Effective Health Care Program

Muscle, Bone, and Joint Conditions
Rheumatoid Arthritis

Drug Therapy for Rheumatoid Arthritis: Comparative Effectiveness

Research Focus for Clinicians

In response to a request from the public to the Agency for Healthcare Research and Quality (AHRQ) concerning the expanding use of disease-modifying anti-rheumatic drugs (DMARDs) to treat rheumatoid arthritis (RA), a systematic review was undertaken to review the effectiveness and safety of the oral and biologic DMARDs. This summary is based on a systematic review prepared as an update to a review published in 2007. In addition to the material reported in 2007, this update includes articles published after the 2007 report and before January 2011 (a total of 211 studies). The full report, listing all studies, is available at www.effectivehealthcare.ahrq.gov/dmardsra.cfm. This summary, based on the full report of research evidence, is provided to clinicians to inform discussions of options with patients and to assist in decisionmaking along with consideration of a patient's values and preferences. Reviews of evidence should not be construed to represent clinical recommendations or guidelines.

Background Information

RA affects 1.3 million adults in the United States, with onset generally between the ages of 30 and 50 years. Women and older adults are most often affected. RA treatment is focused on alleviating pain and inflammation and slowing or preventing the progression of joint destruction. Ultimately, the goal is remission or low disease activity. Nonsteroidal anti-inflammatory drugs and corticosteroids are widely prescribed, but these conventional drugs alone do not prevent disease progression.

Both the oral or injectable nonbiologic drugs and the recently developed biologic DMARDs interfere with rheumatoid disease processes by blocking the production or activity of immune cells and their products that cause joint inflammation and damage. Both oral and biologic DMARDs may be used individually or in combination with anti-inflammatory agents.

DMARDs, and particularly the oral DMARD methotrexate (MTX), have a central position in RA treatment. Their use is increasing with the expectation that they will lead to better disease control and more remissions. Comparing the effectiveness of MTX and other oral and biologic DMARDs will help to clarify the full range of treatment options. An understanding of the most effective drugs and strategies for managing symptoms and improving function and quality of life is needed to support decisionmaking that takes into account the balance between limiting progressive disease and the risks of adverse effects for each patient.

Conclusion

For patients with early RA who have not been treated with MTX, treatment with either MTX or a biologic DMARD provides similar benefits for symptoms and function, but biologic DMARDs are more effective at limiting radiographic evidence of progression. However, the evidence is too limited to permit conclusions about whether one combination strategy is better than another in treating early RA (<3 years). Evidence is accumulating that, as a class, biologic DMARDs offer greater likelihood of remission for patients with longstanding active disease than do the oral ones. Indirect comparisons reveal potential differences in effectiveness of the biologic DMARDS, but the analysis should be interpreted with caution. Combining biologic DMARDs provides no additional benefits and increases the risk of serious adverse effects. In patients with inadequate disease control, biologic DMARDs used in combination with MTX offer greater relief than either monotherapy, without increasing the need to discontinue treatment because of adverse effects.

The oral DMARDs (particularly MTX) remain effective first-line treatments for RA. MTX (at 7.5 to 25 mg/wk) and sulfasalazine are similarly effective for patients with early RA, and leflunomide may provide comparable results. Adding prednisone to treatment with oral DMARDs improves function and may limit radiographic progression, although there is evidence that the combination increases the risks of adverse effects. For patients with longstanding active disease, combining two or three oral DMARDs can provide greater improvement than monotherapy.

DMARDs of both classes are associated with well-known adverse effects (toxicity with oral DMARDs, serious infections with biologic DMARDs), but the comparative risks are not known. Overall tolerability is similar between DMARDs of both classes. The evidence about cancer risks is limited, but the risk for patients with RA does not appear to be elevated by DMARDs of either class.

Direct comparisons of DMARDs—within and between classes, in combination strategies, and in studies of longer duration and followup—are needed to improve understanding of their benefits and safety and to optimize treatment based on disease patterns and patient characteristics.

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Clinical Bottom Line

Biologic DMARDs

Benefits

- Considered as a class, biologic DMARDs provide a greater symptom response and a greater remission rate than do the oral DMARDs for patients with longstanding active disease requiring a change in therapy. ●●○
  - Overall, evidence is insufficient to permit comparisons of these drugs for functional capacity and quality of life outcomes. ○○○
- Combining two biologic DMARDs (**etanercept** [Enbrel®] with **abatacept** [Orencia®] or **anakinra** [Kineret®]) does not add to improvement in disease activity, functional capacity, or symptom response more than one biologic DMARD and increases the risk of serious adverse effects. ●○○
- Comparisons across studies of patients resistant to MTX suggest that there may be clinically observable differences in the efficacy of the biologic DMARDs. Evidence from head-to-head comparisons is too limited to provide guidance for clinical decisionmaking. ●○○

Strength of Evidence Scale

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 the confidence in the estimate of effect and is likely to change the estimate.
Insufficient:	○○○	Evidence either is unavailable or does not permit a conclusion.

Adverse Effects

- The risk of serious infections increases when patients are treated with biologic DMARDs. ●●○
- Combining two biologic DMARDs leads to substantially higher rates of serious adverse events than monotherapy. ●●○
- The rate of adverse events did not increase over time in long-term studies of **adalimumab** (Humira®), **anakinra, etanercept**, and **infliximab** (Remicade®). ●●○
- Studies present no consistent evidence of elevated risk of lymphoma or other cancer types associated with biologic DMARDs (relative to either oral DMARDs or placebo), and the actual risk to patients with RA is not clear (study durations range from 3 months to 5 or more years). ●○○
- For biologic DMARDs, the overall likelihood of withdrawals from trials was about half that of the MTX and placebo groups. Withdrawals due to adverse events were 1.4-fold more likely with biologic DMARDs than with placebo and MTX, but withdrawal due to lack of efficacy was about one-fifth as likely. ●○○
- In indirect comparisons, **certolizumab pegol** (Cimzia®), **etanercept**, and **rituximab** (Rituxan®) have more favorable overall treatment withdrawal profiles than other biologic DMARDs. ●○○
- Withdrawal from treatment due to adverse events is more likely with **certolizumab pegol** and **infliximab** than with **etanercept** or **rituximab**. ●○○
- Withdrawals due to injection site reactions are more likely with **anakinra**, and **infliximab** is associated with a higher rate of infusion reactions. ●○○
- The evidence is insufficient to permit conclusions about the differences in risks for rare but serious adverse effects among the biologic DMARDs (demyelination, autoimmunity, pancytopenia, and hepatotoxicity). ○○○

Oral DMARDs

Benefits

- In patients with longstanding active disease, combining up to three oral DMARDs (**MTX**, **sulfasalazine** [Azulfidine EN-Tabs®], and **hydroxychloroquine** [Plaquenil®]) produces greater improvements in disease activity than one or two oral DMARDs. ●●○
- Adding **prednisone** to treatment with an oral DMARD improves functional capacity ●●○ and radiographic progression ●○○ more than an oral DMARD alone.
- **MTX*** and **sulfasalazine** have similar effects on symptoms, disease activity, functional capacity, and limiting radiographic changes (in patients with RA for less than 3 years). ●●○
- **MTX** and **leflunomide** (Arava®) have similar effects on symptom response, radiographic change, and functional capacity. **Leflunomide** may be superior to **sulfasalazine** for improving functional capacity. ●○○

Adverse Effects

- Oral DMARDs used as monotherapies exhibit similar adverse event rates. ●○○
- Oral DMARDs do not appear to elevate the risk of lymphoma. ●○○
- Adding a corticosteroid to treatment with oral DMARDs does not increase discontinuation rates and may delay discontinuation. ●●○ However, the risk of wound-healing complications may increase, and the risk for increased overall adverse event rates is greater. ●○○

*MTX dosage ranged from 7.5 to 25 mg/week in the evaluated studies.

Clinical Bottom Line *(Continued)*

Combining Oral and Biologic DMARDs

Benefits	Adverse Effects
■ In patients with inadequate disease control who required a change in treatment, combination therapy with a biologic DMARD and MTX achieved greater improvements in some outcomes than either a biologic DMARD or MTX alone. □ Combination therapy achieves greater improvement than biologic DMARDs alone in: ■ Disease activity and radiographic progression ●●○ □ Combination therapy achieves greater improvement than MTX alone in: ■ Clinical response and functional capacity ●●● ■ Quality of life ●●○ ■ In patients whose RA failed to respond to first-line MTX, combination therapy with MTX and a biologic DMARD was not more successful than monotherapy with a biologic DMARD. ●●○ ■ In MTX-naïve patients or those not recently on MTX, combination therapy is superior to monotherapy with a biologic DMARD for functional capacity ●●○ and quality of life ●○○.	■ Combining MTX or other oral DMARDs with a biologic DMARD does not alter the adverse event rate found with the biologic DMARD alone. ●○○ ■ Combining MTX and biologic DMARDs demonstrates a better tolerability profile than MTX alone. ●○○ ■ The evidence is insufficient to estimate differences in rates of specific adverse events between the biologic and oral DMARDS. ○○○

DMARDs for Patients With Early RA

Benefits	Adverse Effects
■ Combination strategies that use corticosteroids plus two or three oral DMARDs are more effective than oral DMARD monotherapy for improving symptom response, disease activity, and functional capacity in the short term and reducing radiographic evidence of progression and joint erosion in the longer term (≥1 year). ●○○ ■ Combining one oral DMARD with **prednisone** reduces radiographic progression and joint erosion more than the DMARD alone. ●○○ ■ For patients with early RA who have not been treated with MTX: □ Effects on symptom response are similar when MTX is compared with **adalimumab** or **etanercept**. ●●○ □ Effects on functional capacity are similar with **MTX** and **adalimumab**. ●○○ ■ Biologic DMARDs more effectively limit radiographic evidence of progression than do oral DMARDs. ●●○ ■ For MTX-naïve patients with early, aggressive RA, combining MTX with a biologic DMARD (**abatacept**, **adalimumab**, **etanercept**, or **infliximab**) provides greater improvement than biologic DMARD monotherapy for symptom response, clinical remission rates, and radiographic progression. ●○○	■ Adding **prednisone** to treatment with one or multiple oral DMARDs does not increase treatment discontinuation rates (treatment durations spanned 2 months to 5 years). ●●○ ■ Combining oral DMARDs (**sulfasalazine** and **MTX**) increases withdrawal from treatment due to adverse events. ●○○

Other Findings: Influence of Patient Characteristics

- Patients with moderate RA had better overall improvement and better functional status than patients with severe RA. However, patients with severe RA had the greatest degree of improvement from baseline. ●○○
- In treatment with MTX, as the age of patients increased, the likelihood of major clinical improvement decreased slightly, but overall age did not affect efficacy or risk of adverse effects. ●○○
- Biologic DMARDs showed no apparent influence on the risk of cardiovascular events in the elderly (≥65 years of age). ●○○
- MTX toxicity (gastrointestinal, liver, and renal) was more likely in patients with greater renal impairment. ●○○
- High-risk comorbidities (cardiovascular disease, diabetes, malignancies, and renal impairment) did not increase the risk of serious adverse effects or infections in patients treated with anakinra. ●○○
- Concomitant antidiabetic, antihypertensive, or statin medications given to patients treated with anakinra did not increase the risk of adverse effects. ●○○

Gaps in Knowledge

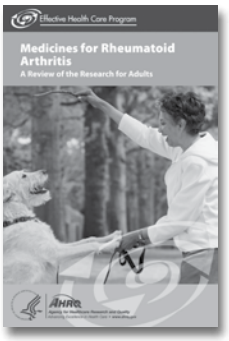
- Applicability of the conclusions is limited, as most evidence comes from efficacy trials that are conducted in ideal settings and exclude many typical patients.
- The evidence about the effects of disease stage, age, concomitant therapies, and comorbidities is limited and is derived from single studies that address these potential modifiers of effectiveness and safety.
- Evidence about response of subgroups defined by health status, age, coexisting conditions, comorbidities, concurrent treatments, sociodemographics, or other variables is inadequate to understand the effects of these characteristics.
- The effect of timing of initiation and duration of treatment, especially whether early use of biologic DMARDs is beneficial, is not well understood.
- Future studies should include measurement of patient-centered, quality-of-life outcomes.
- Head-to-head comparisons of DMARDs and studies that focus on different combination strategies are needed.

What To Discuss With Your Patients

- The natural history of RA and the role of DMARDs in reducing symptoms and improving disease control
- The potential benefits and adverse effects of DMARDs
- Changes in lifestyle that can help relieve symptoms, such as diet and exercise
- Patient and caregiver preferences and values regarding treatment

Resource for Patients

Medicines for Rheumatoid Arthritis, A Review of the Research for Adults is a free companion to this clinician research summary. It covers:



- The types of DMARDs that are used
- The evidence about the short- and long-term benefits and adverse effects associated with DMARDs used to treat patients with RA
- Costs related to biologic and oral DMARDs

Ordering Information

For electronic copies *of Medicines for Rheumatoid Arthritis, A Review of the Research for Adults*, this clinician research summary, and the full systematic review, visit www.effectivehealthcare.ahrq.gov/dmardsra.cfm. To order free print copies, call the AHRQ Publications Clearinghouse at 800-358-9295.

Source

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