX: 7.5 - 30 mg/week D2: • MTX: 7.5 - 30 mg/week • SSZ: 750- 3000 mg daily Number in group D1: 124 D2: 106 Mean age (years) D1: 63.8 D2: 61.8 Sex, % female D1: 70 D2: 74 Race, % white D1: NR D2: NR Race, % black D1: NR D2: NR Ethnicity, Latino D1: NR D2: NR	Mean disease duration, years median (IQR): D1:14 wks (5.3, 67.3) D2: 47 wks (20.2, 109.0) TJC, mean NR SJC, mean NR Corticosteroid use, % D1: 8 D2: 9 DMARD use, %: Previous DMARDS other than SSZ: D1: 15 D2: 13 MTX naïve, %: NR Treatment resistant, %: D1: 100 D2: 100 Patients with early RA, three years or less, %: D1: 100 D2: 100 Baseline DAS score D1: 5.1 (1.3) D2: 4.9 (1.3) Required treatment for latent TB D1: NR D2: NR Other population	ACR mean difference/absolute difference (CI/SD/P Value): NR HAQ, mean difference/absolute difference (CI/SD/P Value): NR DAS, mean difference/absolute difference/absolute difference (CI/SD/P Value): At 6 mo: D1: -0.9 (1.3) D2: -0.8 (1.3) Overall: difference b/t groups: -0.05 (0.16); P=0.737 At 12 mo: D1: -1.1 (1.3) D2: -0.9 (1.2) Overall: difference b/t groups 0.05 (0.15); P=0.756 SF-36, mean difference (CI/SD/P Value): NR Radiographic measures, mean difference/absolute difference (CI/SD/P Value): NR	Overall Overall attrition/withdrawal (n): D1: 42 D2: 53 Overall: 95 Withdrawals due to adverse events (n): D1: 23 D2: 12 Overall: 35 Withdrawals due to lack of efficacy (n): D1: 5 D2: 18 Overall: 23 Serious adverse events: NR Malignancies: NR Respiratory events: NR Other infections: NR Other: NR	Quality rating for efficacy/effectiveness? NR Quality rating for observational studies Fair

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
			characteristics, %, (CI/SD/P value): NR	Quality of life scales, mean difference/absolute difference (CI/SD/P Value): NR		
				Others, (please name); mean difference/absolute difference (CI/SD/P Value): NR		

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
Author, year, study name, if applicable Schneeweiss et al., 2007 152 Country and setting USA, Pennsylvania Medicare beneficiaries Source of funding Engalitcheff Arthritis Outcomes Initiatives, Baltimore, Maryland Research objective Assess association between initiation of anti-TNF therapy and risk of serious bacterial infections in routine care Study design Cohort Study Overall N 15,597 courses of therapy and 5,676 patient years of exposure Duration of study 1/1/1995 - 12/31/2003 Quality rating Fair	Inclusion Criteria • Medicare beneficiaries ages 65 and older with RA who initiated use of a DMARD, including anti- TNF and glucocorticoids, between 1995 and 2003; patients had to demonstrate use of health care system by filling at least 1 prescription for any drug and having at least 1 physician service in each of 2 consecutive 6-month periods in addition to being enrolled in PhDaceutical Assistance Contract for Elderly (PACE) program Exclusion Criteria • < 3 recoreded RA diagnoses: Any cancer (except nonmelanoma skin cancer) or	Interventions, Dose D1: MTX: dosage and frequency NR D2: ETN: dosage and frequency NR IFX: dosage and frequency NR IFX: dosage and frequency NR ADA: dosage and frequency NR D3: Other: Glucocorticoids: dosage and frequency NR D4: LEF: dosage and frequency NR Other: cyclosporine, azathioprine: dosage and frequency NR D5: SSZ: dosage and frequency NR Hydroxychlorquine: dosage and frequency NR Other: gold, penicillamine, minocycline: dosage and frequency NR Number in group D1: 1900 D2: 469 D3: 10617 D4: 654 D5: 1957 Overall: 15,597 Mean age (years) D1: 76 D2: 75 D3: 79 D4: 76 D5: 76	Mean disease duration, years (SD) NR Patients with early RA, three years or less, % NR Treatment resistant, % NR Tender Joint Count, mean (SD) NR Swollen Joint Count, mean (SD) NR Corticosteroid use, % NR DMARD use, % D1: 100 D2: 100 D3: NR D4: 100 D5: 100 MTX naïve, % NR Baseline DAS score, mean (SD) NR Required treatment for latent TB NR Overall: 2 hospitalizations for pulmonary TB Other population characteristics, %, (CI/SD/P value)	ACR NR HAQ, NR DAS NR SF-36 NR Radiographic measures NR Quality of life scales NR Others, (please name); mean difference/absolute difference (CI/SD/P Value) NR	Overall 4.4% of patients dropped out due to disenrollment from PACE plan. Authors also state that most patients dropped out of study because of treatment discontinuation or because they developed study outcome, however, they do not report raw data for that. Overall adverse events reported, n: NR Serious adverse events NR Malignancies NR Respiratory events Pneumonia, n: D1: No. of events: 16, Event rate per 100 patient years (95% CI): 1.47 (0.75 - 2.18) D2: No. of events: 14, Event rate per 100 patient years (95% CI): 2.33(1.12-3.54) D3: No. of events: 67, Event rate per 100 patient years (95% CI): 3.16 (2.41-3.91) D4: No. of events: 6, Event rate per 100 patient years (95% CI): 1.43 (0.29-2.57) D 5: No. of events: 13, Event rate per 100 patient years (95% CI): 1.43 (0.29-2.57) D 5: No. of events: 13, Event rate per 100 patient years (95% CI): 0.91 (0.42-

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics Health Outcon	nes Adverse Events, %
	human immuno- deficiency	Sex, % female D1: 88	Followup, mean years: D1: 0.58	1.40) Overall: No. of events: 116
	virus/acquired immuno- deficiency syndrome	D2: 91 D3: 88 D4: 91 D5: 89 Overall: 89 Race, % white D1: 92 D2: 92 D3: 93	D2: 1.29 D3: 0.20 D4: 0.64 D5: 0.73 Overall: NR Nursing home resident, %: D1: 7 D2: 4 D3: 7	Other infections Septicemia or bacteremia, n: D1: No. of events: 24, Event rate per 100 patient years (95% CI): 2.20(1.33- 3.07); Osteomyelitis, No. of events: 7, Event rate per 100 patient years (95% CI): 0.27 (0.07-
		D4: 92 D5: 92 Overall: 92.5	D4: 7 D5: 5 Overall: 6.5	0.48); Any bacterial infection, No. of events: 41, Event rate per
		Race, % black D1: 7 D2: 7 D3: 6 D4: 7 D5: 7 Overall: 7	Any hospitalization prior to index date, %: D1: 25 D2: 21 D3: 30 D4: 22 D5: 24 Overall: 28	100 patient years (95% CI): 3.77 (2.64-4.9) D2: No. of events: 13, Event rate per 100 patient years (95% CI): 2.16 (1.00-3.32); Osteomyelitis, No. of events: 3, Event rate per 100 patient years
		Ethnicity, Latino NR	Charlson comorbidity score, mean ± SD D1: 1.0 ± 1.5 D2: 0.5 ± 1.2 D3: 1.3 ± 1.9 D4: 0.6 ± 1.4 D5: 1.1 ± 1.5 Overall: NR	(95% CI): 0.49 (000- 1.05); Any bacterial infection, No. of events: 29, Event rate per 100 patient years (95% CI): 4.89 (3.15-6.62) D3: No. of events: 133, Event rate per 100 patient years (95% CI): 6.34 (5.3-7.38); Osteomyelitis, No. of
			No. of physician visits, mean ± SD D1: 6.7 ± 5.3 D2: 7.7 ± 5.5 D3: 6.0 ± 4.9 D4: 7.3 ± 6.0 D5: 6.7 ± 5.3 Overall: NR	events: 17, Event rate per 100 patient years (95% CI): 0.80 (0.42-1.18); Any bacterial infection, No. of events: 196, Event rate per 100 patient years (95% CI): 9.39 (8.14-10.6) D4: No. of events: 15, Event

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics Health Outcomes	Adverse Events, %
			No. of different non-DMARDs used before index date, mean ± SD D1: 6.6 ± 4.4 D2: 8.2 ± 5.1 D3: 8.4 ± 4.8 D4: 8.2 ± 4.9 D5: 6.8 ± 4.5 Overall: NR No. of different DMARD classes used before index date, mean ± SD D1: 0.6 ± 0.7 D2: 1.4 ± 1.0 D3: 0.3 ± 0.5 D4: 1.1 ± 0.9 D5: 0.5 ± 0.6 Overall: NR Any intraarticular procedures, %: D1: 36 D2: 46 D3: 24 D4: 34 D5: 34 Overall: 27.5	rate per 100 patient years (95% CI): 3.66 (1.84-5.48); Osteomyelitis, No. of events: 2, Event rate per 100 patient years (95% CI): 0.48 (000-1.14); Any bacterial infection, No. of events: 22, Event rate per 100 patient years (95% CI): 5.36 (3.18-7.54) D5: No. of events: 33, Event rate per 100 patient years (95% CI): 2.31 (1.53-3.09); Osteomyelitis, No. of events: 9, Event rate per 100 patient years (95% CI): 0.63 (0.22-1.04); Any bacterial infection, No. of events: 53, Event rate per 100 patient years (95% CI): 3.75 (2.70-4.74) Overall: No. of events: 218; Osteomyelitis, No. of events: 38; Any bacterial infection, No. of events: 38; Any bacterial infection, No. of events: 38; Any bacterial infection, No. of events: 341
			Any extraarticular manifestations, %: D1: 3 D2: 4 D3: 2 D4: 4 D5: 3 Overall: 2.5	GI NR Other NR
			At least 1 marker of inflammation tested during previous 180 days, %: D1: 37	

Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
		D2: 39 D3: 20 D4: 36 D5: 33 Overall: 25.2		
		Any orthopedic surgeries, %: D1: 41		
		Diabetes mellitus, %: D1: 8 D2: 9 D3: 9 D4: 10 D5: 8 Overall: 4		
		At least 1 antibiotic dispensed during previous 180 days, %: D1: 30.5 D2: 40 D3: 40 D4: 43 D5: 30 Overall: 28		
		Previous hospitalization for serious bacterial infections, %: D1: 3 D2: 2 D3: 3 D4: 3 D5: 3 Overall: 3.2		
			D3: 20 D4: 36 D5: 33 Overall: 25.2 Any orthopedic surgeries, %: D1: 41 D2: 50 D3: 28 D4: 38 D5: 37 Overall: 32 Diabetes mellitus, %: D1: 8 D2: 9 D3: 9 D4: 10 D5: 8 Overall: 4 At least 1 antibiotic dispensed during previous 180 days, %: D1: 30.5 D2: 40 D3: 40 D4: 43 D5: 30 Overall: 28 Previous hospitalization for serious bacterial infections, %: D1: 3 D2: 2 D3: 3 D4: 3 D4: 3 D5: 3	D3: 20 D4: 36 D5: 33 Overall: 25.2 Any orthopedic surgeries, %: D1: 41 D2: 50 D3: 28 D4: 38 D5: 37 Overall: 32 Diabetes mellitus, %: D1: 8 D2: 9 D3: 9 D4: 10 D5: 8 Overall: 4 At least 1 antibiotic dispensed during previous 180 days, %: D1: 30.5 D2: 40 D3: 40 D4: 43 D5: 30 Overall: 28 Previous hospitalization for serious bacterial infections, %: D1: 3 D2: 2 D3: 3 D4: 3 D5: 3 Overall: 3.2

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
			D1: 8		
			D2: 20		
			D3: 12		
			D4: 12		
			D5: 7		
			Overall: 11		
			Vaccination for		
			Pneumococcal, %:		
			D1: 3		
			D2:4		
			D3: 3%		
			D4: 2		
			D5: 3		
			Overall: 3.1		

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
Author, yr: Setoguchi et al., 2006 153 Country, Setting: US and Canada, 3 databases Funding: Novartis and NIH Research Objective: To estimate association between treatment with biologic DMARDs and development of cancer in pts with RA Study Design: Cohort Study Overall N: 7,830 Study Duration: 1994 to 2004 in US 1996 to 2003 in Canada	Inclusion Criteria: • Age ≥ 65 • 1 claim with a diagnosis of RA and who were dispensed at least 1 prescription of any DMARD or corticosteroid after first RA diagnosis Exclusion Criteria: • Diagnosis of any cancer (except nonmelanoma skin cancer) or human immunodeficiency virus infection	Interventions: D1: Biologic DMARD D2: MTX N: D1: 1152 D2: 7306 Mean age (yrs): D1: 71.4 D2: 73.4 Sex, % female: D1: 75.3 D2: 73.1 Race, % white: NR	Mean disease duration, yrs: NR TJC, mean: NR SJC, mean: NR DMARD use, %: NR Corticosteroid use, %: D1: 51.3 D2: 41.5 MTX naive, %: NR Treatment resistant %: NR Patients with Early RA (≤3 yrs): NR Baseline DAS, mean: NR	RA pts vs. overall population Non-Hodgkin's lymphoma-PY 33,335.0 Observed 58 Expected 26.0 SIR 2.2 95% Cl,1.71-2.87 Multiple myeloma-PY yrs 33,410.0 Observed 19 Expected 9.3 SIR 2.0 95% Cl,1.26-3.12 Melanoma-PY 33,377.7 Observed 29 Expected 12.8 SIR 2.3 95% Cl,1.55-3.22 Colorectal cancer-PY 32,844.9 Observed 118 Expected 97.3 SIR 1.2 95% Cl,1.01-1.45 Lung cancer-PY 31,532.8 Observed 169 Expected 95.6 SIR 1.8 95% Cl,1.52-2.05 Urinary tract/bladder cancer-PY 33,367.0 Observed 54 Expected 26.4 SIR 2.0 95% Cl,1.55-2.65 Biologics vs. MTX Unadjusted Lymphoproliferative HR 1.20 (95% Cl,0.57-2.51) Hematologic HR 1.45 (95% Cl,0.76-2.74) Solid HR 0.91 (95% Cl,0.66- 1.25) Overall HR 1.00 (95% Cl,0.75-1.33)	See health outcomes	Overall Attrition Rate, %: NA ITT Analysis: Not applicable Observational study Quality Rating: Good

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
Characteristics Author, year, study	Exclusion Criteria Inclusion Criteria ≥ 65 years old At least one recorded diagnosis of RA Filled at least 1 prescription of any TNFA (ETN, IFX, ADA) or MTX after first RA diagnosis At least one clinical service during each of 4 consecutive 6-month periods before use of DMARDs Exclusion Criteria Pto who had a			Health Outcomes ACR NR HAQ, NR DAS NR SF-36 NR Radiographic measures NR Quality of life scales NR Others, (please name); mean difference/absolute difference (CI/SD/P Value) NR	Adverse Events, % Overall NA Overall adverse events reported, n: NR Serious adverse events Death, n: NR Overall: All TNFA users: 22; All MTX users: 85; Overall: 107 Cardiovascular events (specify), n: D1: Heart failure admissions: 33 per 304 person-years, incidence rate: 108 D2: Heart failure admissions: 101 per 1333 person-years, incidence rate: 76 D3: Heart failure admissions: 26 per 1375 person-years, incidence rate: 19 D4: Heart failure admissions: 126 per 9290 person- years, incidence rate: 14 Overall: All TNFA users, Heart failure admissions: 59 per 1680 person-years, incidence
observational study, this is quite good with appropriate adjustment and analysis		D1: 89 D2: 84 D3: 90 D4: 89 Race, % white D1: 88	D4: 0 Baseline DAS score, mean (SD) NR Required treatment for		rate: 35 All MTX users, Heart failure admissions: 227 per 10623 person-years, incidence rate: 21
		D1: 88 D2: 92	latent TB		Malignancies NR

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics Health Outcomes	Adverse Events, %
		D3: 89 D4: 91	NR Other population	Respiratory events NR
		Race, % black NR	characteristics, %, (CI/SD/P value)	Other infections NR
		Ethnicity, Latino NR	 Average follow-up, mean (SD): 1.6 (1.5) RA severity-related covariates RA-related surgery: 7% Extra-articular manifestations: 39% Arthocentesis: 64% Injection (joint, tendon, etc): 23% Corticosteorids: 67% Other cytotoxic DMARDs: 24% Noncytotoxic DMARDs: 35% COX2 inhibitors: 48% MI hospitalization: 17% Ischemic heart disease: 66% Valvular heart disease: 45% Cardiac surgery: 10% 1 Prior HF hospitalization: 13% 2 Prior HF hospitalization: 5% 3 Prior HR hospitalizations: 1% Vascular surgery: 29% Ventricular arrhythmia/cardiac arrest: 2% Atrial fibrilation: 39% Other dysrhythmias: 24% 	GI NR Other • Effects of TNFAs compared to MTX on HF and/or death, With previous heart failure, fully adjusted: HR: 1.75, 95% CI (0.86 - 3.56) • Without previous heart failure, fully adjusted: HR: 2.07, 95% CI (1.00 - 4.25) • 2 groups combined: HR: 1.70, 95% CI (1.07 - 2.69) • Risk of death among patients with previous HF (TNFA users compared with MTX users): adjusted HR: 4.19, 95% (CI 1.48 - 11.89)

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
			Intervention for		
			arrhythmia: 4%		
			Cerebrovascular		
			diseases: 29%		
			Hypertension: 92%		
			Hyperlipidemia: 64%		
			Diabetes: 48% Chronic kidney		
			 Chronic kidney diseases: 33% 		
			• Dialysis: 1%		
			Dialysis. 1%Anemia: 64%		
			Hypothyroidism: 17%		
			Chronic airway		
			diseases: 60%		
			Cancer: 22%		
			 Anxiety or depression 55% 		
			D2:		
			 Average follow-up, mean 		
			(SD): 1.7 (1.9)		
			 RA-related surgery: 4% 		
			 Extra-articular 		
			manifestations: 34%		
			 Arthocentesis: 53% 		
			 Injection (joint, tendon, 		
			etc): 12%		
			Corticosteorids: 56%		
			 Other cytotoxic DMARDs: 4% 		
			Noncytotoxic		
			DMARDs: 22%		
			• COX2 inhibitors: 26%		
			MI hospitalization: 15%		
			Ischemic heart		
			disease: 63%		
			Valvular heart		
			disease: 39%		
			 Cardiomyopathy: 19% 		
			 Cardiac surgery: 9% 		
			1 Prior HF		
			hospitalization: 17%		

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
			2 Prior HF		
			hospitalization: 2%		
			• 3 Prior HR		
			hospitalizations: 1%		
			Vascular surgery: 27%		
			Ventricular arrhythmia/		
			cardiac arrest: 2%		
			Atrial fibrilation: 37% Other duarbuthmias: 31%		
			Other dysrhythmias: 21% Intervention for		
			 Intervention for arrhythmia: 6% 		
			Cerebrovascular		
			diseases: 34%		
			Hypertension: 87%		
			Hyperlipidemia: 53%		
			• Diabetes: 47%		
			Chronic kidney		
			diseases: 25%		
			Dialysis: 0%		
			Anemia: 52%		
			 Hypothyroidism: 17% 		
			 Chronic airway 		
			diseases: 53%		
			Cancer: 19%		
			 Anxiety or depression 48% 		
			D3:		
			 Average follow-up, mean 		
			(SD): 1.8 (1.6)		
			 RA-related surgery: 10% 		
			Extra-articular		
			manifestations: 28%		
			Arthocentesis: 58%		
			 Injection (joint, tendon, 		
			etc): 16%		
			Corticosteorids: 59% Other outstaying		
			 Other cytotoxic DMARDs: 24% 		
			Noncytotoxic		
			DMARDs: 32%		
			• COX2 inhibitors: 48%		

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Evente 9/
maracteristics	Criteria	interventions	MI hospitalization: 3%	nealth Outcomes	Adverse Events, %
			Ischemic heart		
			disease: 21%		
			Valvular heart		
			disease: 20%		
			 Cardiomyopathy: 5% 		
			Cardiac surgery: 1%		
			 Vascular surgery: 12% 		
			 Vascalar sargery. 127//li> Ventricular arrhythmia/ 		
			cardiac arrest: 1%		
			 Atrial fibrilation: 8% 		
			Other dysrhythmias: 8%		
			Intervention for		
			arrhythmia: 1%		
			Cerebrovascular		
			diseases: 13%		
			Hypertension: 72%		
			Hyperlipidemia: 58%		
			Diabetes: 31%		
			Chronic kidney		
			diseases: 15%		
			Dialysis: 0%		
			Anemia: 55%		
			Hypothyroidism: 12%		
			Chronic airway		
			diseases: 34%		
			Cancer: 13%		
			Anxiety or		
			depression: 43%		
			D4:		
			 Average follow-up, mean 		
			(SD): 2.5 (2.4)		
			RA-related surgery: 6%		
			Extra-articular		
			manifestations: 23%		
			 Arthocentesis: 48% 		
			 Injection (joint, tendon, 		
			etc): 11%		
			 Corticosteorids: 48% 		
			Other cytotoxic		

Study	Inclusion and Exclusion	Characteristics and	Baseline Disease and		
Characteristics	Criteria	Interventions	Treatment Characteristics	Health Outcomes	Adverse Events, %
	0		DMARDs: 5%		710.10.00 = 10.110, 70
			Noncytotoxic		
			DMARDs: 26%		
			COX2 inhibitors: 24%		
			MI hospitalization: 3%		
			Ischemic heart		
			disease: 19%		
			 Valvular heart 		
			disease: 16%		
			 Cardiomyopathy: 5% 		
			 Cardiac surgery: 1% 		
			 Vascular surgery: 14% 		
			 Ventricular arrhythmia/ 		
			cardiac arrest: 0%		
			 Atrial fibrilation: 8% 		
			 Other dysrhythmias: 6% 		
			 Intervention for 		
			arrhythmia: 1%		
			 Cerebrovascular 		
			diseases: 16%		
			 Hypertension: 70% 		
			 Hyperlipidemia: 46% 		
			Diabetes: 27%		
			 Chronic kidney 		
			diseases: 10%		
			Dialysis: 0%		
			Anemia: 47%		
			 Hypothyroidism: 11% 		
			 Chronic airway 		
			diseases: 29%		
			Cancer: 14%		
			 Anxiety or 		
			depression: 35%		

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
Author, yr: Shin et al., 2006 ¹⁵⁵ Country, Setting: US Funding: NR Research Objective: Review occurence and clinical features of Guillan Barre syndrome and Miller Fisher Syndrome during TNF alpha antagonist therapy	Inclusion Criteria: • TNF alpha antagonist therapy in AERS database Exclusion Criteria: NA	Interventions, dose: NR ETA INF N: NR Mean age, yrs: NR Sex, % female: NR Race, % white: NR	Mean disease duration, yrs: NR TJC, mean: NR SJC, mean: NR DMARD use, %: NR Corticosteroid use, %: NR MTX naive, %: NR Txt resistant %: NR	Guillain-Barre was temporally associated with INF in 10 pts, ETA in 5 pts. This compares to an annual incidence of Guillain Barre Syndrome of 1-3/100,000 population	NR	Overall Attrition Rate, %: NR ITT Analysis: NA Quality Rating: Fair
Study Design: Database analysis; AERS			Pts with Early RA (≤3 yrs): NR			
Overall N: 16 cases Study Duration: NR			Baseline DAS, mean: NR			

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
Author, yr: Slifman, 2003 ¹⁵⁶ Country, Setting: Multinational, multicenter Funding: NR Research Objective: To evaluate postlicensure cases of opportunistic infection, including Listeria monocytogenes, in pts treated with TNFs Study Design: Database analysis; AERS Overall N: 15 cases Study Duration: Varied	Inclusion Criteria: • Age: 17 to 80 • Pts with Listeria monocytogenes treated with ETA or INF for RA or Crohn's disease • Concurrent use of immunosuppressant drugs allowed Exclusion Criteria: • NA	Interventions, dose: D1: INF or ETA ETA: varied INF: varied N: D1: 15 Median age, yrs: D1: 69.5 Sex, % female: D1: 53.3 Race, % white: D1: NR	Mean disease duration, yrs: NR TJC, mean: NR SJC, mean: NR DMARD use, %: NR Corticosteroid use, %: NR MTX naive, %: NR Txt resistant %: NR Pts with Early RA (≤3 yrs): NR Baseline DAS, mean: NR RA: D1: 64%	For all ages and indications, the estimated rate of cases (reporting rates) of listeriosis reported to FDA within first yr of starting txt with inf was 43 cases per 1,000,000 persons (8/186,500) RA pts treated with inf (US cases only), estimated rate of cases of listeriosis reported to FDA was 61 cases per 1,000,000 persons (5/82,000) In 2000, annual incidence of listeriosis in US for all ages was estimated to be 3 cases per 1,000,000 deaths reported (5 INF, 1 ETA) Among reports from US only, this series included 8 cases of Listeria infection, all of which were associated with INF txt		Overall Attrition Rate, %: NA ITT Analysis: NA Quality Rating: Fair

Study design Retrospective Cohort Study Overall N PhDetrics (PM) Database: 12272 with RA; UK General Practice General Practice Othoric D1: 75.4 D2: 73.1 NR MTX naïve, % NR MTX naïve, % NR NR MTX naïve, % NR NR MTX naïve, % NR NR Saseline DAS score, mean (SD) NR Required treatment for latent TB NR Oral Corticosteroids, pts in bot databases showed an increased risk for herpes zoster if treated with traditional DMARDS alon (PhDetrics: 1.37, 95%CI:1.10-1.48), NR Oral Corticosteroids alone MTX naïve, % NR Required treatment for latent TB NR Oral Corticosteroids alone	Study Exclusi Characteristics Criteria	ion Characteristics and	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
(GPRD) 38621 with plans, were missing a value for age or sex, had also been set at the control of study. Ethnicity, Latino Other population characteristics, %, plans, were missing a value for age or sex, had also been sex been sex and the control of study. Other population characteristics, %, provided the characteristics, which is a control of the characteristics and the characteristics are characteristics.	Author, year, study name, if applicable Smitten et al., 2007 157 Country and setting US & UK. mulitcenter Source of funding Data provided by Bristol-Myers Squibb Company and Harvard PhDacoepidemiology Program Research objective Determine if RA pts have an elevated risk for herpes zoster & if their risk is associated with DMARD tx Study design Retrospective Cohort Study Overall N PhDetrics (PM) Database: 12272 with RA; UK General Practice Research Database (GPRD) 38621 with RA Duration of study Inclusic Criteria PhDe enroll health plans Coho be 18 have and 18 years at color who have ICD-9 RA. GPRI 18 years at color who have ICD-9 RA. GPRI 18 years at color who have ICD-9 RA. GPRI 18 years at color years at c	con Criteria etrics: led on 1/61 h care	Treatment Characteristics Mean disease duration, years (SD) NR Patients with early RA, three years or less, % NR Treatment resistant, % NR Tender Joint Count, mean (SD) NR Swollen Joint Count, mean (SD) NR Corticosteroid use, % NR DMARD use, % NR MTX naïve, % NR Baseline DAS score, mean (SD) NR Required treatment for latent TB NR Other population characteristics, %,	ACR NR HAQ NR DAS NR SF-36 NR Radiographic measures NR Quality of life scales NR Others, (please name); mean difference/absolute	Overall NR Overall adverse events reported, n: NR Serious adverse events NR Malignancies NR Respiratory events NR Other infections NR GI NR Other • Compared to pts who had not received DMARDS or Corticosteroids, pts in both databases showed an increased risk for herpes zoster if treated with traditional DMARDS alone (PhDetrics: 1.37, 95%CI:1.18-1.59; GPRD 1.27, 95%CI:1.18-1.59; GPRD 1.27, 95%CI:1.10-1.48), Oral Corticosteroids alone (PhDetrics: 2.51 95%CI: 2.05-3.06; GPRD 1.46 95%CI: 1.24-1.70) and

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
Quality rating Fair: Matching did not account for Disease Activity or Severity which could confound results. Higher DAS = increased disregulation of immune sys? or different dose of drugs could lead to levels of impact on immune system response?	to cohort entry were excluded				DMARDS + Corticosteroids (2.44, 1.26- 4.73), and or Biologics + Traditional DMARDS + Corticosteroids (1.96, 0.99- 3.86) showed an increased risk for herpes zoster while pts treated with a combination of Biologics + Traditional DMARDS (1.38,0.83-2.27) did not show a significantly increase risk. (referant for all comparisons - no DMARD or Corticosteroid)

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
	Exclusion	Interventions Interventions, Dose D1: Biological DMARDs (IFX, ETN, ADA, ANK) D2: MTX: dose NR D3: Hydroxychlorquine: dose NR D4: LEF: dose NR D5: SSZ: dose NR D6: Oral Corticosteroids (separate D) Number in group D1: 2,248		Health Outcomes ACR NR HAQ NR DAS NR SF-36 NR Radiographic measures NR Quality of life scales NR Others, (please name); mean difference/absolute difference (CI/SD/P Value)	Adverse Events, % Overall NA Overall adverse events reported, n: D1: 254 D2: 352 D3: 172 D4: 90 D5: 44 D6: 442 Overall: 1,993 Serious adverse events NR Malignancies NR Respiratory events Tuberculosis: NR Pneumonia, n: D1: NR D2: NR D3: NR D4: NR D5: NR D6: NR Overall: 434 Upper respiratory infection, n: NR Other infections
follow-up time of RA cohort) Quality rating Good: large sample size but unevenly distributed between treatment Ds; disease severity not	that provide supplementary insurance to Medicare	Sex, % female D1: NR D2: NR D3: NR D4: NR D5: NR D6: NR Overall: 75.7	D6: NR Overall: Traditional: 41.17 Biologic: 9.17 MTX naïve, % NR Baseline DAS score, mean (SD) NR		Urinary tract infection, n: D1: NR D2: NR D3: NR D4: NR D5: NR D6: NR Overall: 250 Other infections (specify), n:

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics Health Ou	utcomes Adverse Events, %
accounted for	Criteria	Race, % white NR Race, % black NR Ethnicity, Latino NR	Required treatment for latent TB NR Other population characteristics, %, (CI/SD/P value) Overall: 0 comorbid conditions: 77.0% 1-2 comorbid conditions: 21.8%; 3+ comorbid conditions: 59.4%	D1: Hospitalized infections:

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
					 D6: 1.83 (1.62-2.07); 1.92 (1.67-2.21) 5 mg/day or less oral corticosteroids: 1.28 (1.06-1.55); 1.32 (1.06-1.63); 6-10 mg/day oral corticosteroids: 1.79 (1.44-2.21); 1.94 (1.53-2.46); greater than 10 mg/day oral corticosteroids: 2.89 (2.39-3.49); 2.98 (2.41-3.69)

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events (%)	Analysis and Quality Rating
Author, year: Smolen et al., 1999; 159; Smolen et al., 1999 160; Sharp et al., 2000 161; Larsen et al., 2001 162; Scott et al., 2001 163 Country, Setting: Multinational, multicenter Funding: Hoechst Marion Roussel Research Objective: Efficacy and	Inclusion Criteria: • Age: ≥ 18 • Active RA defined by: ≥ 6 tender and swollen joints, based on a 28-joint count, physician and pt global assessments of RA activity of "fair, poor, or very poor", CRP > 2.0 mg/dL or ESR > 28 mm/h • Functional class I – III • Other DMARDs discontinued ≥ 4 wks • Stable doses of NSAIDS permitted -acetylsalicylic	Interventions: D1: LEF D2: SSZ N: D1: 133 D2: 133 Mean age, yrs: D1: 58.3 D2: 58.9 Sex, % female: D1: 75.9 D2: 69.2 Race, % white: NR	Mean disease duration, yrs: D1: 7.6 D2: 7.4 TJC, mean: NR SJC, mean: NR DMARD use, %: D1: 60.2 D2: 48.9 Corticosteroid use, %: D1: 28.6 D2: 27.8 MTX naive, %: NR	At 24 weeks ACR 20, %: D1: 55 D2: 56 ACR 50, %: D1: 33 D2: 30 Improving HAQ scores, change (%): D1: -0.50 (45) D2: -0.29 (29) (P = 0.0086) Change in Sharp; number, change (SD): D1: 87 1.23 (2.85) D2: 84 2.32 (10.11) Larsen score change: D1: 0.01 D2: 0.01 (P = NS)	SAEs: D1: 5 D2: 7 Headache: D1: 7 D2: 11 Nausea: D1: 10 D2: 17 URTI: D1: 14 D2: 15 Diarrhea: D1: 17 D2: 9 Alopecia:	Overall Attrition Rate, %: 33% at 24 wks ITT Analysis: Yes Quality Rating: Fair
safety of LEF was compared to placebo and SSZ Study Design: RCT Overall N: 266 (358 including placebo arm) Study Duration: 24 wks (12 and 24 month followup)	acid, oral steroids (prednisolone ≤ 10 mg/day), and up to 3 intra-articular steroid injections, not exceeding 60 mg triamcinolone • Intra-articular steroid injections not permitted during first 6 mos		Treatment resistant, %: NR Pts with Early RA (≤3 yrs): NR Baseline DAS, mean: NR RF positive: D1: 79% D2: 80%	At 1 year Change in Sharp; number, change (SD): D1: 60 0.97 (6.11) D2: 53 1.38 (2.88) Larsen score change: D1: 0.02 D2: 0.02 (P = NS) At 2 years Larsen score change: D1: -0.07 D2: -0.02 (P = NS) Similar ACR20 response rates D1: 48; D2: 44; P=NR	D1: 8 D2: 5 Rash: D1: 10 D2: 9 Withdrawal due to AEs: D1: 14 D2: 19 2 cases of reversible agranulocytosis in SSZ	

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
Author, year, study name, if applicable Smolen et al., 2008,	Inclusion Criteria Treatment resistant, adult	Interventions, dose D1: • MTX: 10 - 25 mg	Mean disease duration, years D1: 7.4	ACR ACR 20: D1: 48	Attrition/withdrawal Overall, n: D1: 25
OPTION ¹⁶⁴	patients	once/week	D2: 7.5 D3: 7.8	D2: 59 D3: 26	D2: 13 D3: 12
Country and setting International,	 Inadequate response to 	 Tocilizumab: 4 mg/kg every 4 wks 	Overall: NR	Overall: 4 mg/kg vs. Placebo	Overall: 50
multicenter	MTX • Moderate to	D2: • MTX: 10 - 25 mg	Patients with early RA, three years or less, %	(P = 0.0001), 8 mg/kg vs. Placebo $(P = 0.0001)$	Withdrawals due to adverse events, n:
Source of funding F Hoffman-La Roche	severe active RA (diagnosed	once/week Tocilizumab: 8 mg/kg	NR	ACR 50:	D1: 14
and Chugai Pharmaceutical	according to ACR criteria)	every 4 wks	Treatment resistant, %	D1: 31 D2: 44	D2: 12 D3: 6
Research objective	criteria of more	• MTX: 10 - 25 mg	Tender Joint Count, mean	D3: 11 Overall: 4 mg/kg vs. Placebo	Overall: 32
Assess efficacy of tocilizumab in RA pts	than 6 mos' duration Inadequate	once/week • Placebo	D1: 33.2 (15.6) D2: 31.9 (15.5)	(P = 0.0001), 8 mg/kg vs. Placebo $(P = 0.0001)$	Withdrawals due to lack of efficacy, n: D1: 2
who were receiving background MTX	response to	Number in group D1: 213	D3: 32.8 (16.1) Swollen Joint Count, mean	ACR 70: D1: 12	D2: 0 D3: 3
therapy	 Active disease 	D2: 205 D3: 204	D1: 20.0 (10.9)	D2: 22 D3: 2	Overall: 5
Study design Controlled Trials	was defined by an SJC of 6 or	Overall: 622	D2: 19.5 (11.3) D3: 20.7 (11.7)	Overall: 4 mg/kg vs. Placebo $(P = 0.0001)$, 8 mg/kg vs.	Adherent/compliant, n: D1: 186
Overall N 622 (623 were	more plus a TJC of 8 or more and		Corticosteroid use, % D1: 55	Placebo ($P = 0.0001$)	D2: 191 D3: 189
randomized, however 1 subject	CRP over 10 mg/L or ESR of	D2: 50.8 D3: 50.6	D2: 55 D3: 54	HAQ, D1: -0.52	Overall: 566
never received study	28 mm/h or more	Overall: NR	Overall: 55	D2: -0.55 D3: -0.34	Overall adverse events reported, n:
drug and was withdrawn. Data tables have total n of 622)	 Patients had to have received MTX for 12 weeks or longer 	Sex, % female D1: 82 D2: 85 D3: 78	DMARD use, % D1: 100 D2: 100 D3: 100	Overall: 4 mg/kg vs. Placebo $(P = 0.0296)$, 8 mg/kg vs. Placebo $(P = 0.0082)$	D1: 151 D2: 143 D3: 129 Overall: 423
Duration of study	beforestart	Overall: 82	Overall: 100	DAS28 = 2.6 (%) D1: 13	Serious adverse events
24 wks (Safety: 32 wks)	ofstudy (stable dose of 10-25	Race, % white NR	MTX naïve, % D1: 0	D1: 13 D2: 27 D3: 0.8	Cardiovascular events (specify), n:
Quality rating Fair	mg/week for 8 weeks or longer)	Race, % black NR	D2: 0 D3: 0 Overall: 0	Overall: 4 mg/kg vs. Placebo $(P = 0.0002)$, 8 mg/kg vs. Placebo $(P = 0.0001)$	D1: 0 D2: 1 D3: 1
	Exclusion Criteria • Autoimmune	Ethnicity, Latino NR	Baseline DAS score D1: 6.8	SF-36 Physical	Malignancies Skin cancer (basal cell or

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
•		Interventions		## D1: 9.7 D2: 9.5 D3: 5.0 Overall: 4 mg/kg vs. Placebo	squamous cell), n: D1: 0 D2: 0 D3: 1 Other cancer (specify), n: D1: 0 D2: 0 D3: 1 (unspecified) Respiratory events Tuberculosis, n: 3,570 Pneumonia, n: D1: 0 D2: 1 D3: 1 Overall: Pneumocystis jirovecii pneumonia, n: D1: 0 D2: 0 D3: 1 Overall: D1: 2 D2: 1 Upper respiratory infection, n: D1: 12 D2: 17 D3: 13 Overall: 42 Other infections Urinary tract infection, n: D1: 0 D2: 0 D2: 0
	investigators were encouraged to exclude			4 mg/kg: 418 mg/kg: 41Placebo: 32	D3: 1 Overall: 1 Nasopharyngitis, n: D1: 11

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
	potential pts if, in their judgment, they had a history of unacceptably frequent recurrent infections.) • Active liver disease, indicated by screening and baseline concentrations of alanine or aspartate aminotransferas e of 1 - 5 time supper limit of normal or more • Previous unsuccessful treatment with an anti-TNF agent (i.e., lack of efficacy or significant safety issues, terminations due to cost or injection discomfort were not excluded)			No response (%) 4 mg/kg: 38 8 mg/kg: 20, Placebo 65 Overall: 4 mg/kg vs. Placebo (P = 0.0001) 8 mg/kg vs. Placebo (P = 0.0001) SJC Mean change from baseline 4 mg/kg: -8.5 8 mg/kg: -10.5 Placebo: -4.3 Overall: 4 mg/kg vs. Placebo (P = 0.0001), 8 mg/kg vs. Placebo (P = 0.0001) TJC Mean change from baseline 4 mg/kg: -14.5 8 mg/kg: -17.1 Placebo: -7.4 Overall: 4 mg/kg vs. Placebo (P = 0.0001), 8 mg/kg vs. Placebo (P = 0.0001)	D2: 12 D3: 10 GI Dyspepsia and abdominal pain, n: D1: 17 D2: 20 D3: 11 Overall: 48 Any GI disorder, n: D1: 46 D2: 48 D3: 44 Overall: 138 Other Skin rash, n: D1: 13 D2: 11 D3: 3 Overall: 27 Headache, n: D1: 15 D2: 14 D3: 9 Overall: 28 Mouth ulcers, n: D1: 4 D2: 5 D3: 1 Overall: 10 Peptic ulcers, n: D1: 1 D2: 0 D3: 2 Overall: 3 Raised anlanine

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
					D1: 12 D2: 11 D3: 3 Overall: 26
					Raised aspartate aminotransferase, n: D1: 1 D2: 2 D3: 1 Overall: 4
					Cough: • 4 mg/kg: 7 • 8 mg/kg: 3 • Placebo: 3 • Overall: 13
					Pharyngeal pain, • 4 mg/kg: 2 • 8 mg/kg: 4 • Placebo: 3 • Overall: 9
					Dyspnoea • 4 mg/kg: 3 • 8 mg/kg: 3 • Placebo: 0 • Overall: 6
					Aggravation of RA • 4 mg/kg: 7 • 8 mg/kg: 7 • Placebo: 13 • Overall: 27

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %		
Author, year, study name, if applicable Smolen et al., 2009, RAPID 2 ¹⁶⁵	Inclusion Criteria • ≥ 18 years old • Diagnosis of RA by ACR criteria, prior MTX ≥ 6	Interventions, dose D1: MTX: ≥ 10 mg/wk Placebo: saline SC q 2 weeks D2: MTX: ≥ 10 mg/wk	Mean disease duration, years D1: 5.6 yr (3.9) D2: 6.1 (4.1) D3: 6.5 (4.3)	ACR mean difference/ absolute difference (CI) ACR 20: D1: 8.7 D2: 57.3, OR 14.4 (6.7-31.0),	Overall Overall attrition/withdrawal, n: D1: 110 D2: 72 D3: 65		
Country and setting Multinational Source of funding	mos (stable dose ≥ 10 mg/wk for ≥ 2	Certolizumab 400 mg SC at weeks 0, 2, and 4 then 200	Patients with early RA, three years or less, % NR	P = 0.001 D3: 57.6, 14.3 (6.7-30.8), P = 0.001	Withdrawals due to adverse events, n: D1: 2		
UCB Research objective Evaluate efficacy	mos) Exclusion Criteria	mg q 2 weeks D3: MTX: ≥ 10 mg/wk Certolizumab: 400 mg SC at weeks 0,	Treatment resistant, %	ACR 50: D1: 3.1 D2: 32.5, OR 14.8 (5.3-41.6),	D2: 11 D3: 6		
and safety of CZP vs. placebo, + MTX, in pts with active RA	 Other biological agent for RA within 6 mos 	2, and 4 then 400 mg q 2 weeks	Tender Joint Count, mean D1: 30.4 (3.4) D2: 30.1 (14.5)	P = 0.001 D3: 33.1, 15.3 (5.5-42.9), P = 0.001	Withdrawals due to lack of efficacy, n: D1: 107 D2: 54		
Study design Controlled Trials	before enrollment (3 mos for ETN	Number in group D1: 127 D2: 246 D3: 246	D3: 30.0 (13.9) Swollen Joint Count, mean D1: 21.9 (9.7)	ACR 70: D1: 0.8 D2: 15.9, OR 23.8 (3.2-	D3: 53 Adherent/compliant, n:		
Overall N 619 Duration of study	and ANK), previous treatement with biological with	Mean age, years (SD) D1: 51.5 yr (11.8)	D2: 20.5 (9.6) D3: 21.0 (10.2) Corticosteroid use, %	175.9), <i>P</i> = 0.01 D3: 10.6, 15.5 (2.1-115.4), <i>P</i> = 0.01	D1: 1 D2: 1 D3: 2		
24 weeks Quality rating	severe hypersensitivity or anaphylactic	D2: 52.2 (11.1) D3: 51.9 (11.8) Sex, % female	D1: 59.8 D2: 55.3	HAQ-DI, adj mean change (SE) D1: -0.14 (0.04)	Withdrawal due to patient indecision or other: D1: NR		
Good	reaction No initial	D1: 84.3 D2: 83.7	D3: 61.8 DMARD use, %	D2: -0.50 (0.03), P = 0.001 D3: -0.50 (0.03), P = 0.001	D2: 6 D3: 4		
previous anti- TNF therapy, chest x-ray	D3: 78.0 Race, % white NR	revious anti- NF therapy, hest x-ray ndings for TB, ositive PPD unless thought b be due to CG Race, % white NR Race, % black NR Ethnicity, Latino NR	anti- apy, NR D1: 0 Bay D3: 0 Or TB, Race, % black PPD NR Baseline DAS score D1: 6.83 (0.87) Ethnicity, Latino NR D2: 6.85 (0.84) NR D3: 6.80 (0.79)	previous anti- TNF therapy, chest x-ray positive PPD (unless thought to be due to PNR previous anti- Race, % white D1: 0 D2: 0 D3: 0 Baseline DAS score D1: 6.83 (0.87) D2: 6.85 (0.84)	HAQ-DI, % mean % improvement (SD) D1: 3.7 (59.4) D2: 31.8 (38.5), P = 0.001	Overall adverse events reported, n: D1: 66 D2: 139 D3: 125	
	positive PPD (unless thought to be due to BCG				tive PPD NR Baseline DAS score ess thought e due to Ethnicity, Latino D1: 6.83 (0.87) D2: 6.85 (0.84)	D1: 6.83 (0.87) D2: 6.85 (0.84)	D3: 32.0 (35.1) $P = 0.001$ DAS28 (SD) D1: -0.50 (1.05) D2: -2.27 (1.38), $P = 0.001$
	vaccination).			D3: -2.46, <i>P</i> = 0.001	D2: 1 D3: 1		
			Other population characteristics, %, (SD)	SF-36 PCS, adj mean change, n D1: 0.9	Hepatotoxicity/elevated liver enzymes, n: D1: 4		

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
			MTX (mg/wk) mean: D1: 12.2 (3.3), D2: 12.5 (3.6) D3: 12.6 (3.7)	D2: 5.2 (<i>P</i> = 0.001) D3: 5.5 (<i>P</i> = 0.001) SF-36 PCS, adj mean	D2: 3 D3: 3 Overall: 4 Malignancies
			HAQ-DI mean: D1: 1.6 (0.6) D2: 1.6 (0.6) D3: 1.6 (0.6) mTSS mean: D1: 46.5 (58.6) D2: 39.6 (50.1)	change, PF D1: 0.6 D2: 12.1 (P = 0.001) D3: 12.4 (P = 0.001) Radiographic measures (CI) mTSS: D1: 1.2 (0.5-2.0) D2: 0.2 (-0.1-0.6), P = 0.01 D3: -0.4 (-0.7- to 0.1), P = 0.001 Quality of life scales NR	NR Other cancer (specify), n: D1: 1 (bladder) D2: 1 (testicular) D3: 1 (colon) Respiratory events Tuberculosis: NR
			D3: 46.7 (56.0)		Pneumonia, n: D1: 0 D2: 0 D3: 1 Upper respiratory infection, n: D1: 2 D2: 11 D3: 4
					Other infections Urinary tract infection, n: D1: 9 D2: 11 D3: 5
					Other infections (specify), n: D1: 0 D2: 1 case each of erysipelas, gastroenteritis, postop wound infection, tooth abscess D3: 1 case of erysipelas, 2 cases of sinusitis
					GI NR
					Other

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
					Headache, n: D1: 1 D2: 9 D3: 8
					Any other AEs: For safety analysis two patients inplacebo group that received CZP 200 mg were included inCZP 200 mg group.

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
Author, year, study name, if applicable Smolen et al., 2009 ¹⁶⁶ ASPIRE Country and setting Multinational Unversity hospitals Source of funding	Inclusion Criteria: • Age: 18-75 • Diagnosed according to 1987 ACR criteria • Persistent synovitis for > 3	Interventions, dose D1: MTX: wk 54 mean: 15.1mg/wk Placebo D2: MTX wk54 mean: 15.5mg/wk IFX: 3mg/kg D3: MTX: mean wk 54: 14.9mg/wk	Mean disease duration, years NR Patients with early RA, three years or less, % D1: 100 D2: 100 D3: 100	ACR NR HAQ NR DAS D1: % remission at 54 wks by DAS28-ESR: MTX: 16.3%	Attrition/withdrawal NR Overall adverse events reported, n: NR Serious adverse events NR
Centocor Research objective Examine radiographic progression and disease activity states in pts treated with MTX or INF + MTX Study design Controlled Trials Overall N 1049 Duration of study 54 wks Quality rating Fair	synovitis for > 3 mos and < 3 yrs > 10 swollen joints, and > 12 tender joints 1 or more of following: a positive test result for serum RF, radiographic erosions of	synovitis for > 3 mos and < 3 yrs > 10 swollen joints, and > 12 tender joints 1 or more of following: a positive test result for serum RF, radiographic erosions of hands or feet, or a serum C- reactive protein level of > 2.0 mg/dl Oral corticosteroids; NSAIDS Sev. 414.9mg/wk IFX: 6mg/kg Number in group D1: 298 D2: 373 D3: 378 Mean age, years (SD) D2: 51 D3: 49 Sex, % female D1: 74.8 D2: 71.6 D3: 67.7 Race, % white NR Race, % black	Treatment resistant, % NR TJC, mean NR SJC, mean NR Corticosteroid use, % NR DMARD use, % D1: 100 D2: 100 D3: 100 Overall: 100 MTX naïve, % NR Baseline DAS-ESR score (SD)	D2: MTX+INF: 24.7% SF-36 NR Radiographic measures D1: Changes in TSS wk 14/54 by disease activity (remission, low, moderate, high) wk 14/wk54. MTX 0.1, 2.8*, 2.1**, 6.5**/1.1, 2.2**, 3.9**, 5.8** MTX+IFX -0.3, 0.0, 0.3, 1.3/-0.2, -0.4, 0.6, 2.1. [COMPARED TO IFX+MTX *P = 0.05, **P = 0.01] D2: MTX+IFX -0.3, 0.0, 0.3, 1.3/-0.2, -0.4, 0.6, 2.1.	Malignancies NR Respiratory events Tuberculosis: NR Other infections NR GI NR
	Exclusion Criteria: Prior txt with: MTX, received other DMARDs within 4 wks of entry Used ETN, INF, ADA or other anti-TNF-á agent	Ethnicity, Latino NR	D1: 6.69 (1.04) D2: 6.62 (1.07) D3: 6.72 (1.01) Required treatment for latent TB NR	Quality of life scales NR Others, (please name) • % remission, low, mod, or high disease by SDAI at wk 14/54 MTX: 2.8, 14.6, 45.5, 37.2/ 12.3, 29.5, 29.5, 28.6 (14 & 54 wks between groups, Ps: 0.001)	

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
	hepatitis B or C virus, CHF, or lymphoma or other malignancy within past 5 yrs (excluding excised skin cancers)			• MTX+INF: 10.7, 26.0, 37.4, 25.9/21.3, 35.5, 28.5, 14.7.	

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
name, if applicable Smolen et al., 2009 167 GO-AFTER Study Country and setting multinational; clinics; hospitals Source of funding Centocor Research and Development; Schering-Plough Research Institute Research objective To assess the efficacy and safety of GOL for patients with active RA who had previously received one or more TNF- alpha inhibitors Study design RCT Overall N 461 Duration of study 24 wks Quality rating Fair	Inclusion Criteria	Interventions, Dose D1: GOL: 50 mg every 4 wks D2: GO: 100 mg every 4 wks D3: Placebo Number in group D1: 153 D2: 153 D3: 155 Mean age (years) D1: 55 D2: 55 D3: 54 Sex, % female D1: 74 D2: 80 D3: 85 Race, % white NR Race, % black NR Ethnicity, Latino NR	D1: 9.6 (5.6 - 17.2)	ACR: ACR 20: Week 14 D1: 35 D2: 38 D3: 18 Week 24 D1: 34 D2: 44 D3: 17 ACR 50: Week 14 D1: 16 D2: 20 D3: 6 Week 24 D1: 18 D2: 20 D3: 5 ACR 70: Week 14 D1: 10 D2: 9 D3: 2 Week 24 D1: 12 D2: 10 D3: 3 HAQ: HAQ-DI Week 14 D1: -13.4 (-27.3 to 0.0 (P = 0.0005)) D2: -17.6 (-43.8 to D3: 0 (P < 0.0001)	Overall Overall attrition/withdrawal (n): D1: 13 D2: 15 D3: 31 Overall: 59 Withdrawals due to adverse events (n): D1: 4 D2: 2 D3: 10 Overall: 16 Withdrawals due to lack of efficacy (n): D1: 6 D2: 5 D3: 11 Overall: 22 Adherent/compliant (n): NR Other attrition related comments? Attrition numbers include those that received rescue tx Overall adverse events reported (n): D1: 101 D2: 119 D3: 112 Serious adverse events (specify) (n): HTN D1: 5 D2: 10 D3: 2

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
	infection < 6 mos before screening • Serious infection < 2			D1: -13.3 (-33.3 to 0.0 (<i>P</i> = 0.0003) D2: -14.3 (-44.1 to 0.0 (<i>P</i> < 0.0001) D3: 0 (-25 to 17.6)	Malignancies: D1: 1 D2: 1 D3: 1
	mos before screening History of chronic infection Demyelinating disease Congestive heart failure Severe, progressive, uncontrolled renal, hepatic, haematological, GI, endocrine, pulmonary, cardiac, neurological, psychiatric, or cerebral			DAS: Week 14 D1: -15.7 (-31.6 to -6.8	Respiratory events: Pneumonia (n): D1: 2 D2: 0 D3: 1 Upper respiratory infection (n): D1: 11 D2: 21 D3: 10 Other infections: Urinary tract infection (n): D1: 1 D2: 0 D3: 0 Other infections (specify) (relifections)
	disease • Had			Quality of life scales:	D1: 53 D2: 55 D3: 51
	transplanted organ or malignancy in past 5 yrs			Others:	GI: Bowel obstruction (n): Diaherra D1: 5 D2: 12 D3: 7
					Gastroenteritis D1: 0 D2: 0 D3: 1
					Other: Infusion/injection site reactions (n):

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
					D1: 9 D2: 16 D3: 6
					Any other AEs: AE numbers do not include those who received Rescue therapy

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
Author, year, study name, if applicable Sokolove et al., 2010 ¹⁶⁸ Country and setting USA; Multicenter registry Source of funding Consortium of Rheumatology Researchers of North America Research objective To compare LFT elevations in patients with rheumatoid arthritis receiving ADA, ETN or INF enrolled in the Consortium of Rheumatology Researchers of North America from October 2001 to March 2007.	Inclusion Criteria Patients receiving anti- TNF and/or all non- biological DMARDs with normal baseline ALT and/or AST values, including MTX and/or LEF, with available follow-up determinations Exclusion Criteria PSA	Comparisons (dosage and frequency) D1: Oral DMARDs: MTX, LEF and all other non-biological DMARDs as a group (SSZ,HCQ, azathioprine, gold, penicillamine). D2: ADA: NR D3: ETN: NR D4: INF: NR Number in group D1: 4147 D2: 849 D3: 1383 D4: 1449 Mean age (years) D1: 61.2 D2: 56.14 D3: 55.6 D4: 60.4 Sex, % female D1: 72.8 D2: 79.5 D3: 79.9 D4: 73.7	Mean disease duration, years D1: 9.8 (9.8) D2: 11.3 (9.6) D3: 12.0 (9.9) D4: 11.3 (9.3) TJC, mean D1: 3.25 D2: 4.77 D3: 3.81 D4: 3.63 SJC, mean D1: 4.25 D2: 5.67 D3: 4.02 D4: 5.02 Corticosteroid use, % NR DMARD use, %: NR Treatment resistant, %: NR Patients with early RA, three years or less, %: NR	ACR mean difference/ absolute difference (CI/SD/P Value): NR HAQ, mean difference/ absolute difference (CI/SD/P Value): NR DAS, mean difference/absolute difference (CI/SD/P Value): NR SF-36, mean difference/absolute difference (CI/SD/P Value): NR Radiographic measures, mean difference/absolute difference (CI/SD/P Value): NR Quality of life scales, mean difference/absolute difference/absolute difference/absolute	Overall NR Serious adverse events: Hepatotoxicity/elevated liver enzymes (n): LFT >1× ULN, AOR D2: 1.35(95% CI 1.09 to 1.66) D3: 1.00 (95% CI 0.83 to 1.21) D4: 1.58 (95% CI 1.35 to 1.86) ALT and/or AST >2× ULN, AOR D2: 1.72 (95% CI 0.99 to 3.01) D3: 1.10 (95% CI 0.64 to 1.88) D4: 2.40 (95% CI 1.53 to 3.76) AST/ALT >2× ULN: 0.7 Malignancies: NR Respiratory events: NR Other infections: NR GI:	Quality rating for efficacy/effectiveness? NR Quality rating for observational studies Fair
Study design Observational Overall N 6861 Duration of study		Race, % white NR Race, % black NR Ethnicity, Latino NR	D1: 3.47 (1.5) D2: 3.89 (1.7) D3: 3.56 (1.5) D4: 3.56 (1.4) Required treatment for latent TB	Value): NR Others, (please name); mean difference/absolute difference (CI/SD/P Value):	NR Other: Any other AEs: LFT results (AST/ALT) based on primary model #1 of prevalent TNF-I users in patients on MTX, LEF and other	

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
Mean follow-up per person was 17 mos			NR Other population characteristics, %, (CI/SD/P value): NR	NR	non-biological DMARD	

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
			(had 1+ of these procedures) D1: 41% D2: 40%		beta-blockers, use of clopidogrel, and no curren
			D2: 40%		use of immunosup agents]

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
•	Inclusion Criteria: Age: 18 to 75 Diagnosed according to 1987 ACR criteria Persistent synovitis for > 3 mos and < 3 yrs > 10 swollen joints, and > 12 tender joints 1 or more of following: a positive test result for serum RF, radiographic erosions of hands or feet, or a serum C-reactive protein level of > 2.0 mg/dl Oral corticosteroids; NSAIDS 20 mg MTX (required) Exclusion Criteria: Prior txt with: MTX, received other DMARDs	Interventions Interventions, dose: D1: MTX (20 mg/wk) + placebo D2: MTX + INF (3 mg/kg/wk) D3: MTX + INF (6 mg/kg/wk) N: D1: 282 D2: 359 D3: 363 Mean age, yrs: D1: 50 D2: 51 D3: 50 Sex, % female: D1: 75 D2: 71 D3: 68 Race, % white: NR		At weeks 30 to 54 HAQ: D1: 0.68 D2: 0.80 D3: 0.88; (D2 vs. D1; P = 0.03) (D3 vs. D1; P < 0.001) At 54 weeks HAQ > 0.22, %: D1: 65.2 D2: 76.0 D3: 75.5 (D2 vs. D1; P = 0.003) (D3 vs. D1; P < 0.004) ACR20, %: D1: 53.6 D2: 62.4 D3: 66.2 (D2 vs. D1; P = 0.028) (D3 vs. D1; P < 0.001) ACR50, %: D1: 32.1 D2: 45.6 D3: 50.4 (D2 vs. D1; P = 0.001) (D3 vs. D1; P < 0.001) ACR70, %: D1: 21.2 D2: 32.5 D3: 37.2 (D2 vs. D1; P = 0.002) (D3 vs. D1; P < 0.001) ACR70, %:	Adverse Events, % SAEs: D1: 11 D2: 14 D3: 14 Serious Infections: D1: 2.1 D2: 5.6 D3: 5.0 Infusion or injection reaction: D1: 7 D2: 21 D3: 15 TB: D1: 0 D2: 0.8 D3: 0.3 Nausea: D1: 18 D2: 20 D3: 17 URTI: D1: 21 D2: 25 D3: 28	•

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
	within past 5 yrs (excluding excised		HAQ: D1: 1.5	D3: 46.7 (<i>P</i> < 0.001)		
	skin cancers)		D2: 1.5 D3: 1.5	Modified Sharp: D1: 3.7 D2: 0.4 D3: 0.5 (P < 0.001)		
				Increase in radiographic score, %: INF: 39 vs. MTX 61 (P < 0.001)		
				Employability: INF+MTX (OR 2.4, P < 0.001) MTX (P = 0.56) Combo has higher probability of improvement than MTX alone		
				Net increase in employability: MTX+INF: 8% MTX-only: 2%		
				Employability status changed from employable to unemployable, %: INF: 8 MTX-only: 14 (<i>P</i> = 0.05)		
				SF-36 Physical component summary scores D1: 11.7 D2: 13.2 D3: 10.1 D3 vs. D1, <i>P</i> = 0.10 D3 vs. D2; <i>P</i> = 0.003 Modified Sharp/van der Heijde Score change:		

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
				D1: 3.7		
				D2: 0.4		
				D3: 0.5 <i>P</i> < 0.001		
				Erosion Score change:		
				D1: 3.0		
				D2: 0.3		
				D3: 0.1 P < 0.001		
				JSN Score change:		
				D1: 0.6		
				D2: 0.1		
				D3: 0.2 P < 0.001		

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events (%)	Analysis and Quality Rating
Author, year: Strand et al., 1999 ¹⁷² ; Strand et al., 1999 ¹⁷³ ; Cohen et al., 2001 ¹⁷⁴ Country, Setting: US and Canada, multicenter (47 university & private rheumatology practices) Funding: Hoescht Marion Roussel Research Objective: Efficacy and safety of LEF with placebo and MTX in active RA Study Design: RCT Overall N: 482 (active arms- 364) Study Duration:	 Inflammatory joint disease not caused by RA, History of clinically significant drug or alcohol abuse, or 	(7.5 to 15 mg/week) N: D1: 182 D2: 182 Mean age, yrs: D1: 54.1 D2: 53.3 Sex, % female: D1: 72.5 D2: 75.3 Race, % white: NR	Mean disease duration, yrs: D1: 7.0 D2: 6.5 TJC, mean: D1: 15.5 D2: 15.8 SJC, mean: D1: 13.7 D2: 13.0 DMARD use, %: D1: 55.5 D2: 56.0 Corticosteroid use, %: D1: 53.8 D2: 52.7 MTX naive, %: Both groups 100 Treatment resistant, %: NR Pts with Early RA (≤3 yrs): NR Baseline DAS, mean: NR RF positive:	At 12 mos ACR 20, % D1: 52 D2: 46 ACR 50, % D1: 34 D2: 23 ACR 70, % D1: 20 D2: 9 MHAQ mean change D1: -0.3 D2: -0.2 Sharp score change D1: 0.53 (n:131) D2: 0.88 (n= 138) $(P = 0.05)$ Mean change HAQ-DI D1: -0.45 (n= 164) D2: -0,26 (n= 168) $(P \le 0.01)$ Mean change SF-36 physical component D1: 7.6 (n= 157) D2: 4.6 (n=162) Work productivity mean	SAEs: D1: 1.1 D2: 2.7 Infections: D1: 56.6 D2: 59.9 Abdominal Pain: D1: 13.7 D2: 15.4 Nausea: D1: 20.9 D2: 19.2 Back pain: D1: 8 D2: 2 Diarrhea: D1: 36.8 D2: 21.6 Oral Ulcers: D1: 6.8 D2: 10.5 GI Events: D1: 5.5 D2: 1.7 Elevated Transaminases: D1: 7.1	Overall Attrition Rate, %: 51% at 1 year ITT Analysis: Yes Quality Rating: Fair
12 mos (w/ 1 year followup)	admitted to consumption of more than 1 alcoholic drink per day		D1: 64.8 D2: 59.4 MHAQ: D1: 0.8 D2: 0.8	change D1: 9.8 (n= 138) D2: 7.5 (n= 148)	D2: 4.4	

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
Author, year, study name, if applicable Strand et al., 2006 ¹⁷⁵	Inclusion Criteria • Age ≥ 21 years	Interventions, Dose D1: • Methotrexate ≥ 10	Mean disease duration, years (SD) yrs D1: 11.0 (7.1)	ACR mean difference/ absolute difference (%) Week 24	Attrition/withdrawal Overall, n: D1: 34
Country and setting Multinational	 Fulfillment of revised 1987 American Rheumatism 	 Methotrexate ≥ 10 mg/wk Median dose of MTX at study entry was 	D2: 9.3 (5.5) D3: 9.8 (6.1) D4: 11.5 (7.3)	ACR 20: D1: 15 (38) D2: 26 (65), P = 0.05	D1: 34 D2: 36 D3: 32 D4: 22
Source of funding Roche, Genentech	Association criteria	12.5-15 mg/week • Placebo	Patients with early RA,	D3: 31 (76), $P = 0.01$ based on Fisher's exact test for	Overall: 124 Withdrawals due to adverse
Research objective Evaluate long-term impact on physical function of a single	 Active disease (defined as ≥ 8 swollen and ≥ 8 tender joints and at least 2 of 	D2: • Methotrexate: Median dose of MTX at study entry was 12.5-15 mg/week	three years or less, % D1: 0 D2: 0 D3: 0 D4: 0	comparisons with placebo + MTX group; Wk 48: 19 (46%), P < D4: NR	events, n: D1: 4 D2: **5 D3: 4 D4: 1
course of rituximab in rheumatoid factor, seropositive patients	following: a serum CRP	 Rituximab1000 mg days 1 and 15 	Treatment resistant, % NR	ACR50: D1: 5 (13)	Overall: 14 Withdrawals due to lack of
with active rheumatoid arthritis (RA) despite ongoing methotrexate	level ≥1.5mg/dl, ESR ≥ 30mm/h, or morning stiffness ≥45	Methotrexate: Median dose of MTX at study entry was 12.5-15	Tender Joint Count, mean (SD) D1: 32 (12.8) D2: 33.8 (14.8)	D2: 13 (33) D3: 17 (41), $P = 0.01$ based on Fisher's exact test for comparisons with	efficacy, n: D1: 17 D2: 5
treatment. Study design	minutes) despite treatment with > 10mg of MTX	mg/week • Rituximab1000 mg days 1 and 15	D3: 32.7 (13.8) D4: 32.2 (15.9)	placebo + MTX group D4: NR	D3: 4 D4: 4 Overall: 30
Controlled Trials Overall N	per week; RF ≥ 20 IU per ml.;	Other: Cyclophosphamide	Swollen Joint Count, mean (SD)	ACR 70: D1: 2 (5) D2: 6 (15)	Adherent/compliant, n: NR
161 Duration of study	failed at least 1 DMARD.	750 mg days 3 and 17; Median dose of MTX at study entry	D1: 18.6 (9.6) D2: 20.5 (11.2) D3: 19.4 (10.2)	D3: 6 (15) D4: 9 (23), P = 0.05	*OTHER • D1: 13 • D2: 26
2 yrs.	Exclusion Criteria	was 12.5-15 mg/week	D4: 22.7 (12.7)	Week 48: ACR 20 (%):	D2: 26D3: 25D4: 17
Quality rating Poor: very high attrition rate	 Autoimmune disorder other than RA (except 	Methotrexate > or equal to 10 mg/wk;	Corticosteroid use, % NR	D1: 8 (20) D2: 12 (30)	Overall OTHER: 81 *The majority of protocol
	concurrent Sjogren's)	Median dose of MTX at study entry was 12.5-15 mg/week	DMARD DMARDs failed (other than MTX), n (SD) D1: 2.6 (1.3)	D3: ACR 50 (%):	discontinuations classified as 'other' were owing to
	 American Rheumatism Association 	 Rituximab1000 mg days 1 and 15 	D2: 2.5 (1.6) D3: 2.6(1.4) D4: 2.5(1.4)	D1: 2 (5) D2: 5 (13) D3: 10 (24), <i>P</i> = 0.05	requirement for retreatment with rituximab under a separate protocol; **includes
	functional class IV disease • Active	Number in group D1: 40 D2: 40 D3: 41	MTX naïve, % NR	ACR 70: D1: 0% D2: 3(8%)	1 death due to pneumonia. Overall adverse events reported, n:

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
	rheumatoid vasculitis History of systemic diseases associated with arthritis Chronic fatigue syndrome Serious & uncontrolled coexisting diseases Active infection History of recurrent clinically significant infection or of recurrent bacterial infections with encapsulated organisms Primary or secondary immuno- deficiency History of cancer (except basal cell carcinoma of skin that had been excised).	D4: 40 Mean age (years) D1: 53.7 (11.2) D2: 53.5 (10.2) D3: 52.9 (9.9) D4: 53.5 (11.9) Sex, % female D1: 80 D2: 72.5 D3: 82.9 D4: 75.0 Race, % white NR Race, % black NR Ethnicity, Latino NR	Baseline DAS28 score, mean (SD) D1: 6.9 (0.7) D2: 6.8 (1.0) D3: 6.9 (0.8) D4: 6.8 (0.9) Required treatment for latent TB NR Other population characteristics, %, (CI/SD/P value) HAQ-DI baseline mean (± SD): D1: 2.0 (0.5) D2: 2.0 (0.6) D3: 1.8 (0.7) D4: 1.8 (0.6) MD global,(± SD): D1: 66.7 (15.7) D2: 66.7 (16.2) D3: 67.4 (14.5) D4: 65.6 (14.0) Pt global,(± SD): D1: 65.4 (20.3) D2: 67.8 (22.8) D3: 63.4 (20.5) D4: 61.4 (20.4) Pt pain assessment (VAS, mm): D1: 62.6 (16.1) D2: 62.2 (20.2) D3: 57.5 (20.0) D4: 54.6 (17.8) ESR (mm/h): D1: 51.5 (31.8) D2: 46.9 (22.9)	D3: 4 (10) D4: 6 (15%), P = 0.05 Week 104: ACR 20: D1: 5 (13%) D2: 3 (8%) D3:NR ACR 50: D1: 4 (10%) D2: 3 (8%) D3: 4 (ACR 70: D1: 3 (8%) D2: NR D3: 3 (8) D4: 4 (10%) HAQ, mean difference/ absolute difference/ absolute difference (Cl/SD/P Value) D1: Mean change from baseline at Wk 12 (n = 39): -0.3 (P > or equal to 0.0001); Wk 24 (n = 37): -0.4 (P = 0.0002); Wk 48 (n = 25): -0.3 (P > or equal to 0.005); Wk 72 (n = 15): -0.3 (P > or equal to 0.05) D2: Mean change from baseline at Wk 12 (n = DAS SF-36 Radiographic measures NR Quality of life scales NR	D1: 4 D2: 5 D3: 4 D4: 1 Overall: 14 Serious adverse events Death, n: D1: 0 D2: 1 D3: 0 D4: 0 Overall: 1 Malignancies NR Respiratory events Pneumonia, n: D2: 1 (reported above as we as it led to death) Upper respiratory infection, n: D1: 6 (through wk24 for all Ds in this category) D2: 4 D3: 2 D4: 4 Other infections NR GI Nausea or vomiting, n: D1: 1 D2: 2 D3: 4 D4: 0 Other Infusion/injection site reactions, n: (through wk24 for all Ds in this category)

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
	Exclusion			Others % of patients continuing protocol participation Week 24: D1: 92.5 D2: 95.0 D3: 90.2 D4: 97.5 Week 48: D1: 62.5 D2: 77.5 D3: 82.9 D4: 95.0 Week 72: D1: 37.5 D2: 42.5 D3: 53.7 D4: 70.0 Week 104: D1: 15.0 D2: 10.0 D3: 21.9 D4: 45.0 % of patients reporting improvements in HAQ-DI that met or exceeded MCID (a reduction of > or equal to 0.25) Week 12: D1: (n = 39): 38 D2: (n = 39): 63 D3: (n = 40): 61 D4: (n = 40): 55	D1: 12 D2: 18 D3: 13 D4: 13 Skin rash, n: (through wk 24 for all Ds in this category) D1: 1 D2: 4 D3: 4 D4: 1 Other AEs 1, n: D1: Hypotension (through wk24 for all Ds inse categories): 7; hypertension, 6 *a change of more than 30 mm Hg in systolic or diastolic blood pressure from pressure at screening was classified as hypotension or hypertension D2: Hypotension Through wk 24 for all groups in these categories.
				Week 24: D1: (n = 37): 45 D2: (n = 38): 68 D3: (n = 37): 59 D4: (n = 39): 63	D4: 0 Through wk 24 for all groups in these categories. Cough, n:

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
				Week 48: D1: (n = 25): 28 D2: (n = 31): 43 D3: (n = 34): 39 D4: (n = 38): 68 Week 72: D1: (n = 15): 18 D2: (n = 17): 18 D3: (n = 22): 22 D4: (n = 28): 48	D1: 0 D2: 5 D3: 1 D4: 2 Pruritus, n D1: 0 D2: 4 D3: 4 D4: 0 Through wk 24 for all groups in this category. Dyspnea, n: D1: 0 D2: 4 D3: 0 D4: 0 Any event up to Wk 24: D1: 32 D2: 32 D3: 30 D4: 34 Any event up to Wk 48: D1: 34 D2: 36 D3: 35 D4: 35
					Serious adverse event up to week 24: D1: 3 D2: 2 D3: 6 D4: 3
					Serious adverse event up to week 48: D1: 4 D2: 4 D3: 7 D4: 4

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
					Any event associated with
					first infusion
					D1: 12
					D2: 18
					D3: 13
					D4: 13
					Exacerbation of RA through
					wk 24:
					D1: 16
					D2: 6
					D3: 6
					D4: 2

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %			
Author, year, study name, if applicable	Inclusion Criteria • RA pts initiating	Interventions, Dose D1: Oral DMARDS	Mean disease duration, years (SD)	ACR ACR 20: No efficacy	Overall NR			
Strangfeld et al., 2009 ¹⁷⁶	biologic therapy or switching to another	D2: Biologics D3: Corticosteroids D4: Combination	D1: median (IQR): 9 (4-16) D2: 8.5 (4-14) D3: 10 (5-17)	outcomes reported ACR 50: NR ACR 70: NR	Overall adverse events reported, n:			
Country and setting German, multicenter	DMARD (Oral or Biologic)	therapy Number in group	D4: 6 (3-12) Patients with early RA,	HAQ NR	D1: NR - see additional comments for germane analyses			
Source of funding Essex, Wyeth, Abbott,	Exclusion Criteria • Missing follow	D1: 1252 D2: 591 D3: 1423	three years or less, %	DAS NR	Serious adverse events NR			
Amgen, Hoffman-La Roche, Bristol- Meyers Squibb	up data • (152 patients or	D4: 1774 Mean age (years)	Treatment resistant, %	SF-36 NR	Malignancies NR			
Research objective Investigate if TNF-	2.9% of eligible)	D1: 53.8 D2: 52.9	D1: 53.8	D1: 53.8 D2: 52.9	D1: 53.8 (SD)		Radiographic measures NR	Respiratory events NR
alpha inhibitors as a class, or by mode of impact, are related to		D3. 54.2 D4: 56.2 Sex, % female	Swollen Joint Count, mean (SD)	Quality of life scales NR	Other infections NR			
higher rates of herpes zoster in RA		D1: 77.8 D2: 73.3	NR Corticosteroid use, %	Others, (please name); mean difference/absolute difference (CI/SD/P Value)	GI NR			
pts Study design		D3: 80.2 D4: 78.6	Glucocorticoid/ Prenisolone: D1: 86.1/35.1 D2: 84.4/36.7	NR	Other • Adjusted (Age & Propensity score) HR for			
Prospective Cohort Study		Race, % white NR	D3: 81.6/29.2 D4: 76.5/19.3		Herpes Zoster. • Glucocorticoids 1-9 mgs			
Overall N 5040		Race, % black NR	DMARD use, % NR		1.86 (95%CI 0.92-3.78) • Glucocorticoids 10+mg 2.52 (1.12-5.65) [ref - 0mgs of glucocorticoids]. • Anti-TNF combined D1.63 (0.97-2.74), ETN 1.36 (0.73-2.55), IFX or ADA			
Duration of study varied, up to 36 mos from		Ethnicity, Latino NR	MTX naïve, % NR Baseline DAS score, mean (SD)					
May 2001 to December 2006								
Quality rating Good			D1: 5.8 (1.3) D2: 5.9 (1.2) D3: 5.7 (1.3) D4: 5.0 (1.3)		 1.82 (1.05-3.15) [ref - traditional DMARDs]. Results from subsample (N = 1344) of patients who 			
			Required treatment for latent TB		could act as own control - HR for Herpes Zoster. ETN 1.09 (0.39-3.06); IFX 2.43			

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
			NR Other population characteristics, %, (CI/SD/P value) NR		(0.94-6.26); ADA 3.01 (1.36-6.64) [ref - traditional DMARDs]

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
Author, year,	Inclusion	Comparisons	Mean disease	ACR mean difference/	Overall	Quality rating for
study name, if	Criteria	(dosage and	duration, years	absolute	Overall adverse events	efficacy/effectiveness?
applicable	Treatment	frequency)	D1: median (IQR): 7 (3,	difference (CI/SD/P	reported (n):	NR
Strangfeld et al.,	resistant	D1: Prior	13)	Value):	D1: 5	
2010 ¹⁷⁷	failure of at	malignancies-	D2: median (IQR): 10 (6,	NR	D1: 9	Quality rating for
2010		conventional		INIX	D3: 4	observational studies
Country and	least one	DMARD	16.5)	HAQ, mean difference/	D3: 4 D4: 1	Fair
setting	other DMARD		D3: median (IQR): 6	absolute	= :: :	
Germany	Exclusion	D2: Prior	(2.5, 12)	difference (CI/SD/P	Overall: 19	
,	Criteria	malignancies-	D4: median (IQR): 9 (5,	Value):	Serious adverse	
Source of	• NR	biologic (ETN,	17)	NR	events:	
funding	• IVIX	ADA, INF,	Comparison b/t strata:		Death (n):	
Essex Pharma,		ANK)	P=0.286	DAS, mean	D1: 0	
Wyeth pharma,		D3: Without prior	TJC, mean	difference/absolute	D2: 0	
Amgen,		malignancies-	NR	difference (CI/SD/P	D3: 4	
Biovitrum,		conventional	IVIX	Value):	D4: 1	
Abbott, Bristol-		DMARD	SJC, mean	NR	Overall: 5	
Myers Squibb,		D4: Without prior	NR	05.00	Overall. 5	
Roche, UCB		malignancies-		SF-36, mean	Malignancies:	
,		biologics (ETN,	Corticosteroid use, %	difference/absolute	Recurrent cancer	
Research		ADA, INF,	NR	difference (CI/SD/P	D1: 5; crude incidence	
objective		ANK)	DMARD use, %:	Value):	rates: 31.4 (95%	
To investigate		•	No of previous	NR	CI,10.2 to 73.4)	
the risk of new or		Number in group	DMARDs:	Radiographic	D2: 9; crude incidence	
recurrent		D1: 55	D1: 1.9 (1.0)	measures, mean	rates: 45.5 (95% CI,	
malignancy in		D2: 67		difference/absolute	20.8 to 86.3)	
patients with RA		D3: 1719	D2: 3.7 (1.5)		D3: NR	
receiving		D4: 3279	D3: 1.9 (1.1)	difference (CI/SD/P	D3. NIX	
biologics		Overall: 5120	D4: 3.6 (1.4)	Value):	Overall: (incidence rate	
compared to		Moon age (veers)	Comparison b/t strata:	NR	ratio anti-TNFá agents	
conventional		Mean age (years)	<i>P</i> = 0.656	Quality of life scales,	vs. DMARDs: 1.4 (95%	
DMARDs		D1: 63.2	MTX naïve, %:	mean	CI, 0.5 to 5.5) <i>P</i> =0.63)	
		D2: 64.0	D1: NR	difference/absolute	74 patients among the	
Study design		D3: 55.9	D2: NR	difference (CI/SD/P	4,998 patients who did	
Observational		D4: 53.6	D3: NR	Value):	not have a prior	
Overall N		Overall: comparison	D3. NR D4: NR	NR	malignancy developed	
5120		b/t strata: <i>P</i> <0.001		INIX	an incident tumor.	
5120		Sex, % female	Overall: 2.7	Others, (please name);		
Duration of		D1: 74.5	Treatment resistant,	mean	Respiratory events:	
study		D1: 74.5 D2: 67.2	%:	difference/absolute	NR	
60 mos			NR	difference (CI/SD/P		
		D3: 78.7		Value):	Other infections:	
		D4: 78.2	Patients with early RA,		NR	

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
Characteristics	Criteria	and Interventions Race, % white NR Race, % black NR Ethnicity, Latino NR	three years or less, %: NR Baseline DAS score D1: Mean (SD): 5.4 (1.1) D2: Mean (SD): 5.7 (1.3) D3: Mean (SD): 5.0 (1.3) D4: Mean (SD):5.8 (1.3) Comparison b/t strata: P=0.282 Required treatment for latent TB NR Other population characteristics, %, (CI/SD/P value): NR	Health Outcomes	GI: NR Other: Number of comorbidities, mean (SD): • Pts who developed malignancies during the study: 2.5 (2.1) • Pts who did not developed malignancies during the study: 1.7(1.9) COPD • Pts who developed malignancies during the study: 11/74 (14.9%) • Pts who did not develop malignancies during the study: 223/4924 (4.5%) P<0.0001 Chronic gastrointestinal diseases • Pts who did not developed malignancies during the study: 13/74 (17.6%) • Pts who did not developed malignancies during the study: 13/74 (17.6%) • Pts who did not develop malignancies during the study: 406/4924 (8.2%) P=0.008 Chronic renal diseases • Pts who developed malignancies during the study: 406/4924 (8.2%) P=0.008	Rating
					(17.6%) • Pts who did develop maduring the series 406/4924 (8 P=0.008 Chronic renale • Pts who de	d not alignancies study: 8.2%) diseases eveloped es during

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
					 Pts who did not develop malignancies during the study: 159/4924 (3.2%) P=0.22 	
					The univariate analysis showed that patients with a very active disease (DAS28 >5.1, mean: 5.93) during follow-up had a 2 times higher cancer risk than those with low disease activity (DAS28 <3.2, mean: 2.75)	
					Overall number of observed cancers in patients exposed to anti-TNFá agents: non-significantly lower than the expected number from the general population (standardized incidence rate ratio: 0.75, 95% CI 0.54 to 1.01). No difference was found for patients not exposed to biologics.	

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
Author, yr: Suissa et al., 2004 ¹⁷⁸ Country, Setting: US, 2 large databases Funding: Aventis Research Objective: Assess risk of hepatic events associated with the use of LEF and other DMARDS compared to MTX Study Design:	Age: 18 and older Provious use of	Interventions, dose: NR N: NR Mean age, yrs: NR Sex, % female: NR Race, % white: NR	Mean disease duration, yrs: NR TJC, mean: NR SJC, mean: NR DMARD use, %: NR Corticosteroid use, %: NR MTX naive, %: NR Txt resistant %: NR	When compared to MTX, No increased risk with LEF(rate ratio 0.9, 95% CI, 0.2-4.9), or with traditional DMARDS (RR 2.3; 95% CI, 0.8-6.5) There is an increased risk with biologic DMARDS (RR:5.5; 95% CI, 1.2-24.6) Rate of nonserious hepatic events was also increased with biologic DMARDS (RR 1.5; 95% CI, 1.0-2.3), but not LEF (RR:0.9; 95% CI, 0.7-1.3) and traditional DMARDS (RR 1.1; 95% CI, 0.8-1.4)		Overall Attrition Rate, %: NR ITT Analysis: NA: cohort Quality Rating: Fair
Observational Overall N: 41,885			Pts with Early RA (≤3 yrs): NR			
Study Duration: 3 yrs			Baseline DAS, mean: NR			

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
Author, yr: Suissa et al., 2006 ¹⁷⁹ Country, Setting: Canada, PharMetrics claims database Funding: Sanofi-Aventis; Canadian Institutes of Health Research Objective: To assess risk of ILD in pts with RA treated with LEF. Study Design: Retrospective Cohort Study Overall N: 62,734 Study Duration: Sept 1, 1998 through Dec 31, 2003	Age: 18 or older DMARD-treated cohort defined as all subjects who received at least 1 prescription for a DMARD on or after September 1, 1998, mo LEF was approved in US Exclusion Criteria: No DMARD prescription	N: D1: 74 D2: 7400 Mean age, yrs: D1: 62 D2: 61 Sex, % female: D1: 70 D2: 74 Race, % white: NR	Mean disease duration, yrs: NR TJC, mean: NR SJC, mean: NR DMARD use, %: NR Corticosteroid use, %: NR MTX naive, %: NR Txt resistant %: NR Pts with Early RA (≤3 yrs): NR Baseline DAS, mean: NR	Risk of ILD in pts treated with LEF compared with those not treated with LEF; adjusted OR 1.9, 95% CI,1.1-3.6 (all ORs reported here were adjusted for the concurrent use of the other DMARDs, the other anti-RA drugs, as well as sex and comorbid conditions) Increase was less and was not significant with use of MTX (OR 1.4; 95% CI,0.8-2.3) No increase in risk of ILD with LEF among pts who had no previous MTX use and no interstitial lung disease prior to cohort entry (37 cases and 4,259 controls); OR 1.2; 95% CI,0.4-3.1. This group did have an increased risk of ILD with MTX treatment (OR 3.1; 95% CI,1.5-6.4). Among those who had previously taken MTX or who had a previous diagnosis of ILD (37 cases and 3,141 controls), the risk of ILD was elevated with LEF treatment (OR 2.6; 95% CI,1.2-5.6) but was decreased with MTX treatment (OR 0.4; 95% CI,0.2-0.9)	NR	Overall Attrition Rate, %: NA ITT Analysis: NA: nested case control design Quality Rating: Fair

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
Author, year, study name, if applicable Suissa et al., 2006 ¹⁸⁰	Inclusion Criteria • RA pts with 1 year of eligibility	D1: Other: Case (Acute Myocardial	Mean disease duration, years (SD) NR	ACR ACR 20: D1: Efficacy outcomes NR	Overall Overall attrition/withdrawal, n: D1: NA, LTF NR for database
Country and setting North America - claims data Source of funding	in database Exclusion Criteria • AMI during 1 vear prior to	Infarction - AMI) D2: Other: Control Number in group D1: 558 D2: 5580	Patients with early RA, three years or less, % NR Treatment resistant, %	ACR 50: NR ACR 70: NR HAQ NR	Overall adverse events reported, n: NR - see additional comments for germane analyses
Sanofi-Aventis Canadian Institutes of Health Research, Fonds de la	year prior to cohort entry	Mean age (years) D1: 65 D2: 65	NR Tender Joint Count, mean (SD) NR	DAS NR SF-36	Serious adverse events NR Malignancies
recherche en sante du Quebec Research objective Assess risk of AMI		Sex, % female D1: 55 D2: 55	Swollen Joint Count, mean (SD) NR	NR Radiographic measures NR	NR Respiratory events NR
associated with use of DMARDS and other RA txt		Race, % white NR Race, % black NR	Corticosteroid use, % Glucocorticoid therapy: D1: 15.1 D2: 12.0	Quality of life scales NR Others, (please name); mean difference/absolute	Other infections NR GI
Study design Nested Case control Cohort		Ethnicity, Latino NR	DMARD use, % D1: 25.4 D2: 30.4	difference NR	NR Other Adjusted* RR of AMI for
Overall N 6138 for case-control with 1:10 ratio selected from eligible RA cohort of 107,908 subjects			MTX naïve, % NR Baseline DAS score, mean (SD) NR		current users of RA medications: MTX monotherapy 0.81 (95%CI 0.60-1.08) • LEF 0.28 (0.12-0.64) • Biologic Agents (IFX, ETN,
Duration of study vaired, mean = 14 mos (11). All subjects were followed from date of cohort entry until one of following occurred: termination of health			Required treatment for latent TB NR Other population characteristics, %, (CI/SD/P value) D1: Mean follow up: 14 mos		 & ANA combined) 1.30 (0.92-1.83) All other DMARDS (includes HCQ, SSZ, & 10 other txt) 0.67 (0.46-0.97) Glucocorticoids 1.32 (1.02-1.72) [*Adjusted for age &

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
plan enrollment,			(11)		
death, end of study period (December 31, 2003), or outcome of interest, namely AM			D2: 14 mos (11)		
Quality rating Fair					

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
Author, yr: Svennsson et al 2003 ¹⁸¹ Country, Setting: Sweden, multicenter (5 cheumatologic units covering both urban and rural districts) Funding: Swedish Rheumatism Association and Vardal Foundation Research Objective: To study and compare butcomes of 2 different DMARD/corticost eroid options in ext of early RA in clinical practice Study Design: RCT Overall N: 245 Study Duration: 2 yrs	 Diagnosed according 1987 revised ACR Duration of condition: less than 2 yrs Considered to be in need of Css or DMARDS by treating physician's judgment NSAIDS and analgesics allowed Exclusion Criteria: Prior txt with: DMARDS or Cxs 	Interventions: D1: PNL + MTX D2: SSZ + PNL at lowest possible dose Overall: PNL: 7.5 to 15 mg daily for 1 to 3 mos. with subsequent reduction to lowest possible dose MTX: 5 to 15 mg per wk SSZ: 2 to 3 grams daily N: D1: 113 D2: 108 Mean age (yrs): D1: median 54 D2: median 52 Sex, % female: D1: 59 D2: 67 Race, % white: NR Mean disease duration, yrs: D1: 6 mos. D2: 7 mos	TJC, mean: NR SJC, mean: NR DMARD use, %: D1: 0 D2: 0 Corticosteroid use, %: D1: 0 D2: 0 MTX naive, %: NR Treatment resistant %: NR Patients with Early RA (≤3 yrs): NR DAS28 median: D1: 5 D2: 4.9 Larsen: D1: 5 D2: 3 HAQ: D1: 0.9 D2: 0.9 RF +: D1: 71 D2: 39	No significant differences between txt groups for individual response, remission, function, or radiologic progression Response (EULAR individual response criteria for good/moderate/no response, %) D1: 30/40/30. D2: 33/30/37% (P = 0.319) Remission, % D1: 29 D2: 19 (P = 0.095) Mean change in HAQ D1: 0.35 D2: -0.38 (P = 0.752) Mean change in Larsen score 6.2 vs. 4.1 (P = 0.298) Completers, % D1: 81% D2: 53% Survival analysis between 2 groups (using withdrawals due to AEs or inefficacy as terminal event) showed a highly significant difference in survival times between 2 groups (P = 0.0005)	Overall: D1: 9.9 D2: 31.6	Overall Attrition Rate, %: 39.6 ITT Analysis: No another type of analysis was used (define): Although they state it was an ITT analysis, statistical analysis based on 221 of the 245 pts with available data for clinical outcomes and for about 72% of the cases for Larsen score (based on available Quality Rating: Poor for efficacy, fair for adverse events

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events (%)	Analysis and Quality Rating
Author, yr: Svensson et al., 2005 ¹⁸² Country, Setting Sweden, multicenter Funding: Swedish Rheumatism Association and others Research Objective Efficacy of low-dose PNL on joint damage and disease activity in pts with early RA being treated concomitantly with DMARDs Study Design: RCT Overall N: 250 Study Duration: 2 yrs	DMARD	Interventions, dose: D1: DMARD (SSZ 2 g/day or MTX mean dose 10 mg/week, dosages NR) + PNL (7.5 mg/d) D2: DMARD only N: D1: 119 D2: 131 Mean age, yrs: D1: 51 D2: 59 Sex, % female: D1: 65 D2: 63 Race, % white: D1: NR D2: NR	Mean disease duration, yrs: D1: 6.5 mos D2: 5.8 mos TJC, mean: NR SJC, mean: NR DMARD use, %: Overall: 100 Corticosteroid use, %: NR MTX naive, %: NR Txt resistant, %: NR Pts with Early RA (≤3 yrs): Overall: 100 Baseline DAS, mean: D1: 5.28 D2: 5.42 HAQ: D1: 1.01 D2: 0.98 SOFI: D1: 8 D2: 9	At 2 yrs: DAS < 2.6 disease remission, % achieved D1: 55.5 D2: 32.8 (P = 0.0005) DAS28, scores over time ± SD D1: 5.3 ± 1.1 at baseline to 2.7 ± 1.5 after 1 yr and 2.7 ± 1.3 after 2 yrs D2: 5.4 ± 1.0, 3.3 ± 1.5, and 3.2 ± 1.4 HAQ scores mean decrease over time: D1: 1.0 at baseline to 0.4 at 1 year and 0.5 D2: 1.0, 0.6, and 0.7 (P value NR) Improvement in mean SOFI index D1: mean decreased from 8 at baseline to 4 at 1 year and 4 after 2 years D2: 9, 6, and 7 respectively (P value NR) Total sharp score, median IQR change i D1: 1.8 (IQR 0.5-6.0) D2: 3.5 (IQR 0.5-10.0) (P = 0.019) Newly eroded joints per pt, median D1: 0.5 (IQR 0-2) D2: 1.25 (IQR 0-3.25) (P = 0.007)	NR	Overall Attrition Rate, %: 6.6% ITT Analysis: Yes Quality Rating: Fair

cation for
glucocorticoid
therapy

• Previous
fragility
fractures, pts
< 65 years
with T score
<-2.5 on bone
mineral
densitometry

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
Characteristics Author, year, study name, if applicable van Halm, V.P. et al.; 2006 ¹⁸³ Country and setting Amsterdam, Netherlands; outpatient clinic Source of funding Not reported Research objective Investigate possible associations between CVD and use of conventional DMARDs in RA Study design	Exclusion		Mean disease duration, years (SD) D1: 7.7 yrs, IQR: 5-11 D2: 10.6, IQR: 8-13 P = 0.001 Patients with early RA, three years or less, % NR Treatment resistant, % NR Tender Joint Count, mean (SD) NR Swollen Joint Count, mean (SD) NR	Health Outcomes ACR NR HAQ NR DAS NR SF-36 NR Radiographic measures NR Quality of life scales NR Others, (please name); mean difference/absolute difference (CI/SD/P Value) NR	Overall NA Overall adverse events reported, n: NR Serious adverse events NR Malignancies NR Respiratory events NR Other infections NR
Case Control Cohort Overall N 613 Duration of study Recruitment: 1953 - 2002; Follow-up: 2002 - 2004. Quality rating Fair		dosage and frequency NR Number in group D1: 541 D2: 72 Mean age (years) D1: 62, SD 11 D2: 67, SD 10 P = 0.001 Sex, % female D1: 72 D2: 58 P = 0.02 Race, % white NR Race, % black NR Ethnicity, Latino	Corticosteroid use, % D1: PRED ever: 31 D2: PRED ever: 25 Overall: PRED ever: $P = 0.32$ DMARD use, % D1: • Median use: 2 • IQR: 2-3 • SSZ HCQ or MTX never: 5 • SSZ ever: 78 • HCQ ever: 40 • MTX ever: 72 D2: • Median use: 3, IQR: 1-3 • SSZ HCQ or MTX never: 17 • SSZ ever: 65 • HCQ ever: 38 • MTX ever: 44 Overall: • Median use: $P = 0.01$		Other Model 2 OR (95% CI) corrected for age, gender, smoking, RA duration, htn, diabetes, and hypercholesteremia with all comparisons to never MTX, SSZ, or HCQ; MTX 0.47 (0.07-3.23) SSZ 0.31 (0.07-1.33) HCQ 0.45 (0.10-2.04) MTX and SSZ 0.24 (0.07-0.85) MTX and HCQ 0.54 (0.08-3.66) SSZ and HCQ 0.34 (0.05-2.16) MTX, SSZ, and HCQ 0.27 (0.07-0.99)

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
		NR	 SSZ HCQ or MTX never: P = 0.001 SSZ ever: P = 0.02 HCQ ever: P = 0.67 MTX ever: P = 0.001 		
			MTX na ïve, % NR		
			Baseline DAS score, mean (SD) NR		
			Required treatment for latent TB NR		
			Other population characteristics, %, (CI/SD/P value) D1: • Erosive pts (%): 80 • DMARD naive (%): 3 • Hypertension: 19% • Hypercholesterolemia: 2% D2: • Erosive pts (%): 92 • DMARD naive (%): 10 • Hypertension: 49% • Hypercholesterolemia: 21% Overall: • Erosive pts: P = 0.02 • DMARD naive: P = 0.002 • Hypertension: P = 0.001 • Hypercholesterolemia: P = 0.001		

Study Inclusion a Characteristics Exclusion		Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events (%)	Analysis and Quality Rating
Setting: Multinational, multicenter Funding: Wyeth Research Objective: Evaluate efficacy and safety of ETA monotherapy vs. ETA + MTX in RA pts with inadequate response to MTX Criteria Function of: I-III Previous DMARDs on MTX Exclusion Exclusion DMARDs than MTX 12 wks of screening predniso mg/d Corticost	8 D1: ETA (25 mg s twice wkly) g to ACR 9 to ACR 10 D2: ETA (25 mg s twice wkly) + MTX 11 class 12 L2.5 mg/wk) 13 use of s D1: 159 D2: 155 14 control mptoms ≥ 12.5 D1: 53 D2: 54 15 Criteria: 15 Sother 15 Sother 17 Sex, % female: 16 D1: 79.2 17 D2: 76.8 17 Race, % white: 17 Useroid 18 within 6 19 Sother 19 Sex, % female: 19 D1: 99.4 19 D2: 98.7 10 deroid 18 within 6 19 Sother 19 Sex, % female: 10 Sex, % white: 11 Sex, % white: 12 Sex, % white: 13 Sex, % white: 14 Sex, % white: 15 Sex, % white: 16 Sex, % white: 17 Sex, % white: 18 Sex, % white: 19 Sex, % white	.c. duration, yrs: D1: 10.0 .c. D2: 9.8	DAS28 improvement of > 1.2 units, %: D1: 72.8 D2: 75.2 Difference -2.3 (95% CI, -13.1-8.2; P = 0.658) EULAR response maintained, %: D1: 80.0 D2: 82.4 (P = NR) ACR 20, %: D1: 71.0 D2: 67.1 Difference 3.9 (95% CI, -6.4-14,2; P = 0.46) ACR 50, %: D1: 41.9 D2: 40.1 Difference 1.8,(95% CI, -9.2-12.8; P = 0.75) ACR 70, %: D1: 17.4 D2: 18.4 Difference -1.0 (95% CI, -9.6-7.6; P = 0.82)	D1: 6.3 D2: 6.5 Dizziness: D1: 0.6%	Overall Attrition Rate, %: 17.2 ITT Analysis: Yes Quality Rating: Fair

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
Author, year, study	Inclusion Criteria • Treatment resistant, unsatisfactory response to MTX 12.5 mg a week for at least 3 mos • 18 years old or older • ACR functional class I-III • DAS28 of 3.2 or greater or combination of ≥ 5 swollen joints • ≥ 5 painful joints • ESR of 10 mm/h or more • 16 years old or older during onset of RA • No DMARD use other than MTX within 12 weeks of screening Exclusion Criteria • Patients requiring concurrent use of PRED greater than 10 mg/day or equivalent	Interventions, Dose D1: ETN: 25 mg twice a week D2: MTX: 12.5 mg per week ETN: 25 mg twice a	Mean disease duration,	ACR NA HAQ, mean change from baseline (SD) D1: -0.59 (0.69) D2: -0.59 (0.58) Overall: NS, Difference between groups (95% CI): 0.029 (-0.115, 0.172) DAS NA SF-36 NR Radiographic measures NA Quality of life scales EQ-5D VAS (0-100): D1: 19.76 (27.24) D2: 21.00 (26.61) Difference between groups (95% CI): -2.593 (-7.667, 2.482);- EQ-5D (0-1): D1: 0.1883 (0.33) D2: 0.2399 (0.32) Difference between groups (95% CI): -0.024 (-0.82, 0.034) EQ-5D Usual Activities: D1: 0.3077 (0.61) D2: 0.2867 (0.55) Difference between groups	Overall Overall attrition/withdrawal, n: D1: 18 D2: 13 Overall: 30 Withdrawals due to adverse events, n: D1: 6 D2: 9 Overall: 15 Withdrawals due to lack of efficacy, n: D1: 9 D2: 0 Overall: 9 Overall adverse events reported, n: NR Serious adverse events NR Malignancies NR Respiratory events NR Other infections NR Other NR
			Required treatment for	(95% CI): 0.017 (-0.102, 0.137)	

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
Author, year, study name, if applicable van Riel et al., 2008, ADORE trial 185 (original ADORE publication was van Riel 2006) (continued)	Presence of known relevant concurrent diseases Use of bolus corticosteroids within 6 weeks or intra-articular corticosteroid injection within 9 weeks of screening Previous treatment with ETN or other biological treatments		NR Other population characteristics, %, (CI/SD/P value) Mean HAQ: D1: 1.6 D2: 1.7	EQ-5D Self Care: D1: 0.1731 (0.55) D2: 0.3533 (0.55) Difference between groups (95% CI): -0.129 (-0.233, -0.025; (P = 0.0154) EQ-5D Pain/Discomfort: D1: 0.3718 (0.62) D2: 0.4400 (0.65) Difference between groups (95% CI): -0.04 (-0.159, 0.078) EQ-5D Mobility: D1: 0.3077 (0.50) D2: 0.2318 (0.52) Difference between groups (95% CI): 0.058 (-0.047, 0.164) EQ-5D Anxiety/Depression: D1: 0.2323 (0.59) D2: 0.24 (0.65) Difference between groups (95% CI): 0.029 (-0.089, 0.147) Patient global assessment of disease (PGAD) (0-10): D1: -2.78 (2.60) D2: -2.95 (2.59) Difference between groups (95% CI): -0.174 (-0.692, 0.345) Pain VAS (0-10): D1: -29.40 (25.09) D2: -29.93 (27.25) Difference between groups	

Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
			(95% CI): -1.327 (-7.039,	
				riteria Interventions Treatment Characteristics Health Outcomes

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
Author, year, study name, if applicable van Vollenhoven et al., 2009 186 Swefot Trial Country and setting Sweden; multicenter Source of funding Schering-Plough; Swedish Rheumatism Association Research objective To compare the addition of SSZ and HCQ versus the addition of INF to MTX in patients with early RA Study design Controlled Trials Overall N 258 Duration of study 12 mos	Inclusion Criteria Early RA; symptom duration <1 yr Treatment resistant resistant to 3- 4 mos of MTX treatment indicated by DAS28>3.2 ≥18 yrs old ACR dx of RA no previous treatment with DMARDs No oral glucocorticoid or stable glucocorticoid therapy for at least 4 wks of at most 10 mg daily PNL or equivalent DAS28 >3.2 Exclusion Criteria Contraindicati ons of any trial drugs	Comparisons (dosage and frequency) D1: • MTX: up to 20 mg per wk • SSZ: 1000 mg twice a day • HCQ: 400 mg a day D2: • MTX: up to 20 mg a week • INF: 3 mg/kg at wk 0, 2, 6 and every 8 wks thereafter Number in group D1: 130 D2: 128 Overall: 258 Mean age (years) D1: 52.9 D2: 51.1 Overall: NR Sex, % female D1: 78 D2: 76 Overall: NR Race, % white NR Race, % black NR Ethnicity, Latino NR	Mean disease duration, years D1: 6.3 mos (3.6) D2: 6.2 mos (3.5) Overall: NR TJC, mean NR SJC, mean NR Corticosteroid use, % D1: 8 D2: 6 Overall: NR DMARD use, %: D1: 100 D2: 100 Overall: 0 MTX naïve, %: D1: 0 Overall: 0 Treatment resistant, %: D1: 100 D2: 100 Overall: 100 Patients with early RA, three years or less, %: D1: 100 D2: 100 Overall: 100 Baseline DAS score At baseline: D1: 5.98 (0.96) D2: 5.91 (0.93)	ACR mean difference/absolute difference (CI/SD/P Value): ACR 20: ITT population: D1: I28 D2: 42 Overall: RR 1.48 (1.06 to 2.08; P=0.0266) mITT population: D1: 45 D2: 59 Overall: RR 1.31 (1.03 to 1.66; P=0.0257) ACR 50: ITT population: D1: 15 D2: 25 Overall: RR 1.71 (1.02 to 2.86; P=0.0424) mITT population: D1: 34 D2: 48 Overall: RR 1.43 (1.06 to 1.93; P=0.0226) ACR 70: ITT population: D1: 7 D2: 12 Overall: RR 1.69 (0.77 to 3.73; P=0.2044) mITT population: D1: 15 D2: 28 Overall: RR 1.83 (1.12 to 2.98; P=0.0156) HAQ, mean difference/absolute	Overall: 64 Withdrawals due to adverse events (n): D1: 14 D2: 10 Overall: 24 Withdrawals due to lack of efficacy (n): D1: 18 D2: 3 Overall: 21 Adherent/compliant (n): D1: NR D2: NR Overall: NR Other attrition related comments? D1: 5 pts received treatment and 5 switched treatment D2: 8 never received treatment and 5 switched treatment Overall adverse events reported (n): D1: 48 D2: 32 Serious adverse events:	Quality rating for efficacy/effectiveness? Fair Quality rating for observational studies NR

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
	Exclusion		Treatment	Value): NR DAS, mean difference/absolute	Cardiovascular events (specify) (n): HTN D1: 2 D2: 0 Hepatotoxicity/elevated liver enzymes (n): Liver D1: 1 D2: 5 Malignancies: NR Respiratory events: Upper respiratory infection (n): D1: 2 D2: 2 Other infections: Other infections (specify) (n): D1: 0 D2: 5 GI: Other GI symptoms (specify) (n): D1: 15 D2: 1 Other: Fractures (n): Musculoskeletal	
					D1: 0 D2: 1 Skin rash (n): Skin and allergic reactions D1:3 D2: 11	

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
					Demyelenation or multiple sclerosis (n): Central and peripheral	
					nervous system D1: 6 D2: 1	

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
•		Interventions Interventions, dose: D1: INF (various) D2: ETA (various) N: D1: 566 cases (>233,000 treated) D2: 83 cases (>113,000 treated) Mean age, yrs: D1: 60 D2: 58 Sex, % female: D1: 66 D2: 59 Race, % white: NR		NR	Adverse Events, % Granulomatous infections, rate per 100,000 D1: 239 D2: 74 (P < .001) D1 risk of granulomatous infection was 3.25-fold greater among pts than D2. Tuberculosis infections, rate per 100,000 D1: 144 D2: 35 (P < .001)	
Study Design: Database analysis;AERS Overall N: 649 cases Study Duration: various		NR	NR Pts with Early RA (≤3 yrs): NR Baseline DAS, mean: NR MTX use: D1: 43 D2: 41			

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
Author, yr: Wasserman et al., 2004 ¹⁸⁸ Country, Setting: Canada, Quaternary care center Funding: Schering- Plough Research Objective: Description of infusion-related reactions to INF (during or within 1 hour of infusion) in pts with active rheumatoid arthritis Study Design: Case series Overall N: 113 pts, 1,183 infusions Study Duration: Mean 60.6 wks	 Age: 18 to 75 Diagnosed according to ACR; failed at least 3 DMARDs Active disease; stable doses of corticosteroids (10 mg/d) and/or NSAIDs Exclusion Criteria: Biologically-based therapies 	Interventions, dose: D1: INF INF: 3 mg/kg wks 0,2,6 then every 8, dose could be increased to 5 mg/kg at wk 14 based on clinical grounds N: D1: 113 pts; 1,183 infusions Mean age, yrs: D1: 45.7 Sex, % female: D1: 87 Race, % white: NR	Mean disease duration, yrs: D1: 13.6 TJC, mean: D1: 21.3 SJC, mean: D1: 10.8 DMARD use, %: NR PRE use, %: D1: 59 MTX naive, %: NR Txt resistant %: NR Pts with Early RA (≤3 yrs): NR Baseline DAS, mean: NR MTX use: D1: 100	104 infusion-related reactions out of 1183 infusions performed (8.8%) and 60 of 113 pts (53%) experienced at least one reaction during course of txt Infusion related reactions; Allergic-45 (3.8%); Cardiopulmonary-35 (3.0%); Misc24 (2.0%) Reactions following pretxt or not with diphenhydramine at infusions 3 and 4 Pretreated 14.7% vs. Not pretreated 14.3%	Overall: D1: 8.8 Headache: D1: 9	Overall Attrition Rate, %: ITT Analysis: NA Quality Rating: Fair

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events (%)	Analysis and Quality Rating
Author, yr:	Inclusion Criteria:	Interventions, dose:	Mean disease	mACR20, %:	NR	Overall
Weaver et al.,	 Age: 18 or older 	D1: MTX (10 to 15	duration, yrs:	D1: 37		Attrition
2006 ¹⁸⁹	 Diagnosed with 	mg/wk)	D1: 3.5	D2: 41		Rate, %:
Country	RA according to	D2: ETN (50 mg/wk)	D2: 9.2	D3: 43		33.2
Country,	ACR criteria: 1987	D3: ETN (50 mg/wk)	D3: 7.7	D4 : 26		ITT
Setting:	ACR	+MTX	D4: 10.6	D5: 35		ITT Amalania
US,	 Pts requiring a 	D4: INF (3.8 mg/8wks)	D5: 9.5			Analysis:
Rheumatology	change in RA txt	D5: INF (3.8 mg/8wks)	D6: 10.1	Adjusting for baseline		Yes
practices (509)	•	+ MTX (15 mg/wk)	D7: 7.4	covariates		Quality
Funding:	Exclusion Criteria:	D6: LEF (20 mg/d)	D8: 4.6	D3: vs. D1 (OR, 1.29, 95% CI,		Rating:
Immunex	 Pregnant or 	D7: LEF (20 mg/d)	D9: 7.2	1.09-1.52; P < 0.01)		Fair
Corporation	lactating	+MTX (15 mg/wk)		D2 vs. D1 (OR, 1.23, 95% CI,		ı un
Corporation	 Active infection, 	D8: MTX (15 mg/wk)	TJC, mean:	1.02-1.47; P < 0.05)		
Research	 Concurrent 	+HCQ (400 mg/d)	D1: 13	D1 vs. D5 (OR, 0.96 CI 0.76-		
Objective:	enrollment in a	D9: MTX (15 mg/wk)	D2: 13.4	1.21 P = 0.72		
To evaluate	clinical trial	+HCQ (400 mg/d)	D3: 13.3	D1 vs. D4 (OR, 0.66, 95% CI,		
effectiveness of		+SSZ (2000 mg/d)	D4: 14.8	0.43-1.02; P = 0.06)		
select biologics,			D5: 3.9	,,		
MTX (MTX), and		N:	D6: 12.8	Mean change HAQ		
other DMARDs		D1: 941	D7: 12.2	improvement, %		
in management		D2: 1251	D8: 11.8	D1: 7		
of adult RA in		D3: 1783	D9: 10.1	D2: 17 (P < 0.001)		
routine clinical		D4: 120	SJC, mean:	D3: 17 (P < 0.001)		
practice		D5: 540	•	20. 17 (7 10.001)		
•		D6: 204	D1: 11.3	mACR20 response		
Study Design:		D7: 191	D2: 11.1	D5 vs. D1 : (OR, 0.68, 95% CI,		
Prospective		D8: 325	D3: 11.5	0.48-0.96; <i>P</i> < 0.05)		
cohort study		D9: 42	D4: 13.9	D6 vs. D1 (OR, 0.76, 95% CI,		
Overall N:			D5: 12.0	0.54-1.06; $P = 0.11$)		
5,397		Mean age, yrs:	D6: 11.8	D8 vs, D1 : (OR, 0.94, 95% CI,		
		D1: 56.8	D7: 11.4	0.72-1.23; $P = 0.64$)		
Study Duration:		D2: 53.2	D8: 9.2	,		
12 mos		D3: 52.6	D9: 10.2	D9 vs. D1 : (OR, 0.57, 95% CI, 0.27-1.18; <i>P</i> = 0.13)		
		D4: 60.2	DMARD use, %:	0.27 - 1.16, P = 0.13)		
		D5: 58.5	D1: 25	SIC % improvement		
		D6: 57.7	D2: 75	SJC % improvement		
		D7: 55.5	D3: 96	D1 vs. D1 : 34 (N/A)		
		D8: 53.8	D4: 85	D2 vs. D1 : 53 (<i>P</i> < 0.0001)		
		D9: 47.8	D5: 96	D4 vs. D1 : 29 (<i>P</i> = NS)		
		Sex (% female	D6: 75	D3 vs. D1 : 55 (<i>P</i> < 0.0001)		
		OCA (/0 lelliale	DO. 10	D5 vs. D1 :48 (<i>P</i> < 0.01)		

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events (%)	Analysis and Quality Rating
		D1: 75 D2: 75 D3: 79 D4: 71 D5: 77 D6: 76 D7: 78 D8: 80 D9: 79 Race, % white: D1: 77 D2: 81 D3: 81 D4: 78 D5: 81 D6: 78 D7: 82 D8: 83 D9: 79	D7: 95 D8: 78 D9: 88 Corticosteroid use, % D1: 53 D2: 48 D3: 51 D4: 63 D5: 57 D6: 48 D7: 56 D8: 50 D9: 48 MTX naive, %: NR Treatment resistant, %: NR Pts with Early RA (≤3 yrs): NR Refactor positive: D1: 72 D2: 65 D3: 69 D4: 68 D5: 69 D6: 75 D7: 73 D8: 71 D9: 71	TJC % improvement D1: 34(N/A) D2 vs. D1: 53% (P < 0.001) D4 vs. D1: 29% (P = NS) D3 vs. D1: 55% (P < 0.0001) D5 vs. D1: 48% (P = NS) HAQ % improvement amongst pts < 65 yrs D2: 22 D4: 4 (P = NR)		

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
Author, yr: Weinblatt et al., 2006 190 Country, Setting: Multinational Multicenter ASSURE Trial Funding: Bristol-Myers Squibb Research Objective: To assess safety of ABA in pts with active RA who had been receiving 1 traditional nonbiologic DMARDs Study Design: RCT Overall N: 1456 Study Duration: One yr	Inclusion Criteria: Age: ≥ 18 Diagnosed according to ACR criteria I class I-IV DMARDs Stable, low-dose oral Css and/or stable doses of NSAIDs Stable CHF, asthma, COPD, and DM Exclusion Criteria: Pregnant or lactating History of TB Impaired renal or hepatic system Mycophenolate mofetil, CYP, other calcineurin inhibitors, D-penicillamine, cyclophosphamide, apheresis unstable or uncontrolled diseases, or any autoimmune disorder as the main diagnosis Bacterial infections Active herpes zoster < 2 mos, hepatitis B or C	Interventions, dose: D1: Non-bio and ABA D2: Non-bio and placebo D3: Bio and ABA D4: Bio and placebo ABA: 500 mg a body weight <60 kg, 750 mg for 60-100 kg, and 1 gram for >100 kg N: D1: 856 D2: 418 D3: 103 D4: 64 Mean age, yrs: D1: 52.2 D2: 52.0 D3: 54.6 D4: 52.8 Sex, % female: D1: 83.1 D2: 83.7 D3: 75.7 D4: 75.0 Race, % white: D1: 83.9 D2: 83.3 D3: 97.1 D4: 92.2	Mean disease duration, yrs: D1: 9.5 D2: 9.5 D3: 11.3 D4: 11.3 TJC, mean: NR SJC, mean: NR DMARD use, %: NR Corticosteroid use, %: NR Txt resistant %: NR Pts with Early RA (53 yrs): NR Baseline DAS, mean: NR HAQ: D1: 1.5 D2: 1.5 D3: 1.5 D4: 1.6	ABA and placebo groups exhibited similar frequencies of adverse events (90% and 87%, respectively), serious adverse events (13% and 12%, respectively), and discontinuations due to adverse events (5% and 4%, respectively) Serious infections were more frequent in the ABA group than in the placebo group (2.9% vs. 1.9%) Serious adverse events occurred more frequently in the subgroup receiving ABA plus a biologic agent (22.3%) than in other subgroups (11.7-12.5%) Sub analysis of Pts w/ COPD and DM (placebo vs. ABA)(%) COPD Overall AEs 88.2 vs.97.3 Respiratory oriented 23.5 vs. 23.5 SAEs 5.9 vs. 27 DM Overall AEs 90.3 vs. 93.8 Infections 58.1 vs. 50.8 SAEs 12.9 vs. 21.5 Change in HAQ from baseline Placebo -0.25 vs. ABA- 0.46 (P < 0.001)	D1: 54.9 D2: 53.6 D3: 65.0 D4: 57.8	Overall Attrition Rate, %: 15 ITT Analysis: Yes Quality Rating: Fair

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
Author, year, study name, if applicable Weinblatt, M. et al 2007 ¹⁹¹	Inclusion Criteria • ≥ 18 years of age • Met criteria	Interventions, dose D1: • ETN: 25 mg twice weekly	Mean disease duration, years (SD) D1: 13 (10.1) D2: 12.8 (8.6)	ACR Modified ACR 20: At 6 months: D1: 48.2	Attrition/withdrawal Overall after 1 year, n: D1: 27 D2: 14
Country and setting United States multicenter	ofACR for RA • In functional class, I, II, or III	Abatacept: 2 mg/kg on days 1, 15 and 30, and every 4 weeks	Patients with early RA, three years or less, % NR	D2: 30.6 P = 0.072 At 1 year:	Withdrawals due to adverse events, n: D1: DB Phase: 10
Source of funding Bristol-Myers Squibb	 Must have received ETN 25 mg twice weekly for ≥ 3 	thereafter after 1 year switched to 10 mg/kg D2: • ETN: 25 mg twice	Treatment resistant, % NR	D1: 48.2 D2: 30.6 Overall: NR	LTE: 8 D2: 1 Withdrawals due to lack of
Research objective Investigate efficacy and safety of ABA in combination with	mos and have ≥ 8 swollen joints (66-joint count) and ≥ 10 tender	 Weekly Placebo: after 1 year switch to 10 mg/kg abatacept 	Tender Joint Count, mean (SD) D1: 28.7 (14) D2: 29.2 (13.2)	Modified ACR 50: At 6 months: D1: 25.9 D2: 19.4	efficacy, n: D1: 9 D2: 12
ETN in patients with active RA Study design	joints (68-joint count). • CRP elevation	Number in group D1: 85	Swollen Joint Count, mean (SD) D1: 19.6 (9.4)	P = 0.448 At 1 year:	Adherent/compliant after 1 year, n: D1: 58
Controlled Trials Overall N	was not required for entry.	D2: 36 Overall: 121 Mean age, years (SD)	D2: 20.1 (10.5) Corticosteroid use, %	D1: 28.2 D2: 16.7 Overall: NR	D2: 22 Attrition rate difficult to determine b/c they do not
Duration of study DB Phase: 1 year	Exclusion Criteria • Active or latent	D1: 49.8 (23-73) D2: 54.3 (28-71) Sex, % female	NR DMARD use, % NR	Modified ACR 70: At 6 months: D1: 10.6	clearly indicate how many patients remained in either drug after LTE completion
LTE: 2 years Quality rating Fair	infection Recent opportunist	D1: 78 D2: 72	MTX naïve, % NR	D2: 0.0 P = 0.042 At 1 year:	they list only total LTE completion (N = 61). Overall adverse events
rali	infection TB requiring treatment within	Race, % white D1: 94 D2: 100	Baseline DAS score (SD) D1: 61.8 (17.2) D2: 62.1 (13.5)	D1: 9.4 D2: 5.6 P = 0.481	reported, n: D1: DB Phase: 79 LTE: 78
	previous 3 yearsHistory of cancer within	Race, % black D1: NR D2: 0	Required treatment for latent TB NR	HAQ (SD/P Value) Change from baseline to 1-	D2: 32 Overall: 189
	previous 5 years History of drug or alcohol	Ethnicity, Latino D1: NR	Other population characteristics, n (SD)	year D1: -0.3 (0.5, <i>P</i> = 0.001) D2: -0.2 (0.4, <i>P</i> = 0.040	Serious adverse events Death, n: D1: DB Phase: 0
	misusePregnant and nursing women.	D2: 0	Patient assessment of pain: D1: 66.5 (16.6) D2: 53.2 (23.2)	Change from 1-year to 2- years: D1: -0.1 (0.3, <i>P</i> = NS)	LTE: 1 D2: 0 Overall: 1
	nursing worneri.		·	D2: 0 (0.2, $P = NS$)	Malignancies

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
			mHAQ: D1: 1.0 (0.5) D2: 0.9 (0.5)	DAS Change from baseline to 1- year: D1: -25.7 (27.0, P = 0.001) D2: -18.2 (20.4, P = 0.001)	NR Respiratory events Tuberculosis: NR Upper respiratory infection,
			C y C	Change from 1-year to 2- years: D1: -7.6 (20.6, <i>P</i> = 0.0135) D2: -0.6 (23.1, <i>P</i> = NS)	n: D1: DB Phase: 20, LTE: 10 D2: 5 Overall: 35
				SF-36 Change after 1-year of LTE MCS: D1: 7.08 D2: 2.14	Other infections NR GI Nausea or vomiting, n: D1: DB Phase: 13, LTE: 12 D2: 1
				PCS: D1: 9.11 D2: 3.19 Change after 2 years of LTE	Overall: 26 Other GI symptoms, n: D1: Diarroea: DB Phase: 12, LTE: 13
				MCS: D1: 4.68 D2: 7.54 PCS:	D2: Diarrhea: 2 Overall: 27 Other Skin rash, n:
				D1: 6.65 D2: 3.44 Radiographic measures NR	D1: DB Phase: 11 LTE: 10 D2: 3 Overall: 24
				Quality of life scales NR	Headache, n: D1: DB Phase: 20, LTE: 10 D2: 5 Overall: 35
					Dizziness, n: D1: DB Phase: 13, LTE: 8 D2: 2 Overall: 23
					Fatigue, n: D1: DB Phase: 14, LTE: 14

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
					D2: 6 Overall: 34
					Sinusitis, n: D1: DB Phase: 14, LTE: 18 D2: Sinusitis: 3 Overall: 35
					Arthralgia, n: D1: DB Phase: 13, LTE: 5 D2: 3 Overall: 21
					Cough, n: D1: DB Phase: 11, LTE: 11 D2: 3 Overall: 25
					Vascular disorders: D1: DB Phase: 0, LTE: 6 D2: 1
					Malignancies D1: DB Phase: 0, LTE: 3 D2: 0
					Gastrointestinal disorders: D1: DB Phase: 0, LTE: 3 D2: 0
					Infections and infestations: D1: DB Phase: 3, LTE: 1 D2: 0
					Nervous system disorders: D1: DB Phase: 2, LTE: 1 D2: 0
					Respiratory, thoracic and mediastinal disorders: D1: DB Phase: 30, LTE: 32 D2: 7

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
Author, year, study name, if applicable Wells et al., 2008; ¹⁹²	Inclusion Criteria Treatment resistant	Interventions, Dose D1: Abatacept: 10 mg/kg	Mean disease duration, years (SD) D1: 12.2 (8.5)	ACR NR	Overall NR
Westhovens et al., 2006; 193 Hassett et al., 2008 194	defined as inadequate	DMARDS D2: Placebo	D2: 11.4 (8.9) Patients with early RA,	HAQ, D1: HAQ-DI -0.5 (SD 0.6) D2: -0.1 (0.4)	Overall adverse events reported, n: NR
al., 2008 The ATTAIN Country and setting	response to anti-TNF • ≥10 swollen and	DMARDS Number in group D1: 258	three years or less, %	P = 0.0001 Treatment difference = -0.33, 95% CI, (-0.44 to	Serious adverse events NR
See 458 (from orignal report)	≥12 tender joints • CRP levels of at	D2: 133	Treatment resistant, % 100%	-0.35, 95 % CI, (-0.44 to -0.22)	Malignancies NR
Source of funding Bristol-Meyers	least 1 mg/dl (upper limit of	D1: 53.4 D2: 52.7	TJC, mean (SD) D1: 22.3 (10.2) D2: 22.0 (10.0)	NR SF-36	Respiratory events NR
Squibb Research objective	normal range: 0.5 mg/dl).	Sex , % female D1: 77.1 D2: 79.7	SJC, mean (SD) D1: 31.2 (13.0)	Physical component score, % (SD):	Other infections NR
 To examine impact of ABA on HRQOL 	Exclusion Criteria • Patients not	Race, % white	D2: 32.8 (13.4) Corticosteroid use, %	D1: 6.5 (SD 9.6) D2: 1.0 (SD 7.7)	GI NR
To evaluate patient-recorded outcomes	treated with oral DMARDs or ANK for > 3 mos	D1: 96.1 D2: 93.2	NR DMARD use, %	Patients doing better (%): D1: 44.6 D2: 23.1	Other NR
outcomes including SF-36, activity limitation,	ANK for ≥ 3 mos prior to the study or not receiving	NR	NR MTX naïve, %	Patients doing same (%): D1: 45.8	
fatigue Study design	a stable dose for at least 28 daysUse of myco-	Ethnicity, Latino NR	NR Baseline DAS score, mean	D2: 63.1 Patients doing worse (%):	
Controlled Trials Overall N	phenolate mofetil,		(SD) D1: 6.5 D2: 6.5	D1: 9.6 D2: 13.9 Overall:	
391 Duration of study	cyclosporine, other calcineurin inhibitors		Overall: 6.5 Required treatment for	Mental component score (MCS), % (SD)	
24 weeks Quality rating	and D- penicillamine • Women who		latent TB NR	D1: 5.4 (SD 11.7) D2: 1.7 (SD 10.2)	
Fair	were pregnant or nursing		Other population characteristics, %, (CI/SD/P value)	Patients doing better (%): D1: 43.0 D2: 31.5	
				Patients doing same (%): D1: 45.840.3	

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes D2: 45.4	Adverse Events, %
				Patients doing worse (%): D1: 16.7 D2: 23.1	
				Overall: • Physical Component Score, $P = 0.0001$, Percentage of Patients Doing Better/Same/Worse, $P = 0.0002$, Treatment Difference = 5.5, 95% CI, (3.6 to 7.4) • Mental Component Score, $P = 0.0025$, Percentage of Patients Doing Better/Same/Worse, $P = 0.0723$, Treatment Difference = 3.7, 95% CI, (1.3 to 6.1)	
				Radiographic measures NR	
				Quality of life scales	
				Others, (please name) Fatigue VAS: ABA = -22.1 (SD = 28.6), Placebo = -5.3 (SD = 27.4), P = 0.0001 [From #2964] Fatigue Treatment difference = -16.8, 95% CI, (-22.8 to -10.8) [From #2714] Required Help or Care at Baseline: ABA = 89%, Placebo = 87%	
				 Required Help or Care at Final Visit: ABA = 70%, 	

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
				 Placebo = 76% Percent Difference in Required Help or Care between Baseline and Final Visit: ABA = 19%, Placebo = 11% Psychosocial Independence: Changes in Mean Scores from Baseline to Final Visit in Psychosocial Independence between ABA and Placebo: ABA greater by 0.46 units, 95% CI, (0.17-0.75), P = 0.002 Changes in Mean Scores from Baseline to Final Visit in Physical Independence between ABA and Placebo: ABA greater by 0.59 units, 95% CI, (0.35-0.82), P = 0.001 	

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
Author, yr:	Inclusion Criteria:	Interventions,	Median disease	At week 22	Overall:	Overall
Westhovens et	 Adults w/ RA 	dose:	duration, yrs:	ACD20 0/	D1: 66.2	Attrition
al., 2006 ¹⁹⁵	according to ACR	D1: Placebo + MTX	D1: 8.4	ACR20 response, %	D2: 69.7	Rate, %:
START Trial	criteria	(up to 25 mg/wk)	D2: 7.8	D1: 26	D3: 72.3	17.1
	• MTV > 2 mos	D2: INF 3 mg/kg (at	D3: 6.3	D2: 58	D4: 71.0	
Country, Setting:	 Chloroquine, AZA, 	wks 0, 2, 6, and 14)		D3: 61		ITT
Multinational,	penicillamine, oral	+ MTX (up to 25	IJC, mean:	(<i>P</i> < 0.0001)	SAEs:	Analysis:
multicenter	or intramuscular	mg/wk)	D1: 22	ACR50 response, %	D1: 7.5	Yes
Cundina.		D3: INF 10 mg/kg	D2: 22	D1: 9.7	D2: 7.8	Ouglity
Funding:	gold	(at wks 0, 2, 6, and	D3: 22		D3: 7.5	Quality
Centocor	• HCQ, SSZ, LEF,	14) + MTX (up to 25	0.10	D2: 32.1	D4: 7.8	Rating:
Research	CYP, oral Css, or	14) + W17 (up to 25		D3: 35.4		Good
Objective:	NSAIDS	mg/wk)	D1: 15	(<i>P</i> < 0.0001)	Serious Infections:	
	Exclusion Criteria:	D4: D2 + D3	D2: 15	ACR70 response, %	D1: 1.7	
infections in INF	TB		D3: 15	D1: 4.7	D2: 1.7	
therapy, and		N:	DMARD use, %:	D2: 14.0	D3: 5.0	
safety in	 Opportunistic or 	D1: 363	D1: 70	D3: 16.1	D4: 3.3	
combination with	serious infections	D2: 360	D1: 70 D2: 70.8	(P < 0.0001)	Cardiovascular	
	HIV, lympho-	D0 004		(F < 0.0001)		
background txts	proliferative	D3: 361	D3: 69.8	DAS28 , (+/-)	Events:	
during 1 yr in pts	disease or	Mean age, yrs:	Corticosteroid use,	D1: 4.4 (1.4)	D1: 3.3	
with RA with	malignancy	D1: median 52	%:	D2 and D3: 3.4 (1.3)	D2: 4.5	
various	CHF		D1: 59.2	(P < 0.001)	D3: 5.9	
comorbidities	investigational	D2: 53	D2: 59.2	(1 0.001)	D4: 5.2	
Study Design:	drug (3 mos or 5	D3: 52	D3: 59	Remission, %	Headache:	
RCT	half-lives,	20.02	D3. 39	D1: 14	D1: 6.1	
NO I	whichever was	Sex, % female:	MTX naive, %:	D1: 14 D2: 31	D1: 0:1 D2: 9.7	
Overall N:	greater), with	D1: 83.2	NR .			
1084	cyclophos-	D2: 80.0		D3: 32	D3: 10.2	
	phamide, nitroger	1	Txt resistant %:	(<i>P</i> < 0.0001)	D4: 10.0	
Study Duration:	mustard,	D3: 77.8	NR		Hepatotoxicity (ALT	
54 wks of which	chlorambucil, or	Race, % white:	Pts with Early RA		increase):	
22 wks wast RCT	other alkylating				D1: 2.8	
then open label	, ,	NR	(≤3 yrs):		D1: 2.6 D2: 3.6	
extension	agents more than		NR		D3: 5.3	
	5 mg/kg		Baseline DAS,		D3. 5.3 D4: 4.4	
	cyclosporine, or		mean:		U4. 4.4	
	biologic		NR		Malignancies:	
			INIX		D1: 1.7	
			Median HAQ score:		D2: 4.2	
			D1: 1.5		· ·· -	
			D2: 1.5		Nausea:	

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis an Quality Rating
			D3: 1.5		D1: 8.0	
			% RF positive: D1: 80.7 D2: 82.8 D3: 76.8		D2: 6.4 D3: 6.4 D4: 6.4 URTI: D1: 10.5 D2: 9.7 D3: 11.9 D4: 10.8	
					UTI: D1: 0 D2: 0 D3: 0.6 D4: 0.3	

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
Author, year, study name, if applicable Westhovens et al., 2009 ¹⁹⁶ Country and setting Multinational	 Inclusion Criteria MTX naive or previous exposure of 10mg/wk or less for three wks or 	Interventions, Dose D1: • MTX: 7.5 mg/wk; 15 mg/wk at wk 4 and 20 mg/wk at wk 8 • ABA: 10 mg/kg	Overall: NR	ACR: ACR 20: NR ACR 50: Yr 1 D1: 57.4	Overall Overall attrition/withdrawal (n): D1: 24 D2: 26
Source of funding Bristol-Myers Squibb	less, with none administered for 3 mos before providing	D2: • MTX: 7.5mg/wk; 15 mg/wk at wk 4 and	Patients with early RA, three years or less, %: 100 Treatment resistant, %:	D2: 42.3 D1 vs. 2: <i>P</i> < 0.001 ACR 70: Yr 1 D1: 42.6	Withdrawals due to adverse events (n): D1: 9 D2: 11
Research objective To assess the efficacy and safety of ABA in MTX-naive	informed consent • Early RA of 2 yrs or less	20mg/wk at wk 8 • Placebo Number in group D1: 256	NR Tender Joint Count, mean D1: 31.3 (14.8)	D2: 27.3 D1 vs. 2: <i>P</i> < 0.001 HAQ:	Withdrawals due to lack of efficacy (n): D1: 0 D2: 8
patients with early RA and poor prognostic factors. Study design	 ≥ 12 tender and 10 swollen joints C-reactive 	D2: 253 Overall: 509 Mean age (years)	D2: 30.8 (14.0) Overall: 31.0 Swollen Joint Count, mean D1: 22.9 (11.3	HAQ-DI D1: -0.96 (SE 0.04) D2: -0.76 (SE 0.04) DAS:	Overall adverse events reported (n): D1: 217
RCT Overall N 509	protein (CRP) 0.45 mg/ dl or greater • RF and/or anti-	D1: 50.1 D2: 49.7 Overall: NR	D2: 21.9 (10.1) Overall: 22.4 Corticosteroid use, %	CRP D1: -3.22 (SE 0.09) D2: -2.49 (SE 0.09) P < 0.001	D2: 211 Overall: 428 Serious adverse events: Death (n):
Duration of study 2 yrs Quality rating	CCP2 seropositivity and radiographic	Sex, % female D1: 76.6 D2: 78.7 Overall: NR	D1: 51.2 D2: 49.0 Overall: NR	SF-36: Mental component D1: 8.15 (SE 0.64)	Death (n). D1: 2 D2: 4 Overall: 6
Good	evidence of bone erosion of the hands/ wrists/feet	Race, % white D1: 78.9 D2: 86.6 Overall: NR	DMARD use, %: Other non- biological DMARD (HCQ) D1: 1.6	D2: 6.34 (SE 0.64) D1 vs. 2: <i>P</i> = 0.046 Physical component	Malignancies: Other cancer (specify) (n): Pancreatic D1: 1
	Exclusion Criteria	Race, % black	D2: 2.0 Overall: NR SSZ	D1: 11.68 (SE 0.62) D2: 9.18 (SE 0.63) D1 vs. 2: <i>P</i> = 0.005	D2: 0 Overall: NR
	 Women who were pregnant or breastfeeding 	Ethnicity, Latino NR	D1: 0 D2: 0.4 Overall: NR	Radiographic measures: Yr 1 TS	Respiratory events: Tuberculosis (n): D1: 0 D2: 0
	 Patients with active Mycobacterium 		MTX naïve, %: 100	D1: 0.63 D2: 1.06 D1 vs. 2: <i>P</i> = 0.040	Overall: 0 Pneumonia (n):
	tuberculosis requiring		Baseline DAS score	ES	D1: 1 D2: 3

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
	treatment within 3 yrs.		D1: 6.3 (1.0) D2: 6.2 (1.0) Overall: 6.3	D1: ES:0.50 D2: 0.89 D1 vs. 2: <i>P</i> = 0.033	Overall: 4 Upper respiratory
			Required treatment for latent TB	JSN D1: 0.13 D2: 0.17	infection (n): D1: 26 D2: 26 Overall: 52
			Other population characteristics: HAQ-DI mean (SD) D1: 1.7 (0.7) D2: 1.7 (0.7)	D1 vs. 2: <i>P</i> = 0.353 No radiographic progression D1: (T< or = 0): 61.2% (95% CI, 55.0-67.3) D2: (T< or = 0): 52.9% (95%	Other infections: Other infections (specify) (n): Infections (not specified) D1: 132 D2: 139
			Overall: NR	CI, 46.6-59.2) D1 and D2: 8.3% (95% -1.0 to 17.5)	Serious infections (not including pneumonia) Gastroenteritis
				Quality of life scales: NR	D1: 1 D2: 1
				Others: Yr 1 ACR90	Cellulitis D1: 1 D2: NR
				D1, 16.4% D2: 6.7% D1 vs D2: <i>P</i> < 0.001	Pseduomonal lung infection D1: 1 D2: NR
					Post operative lung infection D1: 1 D2: NR
					Breast cellulitis/staphycocca infection D1: NR D2: 1
					GI: NR
					Other: Infusion/injection site reactions (n): D1: 16 D2: 5

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, % Overall: 21
					Dizziness (n): D1: 5 D2: 2 Overall: 7
					Any other AEs: Most frequently reported adverse events in D1: Nausea:10% pts Upper respiratory tract infection: 10% pts Headache: 10% pts D2: NR
					Pregnancy (protocol violations) D1: 2 D2: NR
					Spontaneous abortion between days 1 and 30 afte 1 infusion of ABA D1: 1 D2: NR

	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
Wolfe and Michaud, 2004 ¹⁹⁷ Country, Setting: US, 908 practices Funding: National Data Bank for Rheumatic Diseases (US) funded by pharma Research Objective: The rate of and standardized incidence ratio for lymphoma in pts with RA and in RA patient subsets by	 Participants in National Data Bank for Rheumatic Diseases (NDB) long-term study of outcomes of RA Cases were identified from this group as those who developed lymphoma during the 2 ½ yr observational period Exclusion 	N: D1: 6433 D2: 2729 D3: 5593 D4: 4474 Mean age, yrs: D1: 60.7 D2: 56.4 D3: 61.2	Mean disease duration, yrs: D1: 13.7 D2: 14.1 D3: 13.5 D4: 13.5 TJC, mean: NR SJC, mean: NR DMARD use, %: NR Corticosteroid use, %: NR Txt resistant %: NR Txt resistant %: NR Pts with Early RA (≤3 yrs): NR Baseline DAS, mean: D1: 1.2 D2: 1.2 D3: 1.1 D4: 1.0 VAS QoL: D1: 65.8 D2: 64.3 D3: 66.7 D4: 65.9 Pain:	SIR for whole population regardless of txt was 1.9 (95%CI, 1.3-2.7); indicating a greater risk for lymphoma in pts with RA • SIR for pts taking biologics (INF or ETA) was 2.9 (95%CI, 1.7-4.9). • No significant differences were observed between txt groups • Only 233 pts received AKA and no lymphomas occurred in this group • Overall, lymphoma incidence rate per 100,000 PY was 99 (95%CI,69-142); for various durations of RA, rates were: 0-5 yrs: 171 (95%CI,82-360), 5-10 yrs: 70 (95%CI,29-168), 10-15 yrs: 20 (95%CI,3-145), >15 yrs: 121 (95%CI,74-198)		Overall Attrition Rate, %: NA ITT Analysis: NA Quality Rating: Fair

Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
		D1: 4.2			
		D2: 4.3			
		D3: 3.7			
		D4: 3.9			

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
Author, yr: Wolfe and Michaud, 2004 ¹⁹⁸ Country, Setting: US, multicenter (National Data Bank for Rheumatic Diseases) Funding: Centocor, Inc Research Objective: To determine frequency of heart failure in pts with RA, and to determine its predictors, particularly use of anti-TNF therapy Study Design: Retrospective cohort study Overall N: 15,739 (RA plus OA subjects) Study Duration:	 Participation in National Data Bank for Rheumatic Diseases study of outcomes of arthritis; patient at participating rheumatology clinic Exclusion Criteria: NR 	Interventions, dose: D1: Any Anti-TNF D2: INF D3: ETA D4: No anti-TNF D5: Total Population Overall N: NR Mean age, yrs: D1: 60 D2: 61.5 D3: 56.7 D4: 61.5 D5: 51 Sex, % female: D1: 78 D2: 77 D3: 80 D4: 76 D5: 77 Race, % white: D1: 95 D2: 96 D3: 92 D4: 92 D5: 94	Mean disease duration, yrs: D1: 14.2 D2: 13.8 D3: 15.2 D4: 15.5 D5: 14.9 TJC, mean: NR SJC, mean: NR DMARD use, %: Overall: 86 PRE use (%) D1: 47 D2: 49 D3: 39 D4: 33 D5: 39 MTX naive, %: NR Txt resistant %: NR Pts with Early RA (≤3 yrs): NR Baseline DAS, mean: D1: 3.7 D2: 3.7 D3: 3.6 D4: 3.5 D5: 3.6 MTX use: D1: 67	 Heart Failure 461 cases in 13,171 pts with RA (overall risk of 3.5%); after adjusting for demographic characteristics; Risk: 3.9% (95% CI,= 3.4% to 4.3%) Among all cases of heart failure, pts receiving anti-TNF therapy were less likely to have heart failure than those not receiving anti-TNF therapy (-1.2%; 95% CI,-1.90.5%) Overall, adjusted frequency of heart failure was 2.8% in those treated with anti-TNF vs. 3.9% in remaining pts (<i>P</i> = 0.03) Frequency of heart failure was 5.2% in men and 3.0% in women In examining incident cases of heart failure in pts under age 50, no increase was found (0/1569 pts using anti-TNF vs. 3/1401 not using anti-TNF therapy) 	NR .	Overall Attrition Rate, %: NR ITT Analysis: NA Quality Rating: Fair

 nclusion and xclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
		D2: 76			
		D3: 44			
		D4: 47			
		D5: 56			

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %	Analysis and Quality Rating
Author, yr: Wolfe et al., 2006 ¹⁹⁹ Country, Setting: US, Rheumatology Clinics Funding: Bristol-Meyers-Squibb Research Objective: To evaluate txt of RA and risk of hospitalization for pneumonia Study Design: Prospective cohort study Overall N: 16,788 Study Duration: 3.5 yrs	Participants in NDB longitudinal study of RA outcomes including 5,317 enrolled as part of an INF safety registry and 1,852 as part of a LEF safety registry Other meds allowed	Interventions, dose: D1: Cohort Prednisone MTX LEF SSZ Hydroxychlorquine ETA INF Adalimumab Other various RA txts N: NR Mean age, yrs: D1: 62 Sex, % female: D1: 77.2 Race, % white: D1: 89.7% white, 4.8% black, 3.0% Hispanic, 1.0 Asian/Pacific Islander, 1.1% American Indian or Alaskan native, 0.5% Other		Effect of txt variables on risk of pneumonia (adjusted for demographic variables-age, sex, smoking, education, and enrollment) • Prednisone HR 1.7 [95% CI, 1.5-2.1]) • LEF HR 1.3 [95% CI, 1.0-1.5], P = 0.036) • •SSZ HR 0.7 [95% CI, 0.4-1.0], P = 0.053) • ETA HR 0.8 [95% CI, 0.6-1.0], P = 0.051) • INF HR 1.1 [95% CI, 0.9-1.4], P = 0.322) • Adalimumab HR 1.1 [95% CI, 0.6-1.9], P = 0.747) • MTX HR 1.0 [95% CI, 0.8-1.2], P = 0.927) • Hydroxychloroquine HR 0.9 [95% CI, 0.7-1.2], P = 0.481)		Overall Attrition Rate, %: NA ITT Analysis: NA Quality Rating: Fair

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
Author, year, study name, if applicable Wolfe et al., 2007 ²⁰⁰ Country and setting	 National Databank for Rheumatic 	Interventions, Dose D1: Hospitilization for Interstitial Lung Disease (HILD)	Mean disease duration, years (SD) D1: 15.3 (11.2) D2: 15.9 (11.2)	ACR ACR 20: D1: No efficacy outcomes reported	Overall Withdrawals due to adverse events, n: D1: 8% of pts drop from
US, multicenter Source of funding Centocor, Amgen,	Diseases (NDB) includes patients receiving	Case/Control (both Ds include treatment with: PRED, MTX, LEF, IFX, HCQ,	Patients with early RA, three years or less, % NR	ACR 50: NR ACR 70: NR HAQ	National Data Bank for Rheumatic Diseases every year Overall adverse events
Abbott, Bristol- Meyers-Squibb, Aventis, NIH	treatment for RA • Patients hospitalized	ETN, SSZ, ADA, & ANK as well as others drugs not included in this	Treatment resistant, % NR Tender Joint Count, mean	NR DAS NR	reported, n: D1: NR - see additional comments for germane analyses
Research objective Investigate association of serious ILD and RA treatments	with interstitial lung diease (HILD) were considered	review D2: Number in group D1: 100	(SD) NR Swollen Joint Count, mean (SD)	SF-36 NR Radiographic measures NR	Serious adverse events NR Malignancies
Study design Retrospective Cohort Study	cases Exclusion Criteria NR	D2: 17498 Mean age (years) D1: 64.4 D2: 61.9	NR Corticosteroid use, % NR	Quality of life scales NR Others, (please name);	NR Respiratory events NR
Overall N 17598 Duration of study		Sex, % female D1: 80.0 D2: 77.0	DMARD use, % NR MTX naïve, %	mean difference/absolute difference (CI/SD/P Value) NR	Other infections NR GI
Varied, cohort followed up to 3.5 yrs beginning in 2001		Race, % white NR	NR Baseline DAS score, mean (SD)		NR Other Hazard Ratio for HILD
Quality rating Fair: Some confounding factors were controlled for		Race, % black NR Ethnicity, Latino NR	NR Required treatment for latent TB NR		from current treatements (adjusted for age, sex, and prior lung disease): PRED 2.5 (95%CI 1.5-4.1,
but authors assert there are others (e.g. dr.s who prescribed a TNF-therapy to treat ILD, Dr.s prescribe LEF instead of MTX in pts with a history of lung disease) that present			Other population characteristics, %, (CI/SD/P value) D1: HAQ/prior lung problems: 1.4 (0.8)/66.7% D2: 1.1 (0.7)/16.7% (for BOTH HAQ & Prior lung problems $P = 0.001$)		 P = 0.000), INX 0.7 (0.4-1.3), ETN 0.9 (0.4-1.7), LEF (1.3 (0.7-2.3), HCQ 1.0 (0.5-1.9), SSZ 1.4 (0.5-3.7), MTX 1.2 (0.7-1.9). Hazard Ratio for HILD from past treatments (adjusted for age, sex, and prior lung disease): PRED

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
problems for assessing c					3.0 (CI: 1.0-8.9, P = 0.044), IFX 2.1 (CI:1.1-3.8, P = 0.019), ETN 1.7 (CI: 1.0-3.0, P = 0.056), LEF 1.4 (0.8-2.4), HCQ 0.7 (0.4-1.2), SSZ 0.7 (0.4-1.2), MTX 0.7 (0.4-1.4), ADA 1.1 (0.4-2.7), AKA 1.0 (0.3-3.3). • Odds Ratio for death from ILD by treatment at time of hospitalization (adjusted for age, sex, and baseline HAQ): ETN 4.9* (CI: 1.0-23.1, P = 0.044), LEF 3.5 (CI: 0.9-13.5, P = 0.073), MTX 0.4 (0.1-1.4), INX 0.6 (0.1-2.5), PRED 0.9 (0.2-4.1). [*ETN OR for death reported differently in text -4.0, CI is same in both places]

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
	Exclusion		Treatment Characteristics Mean disease duration, years (SD)	Health Outcomes ACR ACR 20: D1: No efficacy outcomes reported ACR 50: NR ACR 70: NR HAQ NR DAS NR SF-36 NR Radiographic measures NR Quality of life scales NR Others, (please name); mean difference (CI/SD/P Value) NR	Adverse Events, % Overall NR Overall adverse events reported, n: NR Serious adverse events NR Malignancies Lymphoma or leukemia, n: D1: NR, SEE ADDITIONAL COMMENTS Respiratory events NR Other infections NR GI NR Other • After adjusting for inflammatory activity, pts treated with any Anti-TNF (IFX, ETN, or ADA) did not
Study Overall N 19591 (for RA SIR calculation), 19562 for treatment analysis Duration of study mean 3.7 years Quality rating Fair: additional information about differences in Case/Control			(SD) NR Required treatment for latent TB NR Other population characteristics, %, (CI/SD/P value) D1: HAQ: 1.1 (0.7)		have an increases risk for lymphoma compared to RA pts who had not received Anti-TNFs (OR 1.0, 95%Cl: 0.6-1.8, P = 0.875). IFX vs. all others (OR 1.2 Cl:0.6-2.2, P = 0.646); ETN vs. all others (OR 0.7, Cl:0.3-1.6, P = 0.422); ADA* 4.5 (0.9-23.1, P = 0.064) *Authors questioned reliability of this result based

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
population sociodemographic characteristics & medical history/severity would allow for a better assessment of potential confounding variables					on small sample (N = 56) who had only used ADA

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %				
Author, year, study name, if applicable Wolfe & Muchaud,	Inclusion Criteria • RA Exclusion	D1: All RA pts in NDB database (pts on	Mean disease duration, years (SD) D1: 16.7 yrs (12.7)	ACR ACR 20: D1: No efficacy outcomes	Overall Overall attrition/withdrawal, n: D1: NA, LTF NR for database				
2007 ²⁰² Country and setting US, multicenter	Criteria • < 1 cancer free phase in NDB	biologics including INF, ETN, ADA, & ANK)	Patients with early RA, three years or less, % NR	reported ACR 50: NR ACR 70: NR	Overall adverse events reported, n: D1: NR, SEE ADDITIONAL				
Source of funding Abbott, Amgen, Bristol-Meyers	prior to initiating study or = 2 observational	Number in group D1: 13,001 Mean age (years)	Treatment resistant, % NR	HAQ NR	COMMENTS Serious adverse events NR				
Squibb, Centocor, Merck, Pfizer, and Wyeth Australia	periods recorded in NDB	D1: 58.5 Sex, % female	Tender Joint Count, mean (SD) NR	DAS NR SF-36	Malignancies Other cancer (specify), n:				
Research objective Assess risk of	 Previous diagnoses for individual 	D1: 78 Race, % white D1: 92.5	Swollen Joint Count, mean (SD) NR		D1: NR, SEE ADDITIONAL COMMENTS Respiratory events				
malignancy among biologic treated pts Study design	cancers (e.g. lung) excluded pt from analysis	lung) excluded	lung) excluded pt from analysis	lung) excluded pt from analysis	lung) excluded pt from analysis	Race, % black D1: 3.9	NR	-	NR Other infections
Retrospective Cohort Study	outcome	Ethnicity, Latino D1: 1.9	DMARD use, % D1: combined use of	Others, (please name); mean difference/absolute	NR GI NR				
Overall N 13,869 RA patients (13,001 in			MTX naïve, % NR	difference (CI/SD/P Value) NR	Other • Biologics were associated				
conditional logistic regression)			Baseline DAS score, mean (SD) D1: First Patient Activity		with an increased risk of nonmelanotic skin cancer (OR 1.5, 95% CI 1.2-1.8)				
Duration of study Mean: 4.1 years (minimum 1 year follow up)			Scale score: 3.7 (2.2) Required treatment for latent TB		and melanoma (OR 2.3, 95% CI 0.9-5.4). • No other malignancy was				
Quality rating Fair			NR Other population characteristics, %, NR		associated with biologic use; OR (overall risk) of any cancer was 1.0 (95% CI 0.8-1.2). $P = NS$ for all other cancers and all cancers combined (cancer				
					assessed [with 10+ cases]: bladder, breast, colon, esophogas, leukemia, lung, lymphoma, Non-				

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
					Hodgkins, pancrease, prostate, & solid* [*excludes lymphoma, leukemia, myeloma, and nonmelanoma skil malignancies]. • Stratified by tx: Melanoma - IFX 2.6 (1.0-6.7), ETN* 2.4 (1.0-5.8), ADA* 0.8 (0.1-6.6), ANK* 4.2 (0.9-20.0) • Skin (excludes melanoma)- IFX 1.7 (1.3-2.2), ETN 1.2 (1.0-1.5), ADA 0.9 (0.5-1.8), ANK 1.4 (0.7-2.8) • Other cancers by drug P = NS [*indicates less than 10 cases by treatment]

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
•	Exclusion	Interventions Interventions, dose D1: MTX: stable dose IFX: 3 mg/kg body weight at weeks 0, 2, 6, and 14 D2: MTX: stable dose Placebo: 3 mg/kg body weight at weeks 0, 2, 6, and 14 Number in group D1: 87 D2: 86 Overall: 173 Mean age, years (SD) D1: 47.9, SD: 10.1 D2: 48.9, SD: 8.0 P = 0.461 Sex, % female D1: 85.1 D2: 84.9 Race, % white		## ACR At week 18: ACR 20: D1: 75.86 D2: 48.84 P = 0.0003 ACR 50: D1: 43.68 D2: 25.58 P = 0.011 ACR 70: D1: 22.99 D2: 13.95 P = 0.137 ## AQ, At week 18 vs. baseline: D1: -0.76 D2: -0.45 P = 0.0016 DAS NR SF-36 NR Radiographic measures NR Quality of life scales NR	Adverse Events, % Attrition/withdrawal Overall, n: D1: 9 D2: 15 Overall: 24 Withdrawals due to adverse events, n: D1: 6 D2: 4 Overall: 10 Overall adverse events reported, n: D1: 57 D2: 48 Overall: 105 Serious adverse events Heart failure, n: D1: 0 D2: 0 Malignancies Tumour, n: D1: 0 D2: 0 Respiratory events Tuberculosis: NR Pneumonia, n: D1: NA D2: 1 Other infections Urinary tract infection, n: D1: NR D2: 1
	 Screening laboratory tests had to meet following 				GI Abdominal pain, n: D1: 1 D2: NA

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
	criteria: haemoglobin = 85 g/L, white blood cell count = 4 times				Other Skin rash, n: D1: 2 D2: NA
	10^9/L, serum neutrophils = 1. 5 times 10^9/L, platelets = 100				Demyelenation or multiple sclerosis, n: D1: 0 D2: 0
	times 10^9/L, serum aminotrans- ferase concentration =				Progressive multifocal leukoencephalopathy, n: D1: 1 D2: NA
	1.5 time suppoer limit of normal, serum creatinine of = 120 umol/L				Other AEs 1, n: D1: adult onset of Still's disease: 1 D2: edema of lower limb: 1
	 Stable dose of glucocorticoster oid for 4 weeks before 				Other AEs 2, n: D1: Pharyngitis: 1 D2: Exacerbation of swollen joints: 3
	screening and does not exceed 10 mg/day of PRED or equivalent.				Other AEs 3, n: D1: NR D2: Abnormality in serum alanine transaminase: 1
	Exclusion Criteria • Patients with				Any other AEs Respiratory: D1: 12 D2: 12
	positive TB skin tests (induration = 15 mm), hepatitis,				Liver: D1: 10 D2: 7
	AIDS, tumor, infections, congestive heart failure,				Skin: D1: 9 D2: 4
	demyelinating disease,				Urinary:

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events, %
	commenced on treatment with				D1: 7 D2: 6
	other DMARDs within 4 weeks prior to screening, treatment with thalidomide or other TNF antagonists within 3 mos of entry to study.				Hematological: D1: 7 D2: 2

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes	Adverse Events (%)	Analysis and Quality Rating
Author, yr: Zink, 2005 ²⁰⁴ Country, Setting: Germany, clincal Funding: Essex Pharma, Wyeth Pharma, Amgen, and Abbott Research Objective: To compare drug continuation rates in pts. with RA who start on a biological agent or on a DMARD after previous DMARD failure Study Design: Retrospective cohort study Overall N: 1,523 Study Duration: 1 yr	Previous use of DMARDs: at least 2 Exclusion Criteria: NR	Interventions (dose): D1: ETA D2: INF D3: AKA D4: Total Control Group D5: LEF D6: LEF + MTX Dosages NR N: D1: 511 D2: 343 D3: 70 D4: 599 D5: 120 D6: 141 Mean age, yrs: D1: 53.7 D2: 53.6 D3: 54.3 D4: 56.5 D5: 58 D6: 57.4 Sex, % female: D1: 77.9 D2: 71.1 D3: 77.1 D4: 82.8 D5: 85.8 D6: 78.0 Race, % white: NR	Mean disease duration (yrs): D1: 9 D2: 8.5 D3: 13 D4: 6 D5: 9 D6: 7 TJC, mean: D1: 13.3 D2: 12.6 D3: 12.6 D4: 10 D5: 10.6 D6: 10.9 SJC, mean: D1: 10.4 D2: 10.7 D3: 10.2 D4: 7.7 D5: 7.4 D6: 8.5 DMARD use (#): D1: 3.9 D2: 3.7 D3: 4.2 D4: 2.1 D5: 2.4 D6: 2.2 Corticosteroid use, %: NR MTX naive, %:	Continuation rates D1 and D2 similar D3 significantly lower Txt continuation at 1 yr, % D1: 68.6 ETA+ MTX: 71.6 D2: 65.4 D6: 66.2 D3: 59 AKA vs. ETA; P = 0.004; ANA vs. INF; P = 0.03 Txt discontinuation because of adverse events, %: D2: 18.7 INF+MTX: 18.2 D1: 12.6% ETA+MTX 13.3 D3: 16.3 Txt discontinuation because of lack of efficacy, %: D1: 19.9 ETA + MTX: 16.9; D2: 45 INF+MTX: 17.9 D3: 29.6	NR	Overall Attrition Rate, %: N/A ITT Analysis: N/A: registry Quality Rating: Good
			NR			

Study Characteristics Quality Rating	, Study Information	Study Characteristics	Results	Adverse Events
Author, Year: Alonso-Ruiz et al., 2008 ²⁰⁵	Study design: Systematic Review and meta- analyses	Characteristics of Included Studies: RCTs of INF, ETN, or ADA of at least 6 months duration with efficacy	Any anti-TNFα drug (all doses) vs. control treatment (13	Adverse Events: Any anti-TNFα drug vs. control treatment
Alonso-Ruiz et al.,	Systematic Review and meta-	RCTs of INF, ETN, or ADA of at least 6	Any anti-TNFα drug (all doses) vs. control treatment (13 studies): ACR20: RR, 1.81 (95% CI, 1.43-2.29); NNT, 6 (5-7) ACR50: RR, 2.46 (95% CI, 1.75-3.45); NNT, 5 (5-6) ACR70: RR, 2.77 (95% CI, 1.85-4.15); NNT, 7 (7-9) Any anti-TNFα drug (recommended doses) vs. control treatment : ACR20: RR, 1.8 (95% CI, 1.4-2.3); NNT, 5 (5-6) ACR50: RR, 2.4 (95% CI, 1.7-3.4); NNT, 5 (5-6) ACR70: RR, 2.7 (95% CI, 1.8-4.1); NNT, 7 (7-9) ADA (all doses) vs. control treatment ACR20: RR, 1.9 (95% CI, 1.3-2.8); NNT, 6 (5-7) ACR50: RR, 2.7 (95% CI, 1.6-4.4); NNT, 6 (5-7)	Any anti-TNFα drug vs.
		ADA (ADA doses were 20 mg or 40 mg adminstered once per wk or 2 wks; 1 trial included an 80 mg/2 wk arm)	ACR70: RR, 3.3 (95% CI, 1.8-6.3); NNT, 9 (7-11) ADA (recommended doses) vs. control treatment ACR20: RR, 2.0 (95% CI, 1.3-2.9); NNT, 5 (4-6) ACR50: RR, 2.8 (95% CI, 1.6-4.7); NNT, 5 (5-6) ACR70: RR, 3.5 (95% CI, 1.9-6.7); NNT, 7 (6-8) ETN (all doses) vs. control treatment ACR20: RR, 1.7 (95% CI, 1.1-2.6); NNT, 7 (5-10)	Withdrawal due to adverse event: RR, 1.4 (1.0-2.0); NNH, 47 (26-251) Total adverse event: RR, 1.1 (0.9-1.1); NNH, NS Serious adverse event: RR, 1.0 (0.7-1.4); NNH, NS Infections: RR, 1.1 (0.9-1.2); NNH, NS Serious infections: RR, 1.2 (0.6-2.8); NNH, NS

Study Characterist Quality Rating	tics, Study Information	Study Characteristics	Results	Adverse Events
edulity Nating	Study Information	Study Characteristics	ACR50: RR, 2.1 (95% CI, 1.1- 3.9); NNT, 6 (5-9) ACR70: RR, 2.0 (95% CI, 0.9-	Infusion Reactions: RR, 2.7 (1.7-4.2); NNH, 9 (7-14)
			4.4); NNT, NS ETN (recommended doses) vs.	Malignancies: RR, 1.1 (0.4-2.7); NNH, NS
			control treatment ACR20: RR, 1.7 (95% CI, 1.1-	Mortality: RR, 1.3 (0.4-4.7); NNH, NS
			2.7); NNT, 6 (5-8) ACR50: RR, 2.2 (95% CI, 1.1-	ETN vs. control treatment
			4.3); NNT, 6 (4-7) ACR70: RR, 2.1 (95% CI, 0.9- 4.5); NNT, NS	Withdrawal due to adverse event: RR, 0.7(0.5-0.9); NNH, -26 (-143 to -14)
			INF (all doses) vs. control treatment ACR20: RR, 1.8 (95% CI, 1.2-	Total adverse event: RR, 1.0 (0.9-1.1); NNH, NS
			2.8); NNT, 5 (4-6) ACR50: RR, 2.6 (95% CI, 1.5-	Serious adverse event: RR, 0.9 (0.5-1.6); NNH, NS
			4.7); NNT, 5 (5-6) ACR70: RR, 2.9 (95% CI, 1.4- 5.8); NNT, 8 (6-10)	Infections: RR, 1.0 (0.9-1.0); NNH, NS
			INF (recommended doses) vs. control treatment	Serious infections: RR, 0.9 (0.4-2.3); NNH, NS
			ACR20: RR, 1.7 (95% CI, 1.1- 2.6); NNT, 5 (4-6)	Infusion Reactions: RR, 5.1 (2.9-8.8); NNH, 5(4-6)
			ACR50: RR, 2.2 (95% CI, 1.2- 4.1); NNT, 6 (5-7) ACR70: RR, 2.4 (95% CI, 1.2-	Malignancies: RR, 1.9 (0.6-5.7); NNH, NS
			5.0); NNT, 9 (7-13) Efficacy of anti-TNFα drugs	Mortality: RR, 1.5 (0.2-9.5); NNH, NS
			(recommended doses) in	INF vs. control treatment
			combination with MTX compared with MTX alone in patients with insufficient responses to MTX	Withdrawal due to adverse event: RR, 2.0 (1.3-3.1); NNH, 24 (17-41)
			ACR20: RR, 2 .6 (95% CI, 2.0 5-3.31) ACR50: RR, 4 .13 (95% CI,	Total adverse event: RR, 1.0 (0.9-1.0); NNH, NS
			2.59-6 .59) ACR70: RR, 4.14 (95% CI,	Serious adverse event: RR, 1.4 (1.0-2.0); NNH, 31 (17-

Study Characteristic Quality Rating	es, Study Information	Study Characteristics	Results	Adverse Events
			2.43-7.05)	167)
			Efficacy of anti-TNFα drugs (recommended doses) plus	Infections: RR, 1.2 (1.1-1.3); NNH, 10 (7-24)
			MTX compared to MTX alone in patients with no previous resistance to MTX	Serious infections: RR, 1.8 (0.9-3.4); NNH, NS
			ACR20: RR, 1.15 (95% CI, 1.07-1.22)	Infusion Reactions: RR, 2.7 (1.7-4.2); NNH, 9 (7-14)
			ACR50: RR, 1.56 (95% CI, 1.41-1.72) ACR70: RR, 1.77 (95% CI,	Malignancies: RR, 2.6 (0.6- 11.6); NNH, NS
			1.52-2.05)	Mortality: RR, 0.5 (0.2-1.4); NNH, NS

Study Characteristics, Quality Rating	Study Information	Study Characteristics	Results	Adverse Events
Author, Year: Bergman et al., 2010 ²⁰⁶	Study design: Systematic review and meta- analysis	Characteristics of Included Studies: Double-blind, randomized, placebo controlled trials, 24 to 30 weeks	Study Results: Fixed-Effects Model Relative Risk (95% Crl) / Random-	Adverse Events: NA
Country and setting: Multinational Funding: Hoffmann La-Roche Aims of Review: ACR response between	Number of Patients: 10,419 Studies Included: N = 18	Characteristics of Included Populations Adults with RA Characteristics of Interventions: RCTs - study duration of at least 6	Effects Model Relative Risk (95% Crl) Biologic agent vs.placebo, Fixed-Effects Model Relative Risk (95% Crl) ACR20	
TCZ and other biologic agents in patients with heumatoid arthritis who have inadequate		months;	TCZ: 2.0 (1.9-2.2) TNF- inhibitors :1.9 (1.7-2.1) ABA: 1.9 (1.7-2.1) RTX: 1.8 (1.5-2.2)	
response to disease- modifying antirheumatic drugs Quality Rating: Fair			ACR50 TCZ: 3.5 (3.0, 4.0) TNF- inhibitors: 2.8 (2.4, 3.2) ABA: 2.7 (2.2, 3.3) RTX: 2.8 (1.8, 4.0)	
			ACR70 TCZ: 6.8 (4.9, 9.4) TNF- inhibitors: 3.8 (3.1, 4.8) ABA: 3.4 (2.5, 4.8) RTX: 4.3 (2.2, 8.9)	
			Biologic agent vs.placebo, Random-Effects Model Relative Risk (95% Crl) ACR20 TCZ: 2.1 (1.6-2.5) TNF:- inhibitors: 2.0 (1.7-2.3) ABA: 1.9 (1.4-2.3) RTX: 1.9 (1.3-2.5)	
			ACR50 TCZ: 3.6 (2.5, 5.0) TNF- inhibitors: 3.2 (2.5, 4.3) ABA: 2.7 (1.7, 4.0) RTX: 2.9 (1.5, 4.9)	
			ACR70 TCZ: 6.9 (4.5, 10.8)	

Study Characterist Quality Rating	tics, Study Information	Study Characteristics	Results	Adverse Events
addity hamig	ciacy morniquen	ciacy onalactoricitos	TNF- inhibitors: 4.0 (3.0, 6.0) ABA: 3.6 (2.2, 6.2) RTX: 4.4 (1.9, 10.5)	7.0.1.51.00 E101110
			Pairwise comparison of biologic agents ACR20 TCZ vs.TNF- inhibitors 1.1 (1.0, 1.2) / 1.1 (0.8, 1.3) TCZ vs.ABA 1.1 (1.0, 1.2) / 1.1 (0.8, 1.6) TCZ vs.RTX 1.1 (0.9, 1.4) / 1.1 (0.8, 1.7) ABA vs.TNF- inhibitors 1.0 (0.9 1.1) / 0.9 (0.7, 1.2) RTX vs.TNF- inhibitors 1.0 (0.8 1.2) / 1.0 (0.6, 1.3) RTX vs.ABA 1.0 (0.8, 1.2) / 1.0 (0.7, 1.5)	,
			ACR50 TCZ vs.TNF- inhibitors 1.3 (1.1, 1.5) / 1.1 (0.7, 1.6) TCZ vs.ABA 1.3 (1.0, 1.6) / 1.3 (0.8, 2.3) TCZ vs.RTX 1.3 (0.9, 1.9) / 1.2 (0.7, 2.5) ABA vs.TNF- inhibitors 1.0 (0.8 1.2) / 0.9 (0.5, 1.3) RTX vs.TNF- inhibitors 1.0 (0.7 1.5) / 0.9 (0.5, 1.6) RTX vs.ABA 1.0 (0.7, 1.5) / 1.1 (0.5, 2.1)	,
			ACR70 TCZ vs.TNF- inhibitors 1.8 (1.2, 2.6) / 1.7 (1.0, 2.8) TCZ vs.ABA 2.0 (1.3, 3.1) / 1.9 (1.0, 3.6) TCZ vs.RTX 1.6 (0.7, 3.3) / 1.6 (0.6, 4.0) ABA vs.TNF- inhibitors 0.9 (0.6 1.2) / 0.9 (0.5, 1.5)	

Study Characteristics,				
Quality Rating	Study Information	Study Characteristics	Results	Adverse Events
			RTX vs.TNF- inhibito	ors 1.1 (0.5,
			2.4) / 1.1 (0.4, 2.6)	•
			RTX vs.ABA 1.3 (0.6	5, 2.8) / 1.2
			(0.5, 3.2)	•

Study Characteristics, Quality Rating	Study Information	Study Characteristics	Results	Adverse Events
Author, Year: Bernatsky et al., 2010 ²⁰⁷	Study design: Systematic review and meta- analysis	Characteristics of Included Studies: 5 cohort and 2 nested case-control studies	Study Results: Anti-TNF therapy appeared to significantly increase risk of	Adverse Events: The summary RR, suggested about a 40% increased risk
Country and setting: Study conducted in Canada - components are multinationals Number of Patients: NR Studies Included: N = 7 Funding: NR	NR	Characteristics of Included Populations Patients with RA and serious infections	serious infection (pooled adjusted RR 1 37, 95% CL 1 18-1 60)	of serious infections in patients with RA exposed to TNF antagonists (RR, 1.37; 95% CI, 1.18-1.60).
		Characteristics of Interventions: Anti-TNFs		
Aims of Review: a systematic review and synthesis of observational studies of TNF antagonists and infection risk.				
Quality Rating: Fair				

Study Characteristics	Characteristics of Included Studies	Results	Adverse Events	Assessments, Study Appraisals, and Quality Rating
Author, year, country, funding: Bongartz, 2006, multinational, Mayo foundation, Abbott & Centocor ²⁰⁸ Study Design: Systematic literature search with meta-analysis Aims of the Review: • To assess extent to which anti-TNF antibody therapy may increase risk of serious infection and malignancies in pts with RA by performing a meta-analysis • To derive estimates of sparse harmful events occurring in randomized trials of anti-TNF therapy Number of Pts: 5014 (9 trials)	which pts had ACR- diagnosed RA and were randomized to anti-TNF vs. placebo (or anti-TNF	 In pts with RA, anti-TNF treatment leads to increased risk of serious infections and a dose-dependent increased risk of malignancies. Serious infections reported in 126 anti-TNF- treated pts vs. 26 control group pts (OR, 2.0; 95% CI, 1.3-3.1) Malignancies reported in 24 / 3493 (0.8%) pts who received > 1 dose of anti-TNF vs. 2 / 1512 (0.2%) pts on control Pooled OR for malignancies in anti-TNF group vs. placeborgroup: 3.3 (95% CI, 1.2-9.1) Number needed to harm was 154 (95% CI 91-500) for 1 additional malignancy within a treatment period of 6 to 12 months. For serious infections, the number needed to harm was 59 (39-125) within a treatment period of 3 to 12 months 	(95% CI 1.2 – 9.1) • Serious Infections: Anti-TNF (126/3493) Control (26/1512) OR: 2.0 (1.3-3.1)	Publication Bias Assessed: Not reported Heterogeneity Assessed: Yes Standard Method of Study Appraisals: Yes Comprehensive Search Strategy: Yes - briefly describe in box: EMBASE, MEDLINE, Cochrane Library, and electronic abstracts of the annual scientific meetings both the European League Against Rheumatism and the American College of Rheumatology – through December 2005 Quality Rating: Fair

Study Characteristics, Quality Rating	Study Information	Study Characteristics	Results	Adverse Events
Author, Year: Bongartz et al., 2009 ²⁰⁹ Country and setting: Multinational Funding: Wyeth Aims of Review: To assess the risk of malignancy with ETN Quality Rating: Good	Study design: Systematic review and meta- analysis Number of Patients: 3316 patients, 2244 who received ETN (contributing 2484 person-years of follow-up) and 1072 who received control therapy (1051 person-years). Studies Included: N = 9 (8 published, 1 unpublished)	Characteristics of Included Studies: RCTS at least 12 weeks long Characteristics of Included Populations Patients with RA Characteristics of Interventions: ETA vs. Control	Study Results:	Adverse Events: Malignancies in 26 patients in the ETN group (incidence rate (IR) 10.47/1000 personyears) and 7 in the control group (IR 6.66/1000 personyears). A Cox's proportional hazards, fixed-effect model stratified by trial yielded a hazard ratio of 1.84 (95% CI, 0.79-4.28) for the ETN group compared with the control group.

Study Characteristics	Characteristics of Included Studies	Results	Adverse Events	Assessments, Study Appraisals, and Quality Rating
Author, year, country, funding: Clark, 2004 ²¹⁰ , International: Europe, U.S., Canada, Australia, Health Technology Assessment Programme (U.K.) Study Design: Systematic review and meta-analysis analysis Aims of Review: To review evidence on clinical benefits, hazards, and cost-effectiveness of AKA in adult RA pts Number of Pts: 2,905	Studies included: Efficacy Trials: Bresnihan (1998) Cohen (2001) Cohen (2002) Unpublished report by Amgen (2001; STN 103950 Clinical Review; low-dose for 3 mos) Safety Trial: Fleischmann (2001) Characteristics of included studies: RCTs (except 1) of AKA or AKA + MTX in pts with highly active RA Fleischmann control arm consisted of placebo + DMARD txt Characteristics of included populations: Mean ages 50s Duration 6 mos to 10 yrs Majority had failed at least 1 DMARD and some were taking MTX up to trial start Majority taking low-dose steroids and NSAIDs Characteristics of interventions: AKA alone: AKA from 2.5 mg/day to	Adjusted indirect comparisons with anti TNF agents (ETN, INF) suggested that AKA may be significantly less effective at relieving clinical symptoms than anti-TNF agents (-0.21; 95% CI, -0.32 to -0.10) Adjusted indirect comparisons: RD (95% CI) TNF+MTX vs. MTX 0.37 (0.28 to 0.45) AKA+MTX vs. MTX 0.16 (0.09 to 0.23) AKA+MTX vs. TNF+MTX - 0.21 (-0.32 to -0.10)	Specific adverse events:SAEs: Control: 3.2% to 11.6% AKA: 4.4% to 12.8%	Publication Bias Assessed: NR Heterogeneity Assessed: Yes Standard Method of Study Appraisals: Yes Comprehensive Search Strategy: Yes Quality Rating: Good

Study Characteristics	Characteristics of Included Studies	Results	Adverse Events	Assessments, Study Appraisals, and Quality Rating
	 150 mg/day AKA + MTX: AKA 0.0 mg/kg per day to 2.0 mg/kg per day or fixe dose 100 mg/day 			

Study Characteristics, Quality Rating	Study Information	Study Characteristics	Results	Adverse Events
Author, Year: Devine et al., 2011 ²¹¹	Study design: Systematic review and meta-	Characteristics of Included Studies: RCTs at least 22 weeks outcomes	Study Results: Log Odds Ratio Estimates for the 6-	Adverse Events: NR
Country and setting: Multinational Funding: NR Aims of Review: efficacy of biologic disease-modifying antirheumatic drugs (DMARDs) vs.placebo with or without MTX, in treating rheumatoid arthritis. Quality Rating: Fair	analysis Number of Patients: 6 months: 11,589 12 months: 6051 Studies Included: 6 months: 23 RCTs 12 months: 10 RCTs	Characteristics of Included Populations Patients with RA and and patient populations defined as DMARD-IR or MTX (MTX)-inadequate responders Characteristics of Interventions: Biologic DMARDs with or without MTX or other nonbiologic DMARDs, compared with placebo with or without MTX or other nonbiologic DMARDs	Month and 12-Month Models by Drug 6-month model Certolizumab μ1 2.60 0.44 1.83-3.59 1 TCZ μ2 1.67 0.19 1.31-2.07 2 RTX μ3 1.61 0.59 0.55-2.85 3 INF μ4 1.57 0.27 1.03-2.10 4 ETN μ5 1.43 0.25 1.00-2.00 5 ADA μ6 1.37 0.22 0.94-1.83 6 GOL μ7 1.36 0.38 0.64-2.14 7 ABA μ8 1.16 0.27 0.61-1.68 8 ANK μ9 0.98 0.28 0.47-1.58 9 MTX 0.78 0.19 0.39-1.17 Baseline disease duration 1 0.08 0.04 < 0.01-0.18 Baseline HAQ score 2 -0.45 0.53 -1.49-0.63 Variance 2 0.05 0.02 < 0.01-0.28	
			12-month model Certolizumab μ1 2.02 0.44 1.16-2.83 1 RTX μ2 1.95 0.90 0.47-4.00 2 ADA μ3 1.37 0.28 0.83-1.89 3 INF μ4 1.36 0.31 0.80-1.99 4 ETN μ5 0.86 0.32 0.28-1.43 5 ABA μ6 0.63 0.30 0.08-1.24 6 MTX 0.84 0.21 0.42-1.26 Baseline disease duration 1 0.10 0.04 <	
			0.01-0.17 Baseline HAQ score 2 0.46 0.78 -1.11- 1.89	
			Variance 2 0.02 0.06 < 0.01-0.88	

Study Characteristics	Characteristics of Included Studies	Results	Adverse Events	Assessments, Study Appraisals, and Quality Rating
	Studies Studies included: 26 controlled trials 18 additional studies assessed safety Characteristics of included studies: Often limited to 1 year of follow-up Reported on DAS-28 Radiographic progression,	Adjusted indirect comparison indicate no significant differences in efficacy between antiTNF drugs • Anti-TNF drugs appear to be more efficacious than AKA but do not differ among each other. Inddirect comparisons of INF and of anti-TNF drugs as a class compared to AKA yielded a statistically significant greater efficacy on ACR 20 [RR 0.58 (95%CI 0.38-0.90) and RR 0.61 (95% CI 0.39-0.96), respectively], but not ACR 50 • Few studies assessed longterm radiographic outcomes. In general, rate of radiographic progression was significantly lower in patients treated with biologics than in placebo-	Because of lack of sound long- term safety data, evidence is insufficient to draw firm conclusions about comparative safety of biologics • Higher rates of injection site reactions for AKA than ADA and ETN (56% vs. 19% vs. 25%)	Rating Publication Bias Assessed:
	 All 12 weeks plus of duration (for observational studies it was 3 months or greater and 100 or more patients) 	of concomitant DMARD		

Study Characteristics, Quality Rating Study Information	Study Characteristics	Results	Adverse Events
	Characteristics of Included Studies: RCTs reporting the efficacy on signs and symptoms, disability and/or structure of oral DMARDs vs.placebo (except for MTX) or other nonbiologic DMARDs in patients with RA		Adverse Events: MTX monotherapy vs. MTX combo, DMARD naïve Withdrawals due to lack of efficacy or toxicity were similar in both groups: RR,

Evidence Table 2. Systematic reviews and meta-analyses (continued)

Study Characterist Quality Rating	tics, Study Information	Study Characteristics	Results	Adverse Events
			ACR20: OR, 0.53 (95% CI, 0.21-1.33) • MTX monotherapy vs. MTX combos, DMARD inadequa responders • SJC (3 studies): SRM, -0.7 (95% CI, -1.30 to -0.25) • Pain (3 studies): SRM, -0.6 (95% CI, -1.01 to -0.28) • HAQ (3 studies) SRM, -1.2 (95% CI, -2.07 to -0.36)	e 8 4
			ACR20 (2 studies): RR, = 0.26 (95% CI, 0.16 to 0.40)	
			SSZ monotherapy vs. SSZ combo	
			In 6 trials (657 patients), no significant difference for SJC, function, or ACR20, 50 or 70. Significant finding: Structural damage (1 trial) favoring the combination MTX+SSZ+hydroxychloroquine: SRM, -1.70 (95% CI, -2.03 to -1.37)25	
			Pain (1 trial) favoring SSZ monotherapy: SRM, 4.10 (95% CI, 2.91-5.29)	6

Study Characteristics	Characteristics of Included Studies	Results	Adverse Events	Assessments, Study Appraisals, and Quality Rating
Author, year, country, funding:	Studies included: • Maini et al. 1999	Indirect comparisons, Relative Risk (95% CI)	NR	Publication Bias Assessed: NR
Hochberg et al., 2003 ²¹⁴ Multinational NR	 Lipsky et al. 2000 Weinblatt et al 1999 Weinblatt et al. 2003 	 ETNnercept vs. adalimumab ACR 20 1.10 (0.57 to 2.12) 2.60 (0.35 to 19.0) 		Heterogeneity Assessed: Yes
Study Design: Systematic review and indirect comparisons	Characteristics of included studies:	 Infliximab vs. adalimumab 1.07 (0.66 to 1.73) 1.35 (0.47 to 3.85) 		Standard Method of Study Appraisals: NR
Aims of the Review: Differences in efficacy of	04 = 1.=1	ETNnercept vs. infliximab 1.03 (0.49 to 2.18) 1.92 (0.22 to 17.0)		Comprehensive Search Strategy: Yes - briefly describe in box
TNF alpha blocking agents, as measured by rate ratios for American College of Rheumatology (ACR) 20/50/70 responses, in patients with RA with an incomplete response to methotrexate.	Characteristics of included populations: NR- assuming that it is adults with active RA with lack of response to MTX			Quality Rating: Fair
	Characteristics of interventions: the addition of TNF blocking agents (INF, ETN and ADA) to methotrexate			
Number of Patients: 1053 380 placebo 673 active	in a "step-up" strategy			

Study Characteristics	Study Design	Results Adverse Events	Quality	Comments
Characteristics Author: Kirwan, 2009 ²¹⁵ Country and setting: Multi-national Funding: Chochrane Collaboration	Study design: Systematic Review and meta-analyses Overall study N: 1414 Study aims: To perform a systematic qualitative review of studies evaluating glucocorticoid efficacy in inhibiting the progression of radiological damage in rheumatoid arthritis.	Main results: Comparison 1. Glucocorticoids vs. comparator Erosion outcomes refer to erosion scores expressed as percentage of max possible score for method used by individual studies. Outcome 1. SMD in progression of erosion scores = 0.40 in favor of glucocorticoids (95% Cl 0.27, 0.54) (from abstract) Outcome 2. Change in erosions at 1 year as proportion of maximum score (N = 15, # of Participants = 1421) SMD = 0.39 (95% Cl, 0.27, 0.52) in favor of glucocorticoids Outcome 3. Erosions at 1 year, data from 1 & 2 year studies (N = 10, # of participants = 940) SMD = -0.43 (95% Cl, -0.62, -0.23) in favor of glucocorticoids Outcome 4> Erosions at 2 years, data from 1 & 2 year studies (N = 10, # of participants = 967) SMD = -0.40 (95% Cl, -0.56, -0.24) in favor of glucocorticoids Outcome 5. Joint Space Narrowing at 1 year as a proportion of maximum score (n = 6, # of participants = 711) SMD = -0.27 (95% Cl, -0.50, -0.04) in favor of glucocorticoids	(i.e. comparative studies) and where there was evaluation of radiographs of hands, or hands and feet, or feet by any standardised technique. Eligible studies had at least one treatment arm with glucocorticoids and one without glucocorticoids. Review studies independently reviewed by at least 2 persons?	Comments: Sensitivity analyses looked at several different ways of combining studies, and in all cases a similar benefit for glucocorticoid therapy was demonstrated (concomitant medication, length of study, when only low dose steroid studies were included, when step-down glucocorticoids were used, etc.) Total of 14 comparisons, each with multiple outcomes, reported in review. Comparison 1 was abstracted; others have not been abstracted. The comparisons are: Comp 1. Glucocorticoids vs comparator Comp 2. Glucocorticoids vs nSAID Comp 3. Glucocorticoids vs NSAID Comp 4. Oral low dose Glucocorticoids + DMARD + NSAID vs DMARD = NSAID Comp 5. Step down Glucocorticoids + DMARD = NSAID Comp 6. Studies with less than 26 week of Glucocorticoid treatment Comp 7. Studies with more than 26 weeks of Glucocorticoid vs comparator using modelled SDs

Evidence Table 2. Systematic reviews and meta-analyses (continued)

Study		Results		
Characteristics	Study Design	Adverse Events	Quality	Comments
		Outcome 6. Joint Space	e	Comp 9. Glucocorticoids vs
		Narrowing at 2 years as	s a	comparators using only
		proportion of maximum	score	studies with modelled SDs
		(N = 4, # of participants	; –	Comp 10. Glucocorticoids vs.
		512) SMD = -0.31 -(95°	% CI,	comparator using original
		-0.51, -0.11) in favor of		SDs in studies with
		glucocorticoids		modelled SDs
		 Outcome 7. Joint Space 	е	Comp 11. Glucocorticoids vs
		Narrowing at 1 year da	ta	comparator sensitivity
		from 1 & 2 year studies	(N =	analyses by quality
		4, # of participants = 47	73).	standards - Concealed
		SMD -0.22 (-0.51, 0.07)	treatment
		 Outcome 8. Joint Space 	e	Comp 12. Glucocorticoids vs.
		Narrowing at 2 years da	ata	comparator sensitivity
		from 1 & 2 year studies	(N =	analyses by quality
		3, # of participants = 34	95)	standards - Blinding of
		SMD = -0.28 (95% CI,	-0.57,	Patients
		0.01)		Comp. 13 Glucocorticoids vs
		 Outcome 9. Proportion 	of	comparator sensitivity
		patients progressing at		analyses by quality
		1 (N = 4, # of participar	its =	standards - Intention to
		261). Risk Ratio = 0.60		Treat
		CI, 0.48, 0.74), in favor		Comp 14. Glucocorticoids vs
		glucocorticoids		comparator sensitivity
		Advance		analyses by quality
		Adverse events:		standards - Blinded
		• NR		Assessors

Study Characteristics, Quality Rating	Study Information	Study Characteristics	Results	Adverse Events
Author, Year: Kuriya et al., 2010 ²¹⁶ Country and setting: NR Funding: NR Aims of Review: To examine the efficacy of MTX monotherapy compared with combination therapy with a biologic when used as initial tx in early RA (ERA) pts. Quality Rating:	Study design: Systematic Review and Meta- analysis Number of Patients: 2,763 Studies Included: N = 7	Characteristics of Included Studies: Included studies were double-blind, randomised, active-comparator, controlled clinical trials that studied the efficacy of initial combination therapy (MTX + biologic) compared with MTX monotherapy in adult pts with clinically active ERA Characteristics of Included Populations Pts were adults with clinically active ERA, defined as disease duration < 3 years, and with no or minimal previous exposure to MTX (≤ 4 weeks). Previous treatment with corticosteroids, SSZ or	Study Results: Clinical Remission (Combo vs. Monotherapy, RR, (95% CI): 1.74 (1.54-1.98) Radiographic Non-progression (Combo vs. Monotherapy, RR, (95% CI): 1.30 (1.01-1.68)	Adverse Events: NA
Good Good		hydroxychloroquine/chloroquine was permitted. Characteristics of Interventions: 3 INF trials: 3 mg/kg, q 8 weekly 2 ADA trials: 40 mg, q 2 weekly 1 ETN trial: 50 mg, q weekly 1 ABA trial: 10 mg/kg, q 4 weekly		

Study Characteristics, Quality Rating	Study Information	Study Characteristics	Results	Adverse Events
Author, Year: Leombruno et al., 2009 ²¹⁷ Country and setting: multi-national Funding: NR Aims of Review:	Study design: Meta-analysis Number of Patients: 8,808 Studies Included: N = 18	Characteristics of Included Studies: The study must be an RCT with more than 30 patients randomly assigned to either an anti-TNF or a control group (non-DMARD or placebo) over a minimum of 10 wks. A Jadad score of ≥ 2 was required and tx arms of combination biological therapies were excluded.	Study Results:	Adverse Events: Death, OR (CI) ADA: 2.04 (0.64 - 6.51) ETN: 2.34 (0.67 - 8.12) INF: 0.62 (0.21 - 1.79) Anti-TNF: 1.39 (0.74 - 2.62) Serious adverse events, OR (CI) ADA: 1.12 (0.86 - 1.45)
To evaluate the safety of biological treatments for RA using results		Characteristics of Included Populations Patients with RA		ETN: 1.04 (0.73 - 1.47) INF: 1.17 (0.86 - 1.59) Anti-TNF: 1.11 (0.94 - 1.32)
from RCTs Quality Rating: Fair	om RCTs uality Rating:	 Characteristics of Interventions: ADA: 6 trials doses: 20-80 mg every wk or 20-80 mg every other wk 		Serious infections, OR (CI) ADA: 1.53 (0.83 - 2.81) ETN: 0.89 (0.56 - 1.42) INF: 1.46 (0.86 - 2.47) Anti-TNF: 1.21 (0.89 - 1.63)
		 all but 1 on background of MTX or other DMARD. ETN: 7 trials doses: 10-25 mg twice per wk 		Lymphomas, OR (CI) ADA: 1.07 (0.28 - 4.09) ETN: 1.42 (0.27 - 7.61) INF: 1.42 (.27 - 7.62) Anti-TNF: 1.26 (0.52 - 3.06)
	 2 on background MTX 1 on background SSZ INF: 5 trials doses: 1-10 mg/kq every 4 wks or 3-10 mg/kg every 8 wks 		Non-cutaneous cancers and melanomas, OR (CI) ADA: 1.37 (0.49 - 3.89) ETN: 1.11 (0.42 - 2.96) INF: 1.70 (0.39 - 7.32) Anti-TNF: 1.31 (0.69 - 2.48)	
		all on background of MTX		Non-melanoma skin cancers, OR (CI) ADA: 1.37 (0.49 - 3.89) ETN: 1.03 (0.38 - 2.77) INF: 1.70 (0.39 -7.32) Anti-TNF: 1.27 (0.67 - 2.42)

Study Characteristics	Characteristics of Included Studies	Results	Adverse Events	Assessments, Study Appraisals, and Quality Rating
Author, year, country, funding:	Studies included: 159 studies (71 RCTs, 88	RA patients stay significantly longer on MTX than on other	See main results	Publication Bias Assessed: NR
Maetzel, et al. 2000 ²¹⁸ Multinational Arthritis and Autoimmunity Research	observational studies) (159 satisfied screening criteria; 110 studies included in meta-	DMARDs. (Higher % stay on MTX vs. SSZ because of toxicity [RR 1.68, <i>P</i> < 0.0001]).		Heterogeneity Assessed: NR
Centre, Aventis Canada, Inc.	analysis)	Majority of withdrawals from		Standard Method of Study
Study Design: Meta-analysis	Characteristics of included studies:	SSZ and HCQ result from lack of efficacy. Withdrawal rates		Appraisals: Yes
Aims of Review: To summarize evidence on treatment withdrawal rates	Studies. Studies reporting information on number of patients withdrawing	similar in observational studies vs RCTs.		Comprehensive Search Strategy: Yes
reported in observational studies and RCTs of MTX, SSZ, HCQ (and parenteral gold) among RA patients.	Characteristics of included populations: RA Patients being treated with MTX, parenteral gold (GST),			Quality Rating: Fair
Number of Pts:	SSZ, and HCQ			
Cannot determine	Characteristics of interventions: MTX, GST, SSZ, and HCQ			

Study Characteristics, Quality Rating	Study Information	Study Characteristics	Results	Adverse Events
Author, Year: Martinez Lopez et al., 2009 ²¹⁹ Country and setting: Multinational	Study design: Systematic Review Number of Patients: 366 Studies Included:	Characteristics of Included Studies: RCTs, cohort studies, longitudinal observation studies and surveys Characteristics of Included Populations RA patients who were 18 years or	Study Results: There were 101 MTX exposed pregnancies in the studies. The pooled outcomes (elective abortions not included) demonstrated: 19 miscarriages (23% of pregnancies): 55 live	Adverse Events: N/A
Funding: Abbott Immunology Aims of Review: To analyze the safety of MTX in RA regarding the reproductive system. Quality Rating: Fair	N = 6	older; using MTX at doses usually taken in rheumatology (7.5-25 mg/w) Characteristics of Interventions: No true cohorts, only descriptions of cases obtained from retrospective clinical record searches or from surveys. The studies reported outcomes on male or female fertility; pregnancy complications; malformations, miscarriages, induced abortions, still births and breast feeding complications	(23% of preganancies); 55 live births (66% of preganancies) and 5 of these had neonatal malformations (5% of pregnancies). The rate of induced abortions is 18%. No study filled the selection criteria for MTX and lactation or male fertility. However, there were case reports that generated possible indirect evidence of	

Study		Results		
Characteristics	Study Design	Adverse Events	Quality	Comments
Author: Mertens, 2009 ²²⁰ Country and setting: Multinational (Europe, USA, Canada, Australia) Funding: Internal sources: • Minneapolis VA Medical Center • NIH CTSA Award 1 KL2 RR024151-01 (Mayo Clinic Center for Clinical and Translational Research) • National Institute of Health External sources: • No sources of support supplied	Study design: Systematic review and meta-analysis Overall study N: N = 2872 (788 placebo, 2084 ANK) in systematic review Data not presented for 26 randomized pts (7 placebo, 19 ANK); therefore, N = 2846 (781 placebo, 2065 ANK) for analysis Study aims: What is the clinical effectiveness of Anakinra for the treatment of RA in terms of: a. relieving symptoms? b. delaying disease progression? What are the risks (frequency and severity of adverse events) associated with Anakinra treatment in these patients?	Main results: Result 1. ANK (< 50 mg/day) vs. Placebo, Risk Ratio (M-H, Fixed, 95% CI) ACR 20: 1.38 (1.01, 1.89) ACR 50: 3.37 (0.82, 13.77) ACR 70: 4.45 (0.26, 76.62) Withdrawals: 0.85 (0.62, 1.18) Mean Difference (IV, Fixed, 95% CI) Change in pain VAS score: 0.85 (0.62, 1.18) Change in HAQ score: -0.2 (-0.33, -0.07) Change is ESR: -10.0 (-15.67, -4.33)(1 study) Change in CRP: -0.9 (-1.64, -0.16) (1 study) Change in Larsen score: -2.80 (-5.47, -0.13) Result 2. ANK (50 - 150 mg/day) vs. Placebo, Risk Ratio (M-H, Fixed, 95% CI) ACR 20: 1.61 (1.32, 1.98) ACR 70: 3.71 (1.44, 9.57) Withdrawals: 1.04 (0.86, 1.27) Mean Difference (IV, Fixed, 95% CI) Change in pain VAS score: -0.10 (-0.15, -0.04) Change in HAQ score: -0.19 (-0.30, -0.09) Change is ESR: -10.04 (12.75, -7.33) Change in CRP: -0.6 (-1.26, 0.06) (results from 1 study only) Change in Larsen score: -2.45 (-4.53, -0.36) Adverse events: ANK (50 - 150 mg/day) vs. Placebo, Risk Ratio (M-H, Fixed, 95% CI)	Review based on focused question of interest: Yes Did search strategy employ comprehensive, systematic literature search? Yes Searched Cochrane Central Register of Controlled Trials, MEDLINE (1950 to JanuaryWeek 4 2008), EMBASE (1980 to 2008), and CINAHL (1982 to November 2007); also reviewed reference lists of identified publications, including previous meta-analyses, to identify any additional studies/citations; further information was sought from authors/industry if needed. Eligibility criteria clearly described? Yes Review studies independently reviewed by at least 2 persons? Yes Standard method of critical appraisal before including? Yes	Comments: Due to large variability in doses, 2 groups were created for analysis: data from doses < 50 mg/day of ANK and data from doses 50 to 150 mg/day. This was clinical decision based on fact that recommended daily dose is 100 mg daily. One of 5 included studies separted during analysis because of design differences (included another biologic). Pain VAS and radiographic scales and CRP were reported in just 1 of 5 studies.

Study		Results	Results		
Characteristics	Study Design	Adverse Events	Quality	Comments	
		 Infections: 1.08 (0.80, 1.45) 			
		 Serious Infections: 3.15 (0.81, 12.20) 			
		 Adverse Events: 1.05 (0.94, 1.17) 			
		 Serious Adverse Events: 1.04 (0.70, 			
		1.56)			
		 Injection site reactions: 2.45 (2.17, 2.77) 			
		 Deaths: 1.01 (0.11, 9.04) 			

Study Characteristics Quality Rating	, Study Information	Study Characteristics	Results	Adverse Events
Author, Year: Nam et al., 2010 ²²¹ Country and setting: Multinational Funding: NR Aims of Review: To review the evidence for the effi cacy and safety of biological agents in patients with rheumatoid arthritis (RA) to provide data to develop treatment recommendations by the European League Against Rheumatism (EULAR) Task Force Quality Rating: Fair	Study design: Systematic review and meta- analysis Number of Patients: NR Studies Included: 87 articles and 40 abstracts	Characteristics of Included Studies: For efficacy 1)double-blind randomised controlled trials (RCTs); (2) trials of ≥6 months' duration; (3) studies with ≥ 50 patients; (6) publications in English. And for safety (1) registries and observational studies; (2) inclusion of a control group; (3) report of incidence of events in the context of population-based expected incidences Characteristics of Included Populations Patients with RA Characteristics of Interventions: Studies evaluating 1 of the 9 biological DMARDs	n = 882 RR, 0.25 (95% CI, 0.13-0.48) P = 0.0001 • Sulfasalazine 5 studies n = 434 RR, 0.45 (95% CI, 0.23-0.89) P = 0.02 • Gold salts 2 studies n = 320	 Gold salts 2 studies n = 320 RR, 2.34 (95% CI, 1.10-4.97)

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes
Author, year, country, funding: Osiri et al., 2002 ¹⁴² Multinational Cochrane Collaboration Study Design: Systematic review of RCTs and CCTs Aims of the Review: • To determine efficacy and toxicity of LEF compared to placebo or other DMARDs in txt of RA • META-ANALYSIS-analysis stratified comparison between LEF and Placebo or other DMARDs by outcomes at different length of txts Number of Pts: 1,144 LEF	Studies included: 6 trials Characteristics of included studies: Randomized, double-blind, placebo and/or active controlled Characteristics of included populations: All with active RA Characteristics of interventions: 5,10 or 25 mg/d vs. placebo or MTX or SSZ	 LEF significantly better than placebo at 6,12 and 24 mos. LEF vs. MTX ACR 20: Significantly more responders for MTX than LEF at 12 mos; OR: 1.43 (1.15-1.77) No significant differences at 2 yrs but more responders with MTX than with LEF; OR, 1.28 (0.98-1.67) ACR 50, ACR 70: differences in ACR 50/70 repsonses between LEF and MTX were NS 	Placebo (70/416 vs. 18/311)); LEF not diff in efficacy and tolerability than MTX and SSZ, except that LEF was more efficaious than SSZ at 24 mos; AEs+ GI sympotms, elevated	Publication Bias Assessed: NR Heterogeneity Assessed: Yes Standard Method of Study Appraisals: Yes Comprehensive Search Strategy: Yes Quality Rating: Good
312 to Placebo 680 to MTX 132 to SSZ Only 920 used in meta- analysis-analysis 2 yr extension: LEF:158 SSZ: 60 MTX 101				

Study Characteristics, Quality Rating	Study Information	Study Characteristics	Results	Adverse Events
Author, Year: Osiri et al., 2009 ²²² Country and setting: Multinational Funding: Cochrane Collaboration Aims of Review: To determine the efficacy and toxicity of LEF (monotherapy or combined with another DMARD) compared to placebo or other DMARDs in the treatment of RA. Quality Rating: Good	Study design: Systematic Review and meta- analyses Number of Patients: NR Studies Included: N = 33	Characteristics of Included Studies: All randomized controlled trials (RCTs) or controlled clinical trials (CCTs) comparing LEF as monotherapy or in combination with another DMARD to placebo or other DMARDs. Characteristics of Included Populations Patients were at least 18 yrs old, had a clinical diagnosis of RA according to the ACR 1987 revised criteria, and had active disease as shown by these outcomes: 1) number of 10der joints; 2) number of swollen joints; 3) duration of morning stiffness; 4) acute phase reactants. Characteristics of Interventions: Studies comparing LEF treatment (as monotherapy or in combination with other DMARDs) at a dose of 20 to 25 mg/day (with or without a loading daily dose of 100 mg given in the first 1 to 3 days) with placebo or other DMARDs were included. The duration of treatment in the trials must have been at least 3 mos (or 12 wks).	ACR20, Risk Ratio (M-H, Fixed, 95% CI) • LEF vs. MTX, at 3 mos: 0.96 (0.84-1.10) • LEF vs. MTX, at 4 mos: 0.95 (0.50-1.81) • LEF vs. MTX, at 6 mos (24 wks): 0.96 (0.87-1.06) • LEF vs. MTX, at 12 mos: 1.08 (0.75-1.55)	0.75 (0.53-1.07) • LEF vs.SSZ, at 12 mos: 1.07 (0.43-2.63) • LEF vs. SSZ, at 24 mos: 0.79 (0.39-1.59) • LEF vs. MTX, at 12 mos: 1.26 (1.08-1.48) • LEF vs. MTX, at 2 yrs: 1.15 (0.83-1.61) • LEF + MTX vs. MTX, at • 24 wks: 0.93 (0.60-1.43) • LEF + SSZ vs. placebo + SSZ, at 24 wks: 1.34 (0.77-2.34) • LEF/LEF+ MTX vs. placebo/Lef + MTX, at 48 wks: 1.4 (0.65-3.00) • LEF + MTX vs. MTX, at 3 • mos: 0.75 (0.39-1.43) • LEF+ MTX vs. MTX, at 24 mos: 1.25 (0.52,-3.01) Withdrawals due to adverse events, Risk Ratio (M-H, Fixed, 95% CI) • LEF vs. SSZ, at 6 mos: 0.77 (0.45-1.33) • LEF vs. SSZ, at 12 mos: 0.38 (0.08-1.90) • LEF vs. SSZ, at 24 mos:

Study Characterist Quality Rating	tics, Study Information	Study Characteristics	Results	Adverse Events
adding realing			 LEF+MTX vs.MTX, at 24 wks: 0.23 (0.11-0.48) LEF+SSZ vs. placebo+SSZ, at 24 wks: 0.10 (0.01-1.79) LEF vs. MTX, at 24 wks: 0.83 (0.53-1.32) LEF vs. anti-TNF+MTX, at 24 wks: 1.39 (0.97-1.99) Lef+ADA vs. ADA, at 12 wks 0.84 (0.58-1.20) ACR70, Risk Ratio (M-H, Fixed, 95% CI) LEF vs. MTX, at 12 mos: 0.44 (0.26-0.77) LEF vs. MTX, at 2 yrs: 0.72 (0.44-1.18) LEF vs. SSZ, at 6 mos: 0.66 (0.28-1.55) LEF vs. SSZ, at 12 mos: 1.14 (0.57-2.25) LEF vs. SSZ, at 24 mos: 0.70 (0.34-1.43) LEF+MTX vs.MTX, at 24 wks: 0.23 (0.07-0.77) LEF vs. MTX, at 24 wks: 0.5 (0.10-2.53) LEF vs. anti-TNF+MTX, at 24 wks: 3.75 (1.35-10.43) 	1.38 (0.77-2.47) • LEF + MTX vs. MTX, at 24 wks: 1.82 (0.83-3.97) • LEF/Lef + MTX vs. placebo/LEF + MTX, at 48 wks: 1.0 (0.21-4.83) • LEF vs. LEF + MTX, at 3 • mos: 0.46 (0.03-8.03) :: • LEF + MTX vs. MTX, at 3 • mos: 0.86 (0.41-1.81) • LEF + MTX vs. MTX, at 24 mos: 1.4 (0.46-4.23) Reported adverse events, Risk Ratio (M-H, Fixed, 95% CI) • LEF vs. MTX, at 6 mos:
			HAQ, Mean Difference (IV, Fixed, 95% CI) • LEF vs. MTX, at 3 mos: 0.01 (-0.12, 0.14) • LEF vs. MTX, at 6 mos: -0.0 (-0.11-0.09) • LEF vs. MTX, at 12 mos: -0.02 (-0.09-0.05) • LEF vs. MTX, at 2 yrs: 0.05 (-0.04-0.14) • LEF vs. SSZ, at 6 mos: -0.25	 LEF vs. MTX: 0.50 (0.28-0.92) Allergy or rash, Risk Ratio (M-H, Fixed, 95% CI) LEF vs. SSZ: 1.0 (0.52-

Study Characteris		Study Characteristics	Doculte	Adverse Events
Quality Rating	Study Information	Study Characteristics	(-0.420.08) LEF vs. SSZ, at 12 mos: -0.14 (-0.33-0.05) LEF vs. SSZ, at 24 mos, -0.29 (-0.570.01) LEF+MTX vs. MTX, at 24 wks: -0.30 (-0.420.18) LEF+SSZ vs. placebo+SSZ, at 24 mos: -0.07 (-0.20-0.06) LEF vs. anti-TNF, at 24 wks: 0.49 (0.34-0.64) HAQ-DI, Mean Difference (IV, Fixed, 95% CI) LEF+SSZ vs. placebo+SSZ, at 24 mos: -0.08 (-0.23-0.07) Lef/ILEF+ MTX vs. placebo/LEF + MTX, at 48 wks: 0.21 (0.05-0.37) MHAQ, Mean Difference (IV, Fixed, 95% CI) LEF vs. MTX, at 6 mos: -0.12 (-0.220.02) LEF vs. MTX, at 12 mos: -0.14 (-0.250.03) LEF vs. MTX, at 24 mos: -0.15 (-0.290.01) LEF vs. MTX, at 4 mos: -2.34 (-7.64-2.96) Chinese disability, Mean Difference (IV, Fixed, 95% CI) LEF vs. MTX, at 3 mos: -0.05 (-0.180.00) LEF vs. MTX, at 6 mos: -0.05 (-0.20-0.10) SF-36, Mean Difference, Physical Component Scores (IV, Fixed, 95% CI) LEF vs. MTX, at 12 mos: -3.0 (-0.20-0.10)	Nausea, Risk Ratio (M-H, Fixed, 95% CI) LEF + SSZ vs. placebo + SSZ, at 24 wks: 3.57 (0.41-30.90) LEF/LEF + MTX vs. placebo/LEF + MTX, at 48 wks: 1.33 (0.31-5.80) Diarrhea, Risk Ratio (M-H, Fixed, 95% CI) LEF + SSZ vs. placebo + SSZ, at 24 wks: 2.68 (0.29-24.93) LEF/LEF + MTX vs. placebo/LEF + MTX, at 48 wks: 5.33 (1.61-17.71) Hyper10sion, Risk Ratio (M-H, Fixed, 95% CI) LEF vs. SSZ: 1.0 (0.21-4.87) LEF vs. MTX: 2.29 (1.42-3.69) W8 loss, Risk Ratio (M-H, Fixed, 95% CI) LEF vs. SSZ: 3.0 (0.62-14.60) LEF vs. MTX: 0.81 (0.39-1.66)

Study Characterist		Study Characteristics	Deculto	Advance Events
Quality Rating	Study Information	Study Characteristics	 Results Lef/LEF + MTX vs.placebo/LEF + MTX, at 48 wks: -1.90 (5.14-1.34) 	Fixed, 95% CI) • LEF vs. SSZ: 0.25 (0.03-2.21)
			SF-36, Mean Difference, Mental Component Scores (IV, Fixed, 95% CI) • LEF vs. MTX, at 12 mos: -0.6 (-3.01-1.81) • Lef/LEF + MTX vs.placebo/LEF + MTX, at 48 wks: -2.7 (5.63-0.23)	Elevated liver function tests, Risk Ratio (M-H, Fixed, 95% CI)
			Work Productivity Scores, Mean Difference (IV, Fixed, 95% CI) • LEF vs. MTX, at 12 mos: - 2.30 (-6.37-1.77) • DAS28 response rate, Risk Ratio (M-H, Fixed, 95% CI) • LEF + SSZ vs. SSZ, at 24	 LEF vs. SSZ: 0.6 (0.15-2.46) LEF vs. MTX: 0.66 (0.31-1.39) LEF/LEF + MTX vs. placebo/LEF + MTX, at 48 wks: 1.07 (0.53-2.15) Elevated liver function tests,
			wks: 0.76 (0.47-1.24) DAS28 score change, Mean Difference (IV, Fixed, 95% CI) • LEF + SSZ vs. SSZ, at 24 wks: 0.10 (-0.41-0.61) • LEF vs. MTX, at 16 wks: 0.57 (0.24-0.90) • LEF vs. MTX, at 24 wks: - 0.10 (-0.41-0.21) • LEF vs. anti-TNF+MTX, at 24 wks: 0.80 (0.43-1.17)	reported as adverse event, Risk Ratio (M-H, Random, 95% CI) • LEF vs. SSZ, at 6 mos: 0.6 (0.15-2.46) • LEF vs. MTX, at 6 mos: 0.52 (0.24-1.15) • LEF vs. MTX, at 1 year: 0.65 (0.17-2.45) • LEF vs. MTX, at 2 yrs: 0.80 (0.30-2.14)
			 DAS28 responders, Risk Ratio (M-H, Fixed, 95% CI) LEF + SSZ vs. SSZ, for 24-wk completers: 0.61 (0.36-1.04) 	Elevated liver function tests, withdrawals Risk Ratio (M-H, Random, 95% CI) • LEF vs. SSZ, at 6 mos: 1.0 (0.14-6.99)
			EULAR remission (DAS28 <3.2), Risk Ratio (M-H, Fixed, 95% CI) • LEF vs.MTX, at 16 wks: 1.24	 LEF vs. MTX, at 6 mos: 0.18 (0.02-1.63) LEF vs. MTX, at 1 year: 0.90 (0.28-2.86)

Study Characterist Quality Rating	tics, Study Information	Study Characteristics	Results	Adverse Events
y			(0.64-2.42) • DAS28 remission, Risk Ratio (M-H, Fixed, 95% CI) • LEF vs. MTX, at 24 wks: 1.0 (0.22-4.56) • LEF vs. anti-TNF+MTX, at 24 wks: 1.67 (0.38-7.39) • LEF vs. Lef+MTX, at 3 mos: 1.35 (0.18-10.09)	 LEF vs. MTX, at 2 yr: 0.33 (0.08-1.42) Serious adverse events, (M-H, Fixed, 95% CI) LEF + SSZ vs. placebo + SSZ, at 24 wks: 1.79 (0.47-6.77) LEF/Lef + MTX vs.
			DAS28 low disease activity, Risk Ratio (M-H, Fixed, 95% CI) • LEF vs. MTX, at 24 wks: 1.0 (0.28-3.63) • LEF vs. anti-TNF+MTX, at 24 wks: 3.33 (1.17-9.51)	placebo/Lef + MTX, at 48 wks: 0.87 (0.44,-1.72)
			DAS28 moderate disease activity, Risk Ratio (M-H, Fixed, 95% CI) • LEF vs. MTX, at 24 wks: 1.05 (0.76-1.44) • LEF vs. anti- TNF+MTX, at 24 wks: 0.56 (0.30-1.04)	
			DAS28 high disease activity, Risk Ratio (M-H, Fixed, 95% CI) • LEF vs. MTX, at 24 wks: 0.5 (0.05-5.22) • LEF vs. anti-TNF+MTX, at 24 wks: 0.33 (0.02-6.44)	
			EULAR good response, Risk Ratio (M-H, Fixed, 95% CI) • LEF vs. LEF + MTX, at 3 mos: 0.37 (0.10-1.34) • LEF + ADA vs. ADA, at 12 wks: 0.71 (0.47-1.05)	
			EULAR moderate response, Risk Ratio (M-H, Fixed, 95%	

Study Characteristi Quality Rating	ics, Study Information	Study Characteristics	Results	Adverse Events
, ,			CI) • LEF vs. Lef+MTX, at 3 i 0.80 (0.47-1.35) • LEF + ADA vs. ADA, at wks: 0.83 (0.73-0.93) • EULAR response-no improvement, Risk Rati H, Fixed, 95% CI) • LEF vs. LEF + MTX, at mos: 4.27 (0.64-28.56)	o (M-
			EULAR response rate, Ris Ratio (M-H, Fixed, 95% C • LEF vs. MTX, at 16 wks 1.05 (0.89-1.23)	I)

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes
Author, yr, country, funding: Rheumatoid Arthritis Clinical Trial Archive Group, 1995, 223 Multinational, NIH grants Study Design: Systematic review Aims of the Review: To evaluate whether age and renal impairment affect rate of side effects or efficacy of MTX in RA pts Number of Pts: 496	Studies included: 11 MTX clinical trials: Weinblatt, et al., 1985 Furst, et al., 1989 Schmid, et al., unpublished study Williams, et al., 1985 Wilke, et al., unpublished study Weinblatt, et al., 1990 Williams, et al., 1992 Suarez et al 1988 Morassut, et al., 1989 Hamdy, et al., 1987 Bell, et al., 1988. Characteristics of included studies: RCTs Placebo control or comparative trial MTX as 1 treatment arm Adult RA pts Trial completed (although not necessarily published) by end of 1991, and trial 12 weeks or longer (to end or to crossover) Characteristics of included populations: Adult RA pts treated with MTX Characteristics of interventions: All pts treated with MTX (doses NR)	(referent), 1.4 (0.7, 2.6) for 60-64, 1.0 (0.5, 2.2) for 65-69, and 0.7 (0.3, 1.7) for ≥ 70 (efficacy regression analyses controlled for age group, sex, renal function, study of origin, initial tender joint count, grip strength, steroid dose, NSAID used at baseline, and maximum MTX dose) • Odds of major clinical improvement by creatinine clearance were 1.0 for ≥99.8 ml/min (referent), 0.6 (0.3, 1.0) for 78.6-99.9 ml/min, 1.1 (0.6, 2.0) for 62.6-78.6 ml/min, and 1.0 (0.5, 2.1) for < 62.6 ml/min	1.0 (referent) 1.8 (1.0, 3.4) 1.2 (0.6, 2.3) 1.8 (0.8, 3.7) • Toxicity regressions adjusted for age, sex, creatinine clearance, baseline NSAID use (yes/no), maximum MTX dose, and study of origin	Publication Bias Assessed: NR Heterogeneity Assessed: Yes Standard Method of Study Appraisals: NR Comprehensive Search Strategy: Yes Quality Rating: Fair

Study		Results		
Characteristics	Study Design	Adverse Events	Quality	Comments
Author: Salliot, 2009 ²²⁴	Study design: Systematic Review and	Main results: Pooled ORs Regardless of Dose:	Review based on focused question of interest:	Comments: NR
Country and	meta-analyses	 Rituximab Pooled OR = 1.45 (0.56 - 3.73) Abatacept Pooled OR = 1.35 (0.78 - 		
setting: NR	Overall study N: N = 4,767 (745 rituximab, 1960 abatacept, 2062	2.32) • Anakinra Pooled OR = 2.75 (0.90 - 8.35)	Did search strategy employ comprehensive, systematic literature search?	
Funding: NR	anakinra), 2112 placebo	Pooled ORs Stratified by High and Low	Yes.	
	Study aims: To assess if biological agents, ie rituximab, abatacept, and anakinra increase risk of serious infections.	Dose: Rituximab • High Dose v Placebo 1.68 (0.64 - 4.35) • Low Dose V Placebo 0.24 (0.01 - 4.33) • High Dose v Low Dose 7.20 (0.43 - 120.66)	A systematic literature search of literature published up to December 2007 was performed in PUBMED, EMBASE and Cochrane library databases; without limitation of years of publication or journal, using	
		 Abatacept High Dose v Placebo 1.35 (0.78 - 2.33) Excluding patients receiving concominant treatment with other biologic DMARDs, pooled OR = 1.24 (0.70 - 2.29) Low Dose v Placebo 0.84 (0.13 - 5.30) High Dose v Low Dose 2.16 (0.52 - 8.98) Excluding patients receiving concominant treatment with other biologic DMARDs, pooled OR = 2.0 (0.48 - 8.33) Anakinra High Dose v Placebo 3.40 (1.11 - 10.46) Excluding patients with comorbidity factors, pooled OR = 1.67 (0.51 - 5.41) Low Dose v Placebo 0.51 (0.03 - 8.27) High Dose v Low Dose 9.63 (1.31 - 70.91) Excluding patients with comorbidity factors, pooled OR = 6.41 (0.81 - 50.30) 	followings key-words: "rheumatoid arthritis," "abatacept,' "rituximab,"	
		Adverse events: Rituximab: • Among 17 patients who had 1 serious infection: 5 had bronchopneumonia (1 presented with 2 episodes of	Squibb) were contacted. Eligibility criteria clearly described? Yes.	

Evidence Table 2. Systematic reviews and meta-analyses (continued)

Study		Results		
Characteristics	Study Design	Adverse Events	Quality	Comments
		Pseudomonas aeruginosa pneumonia), 2 septic arthritis (of whom one Staphylococcus aureus septicaemia), 3 pyelonephritis and 2 gastroenteritis and 1 each epiglottitis, cellulitis of a toe, and acute hepatitis B. One fatal bronchopneumonia occurred in a patient receiving rituximab. Abatacept: 49 serious infections occurring with abatacept were mainly bronchopulmonary, streptococcal and pyogenic septicaemia, staphylococcal arthritis, abscesses, gastrointestinal (6 of whom 3 diverticulitis), dermatological infections (6 of whom 1 was a cellulitis) and pyelonephritis. One case of unconfirmed tuberculosis and 1 case of pulmonary aspergillosis were reported. Last patient (who had history of tuberculosis and pulmonary fibrosis) died of aspergillosis and of Pseudomonas aeruginosa septicaemia.	Inclusion criteria were randomised placebo controlled trials in adult patients with RA according to ACR criteria. Publications had to be written in English, French or Spanish. Patients had to be randomised to receive placebo or 1 of 3 biological agents (rituximab, anakinra and abatacept), as monotherapy or with concomitant biological or non-biological DMARDs. Reviews and articles reporting trials that were not placebo-controlled were excluded. Review studies independently reviewed by at least 2 persons? No. One reviewer selected studies and abstracted data. Standard method of critical appraisal before including? NR	
		 Anakinra: Among 30 serious infections occurring in anakinra-treated groups, 11 were pneumonia. Others were osteomyelitis, cellulitis, bursitis, herpes zoster, infected bunion and gangrene (1 of each). No related death or opportunistic infections were described. 		

Study Characteristics, Quality Rating	Study Information	Study Characteristics	Results	Adverse Events
Author, Year: Schipper et al., 2009 ²²⁵ Country and setting: Multinational Funding: NR Aims of Review: To review the effects of the combination of MTX and SSZ in naïve patients and patients with an insufficient response, using the results of published parallel and add-on	Study design: Systematic Review Number of Patients: NR Studies Included: N = 4	Characteristics of Included Studies: RCT of at least 12 weeks duration with a parallel or an add-on design, Characteristics of Included Populations RA patients fulfilling the ACR 1987 revised criteria; either naive to MTX and SSZ (parallel trials) or had failed to 1 of them (add-on trials). Characteristics of Interventions: Placebo-controlled, double blind RCTs and compared the efficacy of combined MTX and SSZ to each individual agent and randomized open study comparing the combination of MTX and SSZ with MTX alone.	Trials with naive patients: Mean DAS changes: sub- additive efficacy (1.3 and 1.9 respectively) ACR 20: 80% ACR50: 33% ACR70: 3%	Adverse Events: From the 2 parallel trials, the first RCT showed more toxicity (nausea) of the MTX-SSZ combination compared with the single-drug arms. The second study showed more adverse events (nausea) in the combination group. The 2 add-on trials showed that the addition of MTX to SSZ in patients who had failed to the latter drug was clinically significantly superior to a switch to MTX alone, without increased toxicity.
clinical trials in RA. Quality Rating: Fair				

Study Characteristics, Quality Rating	Study Information	Study Characteristics	Results	Adverse Events
Author, Year: Singh et al., 2009 ²²⁶	Study design: Overview of SERs using ne2rk	Characteristics of Included Studies: In most of the included trials, each	Study Results: Benefit (ACR 50), Biologic vs.	Adverse Events: Safety (withdrawal due to an
Country and setting: Multinational	meta-analyses of Cochrane SERs	biologic was compared with a placebo, usually in combination with traditional DMARDs (usually MTX) or other	Placebo, OR (95% CI), NNT • ABA: 2.98 (1.79-4.97), NNT, 4 (3-9)	adverse event), OR (95% CI), NNT • ABA: 1.24 (0.88-1.76),
Funding: Government	Number of Patients: NR	biologics Characteristics of Included	• ADA: 3.70 (2.4-5.7), NNT, 4 (3-6)	NNT, NS • ADA: 1.54 (1.12-2.12),
Aims of Review: To provide estimates of the benefits and safety of biologics in patients with RA	Studies Included: 6 SERs; 31 studies	Populations Eligibility criteria and patient populations were similar across reviews: adults with RA who met the ACR criteria for RA	 ANK: 1.68 (0.83-3.41), NNT, NS ETN: 4.97 (2.70-9.13), NNT, 3 (2-5) INF: 2.92 (1.37-6.24), NNT, 4 (2-18) 	 ANK: 1.67 (1.22-2.29), NNT, 31 (17-92) ETN: 0.82 (0.56-1.19),
Quality Rating: Good		Characteristics of Interventions: ADA: All RCTs or CCTs comparing ADA (alone or combo with DMARDs) with placebo or other DMARDs	 RIT: 4.10 (2.02-8.33), NNT, 3 (1-7) Overall (all biologics vs. placebo): 3.35 (2.62-4.2) 	
		ABA: All RCTs comparing ABA (alone or combo with DMARDs) with placebo or other DMARDs; no restrictions on dosage or duration of the intervention	Indirect comparison of ACR 50 between biologics, Ratio of odds ratios (95% CI) • ABA vs. ADA: 0.81 (0.43-	Indirect comparison of withdrawal due to adverse events between biologics, Ratio of odds ratios (95% CI)
		ANK: All RCTs comparing ANK (alone or combo with DMARDs or other biologics) with placebo or other DMARDs or biologics	1.49) • ABA vs. ANK: 1.77 (0.78-4.00) • ABA vs. ETN: 0.60 (0.29-	 ABA vs. ADA: 0.80 (0.51-1.26) ABA vs. ANK: 0.74 (0.47-1.17)
		ETN: All RCTs or CCTs of at least 6 months' duration comparing ETN with placebo, ETN with MTX, or ETN + MTX with MTX alone	1.25) • ABA vs. INF: 1.02 (0.43-2.40) • ABA vs. RIT: 0.73 (0.32-1.65)	 ABA vs. ETN: 1.52 (0.93-2.49) ABA vs. INF: 0.56 (0.30-1.05) ABA vs. RIT: 0.93 (0.43-
		INF: All RCTs comparing INF (1, 3, 5 or 10 mg/kg) + MTX with MTX alone, or INF with placebo, with a minimum duration of 6 months and at least 2 infusions	 ADA vs. ANK: 2.20 (1.01-4.75) ADA vs. ETN: 0.74 (0.37-1.48) ADA vs. INF: 1.26 (0.56- 	2.02) • ADA vs. ANK: 0.92 (0.60-1.42) • ADA vs. ETN: 1.89 (1.18-3.04)
		RIT: All RCTs comparing RIT (300, 350, 500 or 600 mg/m2) (alone or combo with DMARD) with placebo or other DMARDs or biologic	2.86) • ADA vs. RIT: 0.90 (0.41-1.96) • ANK vs. ETN: 0.34 (0.14-0.81)	 ADA vs. INF: 0.70 (0.38-1.28) ADA vs. RIT: 1.15 (0.54-2.48) ANK vs. ETN: 2.05 (1.27-

Study Characterist Quality Rating	tics, Study Information	Study Characteristics	Results	Adverse Events
Quality Rating	Study information	Siduy Characteristics	• ANK vs. INF: 0.58 (0.22-	3.29)
			1.52)	 ANK vs. INF: 0.76 (0.41-
			 ANK vs. RIT: 0.41 (0.16- 	1.39)
			1.05)	• ANK vs. RIT: 1.25 (0.58-
			• ETN vs. INF: 1.70 (0.68-	2.69)
			4.22)	• ETN vs. INF: 0.37 (0.19-
			 ETN vs. RIT: 1.21 (0.51- 2.90) 	0.70) • ETN vs. RIT: 0.61 (0.28-
			• INF vs. RIT: 0.71 (0.27-1.89)	1.35)
			ACR50 Subgroup data, OR (95% CI):	• INF vs. RIT: 1.66 (0.69-3.98)
			Concomitant use of MTX Yes: 3.16 (2.40-4.16) No: 4.18 (2.48-7.06)	Withdrawal due to adverse event Subgroup data, OR (95% CI):
			Rheumatoid arthritis duration Early: 2.05 (1.24-3.38) Established: 3.47 (2.26-5.33)	Concomitant use of MTX Yes: 1.30 (1.02-1.65) No: 1.70 (1.12-2.57)
			Late: 4.02 (2.89-5.59)	Rheumatoid arthritis duration
			Biologic is TNF-inhibitor Yes: 3.57 (2.57-4.97) No: 3.10 (2.12-4.53)	Early: 1.45 (0.92-2.28) Established: 1.25 (0.87-1.78) Late: 1.52 (1.09-2.11)
			Prior drugs failed Biologic: 4.09 (2.17-7.69) DMARD: 3.27 (2.46-4.35)	Biologic is TNF-inhibitor Yes: 1.27 (0.94-1.69) No: 1.55 (1.14-2.11)
			None: 3.00 (1.11-8.13)	Prior drugs failed
			Combination biologic therapy Yes: 1.00 (0.45-2.23) No: 3.60 (2.89-4.49)	Biologic: 1.74 (1.02-2.96) DMARD: 1.41 (1.11-1.79) None: 0.85 (0.41-1.76)
			Duration of randomized trial Short: 4.03 (2.93-5.54) Intermediate: 2.92 (1.91-4.46) Long: 1.73 (0.78-3.82)	Duration of randomized trial Short: 1.46 (1.07-1.99) Intermediate: 1.31 (0.94- 1.82) Long; 1.47 (0.71-3.03)
			Prior failure of TNF biologic Yes: 4.11 (2.21-7.63) No: 3.24 (2.48-4.22)	Prior failure of TNF biologic Yes: 1.76 (1.01-3.06) No: 1.34 (1.06-1.69)

Study Characteristics, Quality Rating	Study Information	Study Characteristics	Results	Adverse Events
Foundation,	Study design: Systematic Review Number of Patients: NR Studies Included: N=6 (Note - 6 Cochrane reviews; data from 7 studies on ABA, 8 on ADA, 5 on ANK, 4 on ETN, 4 on INF, 4 on RIT)	Characteristics of Included Studies: Systematic reviews containing at least 1 RCT, with clinically relevant outcomes, and clear inclusion/exclusion criteria; completed, updated, and available Cochrane Systematic reviews of biologic DMARDs as of May 30, 2009 Characteristics of Included Populations 18 yo or older; RA according to 1987 ACR criteria (populations characteristics similar among reviews) Characteristics of Interventions: Biologic DMARDs along or in combo with other biologics/traditional DMARDs compared to placebo along or placebo + biologics/traditional DMARDs. Biologics were of the following dosing regimens: ADA: 500 mg IV q 4 weeks for 2 weeks if <60 kg (750 mg if 60-100kg; 1000 mg if >100 kg) ADA: 40 mg SQ q 2 wks ANK: 100 mg SQ QD ETN: 25 mg SQ twice a wk INF: 3 mg/kg IV q 8 wks RIT: 2-1000 mg IV doses 2 wks apart	Study Results: ACR50 (OR, 95% CI, reference group is placebo) • ABA: 2.98 (1.79 to 4.97) • ADA: 3.70 (2.40 to 5.70) • ANK: 1.68 (0.83 to 3.41) • ETN: 4.97 (2.70 to 9.13) • INF: 2.92 (1.37 to 6.14) • RIT: 4.10 (2.02 to 8.33) Indirect comparions (only significant OR reported): • ANK less efficacy than ETN: 0.34 (0.14 to 0.81, P = 0.05) • ADA greater efficacy than ANK: 2.20 (1.01 to 4.75, P = 0.046)	Adverse Events: Withdrawals due to ADEs (OR, 95% CI, reference group is placebo): • ABA: 1.24 (0.88-1.76) • ADA: 1.54 (1.12-2.12) • ANK: 1.67 (1.22-2.24) • ETN: 0.82 (0.56-1.19) • INF: 2.21 (1.28-3.82) • RIT: 1.34 (0.65-2.76) Indirect comparisons (only signficant OR reported): ADA more withdrawals due to ADEs than ETN: 1.89 (1.18 to 3.04; P = 0.009) ANK more withdrawals due to ADE than ETN: 2.05 (1.27 to 3.29; P = 0.003) ETN less withdrawals due to ADEs than INF: 0.39 (0.19 to 0.70; P = 0.002)

Study Characteristics Quality Rating	, Study Information	Study Characteristics	Results	Adverse Events
Author, Year: Singh et al., 2010 ²²⁸	Study design: Systematic Review	Characteristics of Included Studies: (RCTs) or Controlled Clinical Trials	Compared to patients treated	Adverse Events: Patients treated with the
Country and setting: Multinational	Number of Patients: 1714	(CCTs) (methods of allocating participants to a treatment which are not strictly random, e.g., date of birth,	with placebo+MTX, patients treated with the FDA-approved dose of GOL+MTX (50 mg	FDA-approved dose of GOL+MTX (50 mg every 4 weeks) no more likely to
Funding: NIH Aims of Review: To compare the	Studies Included: N = 4	hospital record number or alternation) Characteristics of Included Populations Adults 18 years or older, with RA	every 4 weeks) were 2.6 times more likely to reach ACR50 at 14-24 wks (95%confidence interval (CI) 1.3 to 4.9; P = 0.005 and NNT = 5, 95%	have any adverse event (relative risk 1.1, 95% Cl, 0.9-1.2; $P = 0.44$), and 0.5 times as likely to have overall withdrawals (95% Cl 0.3-0.8;
efficacy and safety of GOL in adults with rheumatoid arthritis.		meeting the 1987 American College Rheumatology Classification criteria RA. 1 study was prior mtx failure an biologic failure (smolen 99), 3 studie	CI, 2-20). GOL pts were 1.5 times more likely to reach ACR20 (CI) 1.3-4.9. GOL pts	P = 0.005). No significant differences were noted between GOL and placebo
Quality Rating: Good		were naïve populations Characteristics of Interventions: Interventions compared are GOL alone or in combination with DMARDs or biologics vs.placebo plus MTX or GOL alone or in combination with DMARDs or biologics compared to other DMARDs or biologics. There were no restrictions with regard to dosage or duration of intervention.	were 2.8 times more likely to reach ACR70 (CI) 1.3-5.98. GOL-treated patients were significantly more likely to achieve DAS remission (RR, 5.1 (CI) 1.7-15.7): Absolute risk difference = 10% (95% CI, 6%-14%). NNTB = 6 (95% CI, 2-35). GOL treated patients had a significantly greater change in DAS28 scores compared to placebo (<i>P</i> = 0.0003). GOL +MTX pts had greater improvement in functional ability (HAQ) and HAQ score decrease RR, 1.79 (CI) 1.38-2.31, <i>P</i> < 0.0001: Absolute risk difference, -20% (95% CI, -25%15%). Relative percent change, 11% (95% CI, -14% to-8.3%) NNT, 3 (95% CI, 3-4) compared to MTX + placebo (all statistically significant).	

Study Characterist Quality Rating	ics, Study Information	Study Characteristics	Results	Adverse Events
				difference between the number of serious infections between the GOL and placebo groups ($P = 0.3$). There were no patients experiencing tuberculosis in either treatment or placebo groups. There was no statistically significant difference between the number of lung infections between the GOL and placebo groups ($P = 0.1$). There was no statistically significant difference between the GOL and placebo groups ($P = 0.1$). There was no statistically significant difference between the GOL and placebo groups ($P = 0.7$) for cancer. Patients treated with GOL were 0.7 times less likely to withdraw compared to placebo. There was no statistically significant difference between the number of patients withdrawing due to inefficacy in the placebo and treatment groups ($P = 0.41$), adverse eventss $P = 0.99$.
				GOL 50 mg every 2 weeks + MTX vs.placebo + MTX: No significant differences were noted between GOL and placebo regarding serious adverse events, infections, serious infections $P = 0.97$, cancer $P = 0.5$, withdrawals due to adverse events $P = 0.97$ and inefficacy $P = 0.3$. No deaths in either group.

Study Characterist Quality Rating	tics, Study Information	Study Characteristics	Results	Adverse Events
				GOL 100 mg every 2 weeks + MTX vs.placebo + MTX: No significant differences were noted between GOL and placebo regarding serious adverse events $P = 0.7$, infections, serious infections $P = 0.5$, withdrawals due to adverse events $P = 0.3$ and inefficacy $P = 0.3$. No deaths in either group.
				GOL 100 mg every 4 weeks + placebo (oral) vs.placebo (injections) + MTX: No significant differences were noted between GOL and placebo regarding serious adverse events $P = 0.7$, infections $P = 0.3$, serious infections $P = 0.7$, withdrawals due to adverse events $P = 0.4$ and deaths $P = 0.5$. There were no inefficacy withdrawals.

Study Characteristics, Quality Rating	Study Information	Study Characteristics	Results	Adverse Events
Author, Year: Singh et al., 2010 ²²⁹	Study design: Systematic Review	Characteristics of Included Studies: All multi-center trials; RCTs (or quasi-	Study Results: All results reported for 8 mg/kg	Adverse Events: TCZ 1.2 times more likely to
Country and setting: NR	Number of Patients: 3,334	randomized trials) Characteristics of Included Populations 18 yo or older (some studies 20 yo or older); 1987 ACR criteria for RA for 6 months or more; mean age in early 50s Characteristics of Interventions:	TCZ +MTX vs. placebo +MTX. ACR50 (RR, 95% CI, TCZ vs. placebo): 3.17 (2.72 to 3.67); DAS remission (DAS<2.6): 8.74 (6.26 to 11.8); clinically significant HAQ decrease (HAQ improvement of >0.3 or MHAQ	vs. 65%); serious ADEs: 1.17 (0.83 to 1.64); withdrawals due to ADEs: 1.43 (0.95 to 2.12)
Funding: Cochrane Collaboration; NIH CTSA K12 Award	Studies Included: N = 8			
Aims of Review: To assess the efficacy and safety of TCZ in RA pts			decease >0.22): 1.79 (1.62 to 1.94)	
Quality Rating: Fair		intervention; all patients on stable dose of MTX (10-25 mg a week)		

Evidence Table 2. Systematic reviews and meta-analyses (continued)

Study Characteristics	Inclusion and Exclusion Criteria	Characteristics and Interventions	Baseline Disease and Treatment Characteristics	Health Outcomes
Author, year, country, funding: Wailoo et al., 2006 ²³⁰ AHRQ	Studies included: Disease registry (National Databank for Rheumatic Diseases)	Odds ratio of ACR50 • INF/ETN 1.17 (0.68, 2.08) • ADA/ETN 1.02 (0.54,	NR	Publication Bias Assessed: Yes
Study Design: Decision analytic model	and 6694 in 13 RCTs Characteristics of	1.97) • ADA/INF 0.87 (0.47,		Heterogeneity Assessed: NR
and meta- analysisanalysis	included studies: Treatment duration of at least 6 months	1.57)		Standard Method of Study Appraisals:
Aims of the Review: Cost effectiveness of ETN, ADA,, ANA and INF alone and in	Characteristics of included populations: Adult patients with RA			NR Comprehensive Search Strategy: Yes
sequence Number of Patients: 17,000 in disease registry (National Databank for Rheumatic Diseases) and 6694 in RCTs	Characteristics of interventions: Placebo and MTX controlled			Quality Rating: Fair

Quality Rating Study Information Study Characteristics Results	Adverse Events
Author, Year: Wiens et al., 2009 ²³¹ Country and setting: NR Funding: NR Aims of Review: To evaluate the efficacy and safety of ETN for treating RA Quality Rating: Fair Study design: Systematic review and metaanalysis Number of Patients: 2385 Studies Included: N = 8 Characteristics of Included Studies: RCTs Characteristics of Included Populations • ACR20: 55% RR, 2.94 (95) • ACR50: 26% RR, 5.28 (95) • Mean age: 47.5 to 54 yo • Mean disease duration: 0.7 to 13 years • Mean no. of previous DMARDs: 0.5 to 3.3 • Mean no. of swollen joints: 13.2 to 25 • Mean no. of 10der joints: 14 to 35 • Mean no. of 10der joints: 14 to 35 • Mean baseline HAQ score: 1.1 to 1.9 • ACR70: 34%	Adverse Events: ETN vs. control Serious AEs: RR, 0.88 (95% CI, 0.66-1.17; P = 0.38) Serious infections: RR, 0.87 (95% CI, 0.60-1.26; P = 0.57) Malignancy: RR, 1.48 (95% CI, 0.66-3.35); P = 0.32) Deaths: RR, 1.51 (95% CI, 0.34-6.63; P = 0.58)

Study Characteristics Quality Rating	, Study Information	Study Characteristics	Results	Adverse Events
Author, Year: Wiens et al., 2010 ²³²	Study design: Systematic Review	Characteristics of Included Studies:	Study Results: With short-term treatment (12-30	Adverse Events: No statistically significant
Country and setting: Multinational	Number of Patients: 6503	Characteristics of Included	wks), ETN demonstrated the highest risk ratios (RRs) for reaching ACR20 and ACR50.	differences were noted in the safety of any of the 3 drugs compared with placebo (<i>P</i> >
Funding: Brazilian National Council of Scientific and Technological Development. Aims of Review: To evaluate the efficacy and safety of using the anti-tumor necrosis factor- (anti-TNF-) drugs ADA, ETN, and INF for the treatment of rheumatoid arthritis. Quality Rating: Fair		Populations Mean age 48-57, Disease duration 0.6 to 12 yrs, prior DMARDs 0-3, Treatment duration 12-2yrs Characteristics of Interventions: Studies that compared the anti-TNF-drug with placebo, with or without concomitant MTX in both groups. From these RCTs, those that used the usual dosages for each of the anti-TNF-drugs—ADA 20 mg once/week or 40 mg every other week subcutaneously, ETN 25 mg twice/week or 50 mg once/week subcutaneously, and INF 3 mg/kg intravenously at weeks 0, 2, 6, and then every 8 weeks.	ADA demonstrated the highest RR, for achieving ACR70 ACR 20 ETN: 2.94, 95% CI: 2.27-3.81	0.05 for all parameters). INF had the highest RRs for withdrawing from the study due to lack of efficacy (2.05, 95% CI, 1.33-3.16) and adverse events (0.41, 95% CI, 0.18-0.95).

References

- Askling J, Fored CM, Brandt L, et al. Risk and case characteristics of tuberculosis in rheumatoid arthritis associated with tumor necrosis factor antagonists in Sweden. Arthritis Rheum 2005 Jul;52(7):1986-92.
- 2. Askling J, Fored CM, Brandt L, et al. Risks of solid cancers in patients with rheumatoid arthritis and after treatment with tumour necrosis factor antagonists. Ann Rheum Dis 2005 Oct;64(10):1421-6.
- 3. Askling J, Fored CM, Baecklund E, et al. Haematopoietic malignancies in rheumatoid arthritis: lymphoma risk and characteristics after exposure to tumour necrosis factor antagonists. Ann Rheum Dis 2005 Oct;64(10):1414-20.
- 4. Askling J, van Vollenhoven RF, Granath F, et al. Cancer risk in patients with rheumatoid arthritis treated with anti-tumor necrosis factor alpha therapies: does the risk change with the time since start of treatment? Arthritis Rheum 2009;60(11):3180-9.
- 5. Baecklund E, Iliadou A, Askling J, et al. Association of chronic inflammation, not its treatment, with increased lymphoma risk in rheumatoid arthritis. Arthritis Rheum 2006 Mar;54(3):692-701.
- 6. Bathon JM, Martin RW, Fleischmann RM, et al. A comparison of etanercept and methotrexate in patients with early rheumatoid arthritis. N Engl J Med 2000 Nov 30;343(22):1586-93.
- 7. Genovese MC, Bathon JM, Martin RW, et al. Etanercept versus methotrexate in patients with early rheumatoid arthritis: two-year radiographic and clinical outcomes. Arthritis Rheum 2002 Jun;46(6):1443-50.
- 8. Kosinski M, Kujawski SC, Martin R, et al. Health-related quality of life in early rheumatoid arthritis: impact of disease and treatment response. Am J Manag Care 2002 Mar;8(3):231-40.
- 9. Genovese MC, Bathon JM, Fleischmann RM, et al. Longterm safety, efficacy, and radiographic outcome with etanercept treatment in patients with early rheumatoid arthritis. J Rheumatol 2005 Jul;32(7):1232-42
- 10. Bergstrom L, Yocum DE, Ampel NM, et al. Increased risk of coccidioidomycosis in patients treated with tumor necrosis factor alpha antagonists. Arthritis Rheum 2004 Jun;50(6):1959-66.

- 11. Bernatsky S, Hudson M, Suissa S. Antirheumatic drug use and risk of serious infections in rheumatoid arthritis. Rheumatology (Oxford) 2007;46(7):1157-60.
- 12. Boers M, Verhoeven AC, Markusse HM, et al. Randomised comparison of combined step-down prednisolone, methotrexate and sulphasalazine with sulphasalazine alone in early rheumatoid arthritis. Lancet 1997 Aug 2;350(9074):309-18.
- 13. Landewe RB, Boers M, Verhoeven AC, et al. COBRA combination therapy in patients with early rheumatoid arthritis: long-term structural benefits of a brief intervention.

 Arthritis Rheum 2002 Feb;46(2):347-56.
- 14. Brassard P, Lowe AM, Bernatsky S, et al. Rheumatoid arthritis, its treatments, and the risk of tuberculosis in Quebec, Canada. Arthritis Rheum 2009;61(3):300-4.
- 15. Brassard P, Kezouh A, Suissa S. Antirheumatic drugs and the risk of tuberculosis. Clin Infect Dis 2006;43(6):717-22.
- 16. Breedveld FC, Weisman MH, Kavanaugh AF, et al. The PREMIER study: A multicenter, randomized, double-blind clinical trial of combination therapy with adalimumab plus methotrexate versus methotrexate alone or adalimumab alone in patients with early, aggressive rheumatoid arthritis who had not had previous methotrexate treatment. Arthritis Rheum 2006 Jan;54(1):26-37.
- 17. Breedveld FC, Emery P, Keystone E, et al. Infliximab in active early rheumatoid arthritis. Ann Rheum Dis 2004;63(2):149-55.
- 18. Maini RN, Breedveld FC, Kalden JR, et al. Sustained improvement over two years in physical function, structural damage, and signs and symptoms among patients with rheumatoid arthritis treated with infliximab and methotrexate. Arthritis Rheum 2004 Apr;50(4):1051-65.
- 19. Smolen JS, Han C, Bala M, et al. Evidence of radiographic benefit of treatment with infliximab plus methotrexate in rheumatoid arthritis patients who had no clinical improvement: a detailed subanalysis of data from the anti-tumor necrosis factor trial in rheumatoid arthritis with concomitant

- therapy study. Arthritis Rheum 2005;52(4):1020-30.
- 20. Brown SL, Greene MH, Gershon SK, et al. Tumor necrosis factor antagonist therapy and lymphoma development: twenty-six cases reported to the Food and Drug Administration. Arthritis Rheum 2002 Dec;46(12):3151-8.
- 21. Burmester GR, Mariette X, Montecucco C, et al. Adalimumab alone and in combination with disease-modifying antirheumatic drugs for the treatment of rheumatoid arthritis in clinical practice: the Research in Active Rheumatoid Arthritis (ReAct) trial. Ann Rheum Dis 2007:66(6):732-9.
- 22. Cannon GW, Holden WL, Juhaeri J, et al. Adverse events with disease modifying antirheumatic drugs (DMARD): a cohort study of leflunomide compared with other DMARD. J Rheumatol 2004 Oct;31(10):1906-11.
- 23. Capell H, Madhok R, Porter D, et al.
 Combination therapy with sulphasalazine
 and methotrexate is more effective than
 either drug alone in rheumatoid arthritis (ra)
 patients with a suboptimal response to
 sulphasalazine: Results from the double
 blind placebo controlled mascot study. Ann
 Rheum Dis 2007 Feb;66(2):235-41.
- 24. Chakravarty EF, Michaud K, Wolfe F. Skin cancer, rheumatoid arthritis, and tumor necrosis factor inhibitors. J Rheumatol 2005 Nov;32(11):2130-5.
- 25. Choy EH, Smith CM, Farewell V, et al. Factorial randomised controlled trial of glucocorticoids and combination disease modifying drugs in early rheumatoid arthritis. Ann Rheum Dis 2008;67(5):656-63.
- 26. Chung ES, Packer M, Lo KH, et al.
 Randomized, double-blind, placebocontrolled, pilot trial of infliximab, a
 chimeric monoclonal antibody to tumor
 necrosis factor-alpha, in patients with
 moderate-to-severe heart failure: results of
 the anti-TNF Therapy Against Congestive
 Heart Failure (ATTACH) trial. Circulation
 2003 Jul 1;107(25):3133-40.
- 27. Cohen SB, Emery P, Greenwald MW, et al. Rituximab for rheumatoid arthritis refractory to anti-tumor necrosis factor therapy: results of a multicenter, randomized, double-blind, placebo-controlled, phase III trial evaluating primary efficacy and safety at twenty-four weeks. Arthritis Rheum 2006;54(9):2793-806.

- 28. Keystone E, Burmester GR, Furie R, et al. Improvement in patient-reported outcomes in a rituximab trial in patients with severe rheumatoid arthritis refractory to anti-tumor necrosis factor therapy. Arthritis Rheum 2008:59(6):785-93.
- 29. Keystone E, Emery P, Peterfy CG, et al. Rituximab inhibits structural joint damage in patients with rheumatoid arthritis with an inadequate response to tumour necrosis factor inhibitor therapies. Ann Rheum Dis 2009;68(2):216-21.
- 30. Combe BG, Codreanu C, Fiocco U, et al. Double-blind comparison of Etanercept and Sulphasalazine, alone and combined, in patients with active rheumatoid arthritis despite receiving Sulphasalazine. Ann Rheum Dis 2006 Apr 10.
- 31. Combe B, Codreanu C, Fiocco U, et al. Efficacy, safety and patient-reported outcomes of combination etanercept and sulfasalazine versus etanercept alone in patients with rheumatoid arthritis: a double-blind randomised 2-year study. Ann Rheum Dis 2009;68(7):1146-52.
- 32. Curtis JR, Patkar N, Xie A, et al. Risk of serious bacterial infections among rheumatoid arthritis patients exposed to tumor necrosis factor alpha antagonists. Arthritis Rheum 2007;56(4):1125-33.
- 33. Curtis JR, Xi J, Patkar N, et al. Drugspecific and time-dependent risks of bacterial infection among patients with rheumatoid arthritis who were exposed to tumor necrosis factor alpha antagonists. Arthritis Rheum 2007;56(12):4226-7.
- 34. Curtis JR, Kramer JM, Martin C, et al. Heart failure among younger rheumatoid arthritis and Crohn's patients exposed to TNF-alpha antagonists. Rheumatology (Oxford) 2007;46(11):1688-93.
- 35. De Bandt M, Sibilia J, Le Loet X, et al. Systemic lupus erythematosus induced by anti-tumour necrosis factor alpha therapy: a French national survey. Arthritis Res Ther 2005;7(3):R545-51.
- 36. den Broeder AA, Creemers MC, Fransen J, et al. Risk factors for surgical site infections and other complications in elective surgery in patients with rheumatoid arthritis with special attention for anti-tumor necrosis factor: a large retrospective study. J Rheumatol 2007;34(4):689-95.
- 37. Dixon WG, Watson K, Lunt M, et al. Rates of serious infection, including site-specific and bacterial intracellular infection, in

- rheumatoid arthritis patients receiving antitumor necrosis factor therapy: Results from the British Society for Rheumatology Biologics Register. Arthritis Rheum 2006 Jul 25;54(8):2368-76.
- 38. Dixon WG, Watson KD, Lunt M, et al.
 Reduction in the incidence of myocardial
 infarction in patients with rheumatoid
 arthritis who respond to anti-tumor necrosis
 factor alpha therapy: Results from the
 British Society for Rheumatology Biologics
 Register. Arthritis and Rheumatism
 2007;56(9):2905-12.
- 39. Dixon WG, Hyrich KL, Watson KD, et al. Drug-specific risk of tuberculosis in patients with rheumatoid arthritis treated with anti-TNF therapy: results from the British Society for Rheumatology Biologics Register (BSRBR). Ann Rheum Dis 2010;69(3):522-8.
- 40. Doran MF, Crowson CS, Pond GR, et al. Predictors of infection in rheumatoid arthritis. Arthritis Rheum 2002 Sep;46(9):2294-300.
- 41. Dougados M, Combe B, Cantagrel A, et al. Combination therapy in early rheumatoid arthritis: a randomised, controlled, double blind 52 week clinical trial of sulphasalazine and methotrexate compared with the single components. Ann Rheum Dis 1999;58(4):220-5.
- 42. Maillefert JF, Combe B, Goupille P, et al. Long term structural effects of combination therapy in patients with early rheumatoid arthritis: five year follow up of a prospective double blind controlled study. Ann Rheum Dis 2003:62(8):764-6.
- 43. Duclos M, Gossec L, Ruyssen-Witrand A, et al. Retention rates of tumor necrosis factor blockers in daily practice in 770 rheumatic patients. J Rheumatol 2006;33(12):2433-8.
- 44. Edwards CJ, Cooper C, Fisher D, et al. The importance of the disease process and disease-modifying antirheumatic drug treatment in the development of septic arthritis in patients with rheumatoid arthritis. Arthritis Rheum 2007;57(7):1151-7.
- 45. Emery P, Breedveld FC, Lemmel EM, et al. A comparison of the efficacy and safety of leflunomide and methotrexate for the treatment of rheumatoid arthritis.

 Rheumatology (Oxford) 2000;39(6):655-65.
- 46. Emery P, Fleischmann R, Filipowicz-Sosnowska A, et al. The efficacy and safety of rituximab in patients with active rheumatoid arthritis despite methotrexate

- treatment results of a phase IIb randomized, double-blind, placebocontrolled, dose-ranging trial. Arthritis Rheum 2006 May 1;54(May):1390-400.
- 47. Emery P, Kosinski M, Li T, et al. Treatment of rheumatoid arthritis patients with abatacept and methotrexate significantly improved health-related quality of life. J Rheumatol 2006 04/01/;33(Apr):681-9.
- 48. Emery P, Breedveld FC, Hall S, et al. Comparison of methotrexate monotherapy with a combination of methotrexate and etanercept in active, early, moderate to severe rheumatoid arthritis (COMET): a randomised, double-blind, parallel treatment trial. Lancet 2008;372(9636):375-82.
- 49. Emery P, Keystone E, Tony HP, et al. IL-6 receptor inhibition with tocilizumab improves treatment outcomes in patients with rheumatoid arthritis refractory to antitumour necrosis factor biologicals: results from a 24-week multicentre randomised placebo-controlled trial. Ann Rheum Dis 2008;67(11):1516-23.
- 50. Emery P, Fleischmann RM, Moreland LW, et al. Golimumab, a human anti-tumor necrosis factor alpha monoclonal antibody, injected subcutaneously every four weeks in methotrexate-naive patients with active rheumatoid arthritis: twenty-four-week results of a phase III, multicenter, randomized, double-blind, placebocontrolled study of golimumab before methotrexate as first-line therapy for early-onset rheumatoid arthritis. Arthritis Rheum 2009:60(8):2272-83.
- 51. Emery P, Breedveld F, van der Heijde D, et al. Two-year clinical and radiographic results with combination etanerceptmethotrexate therapy versus monotherapy in early rheumatoid arthritis: a two-year, double-blind, randomized study. Arthritis Rheum 2010;62(3):674-82.
- 52. Emery P, Deodhar A, Rigby WF, et al. Efficacy and safety of different doses and retreatment of rituximab: a randomised, placebo-controlled trial in patients who are biological naive with active rheumatoid arthritis and an inadequate response to methotrexate (Study Evaluating Rituximab's Efficacy in MTX iNadequate rEsponders (SERENE)). Ann Rheum Dis 2010;69(9):1629-35.
- 53. Feltelius N, Fored CM, Blomqvist P, et al. Results from a nationwide postmarketing cohort study of patients in Sweden treated

- with etanercept. Ann Rheum Dis 2005 Feb;64(2):246-52.
- 54. Fernandez-Nebro A, Irigoyen MV, Urena I, et al. Effectiveness, predictive response factors, and safety of anti-tumor necrosis factor (TNF) therapies in anti-TNF-naive rheumatoid arthritis. J Rheumatol 2007;34(12):2334-42.
- 55. Finckh A, Ciurea A, Brulhart L, et al. B cell depletion may be more effective than switching to an alternative anti-tumor necrosis factor agent in rheumatoid arthritis patients with inadequate response to anti-tumor necrosis factor agents. Arthritis Rheum 2007;56(5):1417-23.
- 56. Finckh A, Dehler S, Gabay C. The effectiveness of leflunomide as a co-therapy of tumour necrosis factor inhibitors in rheumatoid arthritis: a population-based study. Ann Rheum Dis 2009;68(1):33-9.
- 57. Fleischmann RM, Schechtman J, Bennett R, et al. Anakinra, a recombinant human interleukin-1 receptor antagonist (rmetHuIL-1ra), in patients with rheumatoid arthritis: A large, international, multicenter, placebo-controlled trial. Arthritis Rheum 2003 Apr;48(4):927-34.
- 58. Tesser J, Fleischmann R, Dore R, et al.
 Concomitant medication use in a large,
 international, multicenter, placebo
 controlled trial of anakinra, a recombinant
 interleukin 1 receptor antagonist, in patients
 with rheumatoid arthritis. J Rheumatol
 2004;31(4):649-54.
- 59. Schiff MH, DiVittorio G, Tesser J, et al. The safety of anakinra in high-risk patients with active rheumatoid arthritis: six-month observations of patients with comorbid conditions. Arthritis Rheum 2004
 Jun;50(6):1752-60.
- 60. Fleischmann RM, Tesser J, Schiff MH, et al. Safety of extended treatment with anakinra in patients with rheumatoid arthritis. Ann Rheum Dis 2006 Aug;65(8):1006-12.
- 61. Fleischmann R, Vencovsky J, van Vollenhoven RF, et al. Efficacy and safety of certolizumab pegol monotherapy every 4 weeks in patients with rheumatoid arthritis failing previous disease-modifying antirheumatic therapy: the FAST4WARD study. Ann Rheum Dis 2009 Jun;68(6):805-11
- 62. Flendrie M, Creemers MC, Welsing PM, et al. Survival during treatment with tumour necrosis factor blocking agents in

- rheumatoid arthritis. Ann Rheum Dis 2003 Nov;62 Suppl 2:ii30-3.
- 63. Flendrie M, Vissers WH, Creemers MC, et al. Dermatological conditions during TNF-alpha-blocking therapy in patients with rheumatoid arthritis: a prospective study. Arthritis Res Ther 2005;7(3):R666-76.
- 64. Fuerst M, Mohl H, Baumgartel K, et al. Leflunomide increases the risk of early healing complications in patients with rheumatoid arthritis undergoing elective orthopedic surgery. Rheumatol Int 2006;26(12):1138-42.
- 65. Furst DE, Schiff MH, Fleischmann RM, et al. Adalimumab, a fully human anti tumor necrosis factor-alpha monoclonal antibody, and concomitant standard antirheumatic therapy for the treatment of rheumatoid arthritis: results of STAR (Safety Trial of Adalimumab in Rheumatoid Arthritis). J Rheumatol 2003 Dec;30(12):2563-71.
- 66. Galloway JB, Hyrich KL, Mercer LK, et al. Anti-TNF therapy is associated with an increased risk of serious infections in patients with rheumatoid arthritis especially in the first 6 months of treatment: updated results from the British Society for Rheumatology Biologics Register with special emphasis on risks in the elderly. Rheumatology (Oxford, England) 2011;50(1):124-31.
- 67. Geborek P, Crnkic M, Petersson IF, et al. Etanercept, infliximab, and leflunomide in established rheumatoid arthritis: clinical experience using a structured follow up programme in southern Sweden. Ann Rheum Dis 2002 Sep;61(9):793-8.
- 68. Geborek P, Bladstrom A, Turesson C, et al. Tumour necrosis factor blockers do not increase overall tumour risk in patients with rheumatoid arthritis, but may be associated with an increased risk of lymphomas. Ann Rheum Dis 2005 May;64(5):699-703.
- 69. Genovese MC, Cohen S, Moreland L, et al. Combination therapy with etanercept and anakinra in the treatment of patients with rheumatoid arthritis who have been treated unsuccessfully with methotrexate. Arthritis Rheum 2004 May;50(5):1412-9.
- 70. Genovese MC, McKay JD, Nasonov EL, et al. Interleukin-6 receptor inhibition with tocilizumab reduces disease activity in rheumatoid arthritis with inadequate response to disease-modifying antirheumatic drugs: the tocilizumab in combination with traditional disease-modifying antirheumatic

- drug therapy study. Arthritis and Rheumatism 2008;58(10):2968-80.
- 71. Goekoop-Ruiterman YP, de Vries-Bouwstra JK, Allaart CF, et al. Clinical and radiographic outcomes of four different treatment strategies in patients with early rheumatoid arthritis (the BeSt study): a randomized, controlled trial. Arthritis Rheum 2005 Nov;52(11):3381-90.
- 72. Allaart CF, Goekoop-Ruiterman YP, de Vries-Bouwstra JK, et al. Aiming at low disease activity in rheumatoid arthritis with initial combination therapy or initial monotherapy strategies: the BeSt study. Clin Exp Rheumatol 2006 Nov-Dec;24(6 Suppl 43):S-77-82.
- 73. Goekoop-Ruiterman YPM, De Vries-Bouwstra JK, Allaart CF, et al. Comparison of treatment strategies in early rheumatoid arthritis: a randomized trial. Ann Intern Med 2007;146(6):406-15.
- 74. van der Kooij SM, de Vries-Bouwstra JK, Goekoop-Ruiterman YP, et al. Patientreported outcomes in a randomized trial comparing four different treatment strategies in recent-onset rheumatoid arthritis. Arthritis Rheum 2009 Jan 15;61(1):4-12.
- 75. van der Kooij SM, Goekoop-Ruiterman YP, de Vries-Bouwstra JK, et al. Drug-free remission, functioning and radiographic damage after 4 years of response-driven treatment in patients with recent-onset rheumatoid arthritis. Ann Rheum Dis 2009:68(6):914-21.
- 76. Gomez-Reino JJ, Carmona L, Valverde VR, et al. Treatment of rheumatoid arthritis with tumor necrosis factor inhibitors may predispose to significant increase in tuberculosis risk: a multicenter active-surveillance report. Arthritis Rheum 2003 Aug;48(8):2122-7.
- 77. Greenberg JD, Reed G, Kremer JM, et al. Association of methotrexate and tumour necrosis factor antagonists with risk of infectious outcomes including opportunistic infections in the CORRONA registry. Ann Rheum Dis 2010;69(2):380-6.
- 78. Grijalva CG, Chung CP, Arbogast PG, et al. Assessment of adherence to and persistence on disease-modifying antirheumatic drugs (DMARDs) in patients with rheumatoid arthritis. Med Care 2007;45(10 Supl 2):S66-76.
- 79. Grijalva CG, Kaltenbach L, Arbogast PG, et al. Initiation of rheumatoid arthritis

- treatments and the risk of serious infections. Rheumatology (Oxford) 2010;4982-90.
- 80. Haagsma CJ, van Riel PL, de Jong AJ, et al. Combination of sulphasalazine and methotrexate versus the single components in early rheumatoid arthritis: a randomized, controlled, double-blind, 52 week clinical trial. Br J Rheumatol 1997;36(10):1082-8.
- 81. Harley CR, Frytak JR, Tandon N. Treatment compliance and dosage administration among rheumatoid arthritis patients receiving infliximab, etanercept, or methotrexate. Am J Manag Care 2003 Oct:9(6 Suppl):S136-43.
- 82. Harrison MJ, Dixon WG, Watson KD, et al. Rates of new-onset psoriasis in patients with rheumatoid arthritis receiving anti-tumour necrosis factor alpha therapy: results from the British Society for Rheumatology Biologics Register. Ann Rheum Dis 2009;68(2):209-15.
- 83. Hetland ML, Christensen IJ, Tarp U, et al. Direct comparison of treatment responses, remission rates, and drug adherence in patients with rheumatoid arthritis treated with adalimumab, etanercept, or infliximab results from eight years of surveillance of clinical practice in the Nationwide Danish DANBIO Registry. Arthritis Rheum 2010;62(1):22-32.
- 84. Hjardem E, Ostergaard M, Podenphant J, et al. Do rheumatoid arthritis patients in clinical practice benefit from switching from infliximab to a second tumor necrosis factor alpha inhibitor? Ann Rheum Dis 2007;66(9):1184-9.
- 85. Hoff M, Kvien TK, Kalvesten J, et al. Adalimumab therapy reduces hand bone loss in early rheumatoid arthritis: explorative analyses from the PREMIER study. Ann Rheum Dis 2009;68(7):1171-6.
- 86. Hyrich KL, Symmons DP, Watson KD, et al. Comparison of the response to infliximab or etanercept monotherapy with the response to cotherapy with methotrexate or another disease-modifying antirheumatic drug in patients with rheumatoid arthritis: Results from the British Society for Rheumatology Biologics Register. Arthritis Rheum 2006 May 30;54(6):1786-94.
- 87. Hyrich KL, Watson KD, Silman AJ, et al. Predictors of response to anti-TNF-alpha therapy among patients with rheumatoid arthritis: results from the British Society for Rheumatology Biologics Register. Rheumatology 2006;45(Dec):1558-65.

- 88. Hyrich KL, Lunt M, Watson KD, et al. Outcomes after switching from one antitumor necrosis factor alpha agent to a second anti-tumor necrosis factor alpha agent in patients with rheumatoid arthritis: results from a large UK national cohort study. Arthritis Rheum 2007;56(1):13-20.
- 89. Jacobsson LT, Turesson C, Gulfe A, et al. Treatment with tumor necrosis factor blockers is associated with a lower incidence of first cardiovascular events in patients with rheumatoid arthritis. J Rheumatol 2005 Jul;32(7):1213-8.
- 90. Karanikolas G, Charalambopoulos D,
 Vaiopoulos G, et al. Adjunctive anakinra in
 patients with active rheumatoid arthritis
 despite methotrexate, or leflunomide, or
 cyclosporin-A monotherapy: a 48-week,
 comparative, prospective study.
 Rheumatology (Oxford) 2008;47(9):1384-8.
- 91. Kavanaugh A, Klareskog L, van der Heijde D, et al. Improvements in clinical response between 12 and 24 weeks in patients with rheumatoid arthritis on etanercept therapy with or without methotrexate. Ann Rheum Dis 2008;67(10):1444-7.
- 92. Klareskog L, van der Heijde D, de Jager JP, et al. Therapeutic effect of the combination of etanercept and methotrexate compared with each treatment alone in patients with rheumatoid arthritis: double-blind randomised controlled trial. Lancet 2004 Feb 28;363(9410):675-81.
- 93. Kay J, Matteson EL, Dasgupta B, et al. Golimumab in patients with active rheumatoid arthritis despite treatment with methotrexate: a randomized, double-blind, placebo-controlled, dose-ranging study. Arthritis Rheum 2008;58(4):964-75.
- 94. Keane J, Gershon S, Wise RP, et al. Tuberculosis associated with infliximab, a tumor necrosis factor alpha-neutralizing agent. N Engl J Med 2001 Oct 11;345(15):1098-104.
- 95. Keystone E, Heijde D, Mason D, Jr., et al. Certolizumab pegol plus methotrexate is significantly more effective than placebo plus methotrexate in active rheumatoid arthritis: findings of a fifty-two-week, phase III, multicenter, randomized, double-blind, placebo-controlled, parallel-group study. Arthritis Rheum 2008;58(11):3319-29.
- 96. Keystone E, Freundlich B, Schiff M, et al. Patients with moderate rheumatoid arthritis (RA) achieve better disease activity states

- with etanercept treatment than patients with severe RA. J Rheumatol 2009;36(3):522-31.
- 97. Keystone EC, Genovese MC, Klareskog L, et al. Golimumab, a human antibody to tumour necrosis factor {alpha} given by monthly subcutaneous injections, in active rheumatoid arthritis despite methotrexate therapy: the GO-FORWARD Study. Ann Rheum Dis 2009;68(6):789-96.
- 98. Keystone E, Genovese MC, Klareskog L, et al. Golimumab in patients with active rheumatoid arthritis despite methotrexate therapy: 52-week results of the GO-FORWARD study. Annals of the rheumatic diseases 2010(6):1129-35.
- 99. Kievit W, Adang EM, Fransen J, et al. The effectiveness and medication costs of three anti-tumour necrosis factor alpha agents in the treatment of rheumatoid arthritis from prospective clinical practice data. Ann Rheum Dis 2008;67(9):1229-34.
- 100. Kim HY, Lee SK, Song YW, et al. A randomized, double-blind, placebo-controlled, phase III study of the human anti-tumor necrosis factor antibody adalimumab administered as subcutaneous injections in Korean rheumatoid arthritis patients treated with methotrexate. APLAR J Rheumatol 2007;10(1):9-16.
- 101. Kirwan JR, Hallgren R, Mielants H, et al. A randomised placebo controlled 12 week trial of budesonide and prednisolone in rheumatoid arthritis. Ann Rheum Dis 2004;63(6):688-95.
- 102. van der Heijde D, Klareskog L, Boers M, et al. Comparison of different definitions to classify remission and sustained remission: 1 year TEMPO results. Ann Rheum Dis 2005 Nov;64(11):1582-7.
- 103. van der Heijde D, Klareskog L, Singh A, et al. Patient reported outcomes in a trial of combination therapy with etanercept and methotrexate for rheumatoid arthritis: the TEMPO trial. Ann Rheum Dis 2006 Mar;65(3):328-34.
- 104. van der Heijde D, Klareskog L, Rodriguez-Valverde V, et al. Comparison of etanercept and methotrexate, alone and combined, in the treatment of rheumatoid arthritis: two-year clinical and radiographic results from the TEMPO study, a double-blind, randomized trial. Arthritis Rheum 2006 Apr;54(4):1063-74.
- 105. Kremer JM, Genovese MC, Cannon GW, et al. Concomitant leflunomide therapy in patients with active rheumatoid arthritis

- despite stable doses of methotrexate. A randomized, double-blind, placebo-controlled trial. Ann Intern Med 2002;137(9):726-33.
- 106. Kremer JL, Blanco R, Brzosko M, et al.
 Tocilizumab inhibits structural joint damage
 in rheumatoid arthritis patients with
 inadequate responses to methotrexate at 1
 year: The LITHE study. Arthritis Rheum
 2010.
- 107. Kristensen LE, Saxne T, Geborek P. The LUNDEX, a new index of drug efficacy in clinical practice: results of a five-year observational study of treatment with infliximab and etanercept among rheumatoid arthritis patients in southern Sweden.

 Arthritis Rheum 2006 Feb;54(2):600-6.
- 108. Kristensen LE, Saxne T, Nilsson JA, et al. Impact of concomitant DMARD therapy on adherence to treatment with etanercept and infliximab in rheumatoid arthritis. Results from a six-year observational study in southern Sweden. Arthritis Res Ther 2006;8(6):R174.
- 109. Kristensen LE, Christensen R, Bliddal H, et al. The number needed to treat for adalimumab, etanercept, and infliximab based on ACR50 response in three randomized controlled trials on established rheumatoid arthritis: A systematic literature review. Scandinavian Journal of Rheumatology 2007;36(6):411-7.
- 110. Lacaille D, Guh DP, Abrahamowicz M, et al. Use of nonbiologic disease-modifying antirheumatic drugs and risk of infection in patients with rheumatoid arthritis. Arthritis Rheum 2008;59(8):1074-81.
- 111. Langer HE, Missler-Karger B. Kineret: efficacy and safety in daily clinical practice: an interim analysis of the Kineret response assessment initiative (kreative) protocol. Int J Clin Pharmacol Res 2003;23(4):119-28.
- 112. Lebwohl M, Blum R, Berkowitz E, et al. No evidence for increased risk of cutaneous squamous cell carcinoma in patients with rheumatoid arthritis receiving etanercept for up to 5 years. Arch Dermatol 2005 Jul;141(7):861-4.
- 113. Lee JH, Slifman NR, Gershon SK, et al. Life-threatening histoplasmosis complicating immunotherapy with tumor necrosis factor alpha antagonists infliximab and etanercept. Arthritis Rheum 2002 Oct;46(10):2565-70.
- 114. Lee YH, Woo JH, Rho YH, et al. Metaanalysis of the combination of TNF

- inhibitors plus MTX compared to MTX monotherapy, and the adjusted indirect comparison of TNF inhibitors in patients suffering from active rheumatoid arthritis. Rheumatology international 2008;28(6):553-9
- 115. Li T, Gignac M, Wells G, et al. Decreased external home help use with improved clinical status in rheumatoid arthritis: an exploratory analysis of the Abatacept in Inadequate responders to Methotrexate (AIM) trial. Clin Ther 2008;30(4):734-48.
- 116. Kremer JM, Genant HK, Moreland LW, et al. Effects of abatacept in patients with methotrexate-resistant active rheumatoid arthritis a randomized trial. Ann Intern Med 2006 Dec:144:865-76.
- 117. Li P, Blum MA, Von Feldt J, et al. Adherence, discontinuation, and switching of biologic therapies in medicaid enrollees with rheumatoid arthritis. Value Health 2010;13(6):805-12.
- Listing J, Strangfeld A, Kary S, et al.Infections in patients with rheumatoid arthritis treated with biologic agents.Arthritis Rheum 2005 Nov;52(11):3403-12.
- 119. Listing J, Strangfeld A, Rau R, et al. Clinical and functional remission: even though biologics are superior to conventional DMARDs overall success rates remain low-results from RABBIT, the German biologics register. Arthritis Res Ther 2006;8(3):R66.
- 120. Listing J, Strangfeld A, Kekow J, et al. Does tumor necrosis factor alpha inhibition promote or prevent heart failure in patients with rheumatoid arthritis? Arthritis Rheum 2008;58(3):667-77.
- 121. Maini RN, Taylor PC, Szechinski J, et al. Double-blind randomized controlled clinical trial of the interleukin-6 receptor antagonist, tocilizumab, in European patients with rheumatoid arthritis who had an incomplete response to methotrexate. Arthritis Rheum 2006;54(9):2817-29.
- 122. Malysheva OA, Wahle M, Wagner U, et al. Low-dose prednisolone in rheumatoid arthritis: adverse effects of various disease modifying antirheumatic drugs. J Rheumatol 2008;35(6):979-85.
- 123. Marchesoni A, Zaccara E, Gorla R, et al. TNF-alpha antagonist survival rate in a cohort of rheumatoid arthritis patients observed under conditions of standard clinical practice. Ann N Y Acad Sci 2009;1173837-46.

- 124. McDonald JR, Zeringue AL, Caplan L, et al. Herpes zoster risk factors in a national cohort of veterans with rheumatoid arthritis. Clin Infect Dis 2009;48(10):1364-71.
- 125. Mease PJ, Revicki DA, Szechinski J, et al. Improved health-related quality of life for patients with active rheumatoid arthritis receiving rituximab: results of the Dose-Ranging Assessment: International Clinical Evaluation of Rituximab in Rheumatoid Arthritis (DANCER) Trial. J Rheumatol 2008;35(1):20-30.
- 126. Michaud K, Wolfe F. The association of rheumatoid arthritis and its treatment with sinus disease. J Rheumatol 2006;33(12):2412-5.
- 127. Migliore A, Bizzi E, Lagana B, et al. The safety of anti-TNF agents in the elderly. Int J Immunopathol Pharmacol 2009;22(2):415-26.
- 128. Miyasaka N. Clinical investigation in highly disease-affected rheumatoid arthritis patients in Japan with adalimumab applying standard and general evaluation: the CHANGE study. Mod Rheumatol 2008;18(3):252-62.
- 129. Mohan N, Edwards ET, Cupps TR, et al. Demyelination occurring during anti-tumor necrosis factor alpha therapy for inflammatory arthritides. Arthritis Rheum 2001 Dec;44(12):2862-9.
- 130. Mohan AK, Cote TR, Block JA, et al.
 Tuberculosis following the use of
 etanercept, a tumor necrosis factor inhibitor.
 Clin Infect Dis 2004 Aug 1;39(3):295-9.
- 131. Mottonen T, Hannonen P, Leirisalo-Repo M, et al. Comparison of Combination Therapy With Single-Drug Therapy in Early Rheumatoid Arthritis: a Randomised Trial. Lancet 1999:353(9164):1568-73.
- 132. Korpela M, Laasonen L, Hannonen P, et al. Retardation of joint damage in patients with early rheumatoid arthritis by initial aggressive treatment with disease-modifying antirheumatic drugs: five-year experience from the Fin-Raco Study. Arthritis Rheum 2004;50(7):2072-81.
- 133. Puolakka K, Kautiainen H, Mottonen T, et al. Impact of initial aggressive drug treatment with a combination of disease-modifying antirheumatic drugs on the development of work disability in early rheumatoid arthritis: a five-year randomized followup trial. Arthritis Rheum 2004;50(1):55-62.
- 134. Mottonen T, Hannonen P, Korpela M, et al. Delay to Institution of Therapy and

- Induction of Remission Using Single-Drug or Combination-Disease-Modifying Antirheumatic Drug Therapy in Early Rheumatoid Arthritis. Arthritis Rheum 2002;46(4):894-8.
- 135. Nadareishvili Z, Michaud K, Hallenbeck JM, et al. Cardiovascular, rheumatologic, and pharmacologic predictors of stroke in patients with rheumatoid arthritis: a nested, case-control study. Arthritis Rheum 2008;59(8):1090-6.
- 136. Naranjo A, Sokka T, Descalzo MA, et al. Cardiovascular disease in patients with rheumatoid arthritis: results from the QUEST-RA study. Arthritis Res Ther 2008;10(2):R30.
- 137. Nishimoto N, Miyasaka N, Yamamoto K, et al. Study of active controlled tocilizumab monotherapy for rheumatoid arthritis patients with an inadequate response to methotrexate (SATORI): significant reduction in disease activity and serum vascular endothelial growth factor by IL-6 receptor inhibition therapy. Mod Rheumatol 2009;19(1):12-9.
- 138. Nuki G, Bresnihan B, Bear MB, et al. Long-term safety and maintenance of clinical improvement following treatment with anakinra (recombinant human interleukin-1 receptor antagonist) in patients with rheumatoid arthritis: extension phase of a randomized, double-blind, placebo-controlled trial. Arthritis Rheum 2002 Nov;46(11):2838-46.
- 139. O'Dell JR, Haire CE, Erikson N, et al. Treatment of rheumatoid arthritis with methotrexate alone, sulfasalazine and hydroxychloroquine, or a combination of all three medications. N Engl J Med 1996 May 16;334(20):1287-91.
- 140. O'Dell JR, Leff R, Paulsen G, et al.
 Treatment of rheumatoid arthritis with
 methotrexate and hydroxychloroquine,
 methotrexate and sulfasalazine, or a
 combination of the three medications:
 results of a two-year, randomized, doubleblind, placebo-controlled trial. Arthritis
 Rheum 2002;46(5):1164-70.
- 141. O'Dell JR, Petersen K, Leff R, et al. Etanercept in combination with sulfasalazine, hydroxychloroquine, or gold in the treatment of rheumatoid arthritis. J Rheumatol 2006 Feb:33(2):213-8.
- 142. Osiri M, Shea B, Robinson V, et al. Leflunomide for treating rheumatoid

- arthritis. Cochrane Database Syst Rev 2002(3):CD002047.
- 143. Pallavicini FB, Caporali R, Sarzi-Puttini P, et al. Tumour necrosis factor antagonist therapy and cancer development: analysis of the LORHEN registry. Autoimmun Rev 2010;9(3):175-80.
- 144. Pan SM, Dehler S, Ciurea A, et al.
 Comparison of drug retention rates and
 causes of drug discontinuation between antitumor necrosis factor agents in rheumatoid
 arthritis. Arthritis Rheum 2009;61(5):560-8.
- 145. Russell AS, Wallenstein GV, Li T, et al. Abatacept improves both the physical and mental health of patients with rheumatoid arthritis who have inadequate response to methotrexate treatment. Ann Rheum Dis 2007 Feb;66(2):189-94.
- 146. Saag KG, Koehnke R, Caldwell JR, et al. Low dose long-term corticosteroid therapy in rheumatoid arthritis: an analysis of serious adverse events. Am J Med 1994 Feb;96(2):115-23.
- 147. Salliot C, Gossec L, Ruyssen-Witrand A, et al. Infections during tumour necrosis factor-{alpha} blocker therapy for rheumatic diseases in daily practice: a systematic retrospective study of 709 patients. Rheumatology (Oxford) 2007 July 31, 2006;46(2):327-34.
- 148. Schaible TF. Long term safety of infliximab. Can J Gastroenterol 2000 Sep;14(Suppl C):29C-32C.
- 149. Schiff MH, Burmester GR, Kent JD, et al. Safety analyses of adalimumab (HUMIRA) in global clinical trials and US postmarketing surveillance of patients with rheumatoid arthritis. Ann Rheum Dis 2006 Jul;65(7):889-94.
- 150. Schiff M, Keiserman M, Codding C, et al. Efficacy and safety of abatacept or infliximab vs placebo in ATTEST: a phase III, multi-centre, randomised, double-blind, placebo-controlled study in patients with rheumatoid arthritis and an inadequate response to methotrexate. Ann Rheum Dis 2008:67(8):1096-103.
- 151. Schipper LG, Fransen J, Barrera P, et al. Methotrexate therapy in rheumatoid arthritis after failure to sulphasalazine: to switch or to add? Rheumatology (Oxford) 2009;48(10):1247-53.
- 152. Schneeweiss S, Setoguchi S, Weinblatt ME, et al. Anti-tumor necrosis factor alpha therapy and the risk of serious bacterial infections in elderly patients with

- rheumatoid arthritis. Arthritis Rheum 2007;56(6):1754-64.
- 153. Setoguchi S, Solomon DH, Weinblatt ME, et al. Tumor necrosis factor alpha antagonist use and cancer in patients with rheumatoid arthritis. Arthritis Rheum 2006 Sep;54(9):2757-64.
- 154. Setoguchi S, Schneeweiss S, Avorn J, et al. Tumor necrosis factor-alpha antagonist use and heart failure in elderly patients with rheumatoid arthritis. Am Heart J 2008;156(2):336-41.
- 155. Shin IS, Baer AN, Kwon HJ, et al. Guillain-Barre and Miller Fisher syndromes occurring with tumor necrosis factor alpha antagonist therapy. Arthritis Rheum 2006 May:54(5):1429-34.
- 156. Slifman NR, Gershon SK, Lee JH, et al. Listeria monocytogenes infection as a complication of treatment with tumor necrosis factor alpha-neutralizing agents. Arthritis Rheum 2003 Feb;48(2):319-24.
- 157. Smitten AL, Choi HK, Hochberg MC, et al. The risk of herpes zoster in patients with rheumatoid arthritis in the United States and the United Kingdom. Arthritis Rheum 2007;57(8):1431-8.
- 158. Smitten AL, Choi HK, Hochberg MC, et al. The risk of hospitalized infection in patients with rheumatoid arthritis. J Rheumatol 2008;35(3):387-93.
- 159. Smolen JS, Kalden JR, Scott DL, et al. Efficacy and safety of leflunomide compared with placebo and sulphasalazine in active rheumatoid arthritis: a doubleblind, randomised, multicentre trial. Lancet 1999;353(9149):259-66.
- 160. Smolen JS. Efficacy and safety of the new DMARD leflunomide: comparison to placebo and sulfasalazine in active rheumatoid arthritis. Scand J Rheumatol 1999;112(Supplement):15-21.
- 161. Sharp JT, Strand V, Leung H, et al.
 Treatment with leflunomide slows
 radiographic progression of rheumatoid
 arthritis: results from three randomized
 controlled trials of leflunomide in patients
 with active rheumatoid arthritis. Arthritis
 Rheum 2000;43(3):495-505.
- 162. Larsen A, Kvien TK, Schattenkirchner M, et al. Slowing of disease progression in rheumatoid arthritis patients during long-term treatment with leflunomide or sulfasalazine. Scand J Rheumatol 2001;30(3):135-42.

- 163. Scott DL, Smolen JS, Kalden JR, et al.
 Treatment of active rheumatoid arthritis
 with leflunomide: two year follow up of a
 double blind, placebo controlled trial versus
 sulfasalazine. Ann Rheum Dis
 2001:60(10):913-23.
- 164. Smolen JS, Beaulieu A, Rubbert-Roth A, et al. Effect of interleukin-6 receptor inhibition with tocilizumab in patients with rheumatoid arthritis (OPTION study): a double-blind, placebo-controlled, randomised trial. Lancet 2008;371(9617):987-97.
- 165. Smolen J, Landewe RB, Mease P, et al. Efficacy and safety of certolizumab pegol plus methotrexate in active rheumatoid arthritis: the RAPID 2 study. A randomised controlled trial. Ann Rheum Dis 2009;68(6):797-804.
- 166. Smolen JS, Han C, van der Heijde DM, et al. Radiographic changes in rheumatoid arthritis patients attaining different disease activity states with methotrexate monotherapy and infliximab plus methotrexate: the impacts of remission and tumour necrosis factor blockade. Ann Rheum Dis 2009;68(6):823-7.
- 167. Smolen JS, Kay J, Doyle MK, et al. Golimumab in patients with active rheumatoid arthritis after treatment with tumour necrosis factor alpha inhibitors (GO-AFTER study): a multicentre, randomised, double-blind, placebo-controlled, phase III trial. Lancet 2009;374(9685):210-21.
- 168. Sokolove J, Strand V, Greenberg JD, et al. Risk of elevated liver enzymes associated with TNF inhibitor utilisation in patients with rheumatoid arthritis. Ann Rheum Dis 2010;69(9):1612-7.
- 169. Solomon DH, Avorn J, Katz JN, et al. Immunosuppressive medications and hospitalization for cardiovascular events in patients with rheumatoid arthritis. Arthritis Rheum 2006 12/01/;54(Dec):3790-8.
- 170. St Clair EW, van der Heijde DM, Smolen JS, et al. Combination of infliximab and methotrexate therapy for early rheumatoid arthritis: a randomized, controlled trial. Arthritis Rheum 2004 Nov;50(11):3432-43.
- 171. Smolen JS, Han C, van der Heijde D, et al. Infliximab treatment maintains employability in patients with early rheumatoid arthritis. Arthritis Rheum 2006 Mar;54(3):716-22.
- 172. Strand V, Cohen S, Schiff M, et al.

 Treatment of active rheumatoid arthritis with leflunomide compared with placebo

- and methotrexate. Arch Intern Med 1999;159(21):2542-50.
- 173. Strand V, Tugwell P, Bombardier C, et al. Function and health-related quality of life: results from a randomized controlled trial of leflunomide versus methotrexate or placebo in patients with active rheumatoid arthritis. Leflunomide Rheumatoid Arthritis Investigators Group. Arthritis Rheum 1999 Sep;42(9):1870-8.
- 174. Cohen S, Cannon G, Schiff M, et al. Twoyear, blinded, randomized, controlled trial of treatment of active rheumatoid arthritis with leflunomide compared with methotrexate. Utilization of leflunomide in the treatment of rheumatoid arthritis. Arthritis Rheum 2001;44(9):1984-92.
- 175. Strand V, Balbir-Gurman A, Pavelka K, et al. Sustained benefit in rheumatoid arthritis following one course of rituximab: improvements in physical function over 2 years. Rheumatology (Oxford) 2006;45(12):1505-13.
- 176. Strangfeld A, Listing J, Herzer P, et al. Risk of herpes zoster in patients with rheumatoid arthritis treated with anti-TNF-alpha agents. Jama 2009;301(7):737-44.
- 177. Strangfeld A, Hierse F, Rau R, et al. Risk of incident or recurrent malignancies among patients with rheumatoid arthritis exposed to biologic therapy in the German biologics register RABBIT. Arthritis Res Ther 2010;12(1):R5.
- 178. Suissa S, Ernst P, Hudson M, et al. Newer disease-modifying antirheumatic drugs and the risk of serious hepatic adverse events in patients with rheumatoid arthritis. Am J Med 2004 Jul 15;117(2):87-92.
- 179. Suissa S, Hudson M, Ernst P. Leflunomide use and the risk of interstitial lung disease in rheumatoid arthritis. Arthritis Rheum 2006 May;54(5):1435-9.
- 180. Suissa S, Bernatsky S, Hudson M.
 Antirheumatic drug use and the risk of acute myocardial infarction. Arthritis Rheum 2006;55(4):531-6.
- 181. Svensson B, Ahlmen M, Forslind K.
 Treatment of early RA in clinical practice: a comparative study of two different DMARD/corticosteroid options. Clin Exp Rheumatol 2003 May-Jun;21(3):327-32.
- 182. Svensson B, Boonen A, Albertsson K, et al. Low-dose prednisolone in addition to the initial disease-modifying antirheumatic drug in patients with early active rheumatoid arthritis reduces joint destruction and

- increases the remission rate: a two-year randomized trial. Arthritis Rheum 2005;52(11):3360-70.
- 183. van Halm VP, Nurmohamed MT, Twisk JW, et al. Disease-modifying antirheumatic drugs are associated with a reduced risk for cardiovascular disease in patients with rheumatoid arthritis: a case control study. Arthritis Res Ther 2006;8(5):R151.
- 184. van Riel PL, Taggart AJ, Sany J, et al.
 Efficacy and safety of combination
 etanercept and methotrexate versus
 etanercept alone in patients with rheumatoid
 arthritis with an inadequate response to
 methotrexate: The ADORE study. Ann
 Rheum Dis 2006 Feb 7.
- 185. Van Riel PLCM, Freundlich B, MacPeek D, et al. Patient-reported health outcomes in a trial of etanercept monotherapy versus combination therapy with etanercept and methotrexate for rheumatoid arthritis: The ADORE trial. Ann Rheum Dis 2008;67(8):1104-10.
- 186. van Vollenhoven RF, Ernestam S, Geborek P, et al. Addition of infliximab compared with addition of sulfasalazine and hydroxychloroquine to methotrexate in patients with early rheumatoid arthritis (Swefot trial): 1-year results of a randomised trial. Lancet 2009;374(9688):459-66.
- 187. Wallis RS, Broder MS, Wong JY, et al. Granulomatous infectious diseases associated with tumor necrosis factor antagonists. Clin Infect Dis 2004 May 1;38(9):1261-5.
- 188. Wasserman MJ, Weber DA, Guthrie JA, et al. Infusion-related reactions to infliximab in patients with rheumatoid arthritis in a clinical practice setting: relationship to dose, antihistamine pretreatment, and infusion number. J Rheumatol 2004
 Oct:31(10):1912-7.
- 189. Weaver AL, Lautzenheiser RL, Schiff MH, et al. Real-world effectiveness of select biologic and DMARD monotherapy and combination therapy in the treatment of rheumatoid arthritis: results from the RADIUS observational registry. Curr Med Res Opin 2006 Jan;22(1):185-98.
- 190. Weinblatt M, Combe B, Covucci A, et al. Safety of the selective costimulation modulator abatacept in rheumatoid arthritis patients receiving background biologic and nonbiologic disease-modifying antirheumatic drugs: A one-year randomized, placebo-controlled study.

- Arthritis Rheum 2006 Aug 31;54(9):2807-16.
- 191. Weinblatt M, Schiff M, Goldman A, et al. Selective costimulation modulation using abatacept in patients with active rheumatoid arthritis while receiving etanercept: a randomised clinical trial. Ann Rheum Dis 2007 Feb;66(2):228-34.
- 192. Wells G, Li T, Maxwell L, et al.
 Responsiveness of patient reported outcomes including fatigue, sleep quality, activity limitation, and quality of life following treatment with abatacept for rheumatoid arthritis. Ann Rheum Dis 2008:67(2):260-5.
- 193. Westhovens R, Cole JC, Li T, et al.
 Improved health-related quality of life for rheumatoid arthritis patients treated with abatacept who have inadequate response to anti-TNF therapy in a double-blind, placebocontrolled, multicentre randomized clinical trial. Rheumatology 2006;45(Oct):1238-46.
- 194. Hassett AL, Li T, Buyske S, et al. The multi-faceted assessment of independence in patients with rheumatoid arthritis: preliminary validation from the ATTAIN study. Curr Med Res Opin 2008;24(5):1443-53.
- 195. Westhovens R, Yocum D, Han J, et al. The safety of infliximab, combined with background treatments, among patients with rheumatoid arthritis and various comorbidities: a large, randomized, placebocontrolled trial. Arthritis Rheum 2006 Apr;54(4):1075-86.
- 196. Westhovens R, Robles M, Ximenes AC, et al. Clinical efficacy and safety of abatacept in methotrexate-naive patients with early rheumatoid arthritis and poor prognostic factors. Ann Rheum Dis 2009

 Dec:68(12):1870-7.
- 197. Wolfe F, Michaud K. Lymphoma in rheumatoid arthritis: the effect of methotrexate and anti-tumor necrosis factor therapy in 18,572 patients. Arthritis Rheum 2004 Jun;50(6):1740-51.
- 198. Wolfe F, Michaud K. Heart failure in rheumatoid arthritis: rates, predictors, and the effect of anti-tumor necrosis factor therapy. Am J Med 2004 Mar 1;116(5):305-
- 199. Wolfe F, Caplan L, Michaud K. Treatment for rheumatoid arthritis and the risk of hospitalization for pneumonia: associations with prednisone, disease-modifying antirheumatic drugs, and anti-tumor necrosis

- factor therapy. Arthritis Rheum 2006 Feb;54(2):628-34.
- 200. Wolfe F, Caplan L, Michaud K. Rheumatoid arthritis treatment and the risk of severe interstitial lung disease. Scand J Rheumatol 2007;36(3):172-8.
- 201. Wolfe F, Michaud K. The effect of methotrexate and anti-tumor necrosis factor therapy on the risk of lymphoma in rheumatoid arthritis in 19,562 patients during 89,710 person-years of observation. Arthritis Rheum 2007;56(5):1433-9.
- 202. Wolfe F, Michaud K. Biologic treatment of rheumatoid arthritis and the risk of malignancy: Analyses from a large US observational study. Arthritis Rheum 2007;56(9):2886-95.
- 203. Zhang FC, Hou Y, Huang F, et al. Infliximab versus placebo in rheumatoid arthritis patients receiving concomitant methotrexate: a preliminary study from China. APLAR J Rheumatol 2006;9(2):127-30.
- 204. Zink A, Listing J, Kary S, et al. Treatment continuation in patients receiving biological agents or conventional DMARD therapy. Ann Rheum Dis 2005 Sep;64(9):1274-9.
- 205. Alonso-Ruiz A, Pijoan JI, Ansuategui E, et al. Tumor necrosis factor alpha drugs in rheumatoid arthritis: Systematic review and metaanalysis of efficacy and safety. BMC Musculoskeletal Disorders 2008;9.
- 206. Bergman GJ, Hochberg MC, Boers M, et al. Indirect comparison of tocilizumab and other biologic agents in patients with rheumatoid arthritis and inadequate response to disease-modifying antirheumatic drugs. Semin Arthritis Rheum 2010;39(6):425-41.
- 207. Bernatsky S, Habel Y, Rahme E. Observational studies of infections in rheumatoid arthritis: a metaanalysis of tumor necrosis factor antagonists. J Rheumatol 2010;37:928-31.
- 208. Bongartz T, Sutton AJ, Sweeting MJ, et al. Anti-TNF antibody therapy in rheumatoid arthritis and the risk of serious infections and malignancies: systematic review and meta-analysis of rare harmful effects in randomized controlled trials. JAMA 2006 May 17:295(19):2275-85.
- 209. Bongartz T, Warren FC, Mines D, et al. Etanercept therapy in rheumatoid arthritis and the risk of malignancies: a systematic review and individual patient data metanalysis of randomised controlled trials. Ann Rheum Dis 2009;68(7):1177-83.

- 210. Clark W, Jobanputra P, Barton P, et al. The clinical and cost-effectiveness of anakinra for the treatment of rheumatoid arthritis in adults: a systematic review and economic analysis. Health Technol Assess 2004
 May;8(18):iii-iv, ix-x, 1-105.
- 211. Devine EB, Alfonso-Cristancho R, Sullivan SD. Effectiveness of biologic therapies for rheumatoid arthritis: an indirect comparisons approach. Pharmacotherapy 2011;31(1):39-51
- 212. Gartlehner G, Hansen RA, Jonas BL, et al. The comparative efficacy and safety of biologics for the treatment of rheumatoid arthritis: a systematic review and metaanalysis. J Rheumatol 2006 Dec;33(12):2398-408.
- 213. Gaujoux-Viala C, Smolen JS, Landewe R, et al. Current evidence for the management of rheumatoid arthritis with synthetic diseasemodifying antirheumatic drugs: a systematic literature review informing the EULAR recommendations for the management of rheumatoid arthritis. Ann Rheum Dis 2010 Jun:69(6):1004-9.
- 214. Hochberg MC, Tracy JK, Hawkins-Holt M, et al. Comparison of the efficacy of the tumour necrosis factor alpha blocking agents adalimumab, etanercept, and infliximab when added to methotrexate in patients with active rheumatoid arthritis. Ann Rheum Dis 2003 2003;62 Suppl 2:ii13-6.
- 215. Kirwan JR, Bijlsma JW, Boers M, et al. Effects of glucocorticoids on radiological progression in rheumatoid arthritis. Cochrane Database Syst Rev 2007(1):CD006356.
- 216. Kuriya B, Arkema EV, Bykerk VP, et al. Efficacy of initial methotrexate monotherapy versus combination therapy with a biological agent in early rheumatoid arthritis: a meta-analysis of clinical and radiographic remission. Ann Rheum Dis 2010;69(7):1298-304.
- 217. Leombruno JP, Einarson TR, Keystone EC. The safety of anti-tumour necrosis factor treatments in rheumatoid arthritis: meta and exposure-adjusted pooled analyses of serious adverse events. Ann Rheum Dis 2009;68(7):1136-45.
- 218. Maetzel A, Wong A, Strand V, et al. Metaanalysis of treatment termination rates among rheumatoid arthritis patients receiving disease-modifying anti-rheumatic drugs. Rheumatology (Oxford) 2000 Sep;39(9):975-81.

- 219. Martinez Lopez JA, Loza E, Carmona L. Systematic review on the safety of methotrexate in rheumatoid arthritis regarding the reproductive system (fertility, pregnancy, and breastfeeding). Clin Exp Rheumatol 2009;27(4):678-84.
- 220. Mertens M, Singh JA. Anakinra for rheumatoid arthritis. Cochrane Database Syst Rev 2009(1):CD005121.
- 221. Nam JL, Winthrop KL, van Vollenhoven RF, et al. Current evidence for the management of rheumatoid arthritis with biological disease-modifying antirheumatic drugs: a systematic literature review informing the EULAR recommendations for the management of RA. Ann Rheum Dis 2010;69(6):976-86.
- 222. Osiri M, Shea B, Welch V, et al.
 Leflunomide for the treatment of rheumatoid arthritis. Cochrane Database Syst Rev 2003;1:Art. No.: CD002047.
- 223. Rheumatoid Arthritis Clinical Trial Archive Group. The effect of age and renal function on the efficacy and toxicity of methotrexate in rheumatoid arthritis. J Rheumatol 1995;22(2):218-23.
- 224. Salliot C, Dougados M, Gossec L. Risk of serious infections during rituximab, abatacept and anakinra treatments for rheumatoid arthritis: meta-analyses of randomised placebo-controlled trials. Ann Rheum Dis 2009;68(1):25-32.
- 225. Schipper LG, Fransen J, Barrera P, et al. Methotrexate in combination with sulfasalazine is more effective in rheumatoid arthritis patients who failed sulfasalazine than in patients naive to both drugs. Rheumatology (Oxford) 2009;48(7):828-33.

- 226. Singh JA, Christensen R, Wells GA, et al. A network meta-analysis of randomized controlled trials of biologics for rheumatoid arthritis: a Cochrane overview. Can Med Assoc J 2009;181:787.
- 227. Singh Jasvinder A, Christensen R, Wells George A, et al. Biologics for rheumatoid arthritis: an overview of Cochrane reviews. Cochrane Database of Systematic Reviews 2009(4).
- 228. Singh JA, Noorbaloochi S, Singh G. Golimumab for rheumatoid arthritis. Cochrane Database Syst Rev 2010(1):CD008341.
- 229. Singh Jasvinder A, Beg S, Lopez-Olivo Maria A. Tocilizumab for rheumatoid arthritis. Cochrane Database of Systematic Reviews 2010(7).
- 230. Wailoo A, Brennan A, Bansback N, et al. Modeling the cost effectiveness of etanercept, adalimumab and anakinra compared to infliximab in the treatment of patients with rheumatoid arthritis in the Medicare program. AHRQ Technology Assessment Program. 2006.
- 231. Wiens A, Correr CJ, Pontarolo R, et al. A systematic review and meta-analysis of the efficacy and safety of etanercept for treating rheumatoid arthritis. Scand J Immunol 2009;70(4):337-44.
- 232. Wiens A, Venson R, Correr CJ, et al. Metaanalysis of the efficacy and safety of adalimumab, etanercept, and infliximab for the treatment of rheumatoid arthritis. Pharmacotherapy 2010;30(4):339-53.

Appendix F. Criteria for Assessing the Quality of **Individual Studies**

Appendix F. Criteria for Assessing the Quality of Individual Studies

Assessment of Internal Validity

To assess the internal validity of individual studies, the EPC adopted criteria for assessing the internal validity of individual studies from the U.S. Preventive Services Task Force and the NHS Centre for Reviews and Dissemination. To assess the quality of observational studies, we used criteria outlined by Deeks et al., 2003.1

For Controlled Trials:

Assessment of Internal Validity

1. Was the assignment to the treatment groups really random?

Adequate approaches to sequence generation:

Computer-generated random numbers

Random numbers tables

Inferior approaches to sequence generation:

Use of alteration, case record numbers, birth dates or week days

Not reported

2. Was the treatment allocation concealed?

Adequate approaches to concealment of randomization:

Centralized or pharmacy-controlled randomization

Serially-numbered identical containers

On-site computer-based system with a randomization sequence that is not readable until allocation

Other approaches sequence to clinicians and patients

Inferior approaches to concealment of randomization:

Use of alteration, case record numbers, birth dates or week days

Open random numbers lists

Serially numbered envelopes (even sealed opaque envelopes can be subject to manipulation)

Not reported

- 3. Were the groups similar at baseline in terms of prognostic factors?
- 4. Were the eligibility criteria specified?
- 5. Were outcome assessors blinded to the treatment allocation?
- 6. Was the care provider blinded?
- 7. Was the patient kept unaware of the treatment received?

- 8. Did the article include an intention-to-treat analysis or provide the data needed to calculate it (i.e., number assigned to each group, number of subjects who finished in each group, and their results)?
- 9. Did the study maintain comparable groups?
- 10. Did the article report attrition, crossovers, adherence, and contamination?
- 11. Is there important differential loss to followup or overall high loss to followup? (Give numbers in each group.)

Assessment of External Validity (Generalizability)

- 1. How similar is the population to the population to whom the intervention would be applied?
- 2. How many patients were recruited?
- 3. What were the exclusion criteria for recruitment? (Give numbers excluded at each step.)
- 4. What was the funding source and role of funder in the study?
- 5. Did the control group receive the standard of care?
- 6. What was the length of followup? (Give numbers at each stage of attrition.)

For Observational Studies:

Assessment of Internal Validity

- 1. Were both groups selected from the same source population?
- 2. Did both groups have the same risk of having the outcome of interest at baseline?
- 3. Were subjects in both groups recruited over the same time period?
- 4. Was there any obvious selection bias?
- 5. Were ascertainment methods adequate and equally applied to both groups?
- 6. Was an attempt made to blind the outcome assessors?
- 7. Was the time of followup equal in both groups?
- 8. Was overall attrition high ($\geq 20\%$)?
- 9. Was differential attrition high ($\geq 15\%$)?
- 10. Did the statistical analysis consider potential confounders or adjust for different lengths of followup?
- 11. Was the length of followup adequate to assess the outcome of interest?

1. Deeks JJ, Dinnes J, D'Amico R, Sowden AJ, Sakarovitch C, Song F, et al. Evaluating non-randomised intervention studies. Health Technol Assess. 2003;7(27):iii-x, 1-173.

For Systematic Reviews and Meta-analyses:

- 1. Is the review based on a focused question of interest?
- 2. Did the search strategy employ a comprehensive, systematic, literature search?
- 3. Are eligibility criteria for studies clearly described?
- 4. Did at least 2 persons independently review studies?
- 5. Did authors use a standard method of critical appraisal before including studies?
- 6. Was publication bias assessed?
- 7. Was heterogeneity assessed and addressed?
- 8. Did statistical analysis maintain trials as the unit of analysis?

Appendix G. Clinical and Self-Reported Scales and Instruments Commonly Used in Studies of Drug Therapy for Rheumatoid Arthritis and Psoriatic Arthritis

Introduction

This appendix provides a brief overview of the various scales and self-reported measures that investigators used to assess outcomes in all the studies reviewed in this systematic review. The main outcome categories involve radiologic assessments of joint damage (erosion or narrowing) and various instruments that patients or subjects used to report on functional capacity or quality of life; the latter fall into two groups, one related to general health measures and one related to condition- or disease-specific instruments. General measures used in rheumatoid and psoriatic arthritis studies are described first; then the disease-specific measures used in rheumatoid and psoriatic arthritis studies are described separately. The new 2010 American College of Rheumatology ACR criteria are presented at the end of the document.

Radiographic Measures

Radiographic assessment of joint damage in hands (including wrists) or both hands and feet are critical to clinical trials in rheumatoid arthritis. The damage can be both joint space narrowing and erosions, and the underlying construct is sometimes referred to as radiographic progression (i.e., changes, whether positive or negative) as detected by radiography and interpretation. Several approaches exist, but the two commonly used are the Sharp Score (and variants) and the Larsen Score. These and other scoring methods have recently been reviewed by Boini and Guillemin; additional citations or sources are given in the brief descriptions below.

Sharp Score and Sharp/van der Heijde Score

The Sharp Score is a means of evaluating joint damage in joints of the hands, including both erosion and joint space narrowing.² Although it has undergone modifications since its introduction, the version proposed in 1985 has become the standard approach. In this method, 17 joint areas in each hand are scored for erosions; 18 joint areas in each hand are scored for joint space narrowing. The score per single joint for erosions ranges from 0 to 5 and for joint space narrowing from 0 to 4. In both cases, a higher score is worse. Erosion scores range from 0 to 170 and joint space narrowing scores range from 0 to 144. Thus, the "total Sharp Score" is the sum of the erosion and joint space narrowing scores, or 0 to 314.

The Sharp/van der Heijde (SHS) method, introduced in 1989, overcame one drawback to the Sharp Score, namely its focus on only hands, given that feet can also be involved early in rheumatoid arthritis. Therefore, the SHS method was developed to take account of erosions and joint space narrowing in both hands and feet.³⁻⁴ As with the Sharp Score, higher scores reflect worse damage. Erosion is assessed in 16 joints in each hand and 6 joints in each foot. Each joint is scored from 0 to 5 with a maximal erosion score of 160 in the hands and 120 in the feet. Joint space narrowing and subluxation are assessed in 15 joints in the hands and 6 joints in the feet. Each joint is scored from 0 to 4 with a maximal score of 120 in the hands and 48 in the feet. The

erosion and joint space narrowing scores are combined to give a total SHS score with a maximum of 448 (weighted toward hands because more joints are scored).

Numerous variants on the Sharp or SHS scores have been developed, differing subtly in terms of the numbers of joints measured and other details.⁵ Generally, all the Sharp methods are very detailed assessments and the approach, although reliable and sensitive to change, is considered time-consuming and tedious. For a speedier approach, Larsen and colleagues developed a simpler approach.

Larsen Scale for Grading Radiographs

The Larsen Scale is an overall measure of joint damage, originally devised in the 1970s and updated most recently in the late 1990s. ⁶⁻¹⁰ It produces both a score for each joint (hands and feet) and an overall score that reflects measurement and extent of joint damage. Scores range from 0 ("normal conditions," i.e., intact bony outlines and normal joint space) to 5 ("mutilating abnormality," i.e., original bony outlines have been destroyed), so higher scores reflect greater damage. Scores can range from 0 to 250.

General Health Measures

Health Assessment Questionnaire

The Health Assessment Questionnaire (HAQ) is a widely used self-report measure of functional capacity; it is a dominant instrument in studies of patients with arthritis (particularly trials of drugs in patients with rheumatoid arthritis), but it is considered a generic (not disease-specific) instrument. Detailed information on its variations, scoring, etc., can be found at www.chcr.brown.edu/pcoc/EHAQDESCRSCORINGHAQ372.PDF (accessed for this purpose 1/18/2007) or www.hqlo.com/content/1/1/20 (accessed for this purpose 1/18/2007) and in the seminal reports by Fries et al. 11 and Ramey et al. 12

The full, five-dimension HAQ consists of four domains: disability, discomfort and pain, toxicity, and dollar costs, plus death (obtained through other sources). More commonly, "the HAQ" as used in the literature refers to the shorter version encompassing the HAQ Disability Index (HAQ-DI), the HAQ pain measure, and a global patient outcome measure. The HAQ-DI is sometimes used alone.

The HAQ-DI, with the past week as the time frame, focuses on whether the respondent "is able to…" do the activity and covers eight categories in 20 items: dressing and grooming, arising, eating, walking, hygiene, reach, grip, and common daily activities. The four responses for the HAQ-DI questions are graded as follows: without any difficulty = 0; with some difficulty = 1; with much difficulty = 2; and unable to do = 3. The highest score for any component question in a category determines the category score. The HAQ-DI also asks about the use of aids and devices to help with various usual activities. Two composite scores can be calculated, one with and one without the aids/devices element; both range from 0 to 3.

The HAQ pain domain is measured on a doubly-anchored horizontal visual analog scale (VAS) of 15 cm in length; one end is labeled "no pain" (score of 0) and the other is labeled "very severe pain" (score of 100). Patients mark a spot on the VAS, and scores are calculated as the length from "no pain" in centimeters (cm) multiplied by 0.2 to yield a value that can range between 0 and 3.

With respect to interpretation, HAQ-DI scores of 0 to 1 are generally considered to represent mild to moderate disability, 1 to 2 moderate to severe disability, and 2 to 3 severe to very severe disability.

The HAQ global health status scale measures quality of life (essentially, as how the patient is feeling) with a 15 cm doubly-anchored horizontal VAS scored from 0 (very well) to 100 (very poor).

Medical Outcomes Study Short Form 36 Health Survey

The Medical Outcomes Study Short Form 36 Health Survey (SF-36) is an internationally known generic health survey instrument. Information can be found at www.sf-36.org/tools/sf36.shtml (accessed for this purpose 2/18/2007) and in a large number of articles documenting its psychometric properties. [13-19] It comprises 36 items in eight independent domains tapping functioning and well-being: physical functioning, role-physical, bodily pain, and general health in one grouping (physical health) and vitality, role-emotional, social functioning, and mental health in another grouping (mental health). The SF-36 provides a separate scale score for each domain (yielding a profile of health) and two summary scores, one for physical health and one for mental health. Each scale is scored from 0 to 100 where higher scores indicate better health and well-being.

A "version 2" of the SF-36 was introduced in the late 1990s to correct some drawbacks in formatting, wording, and other issues and to update the norm-based scoring with 1998 data. It can be fielded in two versions varying by recall period: 4-week recall (the usual approach) and 1-week recall (acute). More recently, it has been tested and used for computer adaptive testing according to item response theory principles.

EuroQol EQ-5D Quality of Life Questionnaire

A third generic quality-of-life instrument is the EuroQol EQ-5D Quality of Life Questionnaire, typically known just as the EQ-5D. More information can be found at http://www.euroqol.org/ (accessed for this purpose 1/18/2007) and in key descriptive articles, one of which is about patients with rheumatoid arthritis. 21

The EQ-5D covers health status in five domains (three questions each): mobility, self-care, usual activities, pain or discomfort, and anxiety or depression. It is intended for self-response but can be used in other administration modes. Each item can take one of three response levels – no problems, some moderate problems, extreme problems – identified as level 1, 2, or 3, respectively. This yields a profile of one level for each of the five domains; this is essentially a five-digit number, and no arithmetic properties attach to these values. Users can convert health states in the five-dimensional descriptive system into a weighted health state index by applying scores from EQ-5D "value sets" elicited from general population samples to the profile pattern (e.g., 1, 2, 3, 3, 1).

The EQ-5D also has a global health VAS scale (20 cm) scored from 0 to 100.

Rheumatoid Arthritis Measures

American College of Rheumatology 20/50/70

The American College of Rheumatology (ACR) criteria are concerned with *improvement* in counts of tender and swollen joints and several domains of health.²² A principal aim of these criteria is use in studies (particularly trials) of drugs for rheumatoid arthritis. More information can be found at www.rheumatology.org/publications/response/205070.asp and www.hopkins-arthritis.som.jhmi.edu/edu/acr/acr.html#remis_rheum (both accessed for this purpose 1/18/2007). Originally these latter involved patient assessment, physician assessment, erythrocyte sedimentation rate, pain scale, and functional questionnaire.

Today, based on work done in the mid 1990s,²³ values for clinical trial patients are defined as improvement in both tender and swollen joint counts and in three of the following: patient's assessment of pain; patient's global assessment of disease activity, patient's assessment of physical function (sometimes referred to as physical disability), the physician's global assessment of disease activity, and acute phase reactant (C-reactive protein, or CRP). The 20, 50, or 70 designations (sometimes called the ACR Success Criteria) refer to improvements in percentage terms to 20 percent, 50 percent, or 70 percent in the relevant dimensions. A physician's global assessment of 70 percent improvement is considered remission.

Thus, patients are said to meet ACR 20 criteria when they have at least 20 percent reductions in tender and swollen joint counts and in at least three of the domains. ACR 50 and ACR 70 criteria are defined in a manner similar to that for ACR 20, but with improvement of at least 50 percent and 70 percent in the individual measures, respectively. The table illustrates, in a study context, how a patient might be said to have an ACR 50 response.

Outcomes Measured	Baseline	Endpoint
Tender joints count *	12	6
Swollen joints count *	8	3
Patient's pain score*	60	20
Patient's physical function (disability) score	80	60
Physician's global activity score*	50	20
C-reactive protein*	3.6	1.4

^{*} At least 50 percent improvement between baseline and endpoint measurements.

Ritchie Articular Index

This is a long-standing approach to doing a graded assessment of the tenderness of 26 joint regions, based on summation of joint responses after applying firm digital pressure.²⁴ Four grades can be used: 0, patient reported no tenderness; +1, patient complained of pain; +2, patient complained of pain and winced; and +3, patient complained of pain, winced, and withdrew. Thus, the index ranges from 0 to 3 for individual measures and 0 to 78 overall, with higher scores being worse tenderness.

Certain joints are treated as a single unit, such as the metacarpal-phalangeal and proximal interphalangeal joints of each hand and the metatarsal-phalangeal joints of each foot. For example, the maximum score for the five metacarpal-phalangeal joints of the right hand would

be 3, not 15. No weights are used for different types of joints (e.g., by size), because the issue is one of measuring changes (improvements) in tenderness; this is especially relevant for rheumatoid arthritis.

Disease Activity Score

The Disease Activity Score (DAS) is an index of disease activity first developed in the mid 1980s. The history of its development and current definitions, scoring systems, and other details can be found at http://www.das-score.nl/www.das-score.nl/ (accessed for this purpose 1/19/2007) and in recent articles. The DAS originally included the Ritchie Articular Index (see above), the 44 swollen joint count, the erythrocyte sedimentation rate, and a general health assessment on a VAS. A cut-off level of the DAS of 1.6 is considered to be equivalent with being in remission.

More recently, an index of RA disease activity using only 28 joints – the DAS 28 – has been developed, focusing on joint counts for both tenderness (TJC) and swelling (SJC). It also uses either the patient's or a physician's global assessment (PGA) of disease activity (on a 100 mm VAS) and the erythrocyte sedimentation rate (ESR) or C-reactive protein. The formula for calculating a DAS 28 score is as follows: = $(0.56 \times \text{TJC}^{1/2}) + (0.28 \times \text{SJC}^{1/2}) + (0.7 \times \ln{[ESR]}) + (0.014 \times \text{PGA [in mm]})$. Numerous formulas to calculate a variety of DAS and DAS 28 scores exist (see the website above), such as when a global patient assessment of health is unavailable.

The DAS 28 yields a score on a scale ranging from 0 to 10. A DAS 28 of 2.6 is considered to correspond to remission; a DAS 28 of 3.2 is a threshold for low disease activity; and a DAS 28 of more than 5.1 is considered high disease activity

EULAR Response Criteria

The European League Against Rheumatism (EULAR) response criteria classify patients as good, moderate, or nonresponders based on both change in disease activity and current disease activity, using either the DAS or the DAS28 (see description above). For example, to be classified as a good responder a patient must have relevant change in DAS (\geq 1.2) and low current disease activity (\leq 2.4), while a nonresponder must have \leq 0.6 change in DAS and high disease activity (>3.7).

The EULAR criteria have been validated in multiple clinical trials, and confirmed in an analysis of nine clinical trials that concluded a high level of agreement and equal validity between ACR and EULAR improvement classifications. Food and moderate responders showed significantly more improvement in functional capacity and significantly less progression of joint damage than patients classified as nonresponders.

Psoriatic Arthritis Measures

Psoriatic Arthritis Response Criteria

The psoriatic arthritis response criteria (PsARC) was initially designed for use in a clinical trial that compared sulphasalazine to placebo in the setting of the Veterans Administration.²⁹ It has since been used as the primary or secondary outcome in all the studies that examined biologics versus placebo in the treatment of PsA. The PsARC includes improvement in at least two of the following, one of which had to be a joint count, and no worsening of any measure:

tender or swollen joint count improvement of at least 30%, patient global improvement by one point on a five-point Likert scale, or physician global improvement on the same scale.²⁹

American College of Rheumatology 20

The ACR 20 (American College of Rheumatology 20 percent response) is the other outcome that is used as the primary outcome in clinical trials of biologics. The measurement is similar to that of the ACR 20 used for rheumatoid arthritis with modifications made that increased the number of joints tested from 68 tender and 66 swollen to 76 and 78, respectively, with the addition of distal interphalangeal joints of the feet and carpometacarpal joints of the hands.²⁹ The outcomes from the ACR 20 are generally poorer when compared to the PsARC due to the variation in items measured; this is due in part to the need to see an improvement in tender *and* swollen joints in the ACR 20 versus an improvement in tender *or* swollen joint counts.

2010 Rheumatoid Arthritis Criteria

Target population (Who should be tested?)

Patients who

- have at least 1 joint with definite clinical synovitis (swelling)
 - Criteria aimed at classification of newly presenting patients; patients with erosive disease typical of RA with a history compatible with prior fulfillment of the 2010 criteria should be classified as having RA; patients with longstanding disease, including those whose disease is inactive (with or without treatment) who, based on retrospectively available data, have previously fulfilled the 2010 criteria should be classified as having RA
- · with the synovitis not better explained by another disease
 - Differential diagnoses vary among patients with different presentations, but may include conditions such as systemic lupus erythematosus, psoriatic arthritis, and gout. If it is unclear about the relevant differential diagnoses to consider, an expert rheumatologist should be consulted

Classification criteria for RA

Score

Score-based algorithm:

- · Add score of categories: Joint involvement, serology, reactants, duration
 - Differential diagnoses vary among patients with different presentations, but may include conditions such as systemic lupus erythematosus, psoriatic arthritis, and gout. If it is unclear about the relevant differential diagnoses to consider, an expert rheumatologist should be consulted
- Score of ≥6/10 needed for classification of a patient as having definite RA
 - Although patients with a score of <6/10 are not classifiable as having RA, their status can be reassessed and the criteria might be fulfilled cumulatively over time

Joint involvement

Joint involvement refers to any *swollen* or *tender* joint on examination, which may be confirmed by imaging evidence of synovitis; d Distal interphalangeal joints, first carpometacarpal joints, and first metatarsophalangeal joints are *excluded from assessment*; categories of joint distribution are classified according to the location and number of involved joints, with placement into the highest category possible based on the pattern of joint involvement

1 large joint		
 "Large joints" refers to shoulders, elbows, hips, knees, and ankles 		
2-10 large joints	1	
 1-3 small joints (with or without involvement of large joints) "Small joints" refers to the metacarpophalangeal joints, proximal interphalangeal joints, second through fifth metatarsophalangeal joints, thumb interphalangeal joints, and wrists. 	2	
4-10 small joints (with or without involvement of large joints)	3	

•	ints (at least 1 small joint)	5
inc	his category, at least 1 of the involved joints must be a small joint; the other joints can lude any combination of large and additional small joints, as well as other joints not ecifically listed elsewhere (e.g., temporomandibular, acromioclavicular, sternoclavicular, .)	

Negative refers to IU values that are less than or equal to the upper limit of normal (ULN) for the laboratory
and assay; low-positive refers to IU values that are higher than the ULN but ≤3 times the ULN for the
laboratory and assay; high-positive refers to IU values that are >3 times the ULN for the laboratory and
assay; where rheumatoid factor (RF) information is only available as positive or negative, a positive result
should be scored as low-positive for RF. ACPA = anti-citrullinated protein antibody

Negative RF and negative ACPA	0
Low-positive RF or low-positive ACPA	2
High-positive RF <i>or</i> high-positive ACPA	3

Acute-phase reactants (at least 1 test result is needed for classification)

 Normal/abnormal is determined by local laboratory standards. CRP = C-reactive protein; ESR = erythrocyte sedimentation rate

Normal CRP and normal ESR	0
Abnormal CRP <i>or</i> abnormal ESR	1

Duration of symptoms

 Duration of symptoms refers to patient self-report of the duration of signs or symptoms of synovitis (e.g., pain, swelling, tenderness) of joints that are clinically involved at the time of assessment, regardless of treatment status

<6 weeks	0
≥6 weeks	1

Adapted from: 2010 Rheumatoid arthritis classification criteria: An American College of Rheumatology/European League Against Rheumatism collaborative initiative. Arthritis & Rheumatism. 2010 Sep; 62(9): 2569–2581

The Psoriasis Area and Severity Index

The Psoriasis Area and Severity Index (PASI) was developed to measure the effect of treatments in clinical trials of psoriasis and is utilized to capture the psoriasis component found in psoriatic arthritis. The scale was originally published in 1978 in a trial of 27 patients suffering from severe chronic generalized psoriasis that were treated with Ro 10-9359, a retinoic acid derivative. The PASI is a composite index of disease severity incorporating measures of scaling, erythema, and induration, and it is weighted by severity and affected body surface area. A PASI > 12 defines severe, PASI 7-12 moderate, and PASI < 7 mild psoriasis.

References

- 1. Boini S, Guillemin F. Radiographic scoring methods as outcome measures in rheumatoid arthritis: properties and advantages. Ann Rheum Dis. 2001 Sep;60(9):817-27.
- 2. Sharp JT, Young DY, Bluhm GB, Brook A, Brower AC, Corbett M, et al. How many joints in the hands and wrists should be included in a score of radiologic abnormalities used to assess rheumatoid arthritis? Arthritis Rheum. 1985
 Dec;28(12):1326-35.
- 3. van der Heijde D, Dankert T, Nieman F, Rau R, Boers M. Reliability and sensitivity to change of a simplification of the Sharp/van der Heijde radiological assessment in rheumatoid arthritis. Rheumatology (Oxford). 1999
 Oct;38(10):941-7.
- 4. van der Heijde D. How to read radiographs according to the Sharp/van der Heijde method. J Rheumatol. 1999 Mar;26(3):743-5.
- 5. Ory PA. Interpreting radiographic data in rheumatoid arthritis. Ann Rheum Dis. 2003 Jul;62(7):597-604.
- 6. Larsen A. Radiological grading of rheumatoid arthritis. An interobserver study. Scand J Rheumatol. 1973;2(3):136-8.
- 7. Larsen A, Dale K, Eek M. Radiographic evaluation of rheumatoid arthritis and related conditions by standard reference films. Acta Radiol Diagn (Stockh). 1977 Jul;18(4):481-91.
- 8. Scott DL, Coulton BL, Bacon PA, Popert AJ. Methods of X-ray assessment in rheumatoid arthritis: a re-evaluation. Br J Rheumatol. 1985 Feb;24(1):31-9.
- 9. Larsen A. How to apply Larsen score in evaluating radiographs of rheumatoid arthritis in long-term studies. J Rheumatol. 1995;22:1974-5.

- 10. Edmonds J, Saudan A, Lassere M, Scott DL. Introduction to reading radiographs by the Scott modification of the Larsen method. J Rheumatol. 1999;26:740-2.
- 11. Fries JF, Spitz P, Kraines RG, Holman HR. Measurement of patient outcome in arthritis. Arthritis Rheum. 1980 Feb;23(2):137-45.
- 12. Ramey DR, Fries JF, Singh G. The Health Assessment Questionnaire 1995 -- Status and Review. In: Spilker B, ed. *Quality of Life and Pharmacoleconomics in Clinical Trials*. 2nd ed. Philadelphia: Lippincott-Raven Publischers 1996:227-37.
- 13. Stewart AL, Hays RD, Ware JE, Jr. The MOS short-form general health survey. Reliability and validity in a patient population. Med Care. 1988 Jul;26(7):724-35.
- 14. Stewart AL, Ware JE. Measuring
 Functioning and Well-Being: The Medical
 Outcomes Study Approach. Durham, NC:
 Duke University Press 1992.
- Ware JE, Jr., Sherbourne CD. The MOS 36item short-form health survey (SF-36). I. Conceptual framework and item selection. Med Care. 1992 Jun;30(6):473-83.
- 16. McHorney CA, Ware JE, Jr., Rogers W, Raczek AE, Lu JF. The validity and relative precision of MOS short- and long-form health status scales and Dartmouth COOP charts. Results from the Medical Outcomes Study. Med Care. 1992 May;30(5 Suppl):MS253-65.
- 17. McHorney CA, Ware JE, Jr., Raczek AE. The MOS 36-Item Short-Form Health Survey (SF-36): II. Psychometric and clinical tests of validity in measuring physical and mental health constructs. Med Care. 1993 Mar;31(3):247-63.
- 18. McHorney CA, Ware JE, Jr., Lu JF, Sherbourne CD. The MOS 36-item Short-Form Health Survey (SF-36): III. Tests of data quality, scaling assumptions, and

- reliability across diverse patient groups. Med Care. 1994 Jan;32(1):40-66.
- 19. Ware JE, Jr., Kosinski M, Bayliss MS, McHorney CA, Rogers WH, Raczek A. Comparison of methods for the scoring and statistical analysis of SF-36 health profile and summary measures: summary of results from the Medical Outcomes Study. Med Care. 1995 Apr;33(4 Suppl):AS264-79.
- 20. Kind P. The EuroQol instrument: An index of health-related quality of life. Quality of life and PharmacoEconomics in Clinical Trials. 2nd ed. Philadelphia: Lippincott-Rayen Publishers 1996.
- 21. Hurst NP, Kind P, Ruta D, Hunter M, Stubbings A. Measuring health-related quality of life in rheumatoid arthritis: validity, responsiveness and reliability of EuroQol (EQ-5D). Br J Rheumatol. 1997 May;36(5):551-9.
- 22. Felson DT, Anderson JJ, Boers M,
 Bombardier C, Chernoff M, Fried B, et al.
 The American College of Rheumatology
 preliminary core set of disease activity
 measures for rheumatoid arthritis clinical
 trials. The Committee on Outcome Measures
 in Rheumatoid Arthritis Clinical Trials.
 Arthritis Rheum. 1993 Jun;36(6):729-40.
- 23. Felson DT, Anderson JJ, Boers M, Bombardier C, Furst D, Goldsmith C, et al. ACR preliminary definition of improvement in rheumatoid arthritis. Arthritis Rheum. 1995;38(6):727-35.
- Ritchie DM, Boyle JA, McInnes JM, Jasani MK, Dalakos TG, Grieveson P, et al.
 Clinical studies with an articular index for the assessment of joint tenderness in patients

- with rheumatoid arthritis. Q J Med. 1968 Jul;37(147):393-406.
- 25. Aletaha D, Nell VP, Stamm T, Uffmann M, Pflugbeil S, Machold K, et al. Acute phase reactants add little to composite disease activity indices for rheumatoid arthritis: validation of a clinical activity score. Arthritis Res Ther. 2005;7(4):R796-806.
- 26. van Gestel AM, Prevoo ML, van 't Hof MA, van Rijswijk MH, van de Putte LB, van Riel PL. Development and validation of the European League Against Rheumatism response criteria for rheumatoid arthritis. Comparison with the preliminary American College of Rheumatology and the World Health Organization/International League Against Rheumatism Criteria. *Arthritis Rheum*. 1996/01/01 ed 1996:34-40.
- 27. Fransen J, van Riel PL. The Disease Activity Score and the EULAR response criteria. *Rheum Dis Clin North Am.* 2009/12/08 ed 2009:745-57, vii-viii.
- 28. van Gestel AM, Anderson JJ, van Riel PL, Boers M, Haagsma CJ, Rich B, et al. ACR and EULAR improvement criteria have comparable validity in rheumatoid arthritis trials. American College of Rheumatology European League of Associations for Rheumatology. *J Rheumatol.* 1999/03/25 ed 1999:705-11.
- 29. Mease PJ, Goffe BS, Metz J, VanderStoep A, Finck B, Burge DJ. Etanercept in the treatment of psoriatic arthritis and psoriasis: a randomised trial. Lancet. 2000 Jul 29;356(9227):385-90.
- 30. Fredriksson T, Pettersson U. Severe psoriasis--oral therapy with a new retinoid. Dermatologica. 1978;157(4):238-44.

Appendix H. Excluded Studies

Characteristics of Studies with Poor Internal Validity

Characteristics of Studio	es with Poor internal			
Study	Design	Sample Size	Intervention	Reason for Exclusion
Anis et al., 2009 ¹	RCT subanalysis	205	Etanercept	High risk of bias due to loss of effect of randomization
Bathon et al., 2006 ² Poole		2,402 l	Etanercept	Selection bias
Bazzani et al., 2009 ³	analysis Prospective cohort registry study	1010 E	Etanercept Adalimumab Infliximab corticosteroid	Selection bias
Bejarno et al., 2008 ⁴ RCT		148	Adalimumab Methotrexate	Very high LTF
[‡] Burmester et al., 2007 ⁵ F	Prospe ctive cohort open-label study	6610 A	Adalimuma b Combo therapy with 1+ DMARD	high risk of bias; confounding by indication
Chopra et al., 2008 ⁶ Pros	pe ctive cohort study	230 L	eflunomi de Methotrexate	High LTF; completers analysis for outcome of interest; selection bias
Cohen et al, 2010 ⁷	Post hoc analysis of RCT data	468 R	ituximab Methotrexate	High risk of bias due to loss of effect of randomization
Cole et al., 2007 ⁸ R	etrospective cohort study	303 E	tanercept Adalimumab Infliximab Methylprednisolone	Inadequate control for potential confounders; retrospective study with chart review; groups not similar at baseline; small sample size
De Stefano, 2010 ⁹	Non-randomized controlled trial	120 A	nti-TNF therapy Methotrexate Leflunomide	High LTF; no randomization; non-ITT analysis
de Nijs et al., 2001 ¹⁰ Cro	ss-sectional	410	Corticosteroids	Selection bias
Faarvang et al., 1993 ¹¹ Ro	СТ	91	Hydroxychloroquine Sulfasalazine	No ITT analysis; high LTF
Fleischmann et al., 2003 ¹²	Pooled data analysis	1128 E	Etanercept	Selection bias
Flendrie et al., 2005 ¹³ Obs		162	Leflunomide infliximab	High LTF; selection bias
Ghosh et al., 2008 ¹⁴ RCT		110	Methotrexate Sulfasalazine Hydroxychlorquine	Randomization/ allocation not adequately reported; inadequate reporting of baseline measures
Guignard et al., 2008 ¹⁵ R	etrospective cohort study		Anti-TNF therapy Non anti-TNF therapy	No adjustment for confounders and effect modifiers; small sample size; single center
Hafstrem et al., 2009 ¹⁶ RO		150	Prednisolone	High LTF
Hansen et al., 1999 ¹⁷ RC	Γ	102	DMARDs Prednisolone	High attrition; no ITT analysis

Chudu	Decima	Sample	Intoniontion	Decom for Evaluation
Heiberg et al., 2006 ¹⁸	Design Observational	Size 183	Adalimumab Methotrexate	Reason for Exclusion High potential for selection bias and confounding; baseline differences between groups
Iwatani et al., 2006 ¹⁹	vatani et al., 2006 ¹⁹ Cross-sectional prospective cohort		Sulfasalazine Methotrexate Bucillamine	Selection bias; high potential for confounding
Jones, et al., 2010 ²⁰	RCT	570	Tocilizumab Methotrexate	Attrition NR; quality of randomization and allocation concealment unclear
Karlsson et al., 2008 ²¹	Prospective cohort study	473	Second-line anti- TNF therapy Third- line anti-TNF therapy	High LTF; Poor inter- rater reliability
Kimel et al., 2008 ²²	RCT	525	Adalimumab Methotrexate	Selection bias; High LTF; no ITT analysis; analyses do not directly compare the two treatment groups
Lee et al., 2008 ²³	Adjusted indirect comparison	N/A	Anti-TNF therapy Methotrexate	High risk of bias due to small number of studies (3) included in indirect comparisons
Mariette et al., 2010 ²⁴	Case-control study	111	Etanercept Infliximab Adalimumab	Small sample size; control for confounding unclear
Mattey et al., 2009 ²⁵	Observational	154	Infliximab Etanercept	No baseline characteristics reported; no adjustments made for different lengths of treatment
Mertz and Blair, 2007 ²⁶	Retrospective observational Study	287	Anti-TNF therapy Methotrexate Azathioprine Leflunomide Prednisone	Confounding by indication; selection bias; groups not similar at baseline
Nagashima et al., 2006 ²⁷	Prospective cohort	1358	Sulfasalazine Methotrexate	No adjustments for confounding; unequal treatment duration; unclear if groups are similar at baseline
Osiri et al., 2006 ²⁸	Prospective cohort	152	Methotrexate Sulfasalazine Leflunomide	High potential for bias due to confounding by indication
Schoels et al., 2007 ²⁹	Prospective cohort study	1214	Methotrexate Sulfasalazine Leflunomide Other unspecified DMARS	Attrition data not reported; not clear if groups are similar at baseline

Sample							
Study	Design	Size	Intervention	Reason for Exclusion			
Seong et al., 2007 ³⁰	Retrospective cohort study	1478	Anti-TNF naïve Infliximab Etanercept	Selection bias; groups not comparable at baseline; high potential for confounding			
Soderlin et al., 2007 ³¹	Prospective cohort	357	Biologics Methotrexate	High LTF; important potential confounders not accounted for			
[‡] Strand et al., 2006 ³²	RCT	161	Rituximab Methotrexate	Very high LTF			
Todoerti et al., 2010 ³³	RCT	210	Prednisone	Poor reporting of outcomes; statistical methods or study design to reduce confounding unclear			
van der Heijde et al., 2007 ³⁴	RCT	414	Etanercept Methotrexate	High LTF			
van Vollenhoven et al., 2010 ³⁵	Observational	664	Adalimumab Methotrexate	High LTF; important baseline differences between groups; high risk of selection bias			
Weisman et al., 2007 ³⁶	RCT	564	Etanercept Placebo	High LTF; not powered to detect a difference in these rare outcomes; some baseline differences in cardiovascular risk factors			

 $NR, not\ reported; ITT, intention\ to\ treat; LTF, loss\ to\ followup;\ RCT, randomized\ controlled\ trial.$

[‡]Rated fair for adverse events or included in adverse events meta-analysis

References

- 1. Anis A, Zhang W, Emery P, et al. The effect of etanercept on work productivity in patients with early active rheumatoid arthritis: results from the COMET study. Rheumatology (Oxford) 2009;48(10):1283-9.
- 2. Bathon JM, Fleischmann RM, Van der Heijde D, et al. Safety and efficacy of etanercept treatment in elderly subjects with rheumatoid arthritis. J Rheumatol. 2006 Feb;33(2):234-43.
- 3. Bazzani C, Filippini M, Caporali R, et al. Anti-TNFalpha therapy in a cohort of rheumatoid arthritis patients: Clinical outcomes. Autoimmunity Reviews 2009;8(3):260-5.
- 4. Bejarano V, Quinn M, Conaghan PG, et al. Effect of the early use of the anti-tumor necrosis factor adalimumab on the prevention of job loss in patients with early rheumatoid arthritis. Arthritis Rheum 2008;59(10):1467-74.
- 5. Burmester GR, Mariette X, Montecucco C, et al. Adalimumab alone and in combination with disease-modifying antirheumatic drugs for the treatment of rheumatoid arthritis in clinical practice: the Research in Active Rheumatoid Arthritis (ReAct) trial. Ann Rheum Dis 2007;66(6):732-9.
- 6. Chopra A, Saluja M, Lagu-Joshi V, et al. Leflunomide (Arava) is a useful DMARD in Indian (Asian) patients: a clinic-based observational study of 1-year treatment. Clin Rheumatol 2008;27(8):1039-44.
- 7. Cohen SB, Keystone E, Genovese MC, et al. Continued inhibition of structural damage over 2 years in patients with rheumatoid arthritis treated with rituximab in combination with methotrexate. Ann Rheum Dis 2010;69(6):1158-61.
- 8. Cole J, Busti A, Kazi S. The incidence of new onset congestive heart failure and heart failure exacerbation in Veteran's Affairs patients receiving tumor necrosis factor alpha antagonists. Rheumatol Int 2007;27(4):369-73.

- 9. De Stefano R, Frati E, Nargi F, et al.
 Comparison of combination therapies in the treatment of rheumatoid arthritis:
 leflunomide-anti-TNF-alpha versus methotrexate-anti-TNF-alpha. Clin
 Rheumatol 2010;29(5):517-24.
- 10. de Nijs RN, Jacobs JW, Bijlsma JW, et al. Prevalence of vertebral deformities and symptomatic vertebral fractures in corticosteroid treated patients with rheumatoid arthritis. Rheumatology (Oxford). 2001 Dec;40(12):1375-83.
- 11. Faarvang K, Egsmose C, Kryger P, et al. Hydroxychloroquine and Sulphasalazine Alone and in Combination in Rheumatoid Arthritis: a Randomised Double Blind Trial. Annals of the rheumatic diseases. 1993;52(10):711-5.
- 12. Fleischmann RM, Baumgartner SW, Tindall EA, et al. Response to etanercept (Enbrel) in elderly patients with rheumatoid arthritis: a retrospective analysis of clinical trial results. J Rheumatol. 2003 Apr;30(4):691-6.
- 13. Flendrie M, Creemers MC, Welsing PM, et al. The influence of previous and concomitant leflunomide on the efficacy and safety of infliximab therapy in patients with rheumatoid arthritis; a longitudinal observational study. Rheumatology (Oxford). 2005 Apr;44(4):472-8.
- 14. Ghosh B, Halder S, Ghosh A, et al. Early rheumatoid arthritis: Clinical and therapeutic evaluation in a tertiary care centre in India. Indian Journal of Rheumatology 2008;3(2):48-51.
- 15. Guignard S, Gossec L, Bandinelli F, et al. Comparison of the clinical characteristics of vasculitis occurring during anti-tumor necrosis factor treatment or not in rheumatoid arthritis patients. A systematic review of 2707 patients, 18 vasculitis. Clin Exp Rheumatol 2008;26(3 Suppl 49):S23-9.
- 16. Hafstrem I, Albertsson K, Boonen A, et al. Remission achieved after 2 years treatment with low-dose prednisolone in addition to diseasemodifying anti-rheumatic drugs in

- early rheumatoid arthritis is associated with reduced joint destruction still present after 4 years: An open 2-year continuation study. 2009.
- 17. Hansen M, Podenphant J, Florescu A, et al. A Randomised Trial of Differentiated Prednisolone Treatment in Active Rheumatoid Arthritis. Clinical Benefits and Skeletal Side Effects. Annals of the rheumatic diseases. 1999;58(11):713-8.
- 18. Heiberg MS, Rødevand E, Mikkelsen K, et al. Adalimumab and methotrexate is more effective than adalimumab alone in patients with established rheumatoid arthritis:

 Results from a 6-month longitudinal, observational, multicentre study. Annals of the rheumatic diseases 2006;65(10):1379-83.
- 19. Iwatani M, Inoue E, Nakamura T, et al. Efficacy profile of bucillamine in rheumatoid arthritis patients in a large observational cohort study, IORRA. Mod Rheumatol 2006;16(6):376-80.
- Jones G. The AMBITION trial: tocilizumab monotherapy for rheumatoid arthritis.
 Expert Rev Clin Immunol 2010;6(2):189-95.
- 21. Karlsson JA, Kristensen LE, Kapetanovic MC, et al. Treatment response to a second or third TNF-inhibitor in RA: results from the South Swedish Arthritis Treatment Group Register. Rheumatology (Oxford) 2008;47(4):507-13.
- 22. Kimel M, Cifaldi M, Chen N, et al. Adalimumab plus methotrexate improved SF-36 scores and reduced the effect of rheumatoid arthritis (RA) on work activity for patients with early RA. J Rheumatol 2008;35(2):206-15.
- 23. Lee YH, Woo JH, Rho YH, et al. Metaanalysis of the combination of TNF inhibitors plus MTX compared to MTX monotherapy, and the adjusted indirect comparison of TNF inhibitors in patients suffering from active rheumatoid arthritis. Rheumatology international 2008;28(6):553-9.
- 24. Mariette X, Tubach F, Bagheri H, et al. Lymphoma in patients treated with anti-

- TNF: Results of the 3-year prospective French RATIO registry. Annals of the rheumatic diseases 2010;69(2):400-8.
- 25. Mattey DL, Brownfield A, Dawes PT. Relationship between pack-year history of smoking and response to tumor necrosis factor antagonists in patients with rheumatoid arthritis. J Rheumatol 2009;36(6):1180-7.
- 26. Mertz LE, Blair JE. Coccidioidomycosis in rheumatology patients: incidence and potential risk factors. Ann N Y Acad Sci 2007;1111343-57.
- 27. Nagashima M, Matsuoka T, Saitoh K, et al. Treatment continuation rate in relation to efficacy and toxicity in long-term therapy with low-dose methotrexate, sulfasalazine, and bucillamine in 1,358 Japanese patients with rheumatoid arthritis. Clin Exp Rheumatol 2006;24(3):260-7.
- 28. Osiri M, Deesomchok U, Tugwell P. Disease activity and functional changes of RA patients receiving different DMARDs in clinical practice. Clin Rheumatol. 2006;25(5):721-7.
- 29. Schoels M, Kapral T, Stamm T, et al. Stepup combination versus switching of nonbiological disease-modifying antirheumatic drugs in rheumatoid arthritis: results from a retrospective observational study. Ann Rheum Dis 2007;66(8):1059-65.
- 30. Seong SS, Choi CB, Woo JH, et al.
 Incidence of tuberculosis in Korean patients
 with rheumatoid arthritis (RA): effects of
 RA itself and of tumor necrosis factor
 blockers. J Rheumatol. 2007 Apr;34(4):70611.
- 31. Soderlin MK, Lindroth Y, Jacobsson LT. Trends in medication and health-related quality of life in a population-based rheumatoid arthritis register in Malmo, Sweden. Rheumatology (Oxford) 2007;46(8):1355-8.
- 32. Strand V, Balbir-Gurman A, Pavelka K, et al. Sustained benefit in rheumatoid arthritis following one course of rituximab: improvements in physical function over 2

- years. Rheumatology (Oxford) 2006;45(12):1505-13.
- 33. Todoerti M, Scire CA, Boffini N, et al. Early disease control by low-dose prednisone comedication may affect the quality of remission in patients with early rheumatoid arthritis. Ann N Y Acad Sci 2010;1193(1):139-45.
- 34. van der Heijde D, Klareskog L, Landewe R, et al. Disease remission and sustained halting of radiographic progression with combination etanercept and methotrexate in patients with rheumatoid arthritis. Arthritis Rheum 2007;56(12):3928-39.
- 35. van Vollenhoven RF, Cifaldi MA, Ray S, et al. Improvement in work place and household productivity for patients with early rheumatoid arthritis treated with adalimumab plus methotrexate: work outcomes and their correlations with clinical and radiographic measures from a randomized controlled trial companion study. Arthritis Care Res (Hoboken) 2010;62(2):226-34.
- 36. Weisman MH, Paulus HE, Burch FX, et al. A placebo-controlled, randomized, double-blinded study evaluating the safety of etanercept in patients with rheumatoid arthritis and concomitant comorbid diseases. Rheumatology (Oxford) 2007;46(7):1122-5.

Appendix I. Strength of Evidence Tables

Strength of evidence for Disease Activity and Radiographic Progression (KQ1)

For each comparison, the following tables provide the strength of evidence for disease activity and radiographic outcomes within a single row, if both outcomes were available. Information related to disease activity is provided in the upper part of each row; information related to radiographic outcomes is provided in the lower part of each row, when available.

Drug Comparison Number of Studies # of Subjects	Risk of Bias Design/ Quality	Consistency	Directness	Precision	Results	Strength of Evidence
Oral DMARD vs. Oral DMARD: Corticosteroid vs. Corticosteroid 1 RCT	Medium RCT/ fair	Unknown, single study	Direct	Precise	No difference in ACR 20 and DAS for prednisolone and budesonide	Low
N =143						
LEF vs. MTX	Low RCTs/ Fair	Consistent	Direct	Imprecise	No difference in ACR 20 at 1 to 2 years	Low
2 RCTs N = 1481	Low RCTs/Fair	Consistent	Indirect	Precise	No difference in radiographic changes at 2 years	Low
LEF vs. SSZ	Medium RCT/Fair	Unknown, single study	Direct	Imprecise	Mixed results for ACR20 response at 2 yrs	Insufficient
N =358	Medium RCT/Fair	Unknown, single study	Indirect	Imprecise	Similar Radiographic changes at 2 years	Low
SSZ vs. MTX 3 RCTs	Low RCTs/Fair	Consistent	Direct	Precise	No difference in disease activity	Low
N = 1001	Low RCTs/Fair	Consistent	Indirect	Imprecise	No difference in radiographic changes	Low
Oral DMARD Combinations vs. Monotherapy or	Low 1 RCT/Fair	Unknown, single study	Direct	Imprecise	Sulfasalazine + MTX improves disease activity (DAS), but no difference in ACR	Low
Combinations with or without Corticosteroids: SSZ + MTX vs. SSZ or MTX	Low 2RCTs, 1 prospective cohort/Fair	Consistent	Direct	Precise	No differences in disease activity in patients with early RA	Moderate
3 RCTs, 1 Prospective cohort;	Low 2RCTs/Fair	Consistent	Indirect	Precise	No difference in radiographic changes	Low
N = 709						
2 RCTs						
N = 374						

Table 1. Strength of evidence for Disease Activity and Radiographic Progression (KQ1)

(continued)						
Drug Comparison Number of Studies # of Subjects	Risk of Bias Design/ Quality	Consistency	Directness	Precision	Results	Strength of Evidence
MTX + HCQ + SSZ vs. 1 or 2 oral DMARDs	Low RCTs/Good	Consistent	Direct	Imprecise	Improvement in disease activity in 3 versus 2 oral DMARDs	Moderate
2 RCTs						
N = 273						
Oral DMARD + corticosteroid vs. Oral DMARD	Low RCTs/fair	Inconsistent	Direct	Imprecise	Mixed results for disease activity	Insufficient
2RCTs	Low RCT/ Fair	Consistent	Indirect	Imprecise	Less radiographic changes with oral DMARD plus prednisone	Low
N = 717						
Biologic DMARDs vs. Biologic DMARDs Mixed treatment comparison (MTC) 30 RCTs N = 6888*	High MTC	Unknown, Single study	Indirect	Imprecise	No significant differences in disease activity (ACR 50) in MTC analyses for abatacept, adalimumab, golimumab,infliximab rituximab and tocilizumab in patients resistant to MTX	Low
Biologic DMARDs vs. Biologic DMARDs: ABA vs. INF 1 RCT N = 431; (MTC) 30 RCTs N = 6888*	Medium RCT/Fair, MTC	Inconsistent	Direct and Indirect	Imprecise	Abatacept improves disease activity over 1 year more than infliximab No differences in ACR 50 in MTC analyses	Low
ADA vs ETN 1 prospective cohort N = 2326	High Cohort/Fair	Unknown, single study	Direct	Imprecise	No difference in disease activity (ACR 70 respons) after 6 months	Low

Table 1. Strength of evidence for Disease Activity and Radiographic Progression (KQ1)

(continued)	•		•		. .	,
Drug Comparison Number of Studies # of Subjects	Risk of Bias Design/ Quality	Consistency				Strength of Evidence
ADA vs. INF 2 prospective cohorts	High Prospective cohorts/Fair, MTC	Consistent	Direct and Indirect	Imprecise	Adalimumab improves disease activity over 1 year more than infliximab No differences in MTC	Low
N = 3033					analyses	
Mixed treatment comparisons (MTC) 30 RCTs						
N = 6888*						
ANA vs. Biologics (MTC)	High, MTC	Unknown, single study	Indirect	Imprecise	Less improvement in disease activity (ACR 50) for anakinra compared to etanercept and anakinra.	Low
30 RCTs					Comparisons with abatacept, golimumab,	
N = 6888*					infliximab, rituximab and tocilizumab did not reach statistical significance.	
ETN vs. Biologics	High, MTC	Unknown, single study	Indirect	Imprecise	In MTC analyses, greater improvement in disease activity (ACR 50) for	Low
(MTC) 30 RCTs N = 6888*					etanercept compared to abatacept, adalimumab, anakinra, infliximab, rituximab and tocilizumab. No significant differences when compared with golimumab.	
ETN vs. INF	High Open label	Consistent	Direct and indirect	Imprecise	Faster onset of efficacy for ETN but no differences	Low
1 open label trial, 5 prospective cohorts	trial, prospective cohorts/Fair,				at 1 year or later MTC analyses (ACR 50:	
N = 5883	MTC				OR 4.17, 95% CI, 2.00- 11.17)	
(MTC) 30 RCTs						
N = 6888*						
RTX vs. anti TNF	High Prospective cohort/Fair	Unknown, single study	Direct	Precise	RTX reduces DAS 28 at 6 months more than anti-TNF	Low
1 prospective cohort						
N = 116						

Table 1. Strength of evidence for Disease Activity and Radiographic Progression (KQ1)

(continued)			•			
Drug Comparison Number of Studies # of Subjects	Risk of Bias Design/ Quality	Consistency				Strength of Evidence
Biologic DMARDs vs. Oral DMARDs 4RCTs/2Cohorts	Low RCTs/ Cohorts/Fair	Consistent	Direct	Imprecise	Higher response rates for biologic DMARDs (ADA, ANA, ETN, INF,) vs. oral DMARDs (MTX, LEF) in patients with inadequate	Moderate
N = 3696					response to prior DMARDs	
Biologic DMARDs vs. Oral DMARDs:	Low RCT/Fair	Unknown, single study	Direct	Precise	Lower response rates for ADA vs. MTX in early RA	Low
ADA vs. MTX 1 RCT	Low RCT/Fair	Unknown, single study	Indirect	Precise	Less radiographic progression for ADA vs. oral DMARD in early RA	Low
N = 799	NA - di	Opposintent	Discort		0	1
ETN vs. Oral DMARDs 2RCTs,	Medium RCT, nonrandomi zed trial/Fair	Consistent	Direct	Imprecise	Greater improvement in disease activity in ETN vs. oral DMARD	Low
1nonrandomized trial N =1687	Low, RCTs/Fair	Consstent	Indirect	Imprecise	Less radiographic progression for ETN vs. oral DMARD	Low
TCZ vs. MTX 1 RCT N = 127	Low 1 RCT/Fair	Unknown, single study	Direct	Precise	Great improvement in disease activity for Tocilizumab than MTX (8mg/wek) at 24wks	Insufficient ^a
Biologic DMARDs + Biologic DMARDs vs. Biologic DMARDs: (1) ETN + AKA vs. ETN (2) ETN + ABA vs. ETN	Low 2 RCTs/Fair	Consistent	Direct	Imprecise	No difference in disease activity	Low
2 RCTs						
N = 363						

Table 1. Strength of evidence for Disease Activity and Radiographic Progression (KQ1) (continued)

(continued)						
Drug						
Comparison						
Number of	Risk of Bias					
Studies	Design/				_	Strength of
# of Subjects	Quality	Consistency				Evidence
Any Biologic	Low	Consistent	Direct	Imprecise	Improved disease activity	Moderate
DMARDs + Oral	RCTs/Fair,				with biologic plus MTX	
DMARDs vs.	Cohorts/2					
Biologic	good					
DMARDs						
	Low/Fair	Consistent	Indirect	Imprecise	Less radiographic change	Low
5 RCTs,4					with biologic plus MTX	
cohorts;						
N. 0004						
N = 9804						
0.000						
2 RCTs						
N = 1405						
N = 1485	Low	Linknown	Direct	Precise	Higher ACR50 response	Low
Biologic DMARDs + Oral	Low 1RCT/Fair	Unknown,	Direct	Precise	for ADA + MTX	Low
DMARDS + Oral	IRC1/Fall	single study			IOI ADA + IVITA	
Biologic	Low	Unknown,	Indirect	Precise	Loss radiographic change	Low
DMARDs: ADA+		single study	munect	FIECISE	Less radiographic change for ADA + MTX	LOW
MTX vs. ADA	INC I/Fall	single study			IOI ADA + IVITA	
WITA VS. ADA						
1 RCT						
11101						
N = 799						
ETN + DMARD	Medium	Consistent	Direct	Imprecise	Trend toward improved	Low
vs. ETN	RCTs/Fair,				disease activity for ETN+	
	cohorts				MTX vs. ETN	
3 RCTs, 3	/2Good,Fair					
cohorts	•					
	Low	Unknown,	Indirect	Precise	Less radiographic change	
N = 8529	1RCT/Fair	single study			for ETN + MTX vs. ETN	Low
INF + MTX vs.	Medium	Unknown,	Direct	Precise	Improved disease activity	Low
MTX	Prospective	single study			for INF + MTX vs. INF	
	cohort/Good	,				
1 Prospective						
cohort						
N = 2711						
RTX +MTX vs.	Low	Unknown,	Direct	Precise	Improved disease activity	Low
RTX	RCT/Fair	single study			for RTX + MTX vs. RTX	
1 RCT						
N = 161	_					
Any Biologic	Low	Consistent	Direct	Precise	Greater improvement in	High
DMARDs + Oral	RCTs/ 1				disease activity for	
DMAR vs Oral	Good				biologic + oral DMARD	
DMARD						
	Low	Consistent	Indirect	Imprecise	Less radiographic change	Moderate
7 RCTs	3RCTs/1Go				for biologic + oral DMARD	
N. 4:00	od					
N = 4482						

Table 1. Strength of evidence for Disease Activity and Radiographic Progression (KQ1) (continued)

(continued)						
Drug						
Comparison						
Number of	Risk of Bias					
Studies	Design/					Strength of
# of Subjects	Quality	Consistency				Evidence
Biologic	Low	Unknown,	Direct	Precise	Greater improvement in	Low
DMARDs + Oral	RCT/Good	single study			disease activity (ACR50)	
DMARDs vs.					for ABA + MTX vs MTX	
Oral DMARDs:						
ABA + MTX vs.	RCT/Good	Unknown,	Indirect	Precise	Less radiographic change	Low
MTX		single study			for ABA + MTX	
1 RCT						
N = 509						
ADA + MTX vs.	Medium	Unknown,	Direct	Precise	Improved disease activity	Low
MTX	1 RCT/Fair	single study			for ADA + MTX vs. MTX	
1 RCT	Medium	Unknown,	Indirect	Precise	Less radiographic change	Low
	RCT/Fair	single study			for ADA + MTX	
N = 799						
ETN + oral	Low	Consist e nt	Direct	Imprecise	Improved disease activity	Moderate
DMARD vs. oral	3RCTs/Fair				for ETN + oral DMARD	
DMRD (MTX or					vs. oral DMARD	
SSZ)	Mar allinosa	I lada a sana	la dia at	Di		1
0 DOT-	Medium	Unknown,	Indirect	Precise	Less radiographic change	LOW
3 RCTs	1 RCT/Fair	single study			for ETN + MTX vs. MTX	
N = 1488						
N - 1400						
GOL + MTX vs.	Medium	Unknown,	Direct	Precise	Improved disease activity	Low
MTX	1RCT/Fair	single study	Direct	1 10030	(ACR50) for GOL + MTX	LOW
	11.01/1 011	onigic study			vs. MTX	
1 RCT						
N = 637						
INF + MTX vs.	Medium	Unknown,	Direct	Precise	Improved disease activity	Low
MTX	1 RCT/Fair	single study			for INF + MTX vs. MTX	
		,				
1 RCT						
N = 1049						

Table 1. Strength of evidence for Disease Activity and Radiographic Progression (KQ1) (continued)

(continued)						
Drug Comparison Number of Studies # of Subjects	Risk of Bias Design/ Quality	Consistency	Directness	Precision		Strength of Evidence
Biologic DMARDs + Oral DMARDs vs. Biologic DMARDs: ANK + MTX vs. ANT + LEF; ETN + DMARD vs. INF + DMARD; Anti- TNF + MTX vs. anti-TNF vs. LEF	Medium Prospective cohorts/Fair	Consistent	Direct	Imprecise	No significant difference between Biologic DMARD + Oral DMARD vs. Biologic DMARD + oral DMARD (ANK, INF, ETN, ADA with MTX or LEF)	Low
3 prospective cohorts						
N = 4225						
Strategies in Early RA: Two oral DMARDs plus	Low 1RCT/Good	,	Direct	Precise	Improved disease activity in combination group at 28 weeks, but no difference by 52 weeks	Low
corticosteroid vs. oral DMARD	Low 1RCT/Good	Unknown, single study	Indirect	Precise	Less radiographic progression in	Low
1 RCT					combination group up to 5 years	
N = 155 Three oral DMARDs plus corticosteroid vs. oral DMARD	Medium RCT/Fair	Unknown, single study	Direct	Precise	Higher remission in combination group at 2 years but not significant at 5 yrs	Low
1 RCT	Medium RCT/Fair	Unknown, single study	Indirect	Precise	Less radiographic progression in	Low
N = 199					combination group up to 5 years	
Three oral DMARDs vs. Biologic plus oral DMARD	Medium RCT/Fair	Unknown, single study	Direct	Precise	Improved disease activity for Biologic DMARD plus oral DMARD compared to three oral DMARDs	Low
1 RCT						
N = 258						

Table 1. Strength of evidence for Disease Activity and Radiographic Progression (KQ1) (continued)

Drug Comparison Number of Studies # of Subjects	Risk of Bias Design/ Quality	Consistency	Directness	Precision		Strength of Evidence
(1)Sequential monotherapy vs. (2)Step-up combination	Low 1RCT/Good	Unknown, single study	Direct	Precise	No difference in remission by four years.	Low
therapy vs. (3)initial combination therapy with prednisone vs.(4) initial combination therapy with infliximab 1 RCT N = 508	Low 1RCT/Good	Unknown, single study	Indirect	Precise	Less radiographic progression in groups 3 and 4 by four years	Low

ABA, abatacept; ACR, American College of Rheumatology; ADA, adalimumab; ANK, anakinra; DAS, disease activity score; DMARD, disease modifying antirheumatic drug; ETN, etanercept; GOL, golimumab; INF, infliximab; leflunomide, LEF; MTX, methotrexate; MTC, mixed treatment comparison; N, number; RA, rheumatoid arthritis rituximab, RIT; RCT, randomized controlled trial; sulfasalzine, SSZ; TCZ, tocilizumab; TNF, tumor necrosis factor; vs., versus.

^aThe dose of MTX used in this study is below the dose usually considered therapeutic. Thus this study does not provide evidence to determine how tocilizumab compares with MTC as it is generally used in clinical practice.

Strength of evidence for functional capacity and quality of life outcomes (KQ2)

Drug

For each comparison, the following tables provide the strength of evidence for functional capacity and quality of life outcomes within a single row, if both outcomes were available. Information related to functional capacity is provided in the upper part of each row; information related to quality of life is provided in the lower part of each row, when available. If only one study provided all of the evidence for a comparison and had consistent results for functional capacity and quality of life outcomes (i.e. finding no difference or one treatment better than the other), we inserted a single set of entries in the row, rather than repeat the same information twice.

Table 2. Strength of evidence for functional capacity and quality of life outcomes (KQ1 and KQ2)

Comparison Number of Studies # of Subjects Oral DMARD vs. Oral DMARD: Corticosteroid vs.	Risk of Bias Design/ Quality Medium RCT/ fair	Consistency Unknown, single study	Directness Direct	Precision Precise	Results Greater improvement in functional capacity and quality of life with prednisolone than with budesonide	Strength of Evidence
Corticosteroid 1 RCT					budesoriue	
N =143 Leflunomide	Low	Inconsistant	Direct	Impresies*	No alinically aignificant	Low
vs. MTX 2 RCTs	Low RCTs/ 2 fair	Inconsistent	Direct	Imprecise*	No clinically significant difference for change in functional capacity.	Low
N = 1481	Medium	Unknown,	Direct	Precise	Although some results	Low
	RCT/1 fair	single study			reached statistically significant differences favoring leflunomide (mean improvement in HAQ-DI: -0.45 vs0.26, P ≤ 0.01), neither study reported a difference reaching the MCID. Greater improvement in quality of life (SF-36 physical summary score, but not mental summary score) with LEF than MTX	
Leflunomide vs. Sulfasalazine	Medium RCT/fair	Unknown, single study	Direct	Precise	Greater improvement in functional capacity with LEF than SSZ	Low
1 RCT						
N = 358 Sulfasalazine	Low	Consistent	Direct	Precise	No difference in functional	Moderate
vs. MTX	RCTs/Fair				capacity	
3 RCTs	NO 13/1 all					
N = 479						

Table 2. Strength of evidence for functional capacity and quality of life outcomes (KQ1 and KQ2) (continued)

(continued)						
Drug						
Comparison						
Number of	Risk of Bias					0(
Studies	Design/	Consistancy	Directness	Bracisian	Populto	Strength of
# of Subjects Oral DMARD	Quality Low	Consistency Consistent	Directness	Precise	Results No difference in functional	Evidence Moderate
Combinations	LOW	Consistent	Direct	FIECISE	capacity	Moderate
VS.	RCTs/Fair				capacity	
Monotherapy	11010/1 0					
or						
Combinations						
with or without						
Corticoster-						
oids: SSZ + MTX vs. SSZ						
or MTX						
monotherapy						
3 RCTs						
N = 479	1	Operation	Discort	Inches de la constant	0	Madant
Oral DMARD + corticosteroid	Low	Consistent	Direct	Imprecise	Greater improvement in	Moderate
vs. Oral	RCTs/ Good,				functional capacity for subjects treated with oral	
DMARD	Fair				DMARD plus prednisolone	
	ı un				Bivi and prodringoione	
2 RCTs	Low	Unknown,	Direct	Imprecise	No difference in quality of	Low
	RCT/Good	single study			life	
N = 717						
4.507						
1 RCT						
N = 467						
Biologic	Medium	Unknown,	Direct	Imprecise	No difference in functional	Low
DMARD vs.		single study			capacity	
Biologic	RCT/Fair					
DMARD: ABA				Imprecise	Statistically significant	Low
vs. INF					difference between groups	
1 RCT					for quality of life (SF-36 PCS but not MCS) that did	
IRCI					not reach the MCID.	
N = 431					not reach the Wolb.	
ETN vs. INF	Medium	Inconsistent	Direct	Imprecise	Mixed results for	Insufficient
	Prospective				functional capacity (2 of 3	
3 prospective	cohorts/3 Fair				studies reported no	
cohort studies;					difference; 1 favored ETN)	
			5	.	5	
N = 2239	Medium to	Unknown,	Direct	Precise	Reported statistically	Insufficient
	High Prospective	single study			significantly greater improvement in quality of	
	cohort/1 Fair				life with ETN ($P = 0.001$),	
	22				but data NR (in Figure	
					only) and CIs appear to	
					overlap in the Figure	
ADA vs. ETN	Medium to	Unknown,	Direct	Imprecise	No difference in functional	Low
4	High	single study			capacity	
1 prospective	Decements:				No difference in available of	
cohort	Prospective cohort/Fair				No difference in quality of life	
N = 707	COHOLIZEALI				IIIC	

Table 2. Strength of evidence for functional capacity and quality of life outcomes (KQ1 and KQ2) (continued)

(continued)						
Drug						
Comparison						
Number of	Risk of Bias					
Studies	Design/	•	D :		D	Strength of
# of Subjects	Quality Medium to	Consistency			Results	Evidence
ADA vs. INF		Unknown,	Direct	Precise	Statistically significant	Low
1 prospective	High	single study			difference between groups favoring ADA for	
cohort;	Prospective				improvement in functional	
conort,	cohort/Fair				capacity that did not reach	
N = 707					the MCID (mean change	
					in HAQ: -0.42 vs0.26, P	
					< 0.05)	
					Reported statistically	Insufficient
					significantly greater	
					improvement in quality of	
					life with ADA ($P = 0.001$),	
					but data NR (in Figure	
					only) and CIs appear to	
Biologic	Medium	Unknown,	Direct	Precise	overlap in the Figure No difference in functional	Low
DMARD vs.		single study	2001		capacity for MTX naïve	
Oral DMARD:	RCT/Fair	omigro ottale,			subjects with early RA	
ADA vs. MTX					,	
1 RCT						
N = 799	Law		Discort		Missal as sulta for five stinual	l
ETN vs. MTX	Low	Inconsistent	Direct	Imprecise	Mixed results for functional capacity	Insufficient
2 RCTs	RCTs/1					
N. 4040	Good, 1 Fair					
N =1318	Medium	Unknown,	Direct	Improving	Easter improvement in	Low
1 RCT	RCT/1 Fair	single study	Direct	imprecise	Faster improvement in quality of life with ETN	Low
1101	NO1/11 all	Sirigic Study			(greater improvement at	
N = 632					12 weeks, but no	
-					difference from weeks 16	
					to 52)	
TCZ vs. MTX	Medium	Unknown,	Direct	Precise	Greater improvement in	Insufficient ^a
1 DCT	RCT/Fair	single study			functional capacity with TCZ than MTX	
1 RCT	NO I/Fall				(8mg/week) for patients	
N = 127					with active RA and an	
· · · · · ·					inadequate response to	
					MTX	
Biologic	Medium	Unknown,	Direct	Imprecise	No difference functional	Low
DMARD +		single study			capacity	
Biologic	RCT/Fair					
DMARD vs.					Greater improvement in	
Biologic DMARD: ETN +					physical, but not mental,	
ABA vs. ETN	•				health-related quality of life	
-						
1 RCTs						
N = 121						

Table 2. Strength of evidence for functional capacity and quality of life outcomes (KQ1 and KQ2)

(continued)	.g 0. 0		onan oapao	,	, 0 000 (
Drug						
Comparison	District Disc					
Number of Studies	Risk of Bias					Strongth of
# of Subjects	Design/ Quality	Consistency	Directness	Precision	Results	Strength of Evidence
Any Biologic	Low	Consistent	Direct		Greater improvement in	Moderate
DMARDs +	2011	Consistent	2000	p. co.co	functional capacity with	Wodorato
Oral DMARDs	RCTs/1				biologic + MTX	
vs. Biologic	Good, 1 Fair				-	
DMARDs ^D						
0.007	Low	Unknown,	Direct	Precise	Greater improvement in	Low
2 RCTs	RCT/1 Good	single study			quality of life with biologic + MTX	
N = 1495					+ IVITA	
Biologic	Medium	Unknown,	Direct	Precise	Greater improvement in	Low
DMARD + MTX		single study			functional capacity with	#
vs. Biologic	RCT/Fair	,			ADA + MTX for MTX-naïve	
DMARD in					subjects with early RA.	
MTX naïve						
subjects or those not						
recently on						
MTX ^b : ADA+						
MTX vs. ADA						
1 RCT						
N - 700						
N = 799 ETN + MTX vs.	Low	Unknown,	Direct	Precise	Greater improvement in	Low
ETN + IMTX VS.	LOW	single study	Direct	i recise	functional capacity and	LOW
	RCT/ Good	onigio otaay			quality of life with ETN +	
1 RCTs, 1					MTX for subjects with	
cohort study					active RA who failed at	
					least 2 oral DMARDs, but	
N = 696					were not on MTX for at	
Biologic	Low	Consistent	Direct	Precise	least 6 months. No difference in functional	Moderate
DMARD + Oral	LUW	COHSISTERIL	DIIECI	1 10030	capacity	MOUETALE
DMARD vs.	RCTs/2 Fair				capacity	
Biologic	Cohort/Fair				No difference in quality of	
DMARD in					life	
subjects with						
active RA						
despite treatment with						
the same Oral						
DMARD ^b : ETN						
+ DMARD vs.						
ETN						
0 DOT: 4						
2 RCTs, 1						
cohort study						
N = 3609						

Table 2. Strength of evidence for functional capacity and quality of life outcomes (KQ1 and KQ2)

(continued) Drug Comparison Number of Risk of Bias **Studies** Design/ Strength of # of Subjects Quality **Consistency Directness Precision** Results **Evidence** Any Biologic Consistent Direct Precise Greater improvement in High Low DMARDs + functional capacity with **Oral DMARD** RCTs/ 5 Fair. biologic + oral DMARD vs. Oral 2 Good **DMARD** Cohort/Fair 7 RCTs, 1 Consistent Direct Precise Greater improvement in Moderate Low RCTs/3 Fair, quality of life with biologic cohort study + oral DMARD 1 Good N = 7516**Biologic** Low Unknown, Imprecise Statistically significant Direct Low DMARD + Oral single study differences for DMARD vs. RCT/Good improvement in functional Oral DMARD: capacity and quality of life (SF-36 PCS) with ABA + ABA + MTX vs. MTX, but differences did MTX not reach MCIDs 1 RCT N = 509ADA + MTX vs. Medium Unknown, Direct Precise Greater improvement in Low MTX single study functional capacity with RCT/Fair ADA + MTX 1 RCT N = 799ETN + oral Greater improvement in Moderate Low Consistent Direct Precise DMARD vs. functional capacity with oral DMARD RCTs/2 Fair, ETN + oral DMARD (MTX or SSZ) 1 Good Cohort/Fair 3 RCTs. 1 cohort study Consistent Precise Greater improvement in Moderate Low Direct RCTs/ 1 Fair, quality of life with ETN + N = 45221 Good oral DMARD GOL + MTX vs. Medium Unknown. Direct Greater numerical Imprecise Low MTX single study improvement in functional RCT/Fair capacity with GOL 50 + 1 RCT MTX compared with MTX, but difference was not N = 637statistically significantly (Median % improvement in HAQ-DI: 43.65 vs. 36.95, P = 0.141) INF + MTX vs. Greater improvement in Medium Unknown, Direct Precise Low MTX functional capacity and single study RCT/Fair quality of life with INF + 1 RCT MTX N = 1049

Table 2. Strength of evidence for functional capacity and quality of life outcomes (KQ1 and KQ2) (continued)

(continued)						
Drug Comparison Number of Studies	Risk of Bias Design/					Strength of
# of Subjects	Quality	Consistency	Directness	Precision	Results	Evidence
Biologic DMARD + Oral DMARD vs. Biologic DMARD + Oral DMARD: Anti- TNF + MTX vs.	Medium Cohort/Fair	Unknown, single study	Direct	Imprecise	No difference in functional capacity	Low
anti-TNF + LEF 1 cohort						
N = 1218						
Strategies in Early RA: Two oral DMARDs plus corticosteroid vs. oral DMARD	Low RCT/Good	Unknown, single study	Direct	Precise	More rapid improvement in functional capacity (comparing groups at 28 weeks), but no difference by 56 weeks	LOW
1 RCT						
N = 155 Three oral	Medium	Unknown,	Direct	Precise	Less work disability in the	Low
DMARDs plus corticosteroid vs. oral DMARD	RCT/Fair	single study	Zii Got	redice	combination strategy group	2011
N = 199						
Other combination strategies: Sequential monotherapy vs. Step-up combination therapy vs. initial combination therapy with prednisone vs. initial combination	Low RCT/Good	Unknown, single study	Direct	Precise	More rapid improvement in functional capacity in groups 3 and 4 than in groups 1 and 2(statistically significantly better at 3, 6, 9, and 12 months). By two years, improvement was maintained in all groups, but there were no statistically significant differences between groups Similar pattern was found for improvement in physical health-related quality of life	Low
infliximab						
infliximab 1 RCT					quality of life	

ABA, abatacept; ADA, adalimumab; DMARD, disease modifying antirheumatic drug; ETN, etanercept; GOL, golimumab; INF, infliximab; MCID, minimal clinically important difference; MTX, methotrexate; N, number; RCT, randomized controlled trial; TCZ, tocilizumab; vs., versus.

*This was considered imprecise based on the high degree of uncertainty around the effect size, partly due to one of the studies

not reporting any quantitative information.

The dose of MTX used in this study is below the dose usually considered therapeutic. Thus, this study does not provide evidence to determine how tocilizumab compares with MTX as it is generally used in clinical practice.

For Biologic DMARD + Oral DMARD vs. Biologic DMARD, we stratified by population because results differed based on the population

enrolled

Strength of evidence for Harms, Tolerability, Adverse Effects or Adherence for Corticosteroids (KQ3)

For each comparison, the following tables (Table 3 and 4) provide the strength of evidence for harms, tolerability, adverse effects, and adherence. The table is organized by drug comparisons among corticosteroids, oral DMARDs, and biologic DMARDs. Comparisons are further grouped by subheadings for overall tolerability specific adverse event categories, and adherence. Categories with no evidence are excluded from the table.

Outcome Drug Comparison Number of Studies # of Subjects	Risk of Bias Design/ Quality	Consistency	Directness	Precision	Results	Strength of Evidence
Overall Tolerability: Corticosteroid vs. Corticosteroid	Medium RCT/ fair	Unknown, single study	Direct	Precise	Similar tolerability with budesonide and prednisolone	Low
1 RCT						
N = 143	NA . P	11.1	L. P f	1	Described to	L. CC. C.
Overall Tolerability: Corticosteroid vs. no corticosteroid	Medium Retrospective cohort/1 fair	Unknown, single study	Indirect	Imprecise	Dose dependent increased risk of fracture, infection, and GI events	Insufficient
1 cohort study						
N = 224 Cardiovascular	Medium	Inconsistent	Direct	Imprecise	Mixed results; decreased	Low
and	Wediam	medialatent	Direct	Impredise	cardiovascular risk in one	LOW
Cerebrovascular Events:	RCT/fair				study, but increased risk of cardiovascular events	
Corticosteroid vs. no corticosteroid	observational/ 4 fair				and stroke in others	
1 RCT						
N = 467						
4 observational						
N = 122,817			1 12 1	<u> </u>	0 " 1 " 1	
Infection: Corticosteroid vs.	Low	Consistent	Indirect	Precise	Corticosteroids increase risk of serious infection,	Moderate
no corticosteroid	observational/ 7 fair, 2 good				TB, and herpes zoster	
9 observational	, 3					
N = 268,383						
Other Adverse Events: Corticosteroid vs. no corticosteroid	Medium observational/ 3 fair	Unknown, single studies	Indirect	Imprecise	Risk of septic (infectious) arthritis and interstitial lung disease increased with corticosteroids	Low
3 observational						
N = 161,838						

RCT, randomized controlled trial; TB, tuberculosis; vs., versus.

Table 4. Stren	gth of eviden	ce for oral Di	/IARDs (KQ:	3)		
Outcome						
Drug						
Comparison						
Number of	Risk of Bias					
Studies	Design/					Strength of
# of Subjects	Quality	Consistency	Directness	Precision	Results	Evidence

Overall Low Inconsistent Direct Precise Similar tolerability and Low discontinuation rates for Oral DMARD vs. RCTs/3 fair HCQ, LEF, MTX, and Crol DMARD

Oral DMARD

Retrospective

3 RCT

Cohort/1 fair

Retrospective

The Q, LEF, MTX, and SSZ, with the exception of one study noting better tolerability for LEF and one study noting better tolerability with MTX

analysis/2

1 observational good, 1 fair

N = 40,594;

3 meta-analysis

N = 7,245

Overall Low Inconsistent Direct

good, 1 fair

cohort/1fair

Overall Low Inconsistent Direct Precise Similar withdrawal rates Moderate due to adverse events

Oral DMARD vs.RCTs/2 good,with exception of oneOral or Biologic4 fairstudy showing increasedDMARDwithdrawal for SSZ +combinationcohort/2 fairMTX combination;

DMARD combination may 6 RCTs meta- have more adverse

analysis/1 events

2 observational

N = 349

N = 841

2 meta-analysis

N = 1,735

OverallLowConsistentDirectPreciseSimilar tolerability and rates of serious adverseModerate rates of serious adverse events; addition ofOral DMARD +RCTs/1 good,events; addition of

adverse events

Corticosteroid 3 fair corticosteroid to oral vs. Oral DMARD DMARD DMARD oral pmared retrospective withdrawal due to

4 RCT N = 1202

1 observational

N = 154

Drug Comparison Number of Risk of Bias Studies Design/ Strength of	
Number of Risk of Bias	
STIINIGE INCINN	
# of Subjects Quality Consistency Directness Precision Results Evidence Cardiovascular Medium Consistent Indirect Imprecise Oral DMARDs and Low	
and combinations of oral	
Cerebrovascular observational/ DMARDS may reduce	
Events: 4 fair cardiovascular risk; risk	
Oral DMARD vs. reductions were larger in	
Oral DMARD vs. magnitude with LEF	
Oral DMARD combination	
Combination	
4 observational	
N = 119,929	
Hepatic Events: Medium Consistent Indirect Imprecise Similar hepatic event Low	
Oral DMARD vs. rates for LEF, MTX, and	
Oral DMARD vs. observational/ other oral DMARDs Biologic DMARD 2 fair	
Siologio Sintito 2 Ian	
2 observational	
N = 82,479	
Infection: Medium Inconsistent Direct Imprecise Mixed results; Low	
Oral DMARD vs. inconsistent differences	
Oral DMARD observational/ for infection rates for comparisons of HCQ,	
6 observational LEF, MTX, and SSZ	
,,	
N = 142,522	
Oral DMARD vs. Medium Inconsistent Indirect Imprecise Mixed results; increased Insufficient risk of infection in some	
no Oral DMARD risk of infection in some observational/ studies, while other show	
6 observational 6 fair decreased infection risk	
N = 236,151	
Interstitial Lung Medium Inconsistent Direct Imprecise Mixed results; increased Insufficient	
Disease: risk with LEF in one study, while another	
Oral DMARD vs. observational study, while another Oral DMARD / 2 fair study found no	
differences among HCQ,	
2 observational LEF, MTX, and SSZ	
N = 80,332	
Malignancy: Medium Consistent Direct Imprecise No differences in Low Oral DMARD vs.	
Oral DMARD vs. lymphoma for MTX and SSZ, and no difference in	
corticosteroid / 1 good, 1 non-melanoma skin	
fair cancer for LEF and MTX	
2 observational	
N = 16,545	

Table 4. Strength of evidence for oral DMARDs (KQ3)

Outcome Drug Comparison Number of Studies # of Subjects	Risk of Bias Design/ Quality	Consistency	Directness	Precision	Results	Strength of Evidence
Other Adverse Events:	Medium	Unknown,	Indirect	Imprecise		Low
Oral DMARD vs. Oral DMARD	RCT/1 good;	single studies			risk of septic arthritis; LEF + corticosteroids increase risk of wound healing	
1 RCT	observational / 3 fair;				complications; no association of oral DMARDs with sinus	
N = 795	review 1 fair				problems; no increased risk of renal damage with	
3 observational					combination; insufficient information on fertility,	
N = 80,332					pregnancy, and lactation	
1 review						
N = 366						

 $DMARD, disease-modifying \ antirheumatic \ drug; HCQ, hydroxychloroquine; LEF, leflunomide; MTX, methotrexate; RCT, randomized controlled trial; SSZ, sulfasalazine.$

^{*} Eligible RCTs included double-blind, randomized, placebo- or MTX-controlled trials lasting at least 12 weeks to determine comparative tolerability, safety, or efficacy. To be included, trials must have reported on at least one of the following: overall withdrawals, withrawals because of lack of efficacy, or withdrawals because of adverse events.

Table 5. Strength of evidence for biologic DMARDs (KQ3)

Table 5. Streng	th of evidence	e for biologi	c DMARDs	(KQ3)		
Outcome	Diels of Dies					
Drug Comparison Number of Studies						Strength of
# of Subjects	Quality	Consistency	Directness	Precision	Results	Evidence
Overall Tolerability: Withdrawals Total: Biologic DMARD vs. Placebo	Medium	Inconsistent	Indirect	Precise	Odds ratio of withdrawal overall: 0.51 (0.40-0.65) Indirect Comparisons: No differences for most comparisons, except certolizumab pegol, etanercept, and rituximab had more favorable	Low
N = 18,029 Studies included in mixed treatment comparison meta- analysis					overall withdrawal profiles than most other biologic DMARDs	
Overall	Medium	Consistent	Indirect	Precise	Odds ratio of withdrawal	Low
Tolerability: Withdrawals due to Lack of Efficacy: Biologic DMARD vs. Placebo	RCTs*				due to lack of efficacy: 0.21 (0.17-0.27) Indirect Comparisons: Certolizumab pegol had fewer withdrawals due to lack of efficacy than adalimumab, anakinra, and infliximab. All but adalimumab and	
N = 13,079 Studies included in mixed treatment comparison meta-					golimumab had fewer withdrawals than anakinra due to lack of efficacy.	
analysis	Maraliana	0	la dia at	Danaina	Odda astis of with doswal	1
Overall Tolerability: Withdrawals due to Adverse Events: Biologic DMARD vs. Placebo	Medium RCTs*	Consistent	Indirect	Precise	Odds ratio of withdrawal due to adverse events: 1.43 (1.18-1.74) Indirect Comparisons: No differences for most comparisons, except certolizumab pegol and infliximab had more	Low
43 RCT					withdrawals due to adverse events than	
N = 11,243 Studies included in mixed treatment comparison meta-analysis					abatacept, etanercept, and rituximab. Etanercept had fewer withdrawals due to adverse events than adalimumab, anakinra, or tocilizumab	
Overall and	Medium	Consistent	Direct	Precise	Serious adverse events	Low
Serious Adverse Events: Biologic DMARD vs. Biologic DMARD	RCT/fair; retrospective cohort/fair				were more common with INF than with ABA, ADA, or ETN	
1 RCT						
N = 431						
1 observational						
N = 2,364						

Table 5. Strength	n of evidence	for biologic	DMARDs ((KQ3)	(continued)	

Outcome Drug Comparison Number of Studies # of Subjects	Design/ Quality	Consistency		Precision		Strength of Evidence
Overall and Serious Adverse Events: Biologic DMARD vs. No Biologic DMARD 34 RCT N = 18,979 6 observational N = 18,476 6 meta-analysis	Low RCT/31 fair; 3 good; observational /6 fair; meta- analysis/2 good, 4 fair	Inconsistent	Indirect	Precise	Mixed results; similar adverse event profiles among biologic DMARDs, with some studies indicating higher adverse event rates for biologic DMARDs given alone or in combination with oral DMARDs compared with placebo or no treatment.	Low
N = 29,348 Cardiovascular and Cerebrovascular Events: Biologic DMARD vs. No Biologic DMARD 1 RCT N = 150 11 observational N = 159,735	High RCT/1 fair; cohort, case- control, or other design/ 8 fair, 3 good	Inconsistent	Indirect		Mixed results; 1 cohort study found protective effect for heart failure, while 3 others found increased risk of heart failure with biologic DMARDs. 1 nested-case control study found no difference in risk for cardiovascular events, while 2 other studies found a protective effect with biologic DMARDs. 1 case-control study found no increased risk of stroke, and 2 cohort studies found no increased risk of MI.	Low
Infections: Biologic DMARD vs. Biologic DMARD 1 RCT N = 431 2 observational N = 24,369	Medium RCT/1 fair; Prospective cohort/2 fair	Inconsistent	Direct	Imprecise	Mixed results; 1 RCT reported more infections with INF than ABA (<i>P</i> = NR). 2 prospective cohort studies reported no differences in risk of serious infections comparing among ADA, ETA, and INF.	Low

Table 5. Strength of evidence for biologic DMARDs (KQ3) (continued)

Table 5. Streng	tn of evidend	e tor biologi	C DIVIARDS	(NU3) (cor	ninuea)	
Outcome Drug Comparison Number of Studies						Strength of
# of Subjects	Quality	Consistency	Directness	Precision	Results	Evidence
Infections: Biologic DMARD vs. No Biologic DMARD	Low RCT/5 fair, 1 good;	Inconsistent	Indirect	Precise	Mixed results; most studies found either a trend towards increased infections or statistically significant increase in	Moderate
6 RCT	observational / 20 fair, 6				infections with biologic DMARDs. One meta-	
N = 5,014;	good				analysis reported a pooled odds ratio for	
26 observational	meta- analysis/5				serious infections of 2.0 (95% CI, 1.3-3.1) relative	
N = 391,403	fair, 1 good				to placebo, another reported an increased	
6 meta-analysis					risk of infection only with INF, and another found an increased risk of infection only with ANK	
Infusion and Injection Site Reactions: Biologic DMARD vs. Biologic DMARD 1 RCT N = 431 1 observational	Medium RCT/1 fair; prospective cohort/1 fair, meta- analysis/1 good	Consistent	Direct	Precise	Mixed results; 1 RCT reported more infusion reactions with INF than ABA (<i>P</i> = NR) and 1 retrospective cohort study reported more infusion reactions INF than with ADA and ETA. 1 metanalysis found more reactions with ANK than ADA or ETA.	Low
N = 14,013						
1 meta-analysis Interstitial Lung Disease: Biologic DMARD vs. Biologic DMARD	Medium prospective cohort/1 fair	Unknown	Direct	Imprecise	Current treatment with ETA and INF not associated with hospitalization for interstitial lung disease; Past treatment was for ETA (HR, 1.7; 95% CI,	Low
N = 17,598					1.0-3.0; <i>P</i> = 0.056) and INF (HR, 2.1; 95% CI, 1.1-3.8; <i>P</i> = 0.019)	
Malignancies: Biologic DMARD vs. Oral DMARD 6 observational	Medium Cohort/5 fair, 1 good	Inconsistent	Indirect	Imprecise	Mixed results; higher risk of lymphoma with biologic DMARDs in 1 study, but no difference in risk in another study. No increased risk of solid	Low
N = 135,498					cancers or other malignancies for biologic DMARDs	

Table 5. Strength of evidence for biologic DMARDs (KQ3) (continued)

Outcome				, , , , , , , ,	/	
Drug Comparison Number of Studies	Design/					Strength of
# of Subjects	Quality	Consistency	Directness	Precision	Results	Evidence
Malignancies: Biologic DMARD	Medium	Unknown	Direct	Imprecise	Mixed results; some studies suggest small	Low
vs. no Biologic	Observationa				increased risk of	
DMARD	I/ 6 fair,				malignancies including: lymphoma, nonmelanotic	
6 observational	meta- analysis/3				skin cancer, and melanoma	
N = 70,377	fair, 1 good					
4 meta-analysis						
1 AERS data						

ABA, abatacept; ADA, adalimumab; ANK, anakinra; DMARD, disease modifying antirheumatic drug; ETN, etanercept; GOL, golimumab; INF, infliximab; leflunomide, LEF; MTX, methotrexate; N, number; RA, rheumatoid arthritis; RCT, randomized controlled trial; vs., versus.

^aThe dose of MTX used in this study is below the dose usually considered therapeutic. Thus this study does not provide evidence to determine how tocilizumab compares with MTC as it is generally used in clinical practice.

Table 6. Strength of evidence for adherence (KQ3)

Drug Comparison Number of Studies						Strength of
# of Subjects	Quality	Consistency	Directness	Precision	Results	Evidence
Oral DMARD vs. Oral DMARD	High	Inconsistent	Direct	Imprecise	No apparent differences in adherence among oral	Low
5 RCT	RCT/5 fair				DMARDs	
N = 1,924						
Biologic DMARD vs. Biologic	High	Inconsistent	Direct	Imprecise	Better adherence for INF than ETN in 1 study,	Insufficient
DMARD	cohort/5 fair				similar adherence for INF and ETN in a second	
5 observational					study, worse adherence for INF than ETN in a	
N = 14,250					third study	
Biologic DMARD vs. Oral DMARD	High	Unknown	Direct	Imprecise	Better adherence for LEF, ADA, ETN, and INF	Low
1 observational	Cohort/1 fair				monotherapy compared with MTX	
N = 6,018						
Biologic DMARD vs. placebo	Medium	Consistent	Indirect	Imprecise	No apparent differences in adherence	Insufficient
2 RCT	RCT/1 good, 1 fair					
N = 2,066						

ADA, adalimumab; DMARD, disease modifying antirheumatic drug; ETN, etanercept; INF, infliximab; leflunomide, LEF; MTX, methotrexate; N, number; RCT, randomized controlled trial; vs., versus.

Table . Strength of evidence for Benefits and Harms for Selected Populations (KQ4)

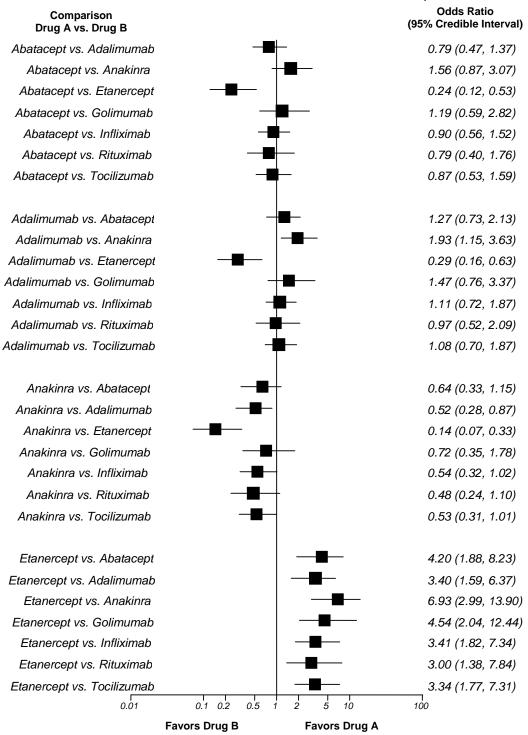
For each comparison, the following table provides the strength of evidence for benefits and harms. The table is organized by subgroup, then by drug comparisons.

Outcome	o organizou	by cabgicap	, thom by an	ag compa	11001101	
Drug Comparison Number of Studies	Risk of Bias Design/					Strength of
# of Subjects	Quality	Consistency	Directness	Precision	Results	Evidence
Stage of Disease: MTX vs. ETA vs. MTX+ETA 1 Post hoc analysis N = 1,091	Medium to High Posthoc analysis/Fair	Unknown, single study	Direct	Imprecise	Moderate RA groups on MTX monotherapy or combinations had better DAS28 scores than those with severe disease; HAQ scores better in moderate RA groups on monotherapy; severe RA monotherapy groups had greater mean change scores in DAS28 from baseline than moderate RA	Low
Age: MTX in age groups	Medium	Unknown, single study	Direct	Imprecise	Inverse relationship between	Low
1 Systematic Review	Systematic Review/Fair	single study			age and risk for major clinical improvement	
N = 496						
Age: Various agents in the elderly	Medium to High	Unknown, single study	Direct	Imprecise	Oral glucocorticoids and cytotoxic immunosuppressive agents (such as LEF) increased risks for cardiovascular events. No differences in cardiovascular events for biologics (ADA, ETN, INF, ANK)	Low
1 Case control study N = 946	Case control study/Fair					
Concomitant Therapies: ANK	Medium	Unknown, single study	Direct	Imprecise	No differences in adverse events when taking	Low
1 RCT	RCT/Fair	onigio olday			antihypertensive, antidiabetic, or statin pharmacotherapies	
N = 1,399					or statin pharmacotherapies	
Comorbidities: ANK use in those with high risk comorbid conditions 1 RCT	Medium RCT/Fair	Unknown, single study	Direct	Imprecise	No differences between treatment groups in regard to serious adverse events or overall infectious events	Low
N = 951						
Comorbidities: MTX use in those with renal impairment 1 Systematic	Medium Systematic Review/Fair	Unknown, single study	Direct	Imprecise	Risk of severe toxicity and respiratory toxicity higher in those with greater renal impairment	Low
Review N = 496						

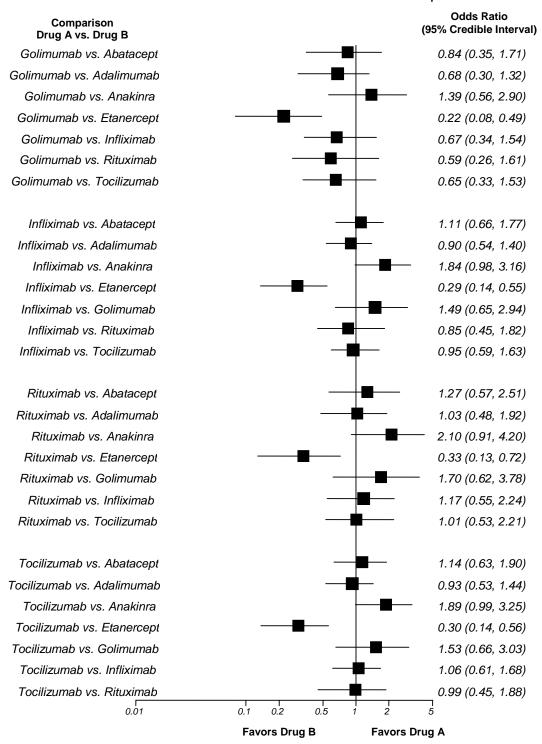
AKA, anakina; CHF, congestive heart failure; DAS, disease activity score; ETA, etanercept; HAQ, health assessment questionnaire, MTX methotrexate; RA, rheumatoid arthritis; RCT, randomized controlled trial; TNF, tumor necrosis factor.

Appendix J. Mixed Treatment Comparisons Results: ACR 20 and ACR 70

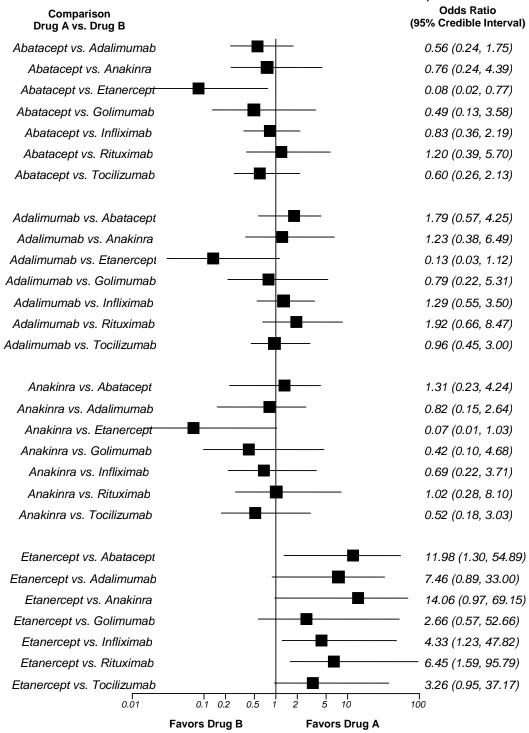
Relative Treatment Effect for ACR20 Response



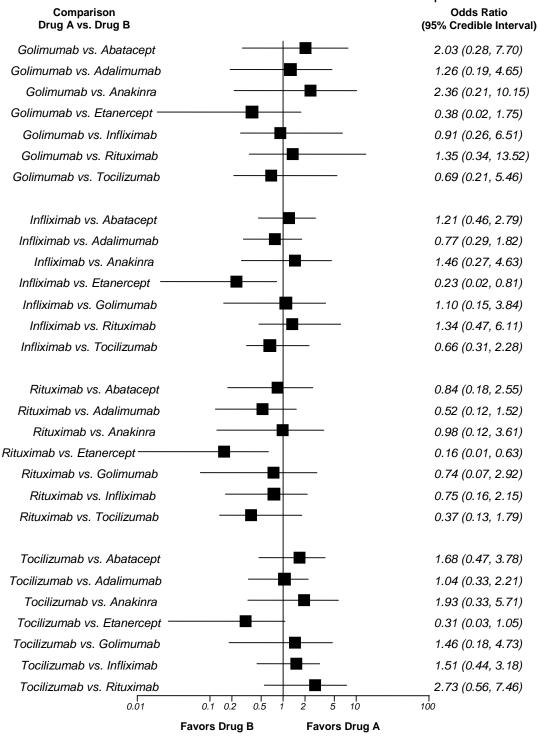
Relative Treatment Effect for ACR20 Response



Relative Treatment Effect for ACR70 Response



Relative Treatment Effect for ACR70 Response



Appendix K. Mixed Treatment Comparisons Sensitivity Analysis Methods

Mixed Treatment Comparison Sensitivity Analysis Methods

A total of 34 studies were identified for potential inclusion in the MTC meta-analysis comparing the efficacy of biologic DMARDs. The potential studies were:

- Three studies evaluating abatacept: AIM 2006, ¹Kremer 2003, ² and ATTEST 2008, ³
- Eight studies evaluating adalimumab: ARMADA 2003, STAR 2003, Keystone 2004, van de Putte 2003, van de Putte 2004, Kim 2007, CHANGE 2008, and Chen 2008.
- Three studies evaluating anakinra: Cohen 2002, ¹² Cohen 2004, ¹³ and Bresnihan 1998. ¹⁴
- Three studies evaluating certolizumab pegol: RAPID-1 2008, ¹⁵ RAPID-2 2009, ¹⁶ and FAST4WARD 2009, ¹⁷
- Four studies evaluating etanercept: Moreland 1999, ¹⁸ Weinblatt 1999, ¹⁹ Lan 2004, ²⁰ Moreland 1997, ²¹
- Two studies evaluating golimumab: GO-FORWARD 2009, ²² and Kay 2008, ²³
- Six studies evaluating infliximab: ATTRACT 1999,²⁴ Abe 2006,²⁵ Kavanaugh 2000,²⁶ START 2006,²⁷ Zhang 2006,²⁸ ATTEST 2008,³ (listed twice as it included comparisons with both abatacept and infliximab)
- Two studies evaluating rituximab: Edwards 2004, ²⁹ and SERENE 2010, ³⁰
- Four studies evaluating tocilizumab: LITHE 2010, 31 OPTION 2008, 32 TOWARD 2008, 33 and CHARISMA 2006, 34

We reviewed all 34 studies for sources of heterogeneity and to consider whether to remove any studies that we did not feel were appropriate to include in the analyses. We considered factors such as handling of missing data, early escape design, unexpected high or low treatment response, study duration, and use of monotherapy treatment. Table 1 summarizes our approach for addressing the potential sources of heterogeneity. Based on our findings, we decided to exclude four studies, CHANGE 2008, ¹⁰ RAPID-1 2008, ¹⁵ RAPID-2 2009, ¹⁶ and FAST4WARD 2009, ¹⁷ because of heterogeneity due to early escape study design. Other sources of heterogeneity were explored through four sensitivity analyses. The results of these analyses are presented and discussed in Chapter 3.

Table 1. Approach	for Addressing Potential Sources of He	eterogeneity
Potential Source of Heterogeneity	Description	Approach
Missing Data	Trials were evaluated for their handling of missing data for ACR50. The majority of trials either used a Last Observation Carried Forward (LOCF) approach for the components that comprise ACR50 or imputed missing ACR data at the endpoint as non-responders (NRI).	Use of different imputation approaches could lead to important differences in estimated treatment effects. Studies were reviewed to investigate whether one biologic exclusively used one approach compared to another biologic. Since ACR data for any one biologic included a mix of studies that used both LOCF and NRI, no trials were excluded based on choice of imputation approach alone.
Early escape design	Trials were evaluated for offering rescue therapy or early escape for patients who failed to achieve a minimal ACR response at a pre-specified time point in the trial.	Several trials offered some sort of rescue therapy at a pre-defined timepoint in the study, but only four trials had a mandatory early escape design and did not report outcomes prior to the early escape. There were a large number of crossovers (from placebo to active treatment) in these studies that might lead to inaccurate calculations of treatment effects. As a result, four studies (CHANGE 2008, 10 RAPID-1 2008, 15 RAPID-2 2009, 16 and FAST4WARD 2009, 17) were not included in our main MTC analysis. These four studies included all three potentially eligible studies of certolizumab pegol. We added the four studies back in a sensitivity analysis to gauge potential impact on overall results. As a result of this approach, certolizumab pegol is now only included in the sensitivity analysis results in Chapter 3. A fifth study, GO-FORWARD 2009, 22 evaluating goliumumab also had a mandatory early escape design, but ACR50 data were available at time of early escape, so this study was kept in the analysis and the outcomes prior to early escape were used.
Monotherapy	Some trials included in the MTC did not have patients in the relevant arms on a	In order to separate out the effects that combination therapy may have on the relative treatment effects, monotherapy trials were
	background dose of Methotrexate.	removed in a sensitivity analysis.
Study Duration	Studies included in the main MTC meta-	In order to evaluate whether study duration
	analysis had durations of three months or	influenced our findings, and to compare
	more.	with other analyses that have used a 6
		month cutoff, the ACR50 analysis was
		rerun with studies of durations of 22 weeks or longer (approximately 6 months).
High or low ACR response	Trials were evaluated for unexpected high treatment response or low placebo response.	Two trials with etanercept, Lan 2004, ²⁰ and Moreland 1997, ²¹ had both a high ACR50 response and low placebo response. Due to the relatively large differences between treatment and placebo response, we removed these two trials in a sensitivity analysis.

References

- 1. Kremer JM, Genant HK, Moreland LW, Russell AS, Westhovens R, et al. Effects of abatacept in patients with methotrexate-resistant active rheumatoid arthritis A randomized trial. Annals of Internal Medicine (USA) 2006:865-76.
- 2. Kremer JM, Westhovens R, Leon M, Di Giorgio E, Alten R, Steinfeld S, et al. Treatment of rheumatoid arthritis by selective inhibition of T-cell activation with fusion protein CTLA4Ig. N Engl J Med 2003:1907-15.
- 3 .Schiff M, Keiserman M, Codding C, Songcharoen S, Berman A, Nayiager S, et al. Efficacy and safety of abatacept or infliximab vs placebo in ATTEST: a phase III, multi-centre, randomised, double-blind, placebo-controlled study in patients with rheumatoid arthritis and an inadequate response to methotrexate. Ann Rheum Dis 2008:1096-103.
- 4. Weinblatt ME, Keystone EC, Furst DE, Moreland LW, Weisman MH, Birbara CA, et al. Adalimumab, a fully human anti-tumor necrosis factor alpha monoclonal antibody, for the treatment of rheumatoid arthritis in patients taking concomitant methotrexate: the ARMADA trial. Arthritis Rheum. 2003 Jan;48(1):35-45.
- 5. Furst DE, Schiff MH, Fleischmann RM, Strand V, Birbara CA, Compagnone D, et al. Adalimumab, a fully human anti tumor necrosis factor-alpha monoclonal antibody, and concomitant standard antirheumatic therapy for the treatment of rheumatoid arthritis: results of STAR (Safety Trial of Adalimumab in Rheumatoid Arthritis). J Rheumatol. 2003 Dec;30(12):2563-71.
- 6. Keystone EC, Kavanaugh AF, Sharp JT, Tannenbaum H, Hua Y, Teoh LS, et al. Radiographic, clinical, and functional outcomes of treatment with adalimumab (a human anti-tumor necrosis factor monoclonal antibody) in patients with active rheumatoid arthritis receiving concomitant methotrexate therapy: a randomized, placebocontrolled, 52-week trial. Arthritis Rheum. 2004 May;50(5):1400-11.
- 7. van de Putte LB, Rau R, Breedveld FC, Kalden JR, Malaise MG, van Riel PL, et al. Efficacy and safety of the fully human anti-tumour necrosis factor alpha monoclonal antibody adalimumab (D2E7) in DMARD refractory patients with rheumatoid arthritis: a 12 week, phase II study. Ann Rheum Dis. 2003 Dec;62(12):1168-77.
 - 8. van de Putte LB, Atkins C, Malaise M, Sany J, Russell AS, van Riel PL, et al. Efficacy and safety of adalimumab as monotherapy in patients with rheumatoid arthritis for whom previous disease modifying antirheumatic drug treatment has failed. Ann Rheum Dis. 2004 May;63(5):508-16.
 - 9. Kim HY, Lee SK, Song YW, Yoo DH, Koh EM, Yoo B, et al. A randomized, double-blind, placebo-controlled, phase III study of the human anti-tumor necrosis factor antibody adalimumab administered as subcutaneous injections in Korean rheumatoid arthritis patients treated with methotrexate. APLAR Journal of Rheumatology 2007:9-16.
 - 10. Miyasaka N. Clinical investigation in highly disease-affected rheumatoid arthritis patients in Japan with adalimumab applying standard and general evaluation: the CHANGE study. Mod Rheumatol 2008:252-62.
 - 11. Chen DY, Chou SJ, Hsieh TY, Chen YH, Chen HH, Hsieh CW, et al. Randomized, double-blind, placebo-controlled, comparative study of human anti-TNF antibody adalimumab in combination with methotrexate and methotrexate alone in Taiwanese patients with active rheumatoid arthritis. 2009.
 - 12. Cohen S, Hurd E, Cush J, Schiff M, Weinblatt ME, Moreland LW, et al. Treatment of rheumatoid arthritis with anakinra, a recombinant human interleukin-1 receptor antagonist, in combination with methotrexate: results of a twenty-four-week, multicenter, randomized, double-blind, placebo-controlled trial. Arthritis Rheum. 2002 Mar;46(3):614-24.
 - 13. Cohen SB, Moreland LW, Cush JJ, Greenwald MW, Block S, Shergy WJ, et al. A multicentre, double blind, randomised, placebo controlled trial of anakinra (Kineret), a recombinant interleukin 1 receptor antagonist, in patients with rheumatoid arthritis treated with background methotrexate. Ann Rheum Dis. 2004 Sep;63(9):1062-8.
 - 14. Bresnihan B, Alvaro-Gracia JM, Cobby M, Doherty M, Domljan Z, Emery P, et al. Treatment of rheumatoid arthritis with recombinant human interleukin-1 receptor antagonist. Arthritis Rheum 1998:2196-204.

- 15. Keystone E, Heijde D, Mason D, Jr., Landewe R, Vollenhoven RV, Combe B, et al. Certolizumab pegol plus methotrexate is significantly more effective than placebo plus methotrexate in active rheumatoid arthritis: findings of a fifty-two-week, phase III, multicenter, randomized, double-blind, placebo-controlled, parallel-group study. *Arthritis Rheum* 2008:3319-29.
- 16. Smolen J, Landewe RB, Mease P, Brzezicki J, Mason D, Luijtens K, et al. Efficacy and safety of certolizumab pegol plus methotrexate in active rheumatoid arthritis: the RAPID 2 study. A randomised controlled trial. *Ann Rheum Dis* 2009:797-804.
- 17. Fleischmann R, Vencovsky J, van Vollenhoven RF, Borenstein D, Box J, Coteur G, et al. Efficacy and safety of certolizumab pegol monotherapy every 4 weeks in patients with rheumatoid arthritis failing previous disease-modifying antirheumatic therapy: the FAST4WARD study. Ann Rheum Dis. 2009 Jun;68(6):805-11.
- 18. Moreland LW, Schiff MH, Baumgartner SW, Tindall EA, Fleischmann RM, Bulpitt KJ, et al. Etanercept therapy in rheumatoid arthritis. A randomized, controlled trial. Ann Intern Med. 1999 Mar 16;130(6):478-86.
- 19. Weinblatt ME, Kremer JM, Bankhurst AD, Bulpitt KJ, Fleischmann RM, Fox RI, et al. A trial of etanercept, a recombinant tumor necrosis factor receptor:Fc fusion protein, in patients with rheumatoid arthritis receiving methotrexate. N Engl J Med. 1999 Jan 28;340(4):253-9.
- 20. Lan JL, Chou SJ, Chen DY, Chen YH, Hsieh TY, Young M, Jr. A comparative study of etanercept plus methotrexate and methotrexate alone in Taiwanese patients with active rheumatoid arthritis: a 12-week, double-blind, randomized, placebo-controlled study. J Formos Med Assoc. 2004 Aug;103(8):618-23.
- 21. Moreland LW, Baumgartner SW, Schiff MH, Tindall EA, Fleischmann RM, Weaver AL, et al. Treatment of rheumatoid arthritis with a recombinant human tumor necrosis factor receptor (p75)-Fc fusion protein. N Engl J Med. 1997 Jul 17;337(3):141-7.
- 22. Keystone EC, Genovese MC, Klareskog L, Hsia EC, Hall ST, Miranda PC, et al. Golimumab, a human antibody to tumour necrosis factor {alpha} given by monthly subcutaneous injections, in active rheumatoid arthritis despite methotrexate therapy: the GO-FORWARD Study. *Ann Rheum Dis* 2009:789-96.
- 23. Kay J, Matteson EL, Dasgupta B, Nash P, Durez P, Hall S, et al. Golimumab in patients with active rheumatoid arthritis despite treatment with methotrexate: a randomized, double-blind, placebo-controlled, dose-ranging study. *Arthritis Rheum* 2008:964-75.
- 24. Maini R, St Clair EW, Breedveld F, Furst D, Kalden J, Weisman M, et al. Infliximab (chimeric anti-tumour necrosis factor alpha monoclonal antibody) versus placebo in rheumatoid arthritis patients receiving concomitant methotrexate: a randomised phase III trial. ATTRACT Study Group. Lancet. 1999 Dec 4;354(9194):1932-9.
- 25. Abe T, Takeuchi T, Miyasaka N, Hashimoto H, Kondo H, Ichikawa Y, et al. A multicenter, double-blind, randomized, placebo controlled trial of infliximab combined with low dose methotrexate in Japanese patients with rheumatoid arthritis. J Rheumatol. 2006 Jan;33(1):37-44.
- Kavanaugh A, St Clair EW, McCune WJ, Braakman T, Lipsky P. Chimeric anti-tumor necrosis factor-alpha monoclonal antibody treatment of patients with rheumatoid arthritis receiving methotrexate therapy. J Rheumatol. 2000 Apr;27(4):841-50.
- 27. Westhovens R, Yocum D, Han J, Berman A, Strusberg I, Geusens P, et al. The safety of infliximab, combined with background treatments, among patients with rheumatoid arthritis and various comorbidities: a large, randomized, placebo-controlled trial. Arthritis Rheum. 2006 Apr;54(4):1075-86.
- 28. Zhang FC, Hou Y, Huang F, Wu DH, Bao CD, Ni LQ, et al. Infliximab versus placebo in rheumatoid arthritis patients receiving concomitant methotrexate: A preliminary study from China. *APLAR Journal of Rheumatology* 2006:127-30.
- Edwards JC, Szczepanski L, Szechinski J, Filipowicz-Sosnowska A, Emery P, Close DR, et al. Efficacy of Bcell-targeted therapy with rituximab in patients with rheumatoid arthritis. N Engl J Med. 2004 Jun 17:350(25):2572-81.

- 30. Emery P, Deodhar A, Rigby WF, Isaacs JD, Combe B, Racewicz AJ, et al. Efficacy and safety of different doses and retreatment of rituximab: a randomised, placebo-controlled trial in patients who are biological naive with active rheumatoid arthritis and an inadequate response to methotrexate (Study Evaluating Rituximab's Efficacy in MTX iNadequate rEsponders (SERENE)). *Ann Rheum Dis.* 2010/05/22 ed 2010:1629-35.
- 31. Kremer JL, Blanco R, Brzosko M, Burgos-Vargas R, Halland AM, Vernon E, et al. Tocilizumab inhibits structural joint damage in rheumatoid arthritis patients with inadequate responses to methotrexate at 1 year: The LITHE study. *Arthritis Rheum* 2010.
- 32. Smolen JS, Beaulieu A, Rubbert-Roth A, Ramos-Remus C, Rovensky J, Alecock E, et al. Effect of interleukin-6 receptor inhibition with tocilizumab in patients with rheumatoid arthritis (OPTION study): a double-blind, placebo-controlled, randomised trial. *Lancet* 2008:987-97.
- 33. Genovese MC, McKay JD, Nasonov EL, Mysler EF, Da Silva NA, Alecock E, et al. Interleukin-6 receptor inhibition with tocilizumab reduces disease activity in rheumatoid arthritis with inadequate response to disease-modifying antirheumatic drugs: The tocilizumab in combination with traditional disease-modifying antirheumatic drug therapy study. *Arthritis and Rheumatism* 2008:2968-80.
- 34. Maini RN, Taylor PC, Szechinski J, Pavelka K, Broll J, Balint G, et al. Double-blind randomized controlled clinical trial of the interleukin-6 receptor antagonist, tocilizumab, in European patients with rheumatoid arthritis who had an incomplete response to methotrexate. *Arthritis Rheum* 2006:2817-29.