Effective Health Care Program

Comparative Effectiveness Review
Number 76

Treatment for Hepatitis C Virus Infection in Adults

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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 www.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 from 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.

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Treatment for Hepatitis C Virus Infection in Adults

Structured Abstract

Objectives. This report systematically reviews the comparative benefits and harms of current antiviral treatment regimens for chronic hepatitis C virus (HCV) infection in treatment-naïve adults.

Data sources. MEDLINE® (1947 to August 2012), the Cochrane Central Register of Controlled Trials (through 3rd quarter 2012), clinical trial registries, and reference lists.

Review methods. We used predefined criteria to determine study eligibility. We selected randomized trials of dual therapy with pegylated interferon (alfa-2a or alfa-2b) plus ribavirin or triple therapy with pegylated interferon (alfa-2a or alfa-2b), ribavirin, and either boceprevir or telaprevir that reported clinical outcomes, sustained virologic response (SVR), or harms. We also selected randomized trials or cohort studies that compared clinical outcomes in patients who experienced an SVR after antiviral therapy with patients who did not experience an SVR.

Results. We included 90 randomized trials and observational studies. No study evaluated the comparative effectiveness of current antiviral regimens on long-term clinical outcomes. In trials of treatment-naïve patients, the likelihood of achieving an SVR was slightly lower for dual therapy with pegylated interferon alfa-2b plus ribavirin than for dual therapy with pegylated interferon alfa-2a plus ribavirin, with a difference in absolute SVR rates of about 8 percentage points. There were no clear differences in estimates of relative effectiveness in patient subgroups defined by demographic or clinical characteristics, although absolute response rates were lower in older patients, Black patients, patients with high viral load, patients with more advanced fibrosis or cirrhosis, and patients with genotype 1 infection. Differences in harms were relatively small, with no difference in withdrawals due to adverse events, although dual therapy with pegylated interferon alfa-2b plus ribavirin was associated with a lower risk of serious adverse events than dual therapy with pegylated interferon alfa-2a plus ribavirin. In patients with genotype 2 or 3 infection, trials found dual therapy with pegylated interferon for 12 to 16 weeks associated with a lower likelihood of achieving SVR as compared with 24 weeks of therapy. Lower doses of pegylated interferon alfa-2b were less effective than standard doses, and limited evidence showed no clear differential effects of ribavirin dosing.

Five trials found triple therapy with pegylated interferon (alfa-2a or alfa-2b), ribavirin, and either boceprevir or telaprevir associated with higher likelihood of SVR (66–80 percent) than dual therapy with pegylated interferon plus ribavirin for genotype 1 infection, with an absolute increase in SVR rate of 22–31 percentage points. Triple therapy with boceprevir was associated with increased risk of hematological adverse events, and triple therapy with telaprevir was associated with increased risk of anemia and rash, including severe rash, versus dual therapy.

A large cohort study that controlled well for confounders found that patients with an SVR after antiviral therapy had a lower risk of all-cause mortality than patients with no SVR, with adjusted hazard ratio estimates ranging from 0.51 to 0.71, depending on genotype. Other, smaller cohort studies also found that SVR was associated with reduced risk of all-cause mortality and long-term complications of HCV infection, but had more methodological shortcomings.

Conclusions. Although there is no direct evidence on the comparative effects of current antiviral regimens on long-term clinical outcomes, SVR rates are substantially higher in patients with HCV genotype 1 infection who receive triple therapy with pegylated interferon (alfa-2a or alfa-2b), ribavirin, and boceprevir or telaprevir compared with dual therapy with pegylated interferon plus ribavirin. Achieving an SVR following antiviral therapy appears to be associated with decreased risk of all-cause mortality compared with no SVR, although estimates are susceptible to residual confounding.

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Executive Summary

Background

Hepatitis C virus (HCV) is the most common chronic bloodborne pathogen in the United States. HCV is primarily acquired by large or repeated percutaneous exposures to blood, with injection drug use being the strongest risk factor. Based on a national survey of households, approximately 1.6 percent of U.S. adults over 20 years of age have antibodies to HCV, indicating prior acute HCV infection.[1] About 78 percent of patients with acute HCV infection develop chronic HCV infection, defined by the presence of persistent viremia.

Chronic HCV infection has a variable course, but it is a leading cause of complications from chronic liver disease, including cirrhosis, liver failure, and hepatocellular carcinoma (HCC). Chronic HCV infection is associated with an estimated 15,000 deaths each year in the United States,[2] and it is the most common indication for liver transplantation among American adults, accounting for more than 30 percent of cases.[3] The prevalence of chronic HCV infection is thought to have peaked in 2001 at 3.6 million people, and the yearly incidence has declined from more than 200,000 cases per year in the 1980s to around 16,000 cases in 2009.[4, 5] However, complications related to chronic HCV infection, which frequently occur only after decades of infection, are expected to rise for another 10 to 13 years.[4]

The goal of antiviral treatment for chronic HCV infection is to prevent the long-term health complications associated with HCV infection, such as cirrhosis, hepatic decompensation, and liver cancer, but it is extremely difficult to design and carry out clinical trials long and large enough to provide direct evidence related to these outcomes. The sustained virologic response (SVR) rate, typically defined as the proportion of patients who experience a decline in HCV-RNA (hepatitis C virus ribonucleic acid) to undetectable levels 24 weeks following completion of antiviral treatment, is the standard marker of successful treatment in clinical trials because an SVR is strongly associated with the long-term absence of viremia.[6, 7] Recent studies have evaluated the association between achieving an SVR and reductions in mortality, liver failure, and cancer.[8, 9]

In the early 2000s, the combination of "pegylated" interferon plus ribavirin became the standard antiviral treatment for HCV infection.[10-12] Pegylation refers to the cross-linking of polyethylene glycol molecules to the interferon molecule, which delays renal clearance and thereby permits less frequent dosing (once weekly vs. three times a week with standard interferon).[13] Dual therapy with pegylated interferon plus ribavirin is associated with higher SVR rates (about 55–60 percent overall) than either standard interferon plus ribavirin or pegylated interferon monotherapy. Currently, two pegylated interferons are available: pegylated interferon alfa-2a and pegylated interferon alfa-2b. Although previous reviews found insufficient evidence to determine whether combination therapy with pegylated interferon alfa-2a or pegylated interferon alfa-2b plus ribavirin is more effective,[14, 15] more head-to-head trials directly comparing these two regimens are now available.[16-19]

A number of factors affect response to antiviral treatment. The two major pretreatment predictors of SVR are the viral genotype and the pretreatment viral load.[11] In the United States, genotype 1 infection is found in around three-quarters of HCV-infected patients.[20] HCV genotype 1 infection is associated with a substantially lower response to antiviral treatment than infection with genotypes 2 and 3, which are present in about 20 percent of HCV-infected patients. A pretreatment viral load of <600,000 international units per milliliter (IU/mL) is

associated with higher likelihood of achieving an SVR.[11] Other factors less consistently or less strongly associated with an increased likelihood of achieving an SVR include female sex, age less than 40 years, non-Black race, lower body weight (≤75 kg), absence of insulin resistance, elevated alanine aminotransferase levels, and absence of bridging fibrosis or cirrhosis on liver biopsy.[11] Effects of race on the likelihood of achieving an SVR may be due in part to polymorphisms in the interleukin-28B (IL28B) gene.[21, 22]

An issue complicating antiviral treatment is the high rate of adverse effects observed with interferon-based therapy, including flulike symptoms, fatigue, and neuropsychiatric and hematologic adverse effects.[23] Such adverse effects can be difficult to tolerate and can lead to premature discontinuation of therapy.

In 2011, the U.S. Food and Drug Administration (FDA) approved the first direct acting antiviral agents, boceprevir (trade name Victrelis™) and telaprevir (trade name Incivek®), for treatment of chronic HCV genotype 1 infection.[24, 25] Both drugs are classified as nonstructural 3/4A protease inhibitors, with a potential advantage of shorter duration of therapy (24 to 28 weeks) compared with standard dual therapy with pegylated interferon (alfa-2a or 2b) plus ribavirin for genotype 1 infection (48 weeks).[26-28] Either drug is administered in combination with pegylated interferon (alfa-2a or 2b) plus ribavirin.

Understanding the comparative benefits and harms of the various antiviral regimens is critical for making informed treatment decisions in patients with chronic HCV infection, particularly given the availability of new treatment options. This review assesses the comparative effectiveness of antiviral treatments in adults with chronic HCV infection who have not received previous antiviral drug treatment. In addition to assessing the comparative effectiveness of different drug regimens, the review evaluates the effects of different medication doses, durations of therapy, and dosing strategies (such as weight-based or response-guided vs. fixed treatment). To help with individualized clinical decisionmaking regarding antiviral therapy for chronic HCV infection, the review also evaluates how comparative effectiveness varies depending on HCV genotype, viral load, and other demographic and clinical characteristics. Given the need to understand the effects of treatment in people with HCV infection identified by screening in order to assess the potential benefits and harms of screening, this review will be used, together with a separate review on HCV screening,[29] by the U.S. Preventive Services Task Force to update its HCV screening recommendations.

Objectives

The following Key Questions are the focus of our report:

Key Question 1

a. What is the comparative effectiveness of antiviral treatment in improving health outcomes in patients with HCV infection?
b. How does the comparative effectiveness of antiviral treatment for health outcomes vary according to patient subgroup characteristics, including but not limited to HCV genotype, age, race, sex, stage of disease, or genetic markers?

Key Question 2

a. What is the comparative effectiveness of antiviral treatments on intermediate outcomes, such as the rate of SVR or histologic changes in the liver?

b. How does the comparative effectiveness of antiviral treatment for intermediate outcomes vary according to patient subgroup characteristics, including but not limited to HCV genotype, age, race, sex, stage of disease, or genetic markers?

Key Question 3

a. What are the comparative harms associated with antiviral treatments?
b. Do these harms differ according to patient subgroup characteristics, including HCV genotype, age, race, sex, stage of disease, or genetic markers?

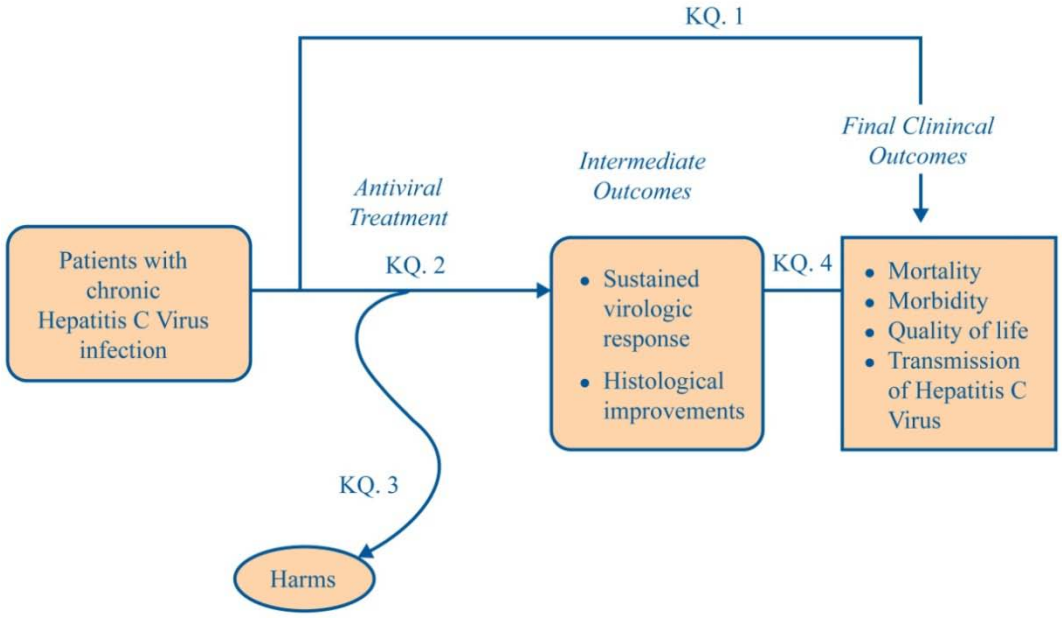
Key Question 4

Have improvements in intermediate outcomes (SVR, histologic changes) been shown to reduce the risk or rates of adverse health outcomes from HCV infection?

Analytic Framework

The analytic framework that guided this report is shown in Figure A. The numbers in the analytic framework indicate the Key Questions listed above. The population was patients with chronic HCV infection who were receiving antiviral therapy. The interventions were dual therapy with pegylated interferon (alfa-2a or alfa-2b) plus ribavirin, or triple therapy with pegylated interferon (alfa-2a or alfa-2b) plus ribavirin plus a protease inhibitor approved by the FDA (either boceprevir or telaprevir). Comparisons were between different regimens, as well as between regimens including the same drugs administered at different doses or for different durations. Intermediate outcomes were sustained virologic response and hepatic histological improvement. Final outcomes were morbidity and mortality from HCV infection (including hepatic cirrhosis, HCC, and liver transplantation rates) and quality of life, as well as harms of antiviral therapies (including flulike symptoms, hematologic effects, rash, and psychiatric effects).

Figure A. Analytic framework for treatment of hepatitis C infection in adults



KQ = Key Question

Methods

Input From Stakeholders

The topic of treatment for HCV infection was nominated for a comparative effectiveness review (CER) in a public process. The Key Questions were proposed in the public nomination process and developed by investigators from the Evidence-based Practice Center (EPC) with contributions from expert Key Informants (KI), who helped refine Key Questions, identify important methodological and clinical issues, and define parameters for the review of evidence. The revised Key Questions were then posted to a public Web site for comment. The Agency for Healthcare Research and Quality (AHRQ) and the EPC agreed on the final Key Questions after reviewing the public comments and receiving additional advice from a Technical Expert Panel (TEP) convened for this report. We then drafted a protocol for this CER, which the TEP reviewed. Access it from the AHRQ Web site, where it was posted in November 2011: (www.effectivehealthcare.ahrq.gov/index.cfm/search-for-guides-reviews-and-reports/?pageaction=displayproduct&productid=855).

A multidisciplinary group of clinicians, researchers, and patient advocates with expertise in hepatitis C treatment and research were selected to serve as the TEP members to provide high-level content and methodological expertise throughout the development of the review. Prior to participation in this report, the TEP members disclosed all financial or other conflicts of interest. The AHRQ Task Order Officer and the authors reviewed all of these disclosures and determined the panel members had no significant conflicts of interest that precluded participation. KIs and TEP members had expertise in hepatology, epidemiology, screening, and primary care. TEP members and other experts were invited to provide external peer review of the draft report.

Search Strategy and Study Selection

To identify articles relevant to each Key Question, a research librarian searched the Cochrane Database of Systematic Reviews, the Cochrane Central Register of Controlled Trials, and Ovid MEDLINE® from 1947 to April 2011 (see Appendix A for the search strategies), and a final updated search was conducted in August 2012. The search strategies were peer reviewed by another research librarian and revised prior to finalization. Unpublished trials were sought by searching clinical trial registries (ClinicalTrials.gov, Current Controlled Trials, Clinical Trial Results, WHO Trial Registries) and grants databases (NIHRePORTER, HSRProj, and AHRQ GOLD)**.** Scientific Information Packets on unpublished and published trials were solicited from manufacturers of included antiviral drugs through the Scientific Resource Center. We also hand-searched the reference lists of relevant studies. Searches were updated before the report was finalized to identify relevant new publications.

Studies were selected according to criteria developed for inclusion and exclusion. The selection criteria were based on the Key Questions and the populations, interventions, comparators, outcomes, timing, and setting (PICOTS) approach. Papers were selected for full review if they were about chronic HCV infection, were relevant to Key Questions in the analytic framework, and met the predefined inclusion criteria. To evaluate the potential effects of publication bias, we included trials published only as conference abstracts of sensitivity analyses. We restricted inclusion to English language articles. Studies of nonhuman subjects were also excluded, and studies had to include original data.

Abstracts and full-text articles were dual reviewed for inclusion and exclusion for each Key Question. Full-text articles were obtained for all studies identified as potentially meeting inclusion criteria. Two investigators independently reviewed all full-text articles for final inclusion or exclusion, and discrepancies were resolved through discussion and consensus, with a third investigator making the final decision if necessary.

Data Extraction and Quality Assessment

We assessed the quality of each study based on predefined criteria (Appendix E). We adapted criteria from methods proposed by Downs and Black (observational studies),[30] the USPSTF,[31] and the Quality Assessment of Diagnostic Accuracy Studies-2 Group.[32] The criteria used are consistent with the approach recommended by AHRQ in the Methods Guide for Effectiveness and Comparative Effectiveness Reviews (Methods Guide).[33] We used the term "quality" rather than the alternate term "risk of bias." Although both refer to internal validity, "quality" may be more familiar to most users and has potential advantages in terms of readability.

We rated the quality of each randomized trial based on the methods used for randomization, allocation concealment, and blinding; the similarity of compared groups at baseline; maintenance of comparable groups; adequate reporting of dropouts, attrition, crossover, adherence, and contamination; loss to followup; the use of intent-to-treat analysis; and ascertainment of outcomes.[31]

We rated the quality of each cohort study based on whether it used nonbiased selection methods to create an inception cohort; whether it evaluated comparable groups; whether rates of loss to followup were reported and acceptable; whether it used accurate methods for ascertaining exposures, potential confounders, and outcomes; and whether it performed appropriate statistical analyses of potential confounders.[31]

Following assessment of individual quality criteria, individual studies were rated good, fair, or poor quality, as defined below.[33]

Good-quality studies are considered likely to be valid. Good-quality studies clearly describe the population, setting, interventions, and comparison groups; use a valid method for allocation of patients to interventions; clearly report dropouts and have low dropout rates; use appropriate methods for preventing bias; and appropriately measure outcomes and fully report results.

Fair-quality studies have some methodological deficiencies but no flaw or combination of flaws judged likely to cause major bias. The study may be missing information, making it difficult to assess its methods or assess limitations and potential problems. The fair-quality category is broad, and studies with this rating vary in their strengths and weaknesses—the results of some fair-quality studies are likely to be valid, while others are only probably valid.

Poor-quality studies have significant flaws that may invalidate the results. They have a serious or fatal flaw in design, analysis, or reporting; large amounts of missing information; or discrepancies in reporting. The results of these studies are judged to be at least as likely to reflect flaws in the study design as true effects of the interventions under investigation. We did not exclude studies rated poor quality a priori, but they were considered to be the least reliable studies when synthesizing the evidence, particularly when discrepancies between studies were present.

We recorded factors important for understanding the applicability of studies, such as whether the publication adequately described the study population, how similar patients were to populations likely to be targeted by screening, whether differences in outcomes were clinically (as well as statistically) significant, and whether the interventions and tests evaluated were

reasonably representative of standard practice.[34] We also recorded the funding source and role of the sponsor. We did not assign a rating of applicability (such as high or low) because applicability may differ based on the user of this report.

Data Synthesis and Rating the Strength of the Body of Evidence

We performed meta-analysis of trials that evaluated similar populations, interventions, comparisons, and outcomes to estimate pooled relative risks.[35] When present, statistical heterogeneity was explored through subgroup and sensitivity analyses, as well as qualitatively. Subgroup analyses were performed in groups stratified by HCV genotype as well as by race, age, body weight, viral load, stage/severity of disease, and IL-28b status when these data were available. We performed sensitivity analysis by excluding poor-quality studies and outlier trials, and by including results from studies published only as abstracts to evaluate the stability of estimates and conclusions. We did not perform meta-analyses for Key Question 4 because all studies were observational and had important methodologic shortcomings. These studies were synthesized qualitatively.

We rated the strength of evidence for each Key Question using the four categories recommended in the AHRQ Methods Guide.[33] We synthesized the overall quality of each body of evidence based on the type and quality of studies (graded good, fair, or poor); the precision of the estimate of effect based on the number and size of studies and confidence intervals for the estimates (graded high, moderate, or low); the consistency of results between studies (graded high, moderate, or low); and the directness of the evidence linking the intervention and health outcomes (graded direct or indirect). We did not downgrade a body of evidence for directness that evaluated an intermediate outcome if the intermediate outcome was the specific focus of the Key Question. We were not able to formally assess for publication bias due to small numbers of studies, methodological shortcomings, or differences across studies in designs, measured outcomes, and other factors.

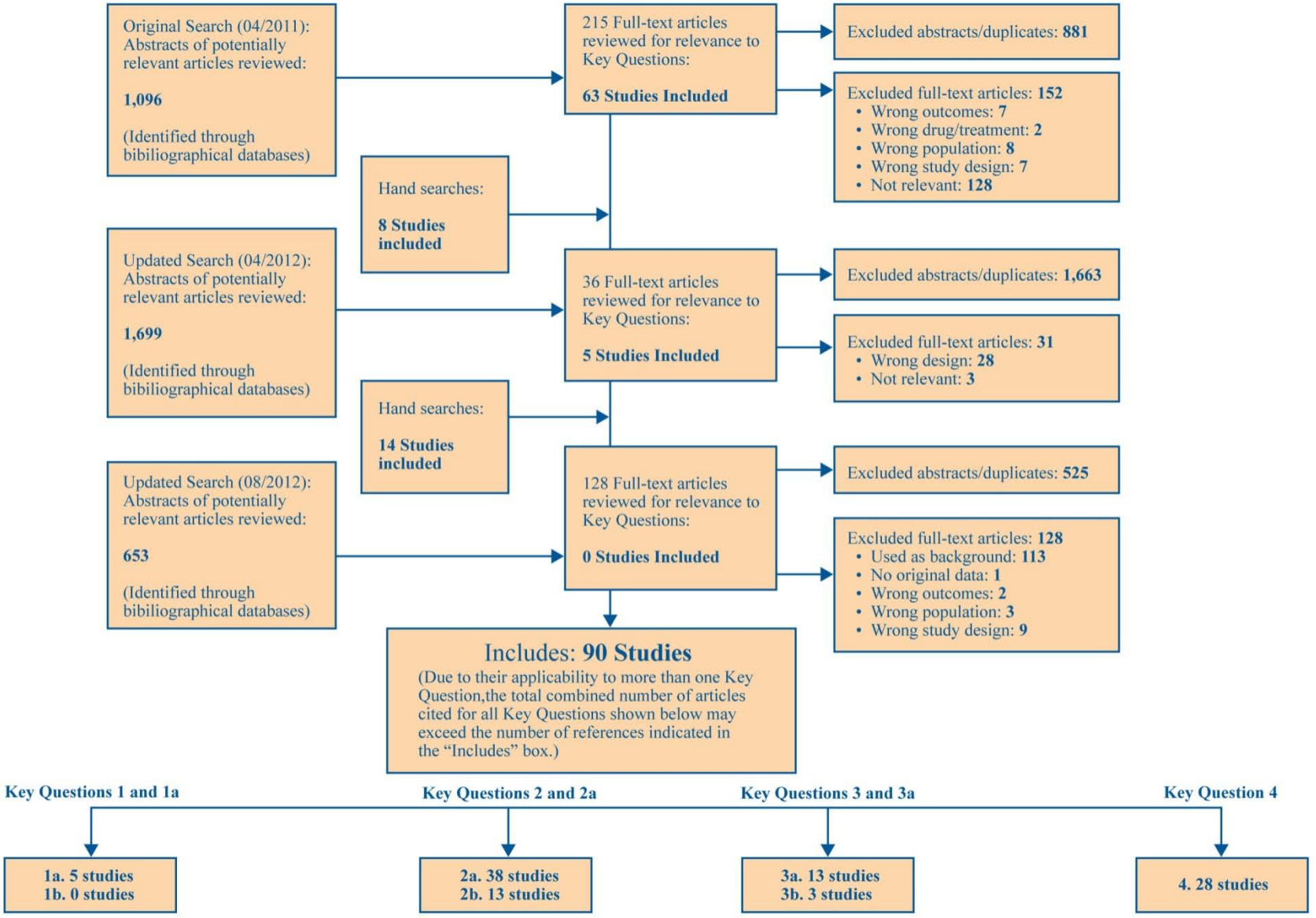
We graded the strength of evidence for each comparison and outcome by using the four categories recommended in the AHRQ Methods Guide:[33] A "high" grade indicates high confidence that the evidence reflects the true effect and that further research is very unlikely to change our confidence in the estimate of effect and will not change the estimate. A "moderate" grade indicates moderate confidence that the evidence reflects the true effect and that further research may change our confidence in the estimate of effect and may change the estimate. A "low" grade indicates low confidence that the evidence reflects the true effect and that further research is likely to change the confidence in the estimate of effect and is likely to change the estimate. An "insufficient" grade indicates evidence either is unavailable or is too limited to permit any conclusion.

Results

The search and selection of articles are summarized in the study flow diagram (Figure B). Of the 1,096 citations identified at the title and abstract level in the original search, 215 articles met inclusion criteria and were selected for further review of the full text. From updated searches and peer reviewer suggested citations, an additional 2,352 citations were identified, and 164 of these met inclusion criteria and were selected for full-text review. Of the 379 articles reviewed at the full-text level, a total of 90 studies met inclusion criteria.

No study evaluated comparative effectiveness of current antiviral regimens on long-term clinical outcomes such as mortality, complications of chronic HCV infection, or quality of life.

Figure B. Study flow diagram: Treatment for hepatitis C virus infection in adults



Dual Therapy Regimens with Pegylated Interferon Plus Ribavirin

In trials of treatment-naïve patients, dual therapy with pegylated interferon alfa-2b plus ribavirin was associated with a slightly lower likelihood of achieving an SVR than dual therapy with pegylated interferon alfa-2a plus ribavirin, with a difference in absolute SVR rates of about 8 percentage points.[16-19, 36-38] In patients with genotype 2 or 3 infection, dual therapy for 12 to 16 weeks appears to be associated with a lower likelihood of SVR, compared with dual therapy for 24 weeks, with no differences between 24 weeks and longer courses of therapy.[39-44] In trials comparing different doses of dual therapy with pegylated interferon plus ribavirin, lower doses of pegylated interferon alfa-2b were less effective than standard doses,[41, 45-49] and limited evidence found no clear differential effects of ribavirin dosing.[39, 50]

There were no clear differences in estimates of relative effectiveness between dual therapy with pegylated interferon alfa-2a plus ribavirin versus dual therapy with pegylated interferon alfa-2b plus ribavirin in patient subgroups defined by demographic or clinical characteristics, although absolute response rates were lower in older patients, Black patients, patients with high viral load, patients with more advanced fibrosis or cirrhosis, and patients with genotype 1 infection.[16, 17, 19, 51]

Differences in harms between dual therapy with pegylated interferon alfa-2a plus ribavirin versus pegylated interferon alfa-2b plus ribavirin were relatively small, with no differences in withdrawals due to adverse events, although dual therapy with pegylated interferon alfa-2b was associated with a lower risk of serious adverse events.[16-19, 38, 52]

Triple Therapy Regimens With Pegylated Interferon, Ribavirin, and Either Boceprevir or Telaprevir

Trials of antiviral regimens including either boceprevir or telaprevir have been primarily conducted in patients with genotype 1 infection. Triple antiviral regimens (pegylated interferon alfa-2a or alfa-2b, ribavirin, and boceprevir or telaprevir) were associated with a substantially increased likelihood of achieving an SVR than dual therapy with pegylated interferon alfa-2a or alfa-2b plus ribavirin).[26-28, 53-57]

Two trials found triple therapy with boceprevir for 48 weeks (dual therapy with pegylated interferon alfa-2b plus ribavirin for 4 weeks followed by 44 weeks of triple therapy with the addition of boceprevir) was associated with a higher likelihood of SVR than dual therapy with pegylated interferon alfa-2b plus ribavirin for 48 weeks (pooled relative risk [RR] 1.81, 95% confidence interval [CI] 1.58 to 2.06, I^2=0.0%) with an absolute increase in SVR rate of 31 percentage points (95% CI 23 to 39).[26, 28]

Three trials found triple therapy with telaprevir for 24 weeks (pegylated interferon alfa-2a, ribavirin, and telaprevir triple therapy for 12 weeks followed by 12 weeks of pegylated interferon alfa-2a plus ribavirin without telaprevir) was associated with a higher likelihood of SVR than dual therapy with pegylated interferon alfa-2a plus ribavirin for 48 weeks (pooled RR 1.48, 95% CI 1.26 to 1.75, I^2=0.0%), with an absolute increase in SVR rate of 22 percentage points (95% CI 13 to 31).[27, 53, 55] One trial found response-guided telaprevir triple therapy (8 or 12 weeks of pegylated interferon alfa-2a, ribavirin, and telaprevir followed by 12 or 36 weeks of response-guided dual therapy with pegylated interferon alfa-2a plus ribavirin) was associated with a higher likelihood of SVR than dual therapy with pegylated interferon alfa-2a plus ribavirin for 48 weeks (RR 1.6, 95% CI 1.4 to 1.9), with an absolute increase in SVR rate of 25–31 percentage points.[54]

Relative estimates of the effects of triple therapy with either boceprevir or telaprevir, compared with dual therapy, were similar across subgroups, except in patients with low viral load, in whom triple therapy was no more effective than dual therapy in achieving an SVR. Triple therapy with boceprevir was associated with increased risk of hematological adverse events and triple therapy with telaprevir with increased risk of anemia and rash (including severe rash) than dual therapy; adverse events were generally self-limited with discontinuation of therapy.[26, 28] All antiviral regimens were associated with a high incidence of flulike symptoms, with small or no clear differences in risk.

Sustained Virologic Response After Antiviral Therapy and Clinical Outcomes

A large cohort study that was well controlled for confounders found that patients with an SVR after antiviral therapy had a lower risk of all-cause mortality than patients with no SVR (adjusted hazard ratio estimates 0.51 to 0.71).[8] Eighteen other cohort studies also found SVR associated with reduced risk of all-cause mortality, liver-related mortality, and other hepatic complications rather than no SVR, but had more methodological shortcomings.[9, 58-74] Ten of the studies were conducted in Asian countries and might not be directly applicable to U.S. populations.

Discussion

Key Findings and Strength of Evidence

The evidence reviewed in this study is summarized in Table A. The specific domain scores used to determine the overall strength of evidence for each body of evidence are shown in Appendix G. We identified no studies that evaluated comparative effectiveness of current antiviral regimens on long-term clinical outcomes such as mortality, complications of chronic HCV infection, or quality of life. Such trials would be difficult to design and carry out due to the long time required for complications of chronic HCV infection to develop in most patients.

Dual Therapy Regimens With Pegylated Interferon and Ribavirin

In lieu of direct evidence on long-term clinical outcomes, SVR rates are the primary outcome to assess comparative benefits of different antiviral regimens. In trials of treatment-naïve patients, the likelihood of achieving an SVR was slightly lower with dual therapy with pegylated interferon alfa-2b plus ribavirin compared with dual therapy with pegylated interferon alfa-2a plus ribavirin (pooled RR 0.87, 95% CI 0.80 to 0.95; I^2=27.4%), with a difference in absolute SVR rates of about 8 percentage points. Although the largest study, the Individualized Dosing Efficacy vs. Flat Dosing to Assess Optimal Pegylated Interferon Therapy (IDEAL) trial, found no difference in SVR rates for dual therapy with pegylated interferon alfa-2a plus ribavirin compared with dual therapy with pegylated interferon alfa-2b plus ribavirin, excluding the IDEAL trial from pooled analyses, resulted in similar effect estimates.[18] Although there was no difference between types of dual therapy regimens in risk of withdrawals due to adverse events, dual therapy with pegylated interferon alfa-2b plus ribavirin was associated with a lower risk of serious adverse events than dual therapy with pegylated interferon alfa-2a plus ribavirin (pooled RR 0.76, 95% CI 0.71 to 0.88, I^2=0.0%), suggesting a potential tradeoff between greater benefits and greater harms. However, serious adverse events were only reported in two trials,[18, 19] and the

rate of serious adverse events was relatively low (about 4 percent overall in IDEAL), with an absolute difference of about 1 percent, and adverse events with antiviral treatments generally resolve following discontinuation of therapy. Trials found no clear difference in estimates of relative effectiveness of dual therapy with pegylated interferon alfa-2a plus ribavirin compared with dual therapy with pegylated interferon alfa-2b plus ribavirin in patient subgroups stratified by age, sex, race, viral load, fibrosis stage, and genotype, although absolute response rates were lower in older patients, Black patients, patients with high viral load, patients with more advanced fibrosis or cirrhosis, and patients with genotype 1 infection.[16-19, 51] SVR rates ranged from 24 to 42 percent lower in patients with genotype 1 infection compared with patients with genotype 2 or 3.

In patients with genotype 2 or 3 infection, dual therapy for 12 to 16 weeks appears to be associated with a lower likelihood of SVR compared with dual therapy for 24 weeks, with no differences between 24 weeks and longer courses of therapy.[39-44] Standard doses of pegylated interferon alfa-2b were more effective than lower doses (no trials compared different doses of pegylated interferon alfa-2a).[41, 45-49] Although trials comparing different ribavirin doses found no clear differences, they evaluated different dose comparisons, precluding firm conclusions.[39, 50, 75, 76]

Triple Therapy Regimens With Pegylated Interferon, Ribavirin, and Either Boceprevir or Telaprevir

Trials of triple therapy regimens with the protease inhibitors boceprevir or telaprevir (both approved by the FDA in 2011) in treatment-naïve patients with genotype 1 infection found each associated with substantially higher SVR rates than standard dual therapy without a protease inhibitor. SVR rates with triple therapy were similar to the 70–80 percent observed with dual therapy in patients with genotype 2 or 3 infection.[23, 26-28, 53-57, 77] Trials that evaluated the telaprevir regimen recommended by the FDA (12 weeks of triple therapy with telaprevir followed by response-guided duration of 12 or 36 weeks of dual therapy) reported SVR rates of 75–80 percent.[54, 56] Trials that evaluated the boceprevir regimen recommended by the FDA for antiviral-naïve patients with cirrhosis (4 weeks of dual therapy lead-in followed by 44 weeks of triple therapy with boceprevir) reported SVR rates of 66–75 percent.[26, 28] Trials that evaluated other regimens in antiviral naïve patients, including fixed duration telaprevir regimens, shorter fixed duration triple therapy boceprevir therapy, and boceprevir without dual therapy lead-in, reported similar or lower SVR rates.

As with the head-to-head trials of dual therapy with pegylated interferon alfa-2a plus ribavirin compared with pegylated interferon alfa-2b plus ribavirin, RR estimates for triple, compared with dual, therapy were similar (or there were no clear differences) in patient subgroups based on age, sex, or race, although absolute SVR rates were lower in older patients and Black patients. In two trials, triple therapy with boceprevir was no more effective than dual therapy in the subgroup of patients with lower HCV-RNA viral load (<600,000 or <800,000 IU/mL),[26, 28] but two trials of triple therapy with telaprevir were inconsistent in showing differential effects depending on baseline viral load.[54, 55] There was insufficient evidence to evaluate relative effectiveness of triple, compared with dual, therapy based on fibrosis stage.

In addition to a higher likelihood of SVR, another advantage of triple therapy regimens in patients with genotype 1 infection is the potential for a shorter duration of treatment (24 or 28 weeks in patients with early virologic response, compared with the standard 48 weeks of dual therapy with pegylated interferon plus ribavirin). Shorter courses of treatment would probably be

appealing to patients, given the frequency of bothersome flulike symptoms associated with interferon-based therapy. On the other hand, triple therapy regimens were associated with increased risk of certain harms, in particular hematological adverse events (neutropenia, anemia, and thrombocytopenia) with boceprevir, and anemia and rash (including severe rash in up to about 10 percent of patients, which could result in treatment discontinuation) with telaprevir. However, there was no clear increase in risk of serious adverse events or overall withdrawal due to adverse events with use of protease inhibitors, and the adverse events appear to be self-limited following drug discontinuation.

Sustained Virologic Response After Antiviral Therapy, and Clinical Outcomes

The strongest evidence on the association between an SVR after antiviral therapy and improved clinical outcomes is a large U.S. Department of Veterans Affairs (VA) cohort study (n=16,864) that adjusted for many confounders and found decreased risk of all-cause mortality compared with no SVR across patient groups stratified by genotype (adjusted hazard ratio [HR] 0.71 [0.60–0.86], 0.62 [0.44–0.87] and 0.51 [0.35–0.75] for genotypes 1, 2, and 3, respectively).[8] Despite controlling for important confounders, the possibility of residual confounding is suggested by the very rapid separation of mortality curves for people with an SVR versus those without an SVR, which was observed at 3 months after assessment for SVR. This is more rapid than expected given the typically prolonged natural history of HCV infection. Therefore, estimates of effects of SVR on clinical outcomes from this study may be exaggerated, although it is not possible to determine to what degree. Eighteen other cohort studies also found an SVR after antiviral therapy associated with decreased risk of all-cause mortality and complications of chronic HCV infection, including studies specifically of patients with baseline cirrhosis, but had more methodological shortcomings. In addition, 10 of the 19 studies were conducted in Asia, where the incidence of HCC in patients with chronic HCV infection is higher than in the United States,[78] potentially limiting their generalizability. Other studies found an SVR after antiviral therapy associated with better scores on measures of quality of life than with no SVR, but those studies focused on short-term outcomes and typically did not adjust for confounders or blind patients to SVR status when assessing outcomes.

Table A. Summary of evidence on comparative effectiveness of treatment for hepatitis C

Key Question	Outcome	Summary of Evidence	Strength of Evidence
Key Question 1a What is the comparative effectiveness of antiviral treatment in improving health outcomes in patients with HCV infection?	Long-term clinical outcomes	No evidence.	Insufficient
	Short-term mortality	Three trials that compared current antiviral regimens[a] found no differences in risk of short-term mortality, but reported very few (20 total) events.	Low
	Short-term quality of life	One open-label randomized trial of patients with genotype 4 infection found dual therapy with pegylated interferon alfa-2a plus ribavirin associated with statistically significant, slightly better short-term scores on some quality of life assessments compared with dual therapy with pegylated interferon alfa-2b plus ribavirin.	Low

Table A. Summary of evidence on comparative effectiveness of treatment for hepatitis C (continued)

Key Question	Outcome	Summary of Evidence	Strength of Evidence
Key Question 1b How does the comparative effectiveness of antiviral treatment for health outcomes vary according to patient subgroup characteristics?	Any clinical outcome	No evidence.	Insufficient
Key Question 2a What is the comparative effectiveness of antiviral treatments on intermediate outcomes?	***Dual Therapy With Pegylated Interferon Alfa-2b Plus Ribavirin vs. Dual Therapy With Pegylated Interferon Alfa-2a Plus Ribavirin***		
	Sustained virologic response	Seven trials found dual therapy with standard doses of pegylated interferon alfa-2b plus ribavirin associated with lower likelihood of achieving an SVR than pegylated interferon alfa-2a plus ribavirin (pooled RR 0.87, 95% CI 0.80 to 0.95; I^2=27.4%), with an absolute difference in SVR rates of 8 percentage points (95% CI 3 to 14).	Moderate
	Dual Therapy With Pegylated Interferon Alfa-2a or Alfa-2b Plus Ribavirin: Duration Effects		
	Sustained virologic response	Two trials of patients with genotype 2 or 3 infection found no difference in likelihood of achieving an SVR between 48 vs. 24 weeks of dual therapy with pegylated interferon alfa-2a plus ribavirin (pooled RR 0.97, 95% CI 0.84 to 1.1; I^2=43%).	Moderate
	Sustained virologic response	Four trials of patients with genotype 2 or 3 infection found 24 weeks of dual therapy with pegylated interferon (alfa-2a or alfa-2b) more effective than 12-16 weeks for achieving an SVR (pooled RR 1.15, 95% CI 1.02 to 1.29; I^2=79.5%). Relative risk estimates ranged from 1.01 to 1.33 in the four trials and may have varied in part due to differences across studies in ribavirin dosing.	Moderate
	Sustained virologic response	Three trials of patients with genotype 2 or 3 infection with a rapid virologic response (undetectable HCV-RNA by week 4) found no differences between 24 vs. 12-16 weeks of dual therapy with pegylated interferon (alfa-2a or alfa-2b) plus ribavirin (pooled RR 0.99, 95% CI 0.86 to 1.14; I^2=66.7%). Relative risk estimates ranged from 0.89 to 1.12.	Moderate

Table A. Summary of evidence on comparative effectiveness of treatment for hepatitis C (continued)

Key Question	Outcome	Summary of Evidence	Strength of Evidence
Key Question 2a What is the comparative effectiveness of antiviral treatments on intermediate outcomes? (continued)	***Dual Therapy With Pegylated Interferon Alfa-2a or Alfa-2b Plus Ribavirin: Dose Effects***		
	Sustained virologic response	Six trials of patients with genotype 2 or 3 infection found lower doses of pegylated interferon alfa-2b (0.75-1.0 mcg/kg or 50 mcg) associated with lower likelihood of achieving an SVR than higher doses (1.5 mcg/kg or 100-150 mcg) (pooled RR 0.90; 95% CI 0.81 to 0.99; I^2=20.2%).	Moderate
	Sustained virologic response	Three trials of patients with genotype 2 or 3 infection who did not specifically have advanced fibrosis or cirrhosis found no clear difference in likelihood of SVR between lower doses of ribavirin (400 or 800 mg flat dose or 600 to 800 mg weight-based dose) vs. higher doses (800 or 1,200 mg flat dose or 800 to 1400 mg weight-based dose).	Moderate
	Sustained virologic response	One small trial of patients with genotype 2 or 3 infection (N=60) and advanced fibrosis or cirrhosis (Ishak stage 4-6) found 600 to 800 mg daily of ribavirin associated with lower likelihood of SVR than 1000 to 1200 mg daily (45 vs. 72 percent, RR 0.62, 95% C I 0.40 to 0.98).	Low
	Triple Therapy With Pegylated Interferon Alfa-2b, Ribavirin, and Boceprevir vs. Dual Therapy With Pegylated Interferon Alfa-2b Plus Ribavirin		
	Sustained virologic response	Two trials of patients with genotype 1 infection found triple therapy with boceprevir (pegylated interferon alfa-2b plus ribavirin for 4 weeks, followed by the addition of boceprevir for 44 weeks) associated with higher likelihood of SVR than dual therapy with pegylated interferon alfa-2b plus ribavirin therapy for 48 weeks (pooled RR 1.81; 95% CI 1.58 to 2.06; I^2=0.0%), with an absolute increase in SVR rate of 31% (95% CI 23 to 39).	Moderate
	Sustained virologic response	One trial of patients with genotype 1 infection found 48 weeks of triple therapy with boceprevir using a low dose of ribavirin (400-1000 mg daily) associated with a non–statistically significant trend toward lower likelihood of SVR compared with 48 weeks of triple therapy with a standard ribavirin dose (800-1400 mg daily) (36% vs. 50%, RR 0.71, 95% CI 0.39 to 1.3).	Low

Table A. Summary of evidence on comparative effectiveness of treatment for hepatitis C (continued)

Key Question	Outcome	Summary of Evidence	Strength of Evidence
Key Question 2a What is the comparative effectiveness of antiviral treatments on intermediate outcomes? (continued)	***Triple Therapy With Pegylated Interferon Alfa-2a or Alfa-2b, Ribavirin, and Telaprevir vs. Dual Therapy With Pegylated Interferon Alfa-2a or Alfa-2b Plus Ribavirin***		
	Sustained virologic response	Three trials of patients with genotype 1 infection found triple therapy with telaprevir for 24 weeks (12 weeks of pegylated interferon alfa-2a, ribavirin, and telaprevir followed by 12 weeks of pegylated interferon alfa-2a plus ribavirin) associated with a higher likelihood of SVR than dual therapy with pegylated interferon alfa-2a plus ribavirin for 48 weeks (pooled RR 1.48, 95% CI 1.26 to 1.75; I^2=0.0%), with an absolute increase in SVR rate of 22% (95% CI 13 to 31).	Moderate
	Sustained virologic response	One trial of patients with genotype 1 infection found no difference in likelihood of SVR between triple therapy with pegylated interferon, ribavirin, and telaprevir for 12 weeks vs. dual therapy with pegylated interferon alfa-2a plus ribavirin for 48 weeks.	Moderate
	Sustained virologic response	One trial of patients with genotype 1 infection found response-guided triple therapy with telaprevir (pegylated interferon alfa-2a, ribavirin, and telaprevir for 8 or 12 weeks followed by a response-guided dual therapy with pegylated interferon alfa-2a plus ribavirin for an additional 12 or 36 weeks) associated with a higher likelihood of SVR than dual therapy with pegylated interferon alfa-2a plus ribavirin for 48 weeks (RR 1.6, 95% CI 1.4 to 1.9), with an absolute increase in SVR rate ranging from 25% to 31%. The regimen with 8 weeks of telaprevir was associated with a slightly lower SVR rate than the 12 week telaprevir regimen (69% vs. 75%).	Low
	Sustained virologic response	One trial of patients with genotype 1 infection found no difference in likelihood of SVR between triple therapy with telaprevir for 48 weeks (12 weeks of triple therapy with pegylated interferon alfa-2a, ribavirin, and telaprevir followed by 36 weeks of dual therapy with pegylated interferon alfa-2a plus ribavirin) vs. triple therapy with telaprevir for 24 weeks (12 weeks of triple therapy followed by 12 weeks of dual therapy).	Low

Table A. Summary of evidence on comparative effectiveness of treatment for hepatitis C (continued)

Key Question	Outcome	Summary of Evidence	Strength of Evidence
Key Question 2a What is the comparative effectiveness of antiviral treatments on intermediate outcomes? (continued)	***Triple Therapy With Pegylated Interferon Alfa-2a, Ribavirin, and Telaprevir: Dose Effects of Pegylated Interferon Alfa-2a vs. Alfa-2b and Duration Effects***		
	Sustained virologic response	One trial of response-guided triple therapy with telaprevir (24 or 48 weeks, based on absence or presence of HCV-RNA from weeks 4 through 20) found similar SVR rates (81–85%) for regimens that varied on telaprevir dose (750 mg tid vs. 1125 mg bid) and type of pegylated interferon (alfa-2a or alfa-2b).	Low
	Sustained virologic response	One trial of patients with an extended rapid virologic response to initial triple therapy with telaprevir reported similar, high (92% and 88%) SVR rates in patients randomized to a total of 24 or 48 weeks of therapy.	Low
Key Question 2b How does the comparative effectiveness of antiviral treatment for intermediate outcomes vary according to patient subgroup characteristics?	***Dual Therapy With Pegylated Interferon Alfa-2b Plus Ribavirin vs. Dual Therapy With Pegylated Interferon Alfa-2a Plus Ribavirin***		
	Sustained virologic response	The largest randomized trial (n=3070) of dual therapy with pegylated interferon alfa-2a plus ribavirin vs. dual therapy with pegylated interferon alfa-2b plus ribavirin found no clear differences in relative risk estimates for SVR in genotype 1 patients stratified by race, sex, age, baseline fibrosis stage, or baseline viral load. Characteristics associated with lower absolute SVR rates across dual therapy regimens were older age, Black race, advanced fibrosis or cirrhosis, and high baseline viral load.	Low
	Sustained virologic response	Four randomized trials of dual therapy with pegylated interferon alfa-2a plus ribavirin vs. dual therapy with pegylated interferon alfa-2b plus ribavirin found no clear differences in relative risk estimates for SVR in patients stratified by genotype. Genotype 1 infection was associated with a lower absolute SVR rate than genotypes 2 or 3.	Moderate
	Triple Therapy With Pegylated Interferon Alfa-2b, Ribavirin, and Boceprevir vs. Dual Therapy With Pegylated Interferon Alfa-2b Plus Ribavirin		
	Sustained virologic response	Two trials of triple therapy with boceprevir for 48 weeks (4 weeks of dual therapy lead-in with pegylated interferon plus ribavirin followed by 44 weeks of triple therapy with pegylated interferon, ribavirin, and boceprevir) found no difference in relative risk estimates for SVR in men vs. women, and no clear difference in relative risk estimates for Black vs. non-Black patients. Black race was associated with a lower absolute SVR rate than non-Black race.	Moderate
	Sustained virologic response	Two trials found triple therapy with pegylated interferon alfa-2b, ribavirin, and boceprevir associated with higher likelihood of achieving SVR than dual therapy with pegylated interferon alfa-2b plus ribavirin in patients with high baseline HCV-RNA viral load (>600,000 or ≥800,000 IU/mL), but found no difference in likelihood of SVR in patients with lower viral load.	Moderate

Table A. Summary of evidence on comparative effectiveness of treatment for hepatitis C (continued)

Key Question	Outcome	Summary of Evidence	Strength of Evidence
Key Question 2b How does the comparative effectiveness of antiviral treatment for intermediate outcomes vary according to patient subgroup characteristics? (continued)	***Triple Therapy With Pegylated Interferon Alfa-2a or Alfa-2b, Ribavirin, and Telaprevir vs. Dual Therapy With Pegylated Interferon Alfa-2a or Alfa-2b Plus Ribavirin***		
	Sustained virologic response	One trial of response-guided triple therapy with telaprevir (12 weeks of pegylated interferon alfa-2a, ribavirin, and telaprevir followed by response-guided dual therapy with pegylated interferon alfa-2a and ribavirin) vs. dual therapy with pegylated interferon plus ribavirin for 48 weeks found no clear differences in relative risk estimates in patients stratified by age, sex, race, baseline fibrosis status, or body mass index. Characteristics associated with lower absolute rates of SVR were older age, Black race, advanced fibrosis or cirrhosis, and higher body mass index. One other trial of 24-week fixed duration triple therapy with telaprevir, pegylated interferon alfa-2b, and ribavirin vs. 48 weeks of dual therapy found no differences in estimates of effect in patients stratified by sex or age.	Moderate (for age and sex) Low (for other factors)
	Sustained virologic response	Two trials of triple therapy with pegylated interferon (alfa-2a or alfa-2b), ribavirin, and telaprevir vs. dual therapy depending reported inconsistent findings for differential relative risk estimates according baseline viral load.	Insufficient
Key Question 3a What are the comparative harms associated with antiviral treatments?	***Dual Therapy With Pegylated Interferon Alfa-2b Plus Ribavirin vs. Dual Therapy With Pegylated Interferon Alfa-2a Plus Ribavirin***		
	Harms	Dual therapy with pegylated interferon alfa-2b was associated with slightly greater risk of headache (three trials, pooled RR 1.1, 95% CI 1.1 to 1.2, I^2=0%), and a lower risk of serious adverse events (two trials, pooled RR 0.76; 95% CI 0.71 to 0.88; I^2=0%), lower risk of neutropenia (five trials, pooled RR 0.61, 95% CI 0.46 to 0.83, I^2=38%), and lower risk of rash (two trials, pooled RR 0.79, 95% CI 0.71 to 0.88, I^2=0.0%) than dual therapy with pegylated interferon alfa-2a plus ribavirin, with no differences in withdrawals due to adverse events.	Moderate

Table A. Summary of evidence on comparative effectiveness of treatment for hepatitis C (continued)

Key Question	Outcome	Summary of Evidence	Strength of Evidence
Key Question 3a What are the comparative harms associated with antiviral treatments? (continued)	***Triple Therapy With Pegylated Interferon Alfa-2b, Ribavirin, and Boceprevir vs. Dual Therapy With Pegylated Interferon Alfa-2b Plus Ribavirin***		
	Harms	Triple therapy with boceprevir for 48 weeks (pegylated interferon alfa-2b plus ribavirin for 4 weeks followed by addition of boceprevir for 44 weeks) was associated with increased risk of neutropenia (two trials, pooled RR 1.8, 95% CI 1.5 to 2.3, I^2=0.0%), dysgeusia (two trials, pooled RR 2.5, 95% CI 2.0 to 3.2, I^2=0.0%), anemia (two trials, pooled RR 2.0, 95% CI 1.4 to 2.8, I^2=0.0%), and thrombocytopenia (two trials, pooled RR 3.2, 95% CI 1.2 to 8.2; I^2=0.0%) than dual therapy with pegylated interferon alfa-2b plus ribavirin. The incidence of anemia was about 25% with triple therapy and the incidence of neutropenia about 33%, with severe anemia in 4–5% and severe neutropenia in 8–15%.	Moderate
	Triple Therapy With Pegylated Interferon Alfa-2a or Alfa-2b, Ribavirin, and Telaprevir vs. Dual Therapy With Pegylated Interferon Alfa-2a or Alfa-2b Plus Ribavirin		
	Harms	In two trials, there were no statistically significant differences between a 12-week regimen of triple therapy with pegylated interferon alfa-2a, ribavirin, and telaprevir vs. dual therapy with pegylated interferon alfa-2a plus ribavirin in risk of any assessed adverse event.	Moderate
	Harms	In three trials, a 24-week regimen of triple therapy with telaprevir (pegylated interferon alfa-2a or alfa-2b, ribavirin, and telaprevir for 12 weeks followed by pegylated interferon alfa-2a plus ribavirin for 12 weeks) was associated with increased risk of anemia (three trials, pooled RR 1.3, 95% CI 1.1 to 1.5, I^2=0%) and rash (three trials, pooled RR 1.4, 95% CI 1.1 to 1.7; I^2=0.0%) vs. dual therapy with pegylated interferon alfa-2a plus ribavirin for 48 weeks. Among patients randomized to the 24-week telaprevir regimen, one to two-thirds experienced a rash (7–10% experienced severe rash) and 27–91% experienced anemia (4–11% experienced severe anemia). There was no difference in risk of withdrawal due to adverse events.	Moderate

Table A. Summary of evidence on comparative effectiveness of treatment for hepatitis C (continued)

Key Question	Outcome	Summary of Evidence	Strength of Evidence
Key Question 3a What are the comparative harms associated with antiviral treatments? (continued)	***Triple Therapy With Pegylated Interferon Alfa-2a or Alfa-2b, Ribavirin, and Telaprevir vs. Dual Therapy With Pegylated Interferon Alfa-2a or Alfa-2b Plus Ribavirin (continued)***		
	Harms	In one trial, response-guided triple therapy with telaprevir (pegylated interferon alfa-2a, ribavirin, and telaprevir for 8 or 12 weeks followed by response-guided duration pegylated interferon alfa-2a and ribavirin) was associated with increased risk of withdrawal due to adverse events (27% vs. 7.2%, RR 3.8, 95% CI 2.6 to 5.7), anemia (38% vs. 19%, RR 2.0, 95% CI 1.6 to 2.5), any rash (36% vs. 24%, RR 1.5 , 95% CI 1.2 to 1.8), and severe rash (5% vs. 1%, RR 4.6, 95% CI 1.6 to 13) vs. therapy with pegylated interferon alfa-2a plus ribavirin for 48 weeks.	Low
Key Question 3b Do these harms differ according to patient subgroup characteristics?	***Dual Therapy With Pegylated Interferon Alfa-2b Plus Ribavirin vs. Dual Therapy With Pegylated Interferon Alfa-2a Plus Ribavirin***		
	Harms	No trial of dual therapy with pegylated interferon alfa-2b plus ribavirin vs. dual therapy with pegylated interferon alfa-2a plus ribavirin reported harms in patients stratified by factors such as HCV genotype, age, race, sex, stage of disease, or genetic markers. Three trials that restricted enrollment to patients with genotype 1 infection reported risk estimates for risk of harms that were similar to the risk estimates based on all trials.	Insufficient
	Triple Therapy With Pegylated Interferon Alfa-2a or Alfa-2b, Ribavirin, and Telaprevir or Boceprevir vs. Dual Therapy With Pegylated Interferon Alfa-2a or Alfa-2b Plus Ribavirin		
	Harms	No trial evaluated harms associated with triple therapy with pegylated interferon, ribavirin, and boceprevir or telaprevir vs. dual therapy with pegylated interferon plus ribavirin in patient subgroups. All trials evaluated patients with genotype 1 infection.	Insufficient

Table A. Summary of evidence on comparative effectiveness of treatment for hepatitis C (continued)

Key Question	Outcome	Summary of Evidence	Strength of Evidence
Key Question 4 Have improvements in intermediate outcomes been shown to reduce the risk or rates of adverse health outcomes from HCV infection?	Mortality and long-term hepatic complications	A large VA hospital study that controlled well for potential confounders found an SVR after antiviral therapy associated with lower risk of all-cause mortality vs. no SVR (adjusted HR 0.71 [0.60-0.86], 0.62 [0.44-0.87] and 0.51 [0.35-0.75] for genotypes 1, 2, and 3, respectively). Eighteen other cohort studies found an SVR associated with decreased risk of all-cause mortality, liver-related mortality, HCC, and other complications of ESLD compared with no SVR, with stronger effect estimates than the VA study (adjusted HRs generally ranged from around 0.10 to 0.33). However, the studies had methodological shortcomings, including inadequate handling of confounders, and 10 were conducted in Asia.	Moderate
	Short-term quality of life	Nine studies found an SVR associated with greater improvement in measures related to quality of life (generic or disease-specific) 24 weeks after the end of antiviral treatment vs. no SVR, with differences averaging less than 5 to 10 points on various SF-36 domains. All studies were poor-quality and were characterized by failure to adjust for confounders, high loss to followup, and failure to blind patients to SVR status.	Low

bid = twice daily; CI = confidence interval; ESLD = end-stage liver disease; HCC = hepatocellular carcinoma; HCV = hepatitis C virus; HCV-RNA = hepatitis C virus ribonucleic acid; HR = hazard ratio; IU = international units; kg = kilograms; mcg = micrograms; mL = milliliters; RR = relative risk; SF-36=Short Form (36) Health Survey; SVR = sustained virologic response; tid = three times daily; VA = U.S. Department of Veterans Affairs

[a] "Current antiviral treatment regimen" refers to dual therapy with pegylated interferon (alfa-2a or alfa-2b) plus ribavirin, or triple therapy with pegylated interferon (alfa-2a or alfa-2b) plus ribavirin and boceprevir or telaprevir.

Findings in Relationship to What Is Already Known

Our findings regarding the comparative effectiveness of dual therapy with pegylated interferon alfa-2b plus ribavirin compared with dual therapy with pegylated interferon alfa-2a plus ribavirin are consistent with recent systematic reviews that also found the former associated with a lower likelihood of SVR.[14, 79] Our findings of no clear difference in comparative effectiveness between 12 to 16 weeks compared with 24 weeks of response-guided dual therapy with pegylated interferon plus ribavirin in hepatitis C genotype 2 or 3 infection with rapid virologic response are discordant with a recent systematic review, which found a shorter duration of treatment associated with a lower likelihood of achieving an SVR.[80] The discrepancy may be explained by the inclusion in the other systematic review of a study that we excluded because it evaluated a nonstandard dose of pegylated interferon,[81] as well as its inclusion of subgroup analyses from trials of patients randomized to different fixed durations of therapy prior to assessment of rapid virologic response,[40, 42, 43] which we considered separately because they did not represent randomized comparisons of response-guided treatment.

Because telaprevir and boceprevir are so new, we are unaware of other published systematic reviews on the comparative benefits and harms of regimens including these drugs, compared with standard dual therapy. Our findings on the association between achieving an SVR and

reduced risk of mortality or complications associated with chronic HCV infection are consistent with a recent review that used some systematic methods.[82]

Applicability

The trials included in this review generally met criteria for efficacy studies based on the exclusion of patients with common comorbidities (such as serious psychiatric conditions or recent or ongoing substance abuse). In addition, the trials may have overestimated efficacy compared with what would be seen in typical practice due to improved adherence as a result of closer followup, effects of trial participation, selection of patients, or other factors. A separate review funded by AHRQ will be focusing on issues related to the screening for HCV infection in adults. [29]

The severity of baseline liver disease in the patients enrolled in the trials suggests a broad range of patients were enrolled. In trials of triple therapy with boceprevir or telaprevir, the proportion of patients with cirrhosis at enrollment ranged from <1 to 11 percent.[26-28, 53, 54, 56, 57] Trials that reported the proportion of patients with minimal or no fibrosis reported rates of 27–39 percent.[27, 53, 54, 56, 57]

Evidence to evaluate potential differences in comparative benefits or harms in patient subgroups based on age, sex, race, and other clinical factors was relatively limited, precluding strong conclusions in these specific subgroups. The strongest evidence on the association between an SVR versus no SVR after antiviral therapy and reduced mortality comes from a study performed in a VA population, which might limit generalizability to other settings.[8] As described above, studies conducted in Asia on the association between an SVR after antiviral therapy and risk of clinical outcomes may be of limited applicability to U.S. populations because of a higher incidence of HCC in Asian patients with chronic HCV infection.[78] However, the incidence of HCC is increasing in the United States in HCV-infected people,[83] which may attenuate such concerns regarding applicability.[78]

The results of this CER are not applicable to populations excluded from the review, including patients previously treated with antiviral therapies and excluded populations such as patients with Human immunodeficiency virus (HIV) coinfection, post-transplant patients, or hemodialysis patients. Antiviral therapy is not recommended in patients following kidney transplant, and ribavirin is not recommended in those with more severe (stage 3 to 5) kidney disease since it is cleared via renal function and associated with increased risk of hemolytic anemia in this setting.[84] Such patients were typically excluded from randomized trials of antiviral treatment.

Implications for Clinical and Policy Decisionmaking

Our review has potential implications for clinical and policy decisionmaking. For patients with genotype 1 infection, triple therapy regimens with pegylated interferon alfa-2a or alfa-2b, ribavirin, and telaprevir or boceprevir may be considered an alternative to dual therapy with pegylated interferon alfa-2a or alfa-2b plus ribavirin as standard treatment due to substantially superior efficacy for achieving SVR compared with dual therapy with pegylated interferon alfa-2a or alfa-2b, as well as a shorter duration of treatment. Factors that may affect decisions to use regimens with boceprevir or telaprevir include cost and specific harms associated with use of these drugs (such as hematologic adverse events with boceprevir and anemia and rash with telaprevir). Dual therapy with pegylated interferon alfa-2a plus ribavirin appears to be associated with a higher likelihood of achieving SVR compared with dual therapy with pegylated interferon

alfa-2b plus ribavirin, but absolute differences were relatively small. Therefore, decisions about which pegylated interferon to use may be affected by other considerations, such as cost, patient preferences, or other factors. For genotype 2 or 3 infection, standard doses and duration (24 weeks) of pegylated interferon as part of dual therapy are more effective than shorter regimens or lower doses, lending support to dosing guidance from the FDA and clinical practice guidelines.[11, 85, 86] Evidence on differential effects of ribavirin dose are too limited to draw strong conclusions about optimal dosing of this component of antiviral regimens, although differences appeared relatively small.

The findings that absolute SVR rates are lower in certain subgroups (such as older patients, Black patients, patients with worse baseline fibrosis, and patients with high viral load) can be used to guide individualized decisionmaking. Patients who are less likely to achieve an SVR may make different informed decisions about therapy compared with those more likely to achieve an SVR, given the adverse effects associated with treatment.

The findings of the review are also relevant to screening recommendations, which are based in part on the effectiveness of treatments in people found through screening to have HCV infection. Important new evidence that may affect assessments regarding potential benefits of screening include stronger evidence on the link between achieving an SVR and improvement in clinical outcomes, as well as evidence showing substantially higher SVR rates with newer triple therapy regimens with boceprevir or telaprevir in patients with genotype 1 infection, the predominant type of HCV infection in the United States.

Limitations of the Comparative Effectiveness Review Process

Our review had some potential limitations. We excluded non–English-language articles, which could result in language bias, although a recent systematic review found little empirical evidence that exclusion of non–English-language articles leads to biased estimates for noncomplementary or alternative medicine interventions.[87]

We did not formally assess for publication bias with funnel plots due to small numbers (<10) of studies for all comparisons. Small numbers of studies can make interpretation of funnel plots unreliable, and experts suggest 10 studies as the minimum number of studies to perform them.[88] We included some studies that were published only as abstracts and found their inclusion or exclusion from analyses did not change conclusions. In addition, we searched trial registries and solicited drug manufacturers for additional unpublished trials and identified none.

Another potential limitation is that we included cohort studies to evaluate the association between SVR and either mortality or hepatic complications associated with chronic HCV infection. Such studies are susceptible to confounding if factors associated with SVR (such as age, race, viral load, or fibrosis stage) are also associated with these outcomes. Therefore, we only included studies that reported adjusted risk estimates, and we evaluated how well studies addressed key potential confounders as part of our quality assessment. Nonetheless, residual confounding is a possibility, even in cohort studies that adjust for potential confounding.

Limitations of the Evidence Base

We identified several important limitations of the evidence base. First, studies assessing important long-term clinical outcomes associated with current antiviral treatments for chronic HCV infection are not available. In the case of antiviral regimens involving newly approved antiviral drugs, such studies are not possible yet because of the extended followup required to adequately evaluate effects on clinical outcomes. Second, no trials directly compared regimens

with boceprevir with regimens with telaprevir. Given the increased efficacy of these regimens for genotype 1 infection, trials directly comparing their effects would be helpful for guiding health care providers' treatment choices between these drugs. Third, few trials have evaluated the regimens approved specifically by the FDA for these drugs, limiting confidence in conclusions regarding estimates of benefits and harms for the regimens likely to be used in clinical practice. Fourth, few methodologically rigorous studies conducted in settings applicable to U.S. populations evaluated the association between achieving an SVR and improvements in clinical outcomes. Such studies would be very helpful for confirming the results of the recent large, well-conducted VA cohort study showing an association between achieving an SVR and reduced mortality risk.[8]

Future Research

Evaluating the comparative effectiveness of current antiviral regimens on clinical outcomes in randomized trials or cohort studies is a challenge due to the long lead time and large sample sizes necessary to adequately assess these outcomes. This might be more feasible if the studies were to focus on populations at higher risk for complications from chronic HCV infection (e.g., patients with baseline cirrhosis, high viral load, or other risk factors for progression).

For all trials of antiviral treatments, studies that enroll broader populations with medical and psychological comorbidities, as frequently encountered in clinical practice, are needed to better understand comparative effectiveness, rather than just comparative efficacy. Studies designed using an effectiveness paradigm would also be helpful for understanding real-world outcomes of antiviral regimens, including effects related to the poorer treatment adherence than expected from efficacy trials.

Trials directly comparing triple therapy with telaprevir compared with triple therapy with boceprevir would be very helpful for understanding comparative effectiveness of these two protease inhibitors. In addition, trials evaluating the boceprevir regimen recommended by the FDA in antiviral-naïve patients without baseline cirrhosis are needed to verify that results from studies of previously treated patients were appropriately generalized. Prolonged followup of patients exposed to telaprevir and boceprevir is needed to understand the long-term harms associated with these medications. A number of other protease inhibitors and other newer drugs for treatment of hepatitis C virus infection are currently in active development, and further studies with new drugs and drug regimens are expected, including regimens without interferon.[89]

It is critical that future studies that evaluate clinical outcomes in patients with an SVR versus no SVR after antiviral therapy adequately control for other factors that influence clinical outcomes in chronic HCV infection. Studies on effects of achieving an SVR on long-term quality of life would be very helpful for understanding other potential clinical benefits of antiviral therapy, but a significant challenge is whether it is possible to ethically blind patients to virologic status, which may have an important effect on assessments of quality of life.

References

1. Armstrong GL, Wasley A, Simard EP, et al. The prevalence of hepatitis C virus infection in the United States, 1999 through 2002. Ann Intern Med. 2006;144:705-14. PMID: 16702586.
2. Ly KN, Xing J, Klevens RM, et al. The increasing burden of mortality from viral hepatitis in the United States between 1999 and 2007. Ann Intern Med. 2012;156(4):271-8. PMID: 22351712.
3. Kim WR. The burden of hepatitis C in the United States. Hepatology. 2002;36(5 suppl. 1): S30-S4. PMID: 12407574.
4. Davis GL, Alter MJ, El-Serag H, et al. Aging of hepatitis C virus (HCV)-infected persons in the United States: a multiple cohort model of HCV prevalence and disease progression. Gastroenterol. 2010 Feb;138(2):513-21. PMID: 19861128.
5. National Center for HIV/AIDS VH, STD & TB Prevention. Disease burden from viral hepatitis A, B, and C in the United States. Centers for Disease Control and Prevention; 2011. www.cdc.gov/hepatitis/PDFs/disease_burden.pdf, Accessed on 6/29/12.
6. Swain M, Lai MY, Shiffman ML, et al. Durability of sustained virological response (SVR) after treatment with peginterferon alfa-2A (40KD) (PEGASYS) alone or in combination with ribavirin (COPEGUS): results of an ongoing long-term follow-up study. Hepatology (Baltimore, MD). 2004;40(4 Suppl 1):400A-1A.
7. Swain MG, Lai MY, Shiffman ML, et al. A sustained virologic response is durable in patients with chronic hepatitis C treated with peginterferon alfa-2a and ribavirin. Gastroenterol. 2010 Nov.;139(5):1593-601. PMID: 20637202.
8. Backus LI, Boothroyd DB, Phillips BR, et al. A sustained virologic response reduces risk of all-cause mortality in patients with hepatitis C. Clin Gastroenterol Hepatol. 2011;9:509-16. PMID: 21397729.
9. Morgan TR, Ghany MG, Kim H-Y, et al. Outcome of sustained virological responders with histologically advanced chronic hepatitis C. Hepatology. 2010 Sep;52(3):833-44. PMID: 20564351.
10. Anonymous. National Institutes of Health consensus development conference statement: management of hepatitis C: 2002--June 10-12, 2002. Hepatology. 2002;36(5 (Suppl 1):S3-S20. PMID: 12407572.
11. Ghany MG, Strader DB, Thomas DL, et al. Diagnosis, management, and treatment of hepatitis C: an update. Hepatology. 2009;49(4):1335-74. PMID: 19330875.
12. Strader DB, Wright T, Thomas DL, et al. Diagnosis, management, and treatment of hepatitis C. Hepatology. 2004; 39(4):1147-71. PMID: 15057920.
13. Foster GR. Review article: pegylated interferons: chemical and clinical differences. Aliment Pharmacol Ther. 2004 Oct 15;20(8):825-30. PMID: 15479353.
14. Awad T, Thorlund K, Hauser G, et al. Peginterferon alpha-2a is associated with higher sustained virological response than peginterferon alfa-2b in chronic hepatitis C: Systematic review of randomized trials. Hepatology. 2010;51(4):1176-84. PMID: 20187106.
15. Chou R CS, Chan BKS. Drug Class Review on Pegylated Interferons for Chronic Hepatitis C Infection. Portland, OR: Oregon Health & Science University; 2007. www.ohsu.edu/drugeffectiveness/reports/final.cfm.
16. Ascione A, De Luca M, Tartaglione MT, et al. Peginterferon alfa-2a plus ribavirin is more effective than peginterferon alfa-2b plus ribavirin for treating chronic hepatitis C virus infection. Gastroenterol. 2010 Jan;138(1):116-22. PMID: 19852964.
17. Escudero A, Rodriguez F, Serra MA, et al. Pegylated alpha-interferon-2a plus ribavirin compared with pegylated alpha-interferon-2b plus ribavirin for initial treatment of chronic hepatitis C virus: prospective, non-randomized study. J Gastroenterol Hepatol. 2008 Jun;23(6):861-6. PMID: 18422960.

18. McHutchison JG, Lawitz EJ, Shiffman ML, et al. Peginterferon alfa-2b or alfa-2a with ribavirin for treatment of hepatitis C infection.[Erratum appears in N Engl J Med. 2009 Sep 3;361(10):1027]. N Engl J Med. 2009 Aug 6;361(6):580-93. PMID: 19625712.

19. Rumi MG, Aghemo A, Prati GM, et al. Randomized study of peginterferon-alpha2a plus ribavirin vs peginterferon-alpha2b plus ribavirin in chronic hepatitis C. Gastroenterol. 2010 Jan;138(1):108-15. PMID: 19766645.

20. Nainan OV, Alter MJ, Kruszon-Moran D, et al. Hepatitis C virus genotypes and viral concentration in participants of a general population survey in the United States. Gastroenterol. 2006;131:478-84. PMID: 16890602

21. Ge D, Fellay J, Thompson AJ, et al. Genetic variation in IL28B predicts hepatitis C treatment-induced viral clearance. Nature. 2009;461(7262):399-401. PMID: 19684573.

22. Suppiah V, Moldovan M, Ahlenstiel G, et al. IL28B is associated with response to chronic hepatitis C interferon-α and ribavirin therapy. Nat Genet. 2009;41(10):1100-4. PMID: 19749758.

23. Fried MW, Shiffman ML, Reddy KR, et al. Peginterferon alfa-2a plus ribavirin for chronic hepatitis C virus infection. N Engl J Med. 2002 Sep 26;347(13):975-82. PMID: 12324553.

24. FDA. Approval of Victrelis (boceprevir) a direct acting antiviral drug (DAA) to treat hepatitis C virus (HCV). 2011. www.fda.gov/ForConsumers/ByAudience/ForPatientAdvocates/ucm255413.htm.

25. FDA. Approval of Incivek (telaprevir), a direct acting antiviral drug (DAA) to treat hepatitis C (HCV). 2011. www.fda.gov/ForConsumers/ByAudience/ForPatientAdvocates/ucm256328.htm.

26. Kwo PY, Lawitz EJ, McCone J, et al. Efficacy of boceprevir, an NS3 protease inhibitor, in combination with peginterferon alfa-2b and ribavirin in treatment-naive patients with genotype 1 hepatitis C infection (SPRINT-1): an open-label, randomised, multicentre phase 2 trial.[Erratum appears in Lancet. 2010 Oct 9;376(9748):1224 Note: SPRINT-1 investigators [added]; multiple investigator names added]. Lancet. 2010 Aug 28;376(9742):705-16. PMID: 20692693.

27. McHutchison JG, Everson GT, Gordon SC, et al. Telaprevir with peginterferon and ribavirin for chronic HCV genotype 1 infection.[Erratum appears in N Engl J Med. 2009 Oct 8;361(15):1516]. N Engl J Med. 2009 Apr 30;360(18):1827-38. PMID: 19403902.

28. Poordad F, McCone J, Jr., Bacon BR, et al. Boceprevir for untreated chronic HCV genotype 1 infection. N Engl J Med. 2011 Mar 31;364(13):1195-206. PMID: 21449783.

29. Chou R, Cottrell E, Wasson N. Screening for Hepatitis C Virus Infection in Adults: Comparative Effectiveness Review. (Prepared by Oregon Evidence-based Practice Center under Contract No. 290-2007-10057-I). Rockville, MD: Agency for Healthcare Research and Quality; Forthcoming 2012.

30. Downs SH, Black N. The feasibility of creating a checklist for the assessment of the methodological quality both of randomised and non-randomised studies of health care interventions. J Epidemiol Community Health. 1998;52(6):377-84. PMID: 9764259.

31. 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;20(3 Suppl):21-35. PMID: 11306229.

32. Whiting PF, Rutjes AW, Westwood ME, et al. QUADAS-2: A Revised Tool for the Quality Assessment of Diagnostic Accuracy Studies. Ann Intern Med. 2011;155(8):529-36. PMID: 22007046.

33. AHRQ. Methods Guide for Effectiveness and Comparative Effectiveness Reviews. Rockville, MD: Agency for Healthcare Research and Quality; 2011. www.effectivehealthcare.ahrq.gov/index.cfm/search-for-guides-reviews-and-reports/?pageaction=displayproduct&productid=318

34. 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;4(1):38. PMID: 15615589.

35. Fu R, Gartlehner G, Grant M, et al. Conducting quantitative synthesis when comparing medical interventions: AHRQ and the effective health care program. J Clin Epidemiol. 2011 Nov;64(11):1187-97. PMID: 21477993.

36. Kamal SM, Ahmed A, Mahmoud S, et al. Enhanced efficacy of pegylated interferon alpha-2a over pegylated interferon and ribavirin in chronic hepatitis C genotype 4A randomized trial and quality of life analysis. Liver Int. 2011;31(3):401-11. PMID: 21281434.

37. Mach TH, Ciesla A, Warunek W, et al. Efficacy of pegylated interferon alfa-2a or alfa-2b in combination with ribavirin in the treatment of chronic hepatitis caused by hepatitis C virus genotype 1b. Polskie Archiwum Medycyny Wewnetrznej. 2011;121(12):434-40.

38. Yenice N, Mehtap O, Gumrah M, et al. The efficacy of pegylated interferon alpha 2a or 2b plus ribavirin in chronic hepatitis C patients. Turk J Gastroenterol. 2006 Jun;17(2):94-8. PMID: 16830289.

39. Hadziyannis SJ, Sette H, Jr., Morgan TR, et al. Peginterferon-alpha2a and ribavirin combination therapy in chronic hepatitis C: a randomized study of treatment duration and ribavirin dose. Ann Intern Med. 2004 Mar 2;140(5):346-55. PMID: 14996676.

40. Lagging M, Langeland N, Pedersen C, et al. Randomized comparison of 12 or 24 weeks of peginterferon alpha-2a and ribavirin in chronic hepatitis C virus genotype 2/3 infection. Hepatology. 2008 Jun;47(6):1837-45. PMID: 18454508.

41. Manns M, Zeuzem S, Sood A, et al. Reduced dose and duration of peginterferon alfa-2b and weight-based ribavirin in patients with genotype 2 and 3 chronic hepatitis C. J Hepatol. 2011b;55(3):554-63. PMID: 21237227.

42. Shiffman ML, Suter F, Bacon BR, et al. Peginterferon alfa-2a and ribavirin for 16 or 24 weeks in HCV genotype 2 or 3. N Engl J Med. 2007 Jul 12;357(2):124-34. PMID: 17625124.

43. Yu M-L, Dai C-Y, Huang J-F, et al. A randomised study of peginterferon and ribavirin for 16 versus 24 weeks in patients with genotype 2 chronic hepatitis C. Gut. 2007 Apr;56(4):553-9. PMID: 16956917.

44. Zeuzem S, Diago M, Gane E, et al. Peginterferon alfa-2a (40 kilodaltons) and ribavirin in patients with chronic hepatitis C and normal aminotransferase levels. Gastroenterol. 2004 Dec;127(6):1724-32. PMID: 15578510.

45. Abergel A, Hezode C, Leroy V, et al. Peginterferon alpha-2b plus ribavirin for treatment of chronic hepatitis C with severe fibrosis: a multicentre randomized controlled trial comparing two doses of peginterferon alpha-2b. J Viral Hepat. 2006 Dec;13(12):811-20. PMID: 17109680.

46. Kawaoka T, Kawakami Y, Tsuji K, et al. Dose comparison study of pegylated interferon-alpha-2b plus ribavirin in naive Japanese patients with hepatitis C virus genotype 2: a randomized clinical trial. J Gastroenterol Hepatol. 2009 Mar;24(3):366-71. PMID: 19032459.

47. Krawitt EL, Gordon SR, Grace ND, et al. A study of low dose peginterferon alpha-2b with ribavirin for the initial treatment of chronic hepatitis C. Am J Gastroenterol. 2006 Jun;101(6):1268-73. PMID: 16771948.

48. Meyer-Wyss B, Rich P, Egger H, et al. Comparison of two PEG-interferon alpha-2b doses (1.0 or 1.5 microg/kg) combined with ribavirin in interferon-naive patients with chronic hepatitis C and up to moderate fibrosis. J Viral Hepat. 2006 Jul;13(7):457-65. PMID: 16792539.

49. Sood A, Midha V, Hissar S, et al. Comparison of low-dose pegylated interferon versus standard high-dose pegylated interferon in combination with ribavirin in patients with chronic hepatitis C with genotype 3: an Indian experience. J Gastroenterol Hepatol. 2008 Feb;23(2):203-7. PMID: 17645472.

50. Jacobson (a) IM, Brown RS, Jr., Freilich B, et al. Peginterferon alfa-2b and weight-based or flat-dose ribavirin in chronic hepatitis C patients: a randomized trial. Hepatology. 2007 Oct;46(4):971-81. PMID: 17894303.

51. Magni C NF, Argenteri B, Giorgi R, Mainini A, Pastecchia C, Ricci E, Schiavini M, Terzi R, Vivirito MC, Resta M. Abstract #883: Antiviral activity and tolerability between pegylated interferon alpha 2a and alpha 2b in naive patients with chronic hepatitis C: Results of a prospective monocentric randomized trial. Hepatology. 2009;50(S4):720A.

52. Miyase S, Haraoka K, Ouchida Y, et al. Randomized trial of peginterferon α-2a plus ribavirin versus peginterferon α-2b plus ribavirin for chronic hepatitis C in Japanese patients. J Gastroenterol. 2012:1-8. PMID: 22382633.

53. Hezode C, Forestier N, Dusheiko G, et al. Telaprevir and peginterferon with or without ribavirin for chronic HCV infection. N Engl J Med. 2009 Apr 30;360(18):1839-50. PMID: 19403903.

54. Jacobson IM, McHutchison JG, Dusheiko G, et al. Telaprevir for previously untreated chronic hepatitis C virus infection. N Engl J Med. 2011;364(25):2405-16. PMID: 21696307.

55. Kumada H, Toyota J, Okanoue T, et al. Telaprevir with peginterferon and ribavirin for treatment-naive patients chronically infected with HCV of genotype 1 in Japan. J Hepatol. 2012;56(1):78-84. PMID: 21827730.

56. Marcellin P, Forns X, Goeser T, et al. Telaprevir is effective given every 8 or 12 hours with ribavirin and peginterferon alfa-2a or -2b to patients with chronic hepatitis C. Gastroenterol. 2011 Feb;140(2):459-68.e1; quiz e14. PMID: 21034744.

57. Sherman KE, Flamm SL, Afdhal NH, et al. Response-guided telaprevir combination treatment for hepatitis C virus infection. N Engl J Med. 2011;365(11):1014-24. PMID: 21916639.

58. Arase Y, Ikeda K, Suzuki F, et al. Long-term outcome after interferon therapy in elderly patients with chronic hepatitis C. Intervirology. 2007;50(1):16-23. PMID: 17164553.

59. Bruno S, Stroffolini T, Colombo M, et al. Sustained virological response to interferon-alpha is associated with improved outcome in HCV-related cirrhosis: a retrospective study. Hepatology. 2007 Mar;45(3):579-87. PMID: 17326216.

60. Cardoso A-C, Moucari R, Figueiredo-Mendes C, et al. Impact of peginterferon and ribavirin therapy on hepatocellular carcinoma: incidence and survival in hepatitis C patients with advanced fibrosis. J Hepatol. 2010 May;52(5):652-7. PMID: 20346533.

61. Coverdale SA, Khan MH, Byth K, et al. Effects of interferon treatment response on liver complications of chronic hepatitis C: 9-year follow-up study. Am J Gastroenterol. 2004 Apr;99(4):636-44. PMID: 15089895.

62. El Braks RE, Ganne-Carrie N, Fontaine H, et al. Effect of sustained virological response on long-term clinical outcome in 113 patients with compensated hepatitis C-related cirrhosis treated by interferon alpha and ribavirin. World J Gastroenterol. 2007;13(42):5648-53. PMID: 17948941.

63. Fernández-Rodríguez CM, Alonso S, Martinez SM, et al. Peginterferon plus ribavirin and sustained virological response in HCV-related cirrhosis: Outcomes and factors predicting response. Am J Gastroenterol. 2010PMID: 20927082.

64. Hasegawa E, Kobayashi M, Kawamura Y, et al. Efficacy and anticarcinogenic activity of interferon for hepatitis C virus-related compensated cirrhosis in patients with genotype 1b low viral load or genotype 2. Hepatol Res. 2007;37(10):793-800. PMID: 17593231.

65. Hung CH, Lee CM, Lu SN, et al. Long-term effect of interferon alpha-2b plus ribavirin therapy on incidence of hepatocellular carcinoma in patients with hepatitis C virus-related cirrhosis. J Viral Hepat. 2006;13(6):409-14. PMID: 16842444.

66. Imazeki F, Yokosuka O, Fukai K, et al. Favorable prognosis of chronic hepatitis C after interferon therapy by long-term cohort study. Hepatology. 2003 Aug;38(2):493-502. PMID: 12883494.

67. Innes HA, Hutchinson SJ, Allen S, et al. Excess liver-related morbidity of chronic hepatitis C patients, who achieve a sustained viral response, and are discharged from care. Hepatology. 2011;54(5):1547-58. PMID: 22045672.

68. Izumi N, Yasuhiro A, Kurosaki M, et al. Development of hepatocellular carcinoma after interferon therapy in chronic hepatitis C. Is it possible to reduce the incidence by ribanirin and IFN combination therapy? Intervirology. 2005;48(1):59-63. PMID: 15785091.

69. Kasahara A, Tanaka H, Okanoue T, et al. Interferon treatment improves survival in chronic hepatitis C patients showing biochemical as well as virological responses by preventing liver-related death. J Viral Hepat. 2004 Mar;11(2):148-56. PMID: 14996350.

70. Maruoka D, Imazeki F, Arai M, et al. Long-term cohort study of chronic hepatitis C according to interferon efficacy. J Gastroenterol Hepatol. 2012b;27(2):291-9. PMID: 21793911.

71. Shiratori Y, Ito Y, Yokosuka O, et al. Antiviral therapy for cirrhotic hepatitis C: association with reduced hepatocellular carcinoma development and improved survival. Ann Intern Med. 2005 Jan 18;142(2):105-14. PMID: 15657158.

72. Veldt BJ, Heathcote EJ, Wedemeyer H, et al. Sustained virologic response and clinical outcomes in patients with chronic hepatitis C and advanced fibrosis. Ann Intern Med. 2007;147(10):677-84. PMID: 18025443.

73. Yoshida H, Arakawa Y, Sata M, et al. Interferon therapy prolonged life expectancy among chronic hepatitis C patients. Gastroenterol. 2002 Aug;123(2):483-91. PMID: 12145802.

74. Yu M-L, Lin S-M, Chuang W-L, et al. A sustained virological response to interferon or interferon/ribavirin reduces hepatocellular carcinoma and improves survival in chronic hepatitis C: a nationwide, multicentre study in Taiwan. Antiver Ther. 2006;11(8):985-94. PMID: 17302368.

75. Ferenci P, Brunner H, Laferl H, et al. A randomized, prospective trial of ribavirin 400 mg/day versus 800 mg/day in combination with peginterferon alfa-2a in hepatitis C virus genotypes 2 and 3. Hepatology. 2008 Jun;47(6):1816-23. PMID: 18454510.

76. Helbling B, Jochum W, Stamenic I, et al. HCV-related advanced fibrosis/cirrhosis: randomized controlled trial of pegylated interferon alpha-2a and ribavirin. J Viral Hepat. 2006 Nov;13(11):762-9. PMID: 17052276.

77. Manns MP, McHutchison JG, Gordon SC, et al. Peginterferon alfa-2b plus ribavirin compared with interferon alfa-2b plus ribavirin for initial treatment of chronic hepatitis C: a randomised trial. Lancet. 2001;358(9286):958-65. PMID: 11583749.

78. Shibuya K, Yano E. Regression analysis of trends in mortality from hepatocellular carcinoma in Japan, 1972-2001. Int J Epidemiol. 2005;34(2):397-402. PMID: 15561746.

79. Singal AK, Jampana SC, Anand BS. Peginterferon alfa-2a is superior to peginterferon alfa-2b in the treatment of naïve patients with hepatitis C virus infection: meta-analysis of randomized controlled trials. Dig Dis Sci. 2011 Aug;56(8):2221-6. PMID: 21643737.

80. Singal AK, Anand BS. Tailoring treatment duration to 12 to 16 weeks in hepatitis C genotype 2 or 3 with rapid virologic response: systematic review and meta-analysis of randomized controlled trials. J Clin Gastroenterol. 2010;44(8):583-7. PMID: 20375729.

81. Mangia A, Santoro R, Minerva N, et al. Peginterferon alfa-2b and ribavirin for 12 vs. 24 weeks in HCV genotype 2 or 3. N Engl J Med. 2005 Jun 23;352(25):2609-17. PMID: 15972867.

82. Pearlman BL, Traub N. Sustained virologic response to antiviral therapy for chronic hepatitis C virus infection: a cure and so much more. Clin Infect Dis. 2011;52(7):889-900. PMID: 21427396.

83. El-Serag HB. Hepatocellular carcinoma. N Engl J Med. 2011;365(12):1118-27. PMID: 21992124.

84. Ghany MG, Kim H-Y, Stoddard A, et al. Predicting clinical outcomes using baseline and follow-up laboratory data from the hepatitis C long-term treatment against cirrhosis trial. Hepatology. 2011 Nov;54(5):1527-37. PMID: 22045670.

85. PEGASYS [package insert]. Hoffmann-La Roche Inc. Nutley, NJ; 2002.

86. PEG-Intron [package insert]. Schering Corporation. Kenilworth, NJ; 2005.

87. Morrison A, Moulton K, Clark M, et al. English-Language Restriction When Conducting Systematic Review-based Metaanalyses: Systematic Review of Published Studies Ottawa: Canadian Agency for Drugs and Technologies in Health; 2009. http://journals.cambridge.org/action/displayAbstract?fromPage=online&aid=8544780

88. Sterne JA, Sutton AJ, Ioannidis JP, et al. Recommendations for examining and interpreting funnel plot asymmetry in meta-analyses of randomised controlled trials. British Medical Journal. 2011 Jul 2011;343(1):d4002. PMID: 21784880.

89. Lok A. Preliminary study of two antiviral agents for hepatitis C genotype 1. N Engl J Med. 2012;366(3):273-5. PMID: 22256811.

Introduction

Hepatitis C virus (HCV) is the most common chronic bloodborne pathogen in the United States. HCV is primarily acquired by large or repeated percutaneous exposures to blood, with injection drug use the strongest risk factor. Based on a national survey of households, approximately 1.6 percent of U.S. adults over 20 years of age have antibodies to HCV, indicating prior acute HCV infection.[1] About 78 percent of patients with acute HCV infection develop chronic HCV infection, defined by the presence of persistent viremia.

Chronic HCV infection has a variable course, but it is a leading cause of complications from chronic liver disease, including cirrhosis, liver failure, and hepatocellular carcinoma (HCC). Chronic HCV infection was associated with an estimated 15,000 deaths in the United States in 2007,[2] and it is the most common indication for liver transplantation among American adults, accounting for more than 30 percent of cases.[3] The prevalence of chronic HCV infection is thought to have peaked in 2001 at 3.6 million people, and the yearly incidence has declined from more than 200,000 cases per year in the 1980s to around 16,000 cases in 2009.[4, 5] However, complications related to chronic HCV infection, which frequently occur only after decades of infection, are expected to rise for another 10 to 13 years.[4]

The goals of antiviral treatment for chronic HCV infection are to prevent the long-term health complications associated with HCV infection, such as cirrhosis, hepatic decompensation, and liver cancer, but it is a challenge to design and carry out clinical trials long and large enough to provide direct evidence related to these outcomes. The sustained virologic response (SVR) rate, typically defined as a decline in HCV-RNA (Hepatitis C virus ribonucleic acid) to undetectable levels 24 weeks following completion of antiviral treatment, is the standard marker for successful treatment in clinical trials because it is strongly associated with long-term absence of viremia.[6, 7] Recent studies have evaluated the association between achieving an SVR and reductions in mortality, liver failure, and cancer.[8, 9]

The treatment of HCV infection has evolved dramatically over the past several decades. Recombinant type I interferons were introduced as monotherapy in the mid-1980s, but were only modestly successful at achieving SVR (overall <20 percent).[10-13] Subsequent trials found dual therapy with interferon and the synthetic nucleoside analogue ribavirin more effective than monotherapy with interferon, although the SVR rates remained under 50 percent.[10-13]

In the early 2000s, the combination of "pegylated" interferon plus ribavirin became the standard antiviral treatment for HCV infection.[14-16] The first pegylated interferon was approved by the FDA in 2001. Pegylation refers to the cross-linking of polyethylene glycol molecules to the interferon molecule, which delays renal clearance and thereby permits less frequent dosing (once weekly vs. three times a week with nonpegylated interferon).[17] Currently, two pegylated interferons are available: pegylated interferon alfa-2a and pegylated interferon alfa-2b. Both are Type I alfa interferons, but differ in the size and structure of the interferon and polyethylene glycol molecules, as well as in their pharmacokinetic properties (Table 1).[17] One pegylated interferon consists of 31-kilodalton (kDa) interferon alfa-2b conjugated to 12-kDa polyethylene glycol (brand name PEG-intron®). The other consists of recombinant 20-kDa interferon alfa-2a linked to 40-kDa polyethylene glycol (trade name Pegasys®). The dosing schedule is fixed for pegylated interferon alfa-2a and is based on weight for pegylated interferon alfa-2b. Each pegylated interferon is approved for dual therapy with ribavirin. Although each pegylated interferon is approved for combination therapy with a specific brand of ribavirin manufactured by the respective manufacturer (Copegus® for pegylated interferon alfa-2a and Rebetol® for alfa-2b), the ribavirin is pharmacologically identical. The FDA-recommended doses of ribavirin are

800 to 1200 mg/day for pegylated interferon alfa-2a, depending on weight and genotype, and 800 to 1400 mg/day for pegylated interferon alfa-2b, depending on weight.

Dual therapy with pegylated interferon (alfa-2a or alfa-2b) plus ribavirin is associated with higher SVR rates (about 55–60 percent overall) than either nonpegylated interferon plus ribavirin or pegylated interferon (alfa-2a or alfa-2b) monotherapy. Although previous reviews found insufficient evidence to determine whether dual therapy with pegylated interferon alfa-2a or pegylated interferon alfa-2b is more effective,[18, 19] more head-to-head trials directly comparing these two regimens are now available.[20-23]

A number of factors affect response to antiviral treatment. The two major pretreatment predictors of SVR are the viral genotype and the pretreatment viral load.[15] In the United States, genotype 1 infection is found in around three-quarters of HCV-infected patients.[24] HCV genotype 1 infection is associated with a substantially lower response to antiviral treatment than infection with genotypes 2 and 3, which are present in about 20 percent of HCV-infected patients. A pretreatment viral load of <600,000 international units per milliliter (IU/mL) is associated with higher likelihood of achieving an SVR.[15] Other factors less consistently or less strongly associated with increased likelihood of SVR include female sex, age less than 40 years, non-Black race, lower body weight (≤75 kg), absence of insulin resistance, elevated alanine aminotransferase (ALT) levels, and absence of bridging fibrosis or cirrhosis on liver biopsy.[15] Effects of race on the likelihood of SVR may be due in part to polymorphisms in the interleukin-28B (IL28B) gene.[25, 26]

An issue complicating antiviral treatment is the high rate of adverse effects observed with interferon-based therapy, including flulike symptoms, fatigue, and neuropsychiatric and hematologic adverse effects.[27] Such adverse effects can be difficult to tolerate and can lead to premature discontinuation of therapy.

In 2011, the U.S. Food and Drug Administration (FDA) approved the first direct acting antiviral agents, boceprevir (trade name Victrelis®) and telaprevir (trade name Incivek®), for treatment of chronic HCV genotype 1 infection (Table 1).[28, 29] Both drugs are classified as nonstructural (NS) 3/4A protease inhibitors, with a potential advantage of shorter duration of therapy (24 to 28 weeks) when used in combination with pegylated interferon (alfa-2a or alfa-2b) compared with standard dual therapy with pegylated interferon (alfa-2a plus -2b) plus ribavirin for genotype 1 infection (48 weeks) (Table 1).[30-32]

Table 1. Pharmacokinetics, indications, and dosing of included drugs[28, 29, 33, 34]

Drug Trade Name	Indications Labeled by the U.S. Food and Drug Administration	Dosing Recommended by the U.S. Food and Drug Administration
Pegylated interferon alfa-2a Pegasys®	Patients 5 years of age and older with chronic HCV infection with compensated liver disease not previously treated with interferon alfa	180 mcg once weekly in combination with ribavirin for 24 weeks with ribavirin for genotypes 2 or 3, or 48 weeks for genotype 1or 4 infection
Pegylated interferon alfa-2b PEG-Intron®	Patients 5 years of age and older with chronic HCV infection with compensated liver disease	1.5 mcg/kg weekly in combination with ribavirin for 24 weeks with ribavirin for genotypes 2 or 3, or 48 weeks for genotype 1 infection
Boceprevir Victrelis®	Adults with chronic HCV genotype 2 infection with compensated liver disease, including cirrhosis, who are previously untreated or who have been previously treated with interferon and ribavirin therapy	Four weeks of treatment with pegylated interferon (alfa-2a or 2b) plus ribavirin, then the addition of boceprevir 800 mg 3 times daily as follows:[a] In treatment-naïve patients without cirrhosis: - If HCV-RNA undetectable from treatment week 8 through week 24, complete triple therapy at treatment week 28 - If HCV-RNA detectable at treatment week 8 and undetectable at treatment week 24, continue triple therapy through treatment week 36 and continue pegylated interferon (alfa-2a or 2b) with ribavirin through treatment week 48 In treatment-naïve patients with cirrhosis: - 44 weeks of triple therapy
Telaprevir Incivek®	Adults with chronic HCV genotype 1 infection with compensated liver disease, including cirrhosis, who are previously untreated or who have been previously treated with interferon and ribavirin therapy	750 mg 3 times a day with pegylated interferon (alfa-2a or 2b) and ribavirin for all patients for 12 weeks, followed by response-guided regimen of pegylated interferon and ribavirin[a] In treatment-naïve patients without cirrhosis: - If HCV-RNA is undetectable at weeks 4 and 12, then continue dual therapy for 12 more weeks (total treatment 24 weeks) - If HCV-RNA is detectable at week 4 and/or week 12, then continue dual therapy for 36 more weeks (total treatment 48 weeks) In treatment-naïve with cirrhosis: - Continue dual therapy for 36 more weeks (total treatment 48 weeks)

HCV = hepatitis C virus; HCV-RNA = hepatitis C virus ribonucleic acid

[a] The manufacturer packaging and dosage information does not specify a particular pegylated interferon (alfa-2a or alfa-2b) for either drug, though in trials conducted to obtain FDA approval, boceprevir was tested with pegylated interferon alfa-2b and telaprevir with pegylated interferon alfa-2a.

Understanding the comparative benefits and harms of the various antiviral regimens is critical for making informed treatment decisions in patients with chronic HCV infection, particularly given the availability of new treatment options. This review will assess the comparative effectiveness of antiviral treatments in adults with chronic HCV infection who have not received previous antiviral drug treatment. In addition to assessing the comparative effectiveness of different drug regimens, the review will evaluate effects of different medication doses, durations of therapy, and dosing strategies (such as weight-based or response-guided vs. fixed treatment). To help with individualized clinical decisionmaking regarding antiviral therapy for chronic HCV infection, it will also evaluate how comparative effectiveness varies depending

on HCV genotype, viral load, and other demographic and clinical characteristics. Because estimating potential benefits and harms of HCV screening requires an understanding of the effects of treatment in people with HCV infection, this review will be used, together with a separate review on HCV screening,[35] by the U.S. Preventive Services Task Force to update its HCV screening recommendations.

Scope and Key Questions

The analytic framework and Key Questions used to guide this report are shown below (Figure 1). The analytic framework shows the target populations, interventions, and intermediate and health outcome measures we examined.

The following Key Questions are the focus of our report:

Key Question 1

a. What is the comparative effectiveness of antiviral treatment in improving health outcomes in patients with HCV infection?
b. How does the comparative effectiveness of antiviral treatment for health outcomes vary according to patient subgroup characteristics, including but not limited to HCV genotype, age, race, sex, stage of disease, or genetic markers?

Key Question 2

a. What is the comparative effectiveness of antiviral treatments on intermediate outcomes, such as the rate of SVR or histologic changes in the liver?
b. How does the comparative effectiveness of antiviral treatment for intermediate outcomes vary according to patient subgroup characteristics, including but not limited to HCV genotype, age, race, sex, stage of disease, or genetic markers?

Key Question 3

a. What are the comparative harms associated with antiviral treatments?
b. Do these harms differ according to patient subgroup characteristics, including HCV genotype, age, race, sex, stage of disease, or genetic markers?

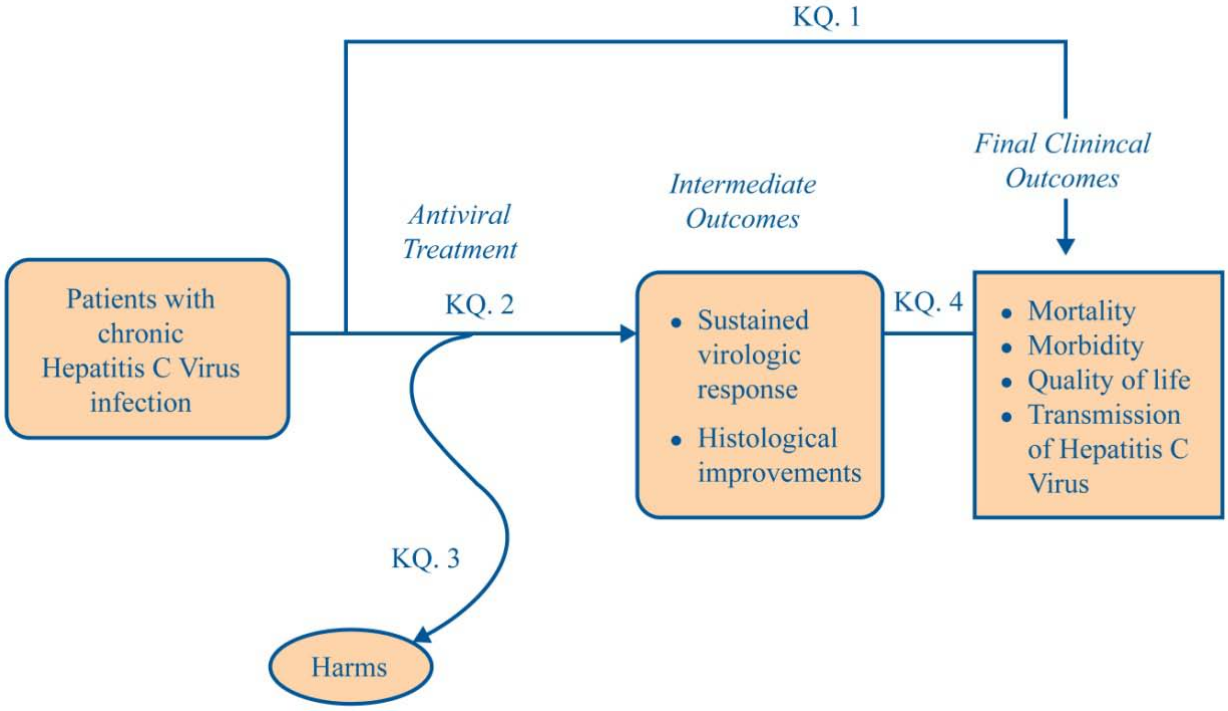
Key Question 4

Have improvements in intermediate outcomes (SVR, histologic changes) been shown to reduce the risk or rates of adverse health outcomes from HCV infection?

Key Question 1 focuses on direct evidence on the comparative effectiveness of antiviral treatments for chronic HCV infection on health outcomes (such as death, cirrhosis, hepatic decompensation, HCC, need for transplantation, or quality of life). Because of the long duration (typically decades) necessary develop major hepatic complications related to chronic HCV infection, it is difficult to assess for such outcomes in clinical trials. In addition, dual therapy with pegylated interferon (alfa-2a or alfa-2b) plus ribavirin has only been available since 2001, and protease inhibitors only became approved by the FDA in 2011, which might not be enough time to adequately evaluate some long-term clinical outcomes. Therefore, Key Question 2 focuses on evidence on the comparative effectiveness of antiviral treatments for chronic HCV infection on intermediate outcomes (SVR and histological improvements). Key Question 4 assesses the link between intermediate and clinical outcomes, in order to facilitate interpretation

of results obtained for Key Question 2. Key Question 3 focuses on the comparative harms of different antiviral treatments.

Figure 1. Analytic framework for treatment of hepatitis C infection in adults



KQ = Key Question

Methods

Input From Stakeholders

The topic of hepatitis C virus (HCV) treatment was nominated for a comparative effectiveness review (CER) in a public process. The Key Questions were proposed in the public nomination process and developed by investigators from the Evidence-based Practice Center (EPC) with input from expert Key Informants (KI), who helped to refine Key Questions, identify important methodological and clinical issues, and define parameters for the review of evidence. The revised Key Questions were then posted to a public Web site for comment. The Agency for Healthcare Research and Quality (AHRQ) and the EPC agreed upon the final Key Questions after reviewing the public comments and receiving additional input from a Technical Expert Panel (TEP) convened for this report. We then drafted a protocol for this CER, which was reviewed by the TEP and is available on the AHRQ Web site where it was posted in November 2011: www.effectivehealthcare.ahrq.gov/index.cfm/search-for-guides-reviews-and-reports/?pageaction=displayproduct&productid=855.

A multidisciplinary group of clinicians, researchers, and patient advocates with expertise in hepatitis C treatment and research were selected to serve as the TEP members to provide high-level content and methodological expertise throughout the development of the review. Prior to participation in this report, the TEP members disclosed all financial or other conflicts of interest. The AHRQ Task Order Officer and the authors reviewed all of these disclosures and determined the panel members had no significant conflicts of interest that precluded participation. KIs and TEP members had expertise in the areas of hepatology, epidemiology, screening, and primary care. TEP members and other experts were invited to provide external peer review of the draft report.

Search Strategy

To identify articles relevant to each Key Question, a research librarian searched the Cochrane Database of Systematic Reviews, the Cochrane Central Register of Controlled Trials, and Ovid MEDLINE® (Appendix A) from 1947 to April 2011 (see Appendix A for the search strategies and a final updated search was conducted in August 2012 following the receipt of peer reviewer comments. The search strategies were peer reviewed by another research librarian and revised prior to finalization. Unpublished trials were sought by searching clinical trial registries (ClinicalTrials.gov, Current Controlled Trials, Clinical Trial Results, WHO Trial Registries) and grants databases (NIHRePORTER, HSRProj, and AHRQ GOLD). Scientific Information Packets on unpublished and published trials were solicited from manufacturers of included antiviral drugs through the Scientific Resource Center. We also hand-searched the reference lists of relevant studies. Searches were updated prior to finalization of the report to identify relevant new publications.

Study Selection

We developed criteria for inclusion and exclusion of studies based on the Key Questions and the populations, interventions, comparators, outcomes, timing, and setting (PICOTS) approach. Inclusion and exclusion criteria, summarized below, are described in more detail by Key Question in Appendix B. Papers were selected for full review if they were about chronic HCV infection, were relevant to Key Questions in the analytic framework, and met the predefined

inclusion criteria. To evaluate potential effects of publication bias, we included trials published only as conference abstracts as sensitivity analyses. We restricted inclusion to English language articles. Studies of nonhuman subjects were also excluded, and studies had to include original data.

Abstracts and full-text articles were dual reviewed for inclusion and exclusion for each Key Question (Appendix B). Full-text articles were obtained for all studies that either investigator identified as potentially meeting inclusion criteria. Two investigators independently reviewed all full-text articles for final inclusion or exclusion (Appendix C). A list of excluded studies with primary reasons for exclusion can be found in Appendix D. Discrepancies were resolved through discussion and consensus, with a third investigator making the final decision if necessary.

Population and Conditions of Interest

The target population for Key Questions 1 through 3 was nonpregnant adults with chronic HCV infection who have not had previous antiviral drug treatment. Pregnant women were excluded as no antiviral treatment for HCV infection is currently recommended during pregnancy due to potential teratogenic effects.[36] We also evaluated comparative benefits and harms in patient subgroups defined by HCV genotype, race, sex, stage or severity of disease, viral load, weight, genetic markers (i.e., polymorphisms in the IL28B gene), and other factors (such as body weight). For Key Question 4, the target population was adults with chronic HCV infection who had received a course of interferon-based antiviral therapy. We excluded post-transplant patients, HIV patients, and hemodialysis patients, because treatment considerations and response to therapy may differ from what is observed in the general population of patients with chronic HCV infection without these conditions.

Interventions and Comparisons

We included antiviral regimens recommended in current guidelines for treatment of HCV infection, specifically dual therapy with pegylated interferon alfa-2a or alfa-2b plus ribavirin for genotype 2 or 3 infection,[15] and triple therapy regimens with the recently approved protease inhibitors telaprevir and boceprevir, which are used in combination with pegylated interferon alfa-2a or alfa-2b plus ribavirin, for genotype 1 infection.[37] We included studies of interferon monotherapy and standard interferon plus ribavirin only for Key Question 4, which evaluated the association between intermediate and clinical outcomes. We excluded regimens that involved antiviral drugs that are not approved in the United States for treatment of chronic HCV infection.

For Key Questions 1 through 3, we included studies that compared dual therapy with pegylated interferon alfa-2a plus ribavirin compared with dual therapy with pegylated interferon alfa-2b plus ribavirin, or that compared triple therapy with pegylated interferon (alfa-2a or alfa-2b), ribavirin, and a protease inhibitor (either telaprevir or boceprevir) compared with dual therapy with pegylated interferon (alfa-2a or alfa-2b) plus ribavirin. We also included studies that evaluated different doses or dosing protocols (i.e., weight-based vs. standardized) of the same antiviral drugs, or different durations of therapy or methods (e.g., response-guided therapy vs. fixed-duration therapy) for guiding duration of therapy. We focused on dose and duration comparisons of dual therapy with pegylated interferon (alfa-2a or alfa-2b) plus ribavirin in patients with HCV genotypes 2 and 3. For Key Question 4, we included studies of patients with chronic HCV infection who received antiviral treatment that compared outcomes between those who achieved an SVR (or improved histological findings) after antiviral therapy and those who did not.

Outcomes

Clinical outcomes were mortality, cirrhosis, hepatic decompensation, HCC, need for transplantation, and quality of life. We classified clinical outcomes assessed 1 year or earlier after the end of antiviral treatment as short-term and those assessed after at least 1 year as long-term. Intermediate outcomes were SVR rates and improvements in histological outcomes. We defined a sustained virologic response as the absence of detectable HCV-RNA in the serum six months after the end of a course of therapy.[15] We did not evaluate measures of earlier virologic response (such as undetectable HCV-RNA before or through week 12 of therapy or at the end of therapy). Although such early virologic outcomes predict whether a patient will achieve an SVR and can be used to guide therapy decisions (e.g., whether to continue therapy or duration of therapy), they are less accurate than the SVR for predicting long-term remission.[15] Histological response has been defined as a 2-point or greater decrease in the inflammatory score or fibrosis score, or a 1-point decrease in the fibrosis score, although relatively few trials evaluate histological response and definitions are less standardized compared with SVR.[15, 38] We did not evaluate improvement in liver function tests as an intermediate outcome (e.g., sustained biochemical response, or normalization of liver transaminases six months after the end of a course of therapy), due to its poor correlation with SVR.[39-42] Harms of treatment included withdrawals due to adverse events, serious adverse events such as neutropenia, anemia, psychological adverse events, flulike symptoms, and dermatologic adverse events.

Timing

We did not apply a minimum threshold for duration of studies. We defined long-term outcomes as those measured one year or more after the completion of antiviral therapy and short-term outcomes as those measured prior to one year after the completion of antiviral therapy.

Setting

Studies conducted in primary care and specialty settings were included.

Types of Studies

We included randomized trials for all Key Questions. For Key Question 4, we included cohort studies that compared clinical outcomes between patients who achieved an SVR compared with those who did not achieve an SVR, or that compared clinical outcome between patients who achieved a histological response compared with those who did not. Many factors (such as age, race, viral load, and fibrosis stage) may be associated with both the likelihood of achieving an SVR as well as the likelihood of hepatic complications.[15] Therefore, we excluded studies on the association between achieving an SVR and mortality or hepatic complications that only reported unadjusted risk estimates, given the strong potential for confounding. Because almost no studies on the association between SVR and quality of life reported adjusted risk estimates, we included studies that reported unadjusted risk estimates for this association.

Data Extraction

We extracted the following data from included studies into Excel spreadsheets: study design, setting, population characteristics, eligibility and exclusion criteria, the antiviral regimen (including duration and dose), and results for each outcome. Data abstraction for each study was

completed by two investigators: the first abstracted the data, and the second reviewed the abstracted data for accuracy and completeness against the original articles.

For Key Question 4, some studies reported adjusted hazard ratios (HRs) for the association between achieving an SVR and clinical outcomes relative to untreated patients, and for no SVR and clinical outcomes relative to untreated patients, but did not report a risk estimate for SVR compared with no SVR. We calculated the HR for SVR compared with no SVR based on the two HRs and their reported confidence intervals, assuming zero correlation between the two reported HRs. Such HRs are usually positively correlated; an assumption of zero correlation results in the most conservative (widest) confidence interval for the HR for SVR compared with no SVR.

Assessing Quality

We assessed quality for each study based on the predefined criteria listed in Appendix E. We adapted criteria from methods proposed by Downs and Black[43] and the USPSTF.[44] The criteria used are consistent with the approach recommended in AHRQ's Methods Guide for Effectiveness and Comparative Effectiveness Reviews (Methods Guide).[45] We used the term "quality" rather than the alternate term "risk of bias." Although both refer to internal validity, "quality" may be more familiar to most users and has potential advantages in terms of readability.

We rated the quality of each randomized trial based on the methods used for randomization, allocation concealment, and blinding; the similarity of compared groups at baseline; maintenance of comparable groups; adequate reporting of dropouts, attrition, crossover, adherence, and contamination; loss to followup; the use of intent-to-treat analysis; and ascertainment of outcomes.[44]

We rated the quality for each cohort study based on whether it used nonbiased selection methods to create an inception cohort; whether it evaluated comparable groups; whether rates of loss to followup were reported and acceptable; whether it used accurate methods for ascertaining exposures, potential confounders, and outcomes; and whether it performed appropriate statistical analyses of potential confounders.[44] For Key Question 4, we considered studies to have performed adequate statistical analyses of potential confounders if they adjusted at a minimum for age, sex, genotype, viral load, and hepatic fibrosis stage in a multivariate model including SVR or histological response; evaluated these factors and excluded them from the multivariate model because there was no association in either univariate or step-wise multivariate analyses; or accounted for these factors using other methods such as stratification or restriction.

Following assessment of individual quality criteria, individual studies were rated as good, fair, or poor quality, as defined below.[44, 45]

Good quality studies are considered likely to be valid. Good quality studies clearly describe the population, setting, interventions, and comparison groups; use a valid method for allocating patients to interventions; clearly report dropouts and have low dropout rates; use appropriate methods for preventing bias; and appropriately measure outcomes and fully report results.

Fair quality studies have some methodological deficiencies, but no flaw or combination of flaws judged likely to cause major bias. The study may be missing information, making it difficult to assess its methods or assess limitations and potential problems. The fair quality category is broad, and studies with this rating vary in their strengths and weaknesses—the results of some fair quality studies are likely to be valid, while others are only probably valid.

Poor quality studies have significant flaws that may invalidate the results. They have a serious or fatal flaw in design, analysis, or reporting; large amounts of missing information; or

discrepancies in reporting. The results of these studies are judged to be at least as likely to reflect flaws in the study design as true effects of the interventions under investigation. We did not exclude poor quality studies a priori, but they were considered the least reliable studies when synthesizing the evidence, particularly when discrepancies between studies were present.

Assessing Research Applicability

We recorded factors important for understanding the applicability of studies such as whether the publication adequately described the study population, the country in which the study was conducted (studies indicate that the rate of HCC in patients with chronic HCV infection is higher in Japan and other Asian countries compared with the United States),[46] how similar patients were to typical populations of those with chronic HCV infection, whether differences in outcomes were clinically (as well as statistically) significant, and whether the antiviral regimens and other aspects of care evaluated were reasonably representative of standard practice.[47] We also recorded the funding source and role of the sponsor. We did not assign a rating of applicability (such as high or low) because applicability may differ based on the user of this report.

Data Synthesis

For Key Questions 1 through 3, we performed meta-analysis of trials that evaluated similar populations, interventions, comparisons, and outcomes to estimate pooled relative risks using the DerSimonian-Laird method in a random effects model.[48] A random effects model results in estimates that are similar to a fixed effects model when there is little or no between-study statistical heterogeneity, but results in more conservative estimates (wider confidence intervals) when statistical heterogeneity is present. Heterogeneity was assessed by calculating the Q-statistic and the percentage of the total variance due to between study variability (I^2 statistic).[49] When present, statistical heterogeneity was explored through subgroup and sensitivity analyses, as well as qualitatively. Subgroup analyses were performed in groups stratified by HCV genotype as well as by race, age, body weight, viral load, stage/severity of disease, and IL-28b status when these data were available. We performed sensitivity analysis by excluding poor-quality studies, excluding outlier trials and including trials that used nonstandard doses of antiviral drugs, and adding results from trials published only as abstracts to evaluate the stability of estimates and conclusions. We did not formally assess for publication bias with funnel plots due to small numbers (<10) of studies for all comparisons. Small numbers of studies can make interpretation of funnel plots unreliable, and experts suggest 10 studies as the minimum number of studies to perform funnel plots.[50] All analyses were performed using Stata 11.0 (StataCorp, College Station, TX, 2009).

For Key Question 4, we did not perform meta-analysis, since all studies were cohort studies, and many had methodological shortcomings (including failure to adjust for important confounders) and varied in populations assessed, treatments received, and other factors. Rather, these studies were synthesized qualitatively.

Strength of the Body of Evidence

We assessed the overall strength of evidence for a body of literature about a particular Key Question in accordance with the AHRQ Methods Guide.[45] The strength of evidence was based on the overall quality of each body of evidence, based on the type and quality of studies (graded good, fair, or poor); the consistency of results within and between study designs (graded high,

moderate, or low); the directness of the evidence linking the intervention and health outcomes (graded direct or indirect); and the precision of the estimate of effect, based on the number and size of studies and confidence intervals for the estimates (graded high, moderate, or low). We did not downgrade a body of evidence for directness that evaluated an intermediate outcome, if the intermediate outcome was the specific focus of the Key Question. We did not grade supplemental domains for cohort studies included in Key Question 4 because they were not relevant (dose-response relationship) or because important methodological shortcomings (in particular failure to adjust for critical confounders) limited their usefulness (magnitude of effect and direction of plausible confounding). We were not able to formally assess for publication bias due to small numbers of studies, methodological shortcomings, or differences across studies in designs, measured outcomes, and other factors.

We graded the strength of evidence for each Key Question using the four key categories recommended in the AHRQ Methods Guide.[45] A "high" grade indicates high confidence that the evidence reflects the true effect and that further research is very unlikely to change our confidence in the estimate of effect. A "moderate" grade indicates moderate confidence that the evidence reflects the true effect and further research may change our confidence in the estimate of effect and may change the estimate. A "low" grade indicates low confidence that the evidence reflects the true effect and further research is likely to change the confidence in the estimate of effect and is likely to change the estimate. An "insufficient" grade indicates evidence either is unavailable or is too limited to permit any conclusion.

Peer Review and Public Commentary

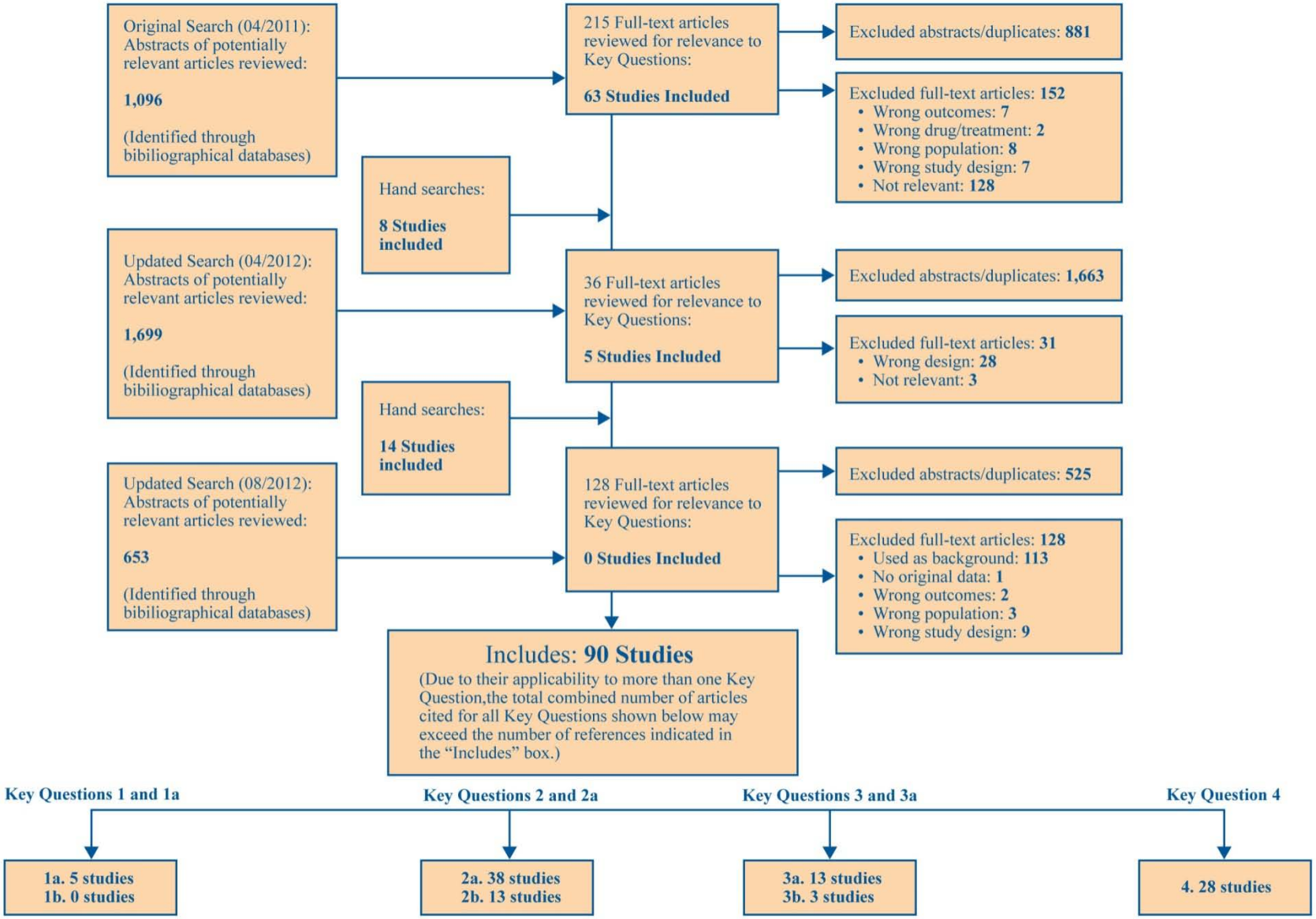
Experts in gastroenterology, hepatology, primary care, and prevention, and individuals representing stakeholder and user communities were invited to provide external peer review of a draft of this CER; AHRQ and an EPC associate editor also provided comments. The draft report was posted on the AHRQ Web site for 4 weeks to elicit public comment. All comments were reviewed and addressed as documented in a disposition of comments report that will be made available 3 months after the Agency posts the final CER on the AHRQ Web site www.effectivehealthcare.ahrq.gov.

Results

Overview

The search and selection of articles are summarized in the study flow diagram (Figure B). Of the 1,096 citations identified at the title and abstract level in the original search, 215 articles met inclusion criteria and were selected for further review of the full text. From updated searches and peer reviewer suggested citations, an additional 2,352 citations were identified, and 164 of these met inclusion criteria and were selected for full-text review. Of the 379 articles reviewed at the full-text level, a total of 90 studies met inclusion criteria.

Figure 2. Study flow diagram: Treatment for hepatitis C virus infection in adults



Key Question 1a. What is the comparative effectiveness of antiviral treatment in improving health outcomes in patients with HCV infection?

- No randomized trial or observational study evaluated the comparative effectiveness of current antiviral treatment regimens for chronic HCV infection on improving long-term clinical outcomes (strength of evidence: insufficient).
- Three trials that compared current antiviral regimens found no differences in risk of short-term mortality, but reported very few (20 total) events (strength of evidence: low).
- One open-label randomized trial of patients with genotype 4 infection found dual therapy with pegylated interferon alfa-2a plus ribavirin associated with statistically significant, slightly better short-term scores on some generic and liver disease-specific quality of life assessments than dual therapy with pegylated interferon alfa-2b plus ribavirin (strength of evidence: low).

No trial evaluated comparative effects of current antiviral treatment regimens for chronic HCV infection (dual therapy with pegylated interferon alfa-2a or alfa-2b plus ribavirin or triple therapy with pegylated interferon alfa-2a or alfa-2b, ribavirin, and a protease inhibitor) on risk of long-term clinical outcomes.

Three trials reported short-term mortality (through 6 months after the completion of antiviral therapy), but reported few deaths (20 total), resulting in very imprecise estimates (Appendix H: Evidence Table 1). One large trial found no difference between dual therapy with standard dose pegylated interferon alfa-2b (1.5 mcg/kg/week) plus ribavirin versus pegylated interferon alfa-2a plus ribavirin in risk of short-term mortality (risk ratio [RR] 0.85, 95% confidence interval (CI) 0.26 to 2.8), based on 11 deaths in over 2000 subjects.[22] Another trial found no difference between triple therapy with boceprevir and dual therapy in risk of short-term all-cause mortality (RR 0.25, 95% CI 0.03 to 2.2), but only reported 5 deaths in over 700 patients.[32] One trial of response-guided triple therapy with telaprevir versus dual therapy reported four deaths in over 1088 patients, resulting in a very imprecise estimate (RR 1.5, 95% CI 0.16 to 14).[51]

Two trials evaluated comparative effects of current antiviral regimens for chronic HCV infection on short-term quality of life (Appendix H: Evidence Table 11).[52, 53] One trial of patients with genotype 4 infection found dual therapy with pegylated interferon alfa-2a plus ribavirin associated with slightly higher (better) scores on some Short-Form 36 (SF-36) health survey subscales than dual therapy with pegylated interferon alfa-2b plus ribavirin 24 weeks after the end of treatment (differences of 3.2 to 5.7 points on the Bodily Pain, Vitality, Social Functioning, and Role Emotional subscales, each on a 0 to 100 scale).[53] Dual therapy with pegylated interferon alfa-2a was also associated with slightly higher scores on the Physical Component Summary score (3.2, points, $p<0.02$), but there was no difference on the Mental Component Summary score, or on five of six domains on the Chronic Liver Disease questionnaire, though dual therapy with pegylated interferon alfa-2a plus ribavirin was associated with a slightly higher overall score (difference 0.4 point on a 1 to 7 scale, $p=0.02$). The trial was open-label and patients do not appear to have been blinded to virologic response status, which could have affected quality of life assessments. A trial of patients with genotype 1 infection with undetectable HCV-RNA after 24 weeks of pegylated interferon alfa-2a plus ribavirin found continuation of dual therapy for another 24 weeks associated with worse quality of life scores at the end of treatment than pegylated interferon alone for the last 24 weeks, but the clinical relevance of this finding is limited since the shorter regimen was associated with lower

likelihood of achieving an SVR and is not considered the standard of care for genotype 1 infection.[52]

Key Question 1b. How does the comparative effectiveness of antiviral treatment for health outcomes vary according to patient subgroup characteristics, including but not limited to HCV genotype, age, race, sex, stage of disease or genetic markers?

- No randomized trial or observational study evaluated comparative effects of current antiviral treatment regimens on any clinical outcomes in patients stratified by HCV genotype, age, race, sex, stage of disease, genetic markers, or other factors (strength of evidence: insufficient).

Key Question 2a. What is the comparative effectiveness of antiviral treatments on intermediate outcomes, such as the rate of SVR or histologic changes in the liver?

Dual Therapy With Pegylated Interferon Alfa-2a or Alfa-2b Plus Ribavirin

- Seven trials found dual therapy with standard doses of pegylated interferon alfa-2b plus ribavirin associated with lower likelihood of achieving an SVR than pegylated interferon alfa-2a plus ribavirin (pooled RR 0.87, 95% CI 0.80 to 0.95, I^2=27.4%), with an absolute difference in SVR rates of 8 percentage points (95% CI 3 to 14) (strength of evidence: moderate).

Dual Therapy With Pegylated Interferon Alfa-2a or Alfa-2b Plus Ribavirin: Duration Effects

- Two trials of patients with genotype 2 or 3 infection found no difference in likelihood of achieving an SVR between 48 versus 24 weeks of dual therapy with pegylated interferon alfa-2a plus ribavirin (pooled RR 0.97, 95% CI 0.84 to 1.11, I^2=42.7%) (strength of evidence: moderate).
- Four trials of patients with genotype 2 or 3 infection found 24 weeks of dual therapy with pegylated interferon (alfa-2a or alfa-2b) more effective than 12-16 weeks for achieving an SVR (pooled RR 1.15, 95% CI 1.02 to 1.29, I^2=79.5%). Relative risk estimates ranged from 1.0 to 1.3 (strength of evidence: moderate).
- Three trials of patients with genotype 2 or 3 infection with a rapid virologic response (undetectable HCV-RNA by week 4) found no differences between 24 versus 12-16 weeks of dual therapy with pegylated interferon (alfa-2a or alfa-2b) plus ribavirin (pooled RR 0.99, 95% CI 0.86 to 1.14, I^2=66.7%). Relative risk estimates ranged from 0.89 to 1.1 (strength of evidence: moderate).

Dual Therapy With Pegylated Interferon Alfa-2a or Alfa-2b Plus Ribavirin: Dose Effects

- Six trials of patients with genotype 2 or 3 infection found lower doses of pegylated interferon alfa-2b (0.75–1.0 mcg/kg or 50 mcg) associated with lower likelihood of achieving an SVR than higher doses (1.5 mcg/kg or 100–150 mcg) (pooled RR 0.90, 95% CI 0.81 to 0.99, I^2=20.2%) (strength of evidence: moderate).
- Three trials of patients with genotype 2 or 3 infection who did not specifically have advanced fibrosis or cirrhosis found no clear difference in likelihood of SVR between lower doses of ribavirin (400 or 800 mg flat dose or 600 to 800 mg weight-based dose) versus higher doses (800 or 1200 mg flat dose or 800 to 1400 mg weight-based dose) (strength of evidence: moderate).
- One small trial of patients with genotype 2 or 3 infection (N=60) and advanced fibrosis or cirrhosis (Ishak stage 4-6) found 600 to 800 mg daily of ribavirin associated with lower likelihood of SVR than 1000 to 1200 mg daily (45 vs. 72 percent, RR 0.62, 95% C I 0.40 to 0.98) (strength of evidence: low).

Trials of Triple Therapy With Pegylated Interferon Alfa-2b, Ribavirin, and Boceprevir

- Two trials of patients with HCV genotype 1 infection found dual therapy lead-in with pegylated interferon alfa-2b plus ribavirin for 4 weeks followed by 44 weeks of triple therapy with boceprevir associated with higher likelihood of SVR than dual therapy for 48 weeks (pooled RR 1.81, 95% CI 1.58 to 2.06, I^2=0.0%), with an absolute increase in SVR rate of 31 percentage points (95% CI 23 to 39) (strength of evidence: moderate).
- One trial of patients with genotype 1 infection found 48 weeks of triple therapy with boceprevir using low dose of ribavirin (400–1000 mg daily) associated with a non–statistically significant trend towards lower likelihood of SVR than 48 weeks of triple therapy with a standard ribavirin dose (800–1400 mg daily) (36 vs. 50 percent, RR 0.71, 95% CI 0.39 to 1.3) (strength of evidence: low).

Trials of Triple Therapy With Pegylated Interferon Alfa-2a or Alfa-2b, Ribavirin, and Telaprevir

- Three trials of patients with genotype 1 infection found triple therapy with telaprevir for 24 weeks (12 weeks of pegylated interferon alfa-2a or alfa-2b, ribavirin, and telaprevir followed by 12 weeks of pegylated interferon alfa-2a or alfa-2b plus ribavirin) associated with higher likelihood of SVR than dual therapy with pegylated interferon alfa-2a or alfa-2b plus ribavirin for 48 weeks (pooled RR 1.48, 95% CI 1.26 to 1.75, I^2=0.0%), with an absolute increase in SVR rate of 22 percentage points (95% CI 13 to 31) (strength of evidence: moderate).
- One trial of patients with genotype 1 infection found no difference in likelihood of SVR between triple therapy with pegylated interferon alfa-2a, ribavirin, and telaprevir for 12 weeks versus dual therapy with pegylated interferon alfa-2a plus ribavirin for 48 weeks (strength of evidence: moderate).
- One trial of patients with genotype 1 infection found response-guided triple therapy with telaprevir (pegylated interferon alfa-2a, ribavirin, and telaprevir for 8 or 12 weeks

followed by response-guided dual therapy with pegylated interferon alfa-2a plus ribavirin for an additional 12 or 36 weeks) associated with higher likelihood of SVR than dual therapy with pegylated interferon alfa-2a plus ribavirin for 48 weeks (RR 1.6, 95% CI 1.4 to 1.9), with an absolute increase in SVR rate ranging from 25 to 31 percent. The regimen with 8 weeks of telaprevir was associated with a slightly lower SVR rate than the 12 week telaprevir regimen (69 vs. 75 percent) (strength of evidence: low).

- One trial of patients with genotype 1 infection found no difference in likelihood of SVR between triple therapy with telaprevir for 48 weeks (12 weeks of triple therapy with pegylated interferon alfa-2a, ribavirin, and telaprevir followed by 36 weeks of dual therapy with pegylated interferon alfa-2a plus ribavirin) versus triple therapy with telaprevir for 24 weeks (12 weeks of triple therapy followed by 12 weeks of dual therapy) (strength of evidence: low).
- One trial of response-guided triple therapy with telaprevir (24 or 48 weeks, based on absence or presence of HCV-RNA from weeks 4 through 20) found similar SVR rates (81–85 percent) for regimens that varied on telaprevir dose (750 mg three times daily vs. 1125 mg two times daily) and type of pegylated interferon (alfa-2a or alfa-2b) (strength of evidence: low).
- One trial of patients with an extended rapid virologic response to initial triple therapy with telaprevir reported similar high (92 and 88 percent) SVR rates (92 and 88 percent) in patients randomized to a total of 24 or 48 weeks of therapy (strength of evidence: low).

Dual Therapy With Pegylated Interferon Alfa-2a Plus Ribavirin Compared With Dual Therapy With Pegylated Interferon Alfa-2b Plus Ribavirin

Ten trials that directly compared dual therapy with pegylated interferon alfa-2a plus ribavirin to dual therapy with pegylated interferon alfa-2b plus ribavirin in patients with genotypes 1, 2, or 3 infection met inclusion criteria (Table 2, Appendix H: Evidence Table 1).[20-23, 53-58] Two of these trials were published only as abstracts and were included only in sensitivity analyses; we could not adequately assess their quality due to limited information in the abstracts.[54, 56] One other trial compared pegylated interferon alfa-2a versus pegylated interferon alfa-2b as part of response-guided triple therapy with telaprevir and was also only included in sensitivity analysis.[59] One trial enrolled a mix of treatment naïve and treatment experienced patients but reported SVR in the treatment-naïve subgroup.[57] Of the eight trials that could be quality rated, two[21, 58] were rated poor quality and six were rated fair quality (Appendix H: Evidence Table 2). Frequent methodologic shortcomings were open-label design,[20, 21, 23, 53, 55, 57] high or unclear loss to followup,[20-23] and unclear or inadequate methods of allocation concealment.[21, 23, 53, 55, 57, 58] Sample sizes ranged from 66 to 3,070. Five trials, including the trial that compared triple therapy regimens, only enrolled patients with genotype 1 HCV infection;[22, 55, 57-59] the others enrolled either a mix of genotypes or a specific genotype other than genotype 1. The proportion of patients with cirrhosis at baseline ranged from <5–20 percent,[20, 23, 59, 60] and the proportion of patients with elevated transaminases ranged from 60–100 percent[20, 21, 23, 53, 58, 60] in trials that reported this information. All but two trials[54, 57] included a comparison of a standard dose of pegylated interferon alfa-2a (180 mcg/week) with a standard dose of pegylated interferon alfa-2b (1.5 mcg/kg/week). One trial evaluated multiple pegylated interferon alfa-2b doses.[22] Ribavirin dosing varied across studies. All trials used weight-based dosing of ribavirin except for one,

which used an 800 mg daily flat dose (it also enrolled only genotype 3 patients).[54] Three trials used different ribavirin doses with pegylated interferon alfa-2a and alfa-2b.[22, 23, 59] Nine trials evaluated fixed-duration regimens, with 48 weeks of treatment for genotypes 1 or 4 and 24 weeks for genotypes 2 or 3.[20, 21, 23, 53-58]

Table 2. Trials of dual therapy with pegylated interferon alfa-2a plus ribavirin versus dual therapy with pegylated interferon alfa-2b plus ribavirin

Trial Country N Quality	Population Characteristics	Genotype Mix	Weekly Pegylated Interferon Dose	Daily Ribavirin Dose	Duration (weeks)	Sustained Virologic Response Rate
Ascione, 2010[20] Italy N=320 Quality: Fair	A vs. B Age (mean): 51 vs. 49 years Female: 49% vs. 61% Race: Not reported Cirrhosis: 21% vs. 16% Minimal or no fibrosis: Not reported Elevated transaminases: 100%	~60% genotype 1 or 4	A. Alfa-2a 180 mcg B. Alfa-2b 1.5 mcg/kg	1000-1200 mg	24-48 by genotype	A. 69% B. 54%
Escudero, 2008[21] Spain N=183 Quality: Poor	A vs. B Age (mean): 44 vs. 44 years Female: 30% vs. 39% Race: Not reported Cirrhosis: Not reported Minimal or no fibrosis: Not reported (100% had at least periportal fibrosis) Elevated transaminases: 100%	~75% genotype 1 or 4	A. Alfa-2a 180 mcg B. Alfa-2b 1.5 mcg/kg	800-1200 mg	24-48 by genotype	A. 66% B. 62%
Kamal, 2011[53] Egypt N=217 Quality: Fair	A vs. B Age (mean): 42 vs. 41 years Female: 46% vs. 56% Race: Not reported Cirrhosis: Not reported Minimal or no fibrosis: Not reported Elevated transaminases: 100%	100% genotype 4	A. Alfa-2a 180 mcg B. Alfa-2b 1.5 mcg/kg	1000-1200 mg	48	A. 71% B. 55%
Khan, 2007[54] Pakistan N=66 Quality: Not assessed[b]	A vs. B Age: Not reported Female: Not reported Race: Not reported Cirrhosis: Not reported Minimal or no fibrosis: Not reported Elevated transaminases: Not reported	100% genotype 3	A. Alfa-2a 180 mcg B. Alfa-2b 1.0 mcg/kg	800 mg	24	A. 79% B. 82%

Table 2. Trials of dual therapy with pegylated interferon alfa-2a plus ribavirin versus dual therapy with pegylated interferon alfa-2b plus ribavirin (continued)

Trial Country N Quality	Population Characteristics	Genotype Mix	Weekly Pegylated Interferon Dose	Daily Ribavirin Dose	Duration (weeks)	Sustained Virologic Response Rate
Mach 2011[55] Poland N=260 Quality: Fair	A vs. B Age: 44 vs. 45.2 years Female: 37.7% vs. 42% Race: Not reported (Polish centers) Cirrhosis: Not reported Minimal or no fibrosis: Not reported (78% vs. 73% F0-F2 fibrosis) Elevated transaminases: Not reported	100% genotype 1b	A: Alfa-2a 180 mcg B:Alfa-2b 1.5 mg/kg	1000-1200 mg	48	A. 49% B. 44%
Magni, 2009[56] Italy N=218 Quality: Not assessed[b]	A vs. B Age: Not reported Female: Not reported Race: Not reported Cirrhosis: Not reported Minimal or no fibrosis: Not reported Elevated transaminases: Not reported	~55% genotype 1 or 4	A. Alfa-2a 180 mcg B. Alfa-2b 1.5 mcg/kg	10.5 mg/kg	24-48 by genotype	A. 68% B. 67%
Marcellin, 2011[59a] Europe N=161 Quality: Fair	A vs. B vs. C vs. D Age (median): 47 vs. 46 vs. 40 vs. 49 years Female: 50% vs. 52% vs. 48% vs. 51 Non-White race: 10% vs. 10% vs. 10% vs. 8% Cirrhosis: 2.5% vs. 2.4% vs. 0% vs. 5.1% Minimal or no fibrosis: 38% vs. 36% vs. 55% vs. 28% Elevated transaminases: Not reported	100% genotype 1	A. Alfa-2a 180 mcg B. Alfa-2b 1.5 mcg/kg C. Alfa-2a 180 mcg D. Alfa-2b 1.5 mcg/kg	A. 1000-1200 mg B. 800-1200 mg C. 1000-1200 mg D. 800-1200 mg	24/48	A. 85% B. 81% C. 83% D. 82%
McHutchison, 2008 (IDEAL)[60] U.S. N=3070 Quality: Fair	A vs. B vs. C Age (mean): 48 vs. 48 vs. 48 years Female: 40% vs. 40% vs. 41% Non-White race: 29% vs. 28% vs. 29% Cirrhosis: Not reported (10% vs. 11% vs. 11% severe fibrosis or cirrhosis) Minimal or no fibrosis: Not reported Elevated transaminases: 80% vs. 81% vs. 81%	100% genotype 1	A. Alfa-2a 180 mcg B. Alfa-2b 1.5 mcg/kg C. Alfa-2b 1.0 mcg/kg	A. 1000-1200 mg B. 800-1400 mg C. 800-1400 mg	48	A. 41% B. 40% C. 38%

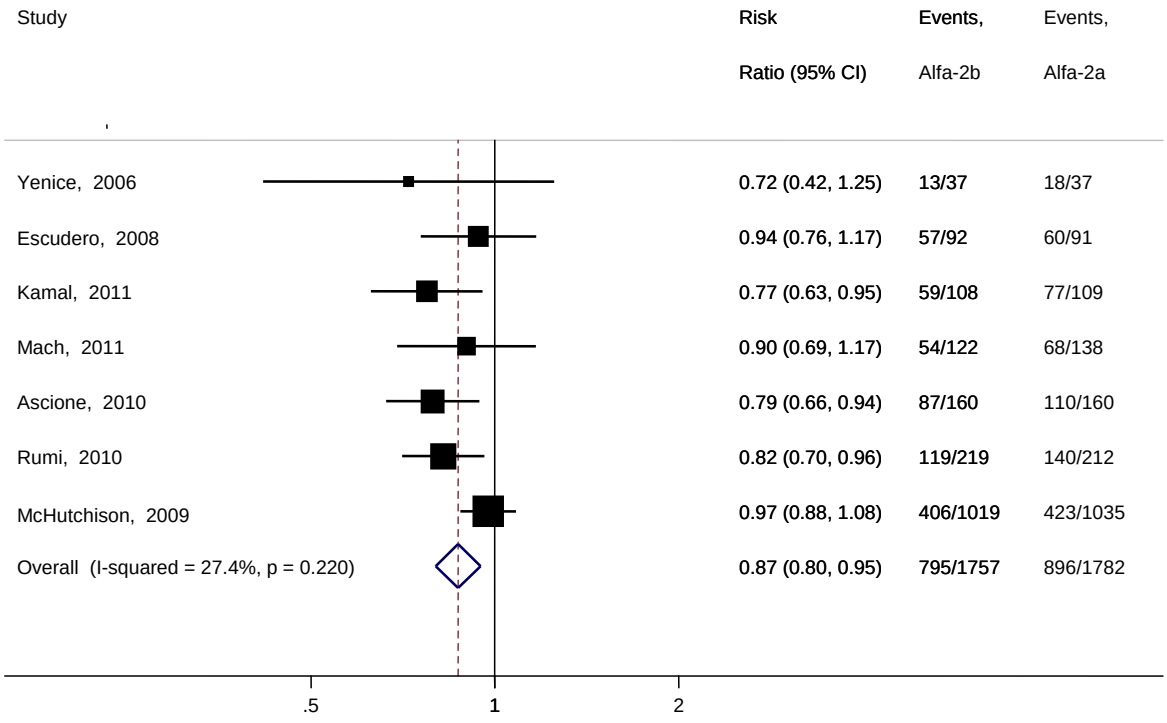
Table 2. Trials of dual therapy with pegylated interferon alfa-2a plus ribavirin versus dual therapy with pegylated interferon alfa-2b plus ribavirin (continued)

Trial Country N Quality	Population Characteristics	Genotype Mix	Weekly Pegylated Interferon Dose	Daily Ribavirin Dose	Duration (weeks)	Sustained Virologic Response Rate
Miyase, 2012[57] Japan N=201 Quality: Fair	A vs. B Age mean: 59.2 vs. 58.9 years Female: 61.4% vs. 60% Nonwhite race: Not reported Cirrhosis: 20% vs. 17% Minimal or no fibrosis: Not reported Elevated transaminases: Not reported	100% genotype 1	A: Alfa-2a 180 mcg B: Alfa-2b 60-150 mcg/kg (weight-based)	600-1000 mg	48	A. 66% B. 51%
Rumi, 2010[23] Italy N=431 Quality: Fair	A vs. B Age (mean): 52 vs. 53 years Female: 40% vs. 45% Race: Not reported Cirrhosis: 20% vs. 18% Minimal or no fibrosis: Not reported Elevated transaminases (>2 times upper limit of normal): 59% vs. 59%	41% genotype 1 33% genotype 2 15% genotype 3 10% genotype 4	A. Alfa-2a 180 mcg B. Alfa-2b 1.5 mcg/kg	Genotype 1/4: A. 1000-1200 mg/day for 48 weeks B. 800-1200 mg/day for 48 weeks Genotype 2/3: A. 800 mg/day for 24 weeks B. 800-1200 mg/day for 24 weeks	24 -48 by genotype	A: 66% B: 54%
Yenice, 2006[58] Turkey N=74 Quality: Poor	A vs. B Age (mean): 48 vs. 51 years Female: 35% vs. 27% Race: Not reported Cirrhosis: Not reported Minimal or no fibrosis: Not reported (all patients had at least minimal fibrosis) Elevated transaminases: 70% vs. 76%	100% genotype 1 (1a vs. 1b vs. 1c)	A. Alfa-2a 180 mcg B. Alfa-2b 1.5 mcg/kg	800-1200 mg	24-48 by genotype	A. 49% B. 35%

Note: Cirrhosis = METAVIR F4, Ishak 5-6, or equivalent. Minimal or no fibrosis=METAVIR F0-F1, Ishak 0-2, or equivalent.
[a] All arms included 12 weeks of telaprevir; because this trial compared triple therapy regimens it was excluded from the primary analysis and only included in sensitivity analysis.
[b] Published as abstract only; only included in sensitivity analysis.

Dual therapy with a standard dose of pegylated interferon alfa-2b (1.5 mcg/kg/week) plus ribavirin was associated with slightly lower likelihood of achieving an SVR than a standard dose of pegylated interferon alfa-2a (180 mcg/week) plus ribavirin (seven trials, pooled RR 0.87, 95% CI 0.80 to 0.95, I^2=27.4%) (Figure 3).[20-23, 53, 55, 58] The pooled absolute reduction in likelihood of SVR was 8 percentage points (95% CI 3 to 14). Results were similar when the meta-analysis included the trial[59] that evaluated pegylated interferon alfa-2b versus pegylated interferon alfa-2a as part of a triple therapy regimen with telaprevir and ribavirin (eight trials, pooled RR 0.89, 95% CI 0.82 to 0.96, I^2=26%) and a trial[56] only available as a conference abstract (nine trials, pooled RR 0.90, 95% CI 0.83 to 0.97, I^2=25%), or excluded two poor-quality trials (five trials, pooled RR 0.86, 95% CI 0.78 to 0.95, I^2=47%).[21, 58] Two trials, one published only as an abstract, compared only a standard dose of pegylated interferon alfa-2a (180 mcg weekly) versus nonstandard doses of pegylated interferon alfa-2b (1.0 mcg/kg/week or 60-150 mcg/week).[54, 57] Pooled estimates were similar when these trials were included in the analysis (nine trials, pooled RR 0.88, 95% CI 0.82 to 0.95, I^2=22%).

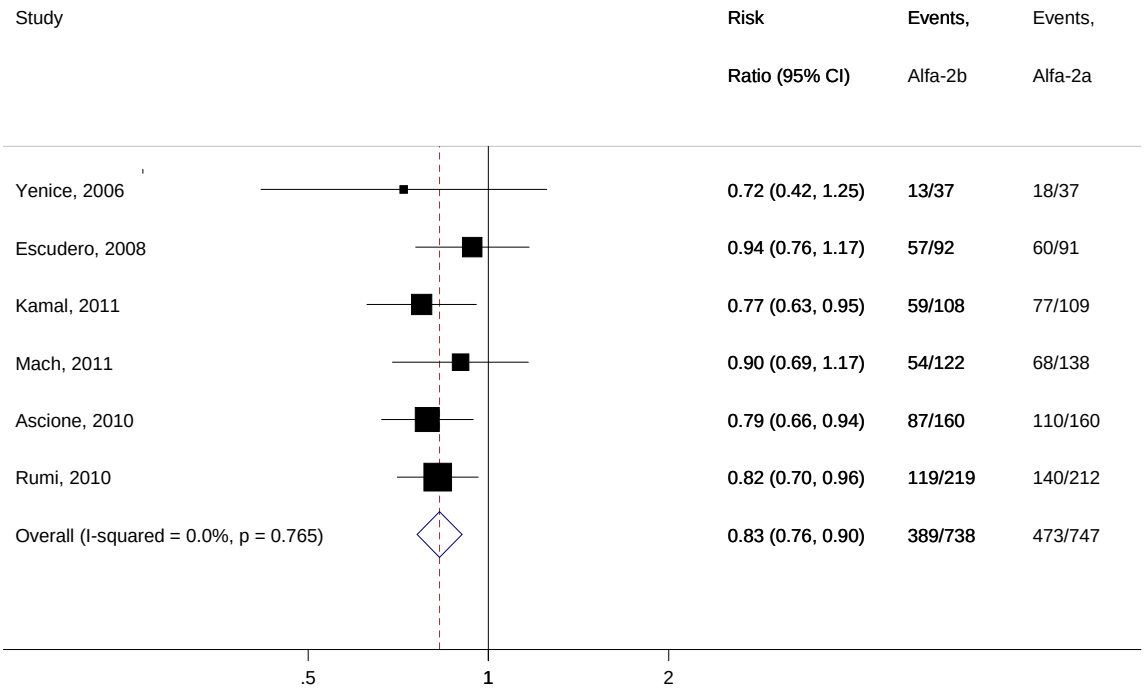
Figure 3. Sustained virologic response: Dual therapy with pegylated interferon alfa-2b plus ribavirin versus dual therapy with pegylated interferon alfa-2a plus ribavirin (standard doses of pegylated interferon only)



The largest head-to-head trial was the Individualized Dosing Efficacy vs. Flat Dosing to Assess Optimal Pegylated Interferon Therapy (IDEAL) study (n=3070, compared with 66 to 477 in the other trials).[22] It was rated fair quality because loss to followup exceeded 20 percent. A three-armed trial, IDEAL randomized patients with HCV genotype 1 infection to one of two doses of pegylated interferon alfa-2b (1.0 mcg/kg/week or 1.5 mcg/kg/week) plus ribavirin 800 to1400 mg daily (800 mg 40 to 65 kg; 1000 mg >65 to 85 kg; 1200 mg >85 to 105 kg; 1400 >105 to 125 kg) or pegylated interferon alfa-2a 180 mcg/week plus ribavirin 1000 to 1200 mg/day (1000 mg <75 kg; 1200 mg ≥75 kg). Overall, SVR rates were similar at 38–41 percent in

the three arms. However, differences in ribavirin dosing could have affected treatment comparability. Excluding IDEAL[22] had little effect on the pooled estimate and eliminated statistical heterogeneity (six trials, pooled RR 0.83, 95% CI 0.76 to 0.90, I^2= 0%) (Figure 4).[20, 21, 23, 53, 55, 58]

Figure 4. Sustained virologic response: Dual therapy with pegylated interferon alfa-2b plus ribavirin versus dual therapy with pegylated interferon alfa-2a plus ribavirin (excluding trials with differential ribavirin dosing or that evaluated triple therapy regimens)



Dual Therapy With Pegylated Interferon Alfa-2a or Alfa-2b Plus Ribavirin: Duration Effects

Eleven trials compared effects of different treatment durations of dual therapy with pegylated interferon (alfa-2a or alfa-2b) plus ribavirin on SVR rates in patients with HCV genotype 2 or 3 infection (Table 3, Appendix H: Evidence Table 5).[61-71] Nine trials[61, 62, 64-70] only enrolled patients with genotype 2 or 3 infection and the other two[63, 71] reported results in the subgroup of patients with genotype 2 or 3 infection. Sample sizes ranged from 117 to 1,465 subjects. One trial[68] was rated good quality, one trial poor quality,[66] and the remainder fair quality (Appendix H: Evidence Table 6). Common methodological shortcomings included open-label design[61, 62, 64, 65, 67, 70-72] and inadequately described randomization or treatment allocation procedures[62, 64-67, 69-71] One trial also reported high attrition.[66] Most trials evaluated standard dosing of pegylated interferon alfa-2a (180 mcg/week) and pegylated interferon alfa-2b (1.5 mcg/kg/week), although ribavirin dosing varied across the trials.

Table 3. Trials on effects of duration with dual therapy with pegylated interferon (alfa-2a or alfa-2b) plus ribavirin[a]

Trial Country N Quality	Population Characteristics	Percent Genotype 2 or 3	Weekly Pegylated Interferon Dose	Daily Ribavirin Dose	Duration	Sustained Virologic Response Among Patients with Genotype 2 or 3 Infection
48 Weeks vs. 24 Weeks						
Hadziyannis, 2004[63] World-wide N=492 with genotype 2 or 3 infection N(total) = 1284 Quality: Fair	A vs. B vs. C vs. D: Age (mean): 41 vs. 42 vs. 43 vs. 43. years Female: vs. 32% vs. 34% vs. 27% vs. 34% Non-White race: 13% vs. 10% vs. 12% vs. 9% Cirrhosis: 7% vs. 8% vs. 5% vs. 7% Minimal or no fibrosis: Not reported	38%	Alfa-2a 180 mcg	A. 800 mg B. 1200 mg C. 800 mg D. 1200 mg	A/B. 48 weeks C/D. 24 weeks	A/B. 75% C/D. 82%
Zeuzem, 2004[71] (PEGASYS) Australia, Europe, New Zealand, North & South America N=117 with genotype 2 or 3 infection N(total) = 491 Quality: Fair	A vs. B Age (Mean): 44 vs. 44 Female: 61% vs. 58% Non-White race: 14% vs. 14% Cirrhosis: 1% vs. 0% Minimal or no fibrosis: 69% vs. 66%	28%	Alfa-2a 180 mcg	800 mg	A. 48 weeks B. 24 weeks	A. 78% B. 72%
24 Weeks vs. 12-16 Weeks						
Lagging, 2008[64] Denmark & Finland N=382 Quality: Fair	A vs. B: Age (mean): 42 vs. 42 years Female: 44% vs. 37% Non-White race: Not reported Cirrhosis: 13% vs. 13% Minimal or no fibrosis: Not reported	100%	Alfa-2a 180 mcg	800 mg	A. 24 weeks B. 12 weeks	A. 78% B. 59%
Manns, 2011[66] International N=458 Quality: Poor	A vs. B Age (Mean): 40 vs. 40 years Female: 35% vs. 36% Non-White race: Not reported Cirrhosis: Not reported Minimal or no fibrosis: Not reported	100%	Alfa-2b 1.5 mcg	800-1400 mg	A. 24 weeksB. 16 weeks	A. 67% B. 57%

Table 3. Trials on effects of duration with dual therapy with pegylated interferon (alfa-2a or alfa-2b) plus ribavirin[a] (continued)

Trial Country N Quality	Population Characteristics	Percent Genotype 2 or 3	Weekly Pegylated Interferon Dose	Daily Ribavirin Dose	Duration	Sustained Virologic Response Among Patients with Genotype 2 or 3 Infection
24 Weeks vs. 12-16 Weeks (continued)						
Shiffman, 2007[68] 132 Centers World-wide N=1465 Quality: Good	A vs. B: Age (mean): 45.6 vs. 46 years Female: 37% vs. 39% Non-White race: 13% vs. 13% Cirrhosis: Not reported (23% vs. 25% severe fibrosis or cirrhosis) Minimal or no fibrosis: Not reported	100%	Alfa-2a 180 mcg	800 mg	A. 24 weeks B. 16 weeks	A. 70% B. 62%
Yu, 2007[70] Taiwan N=150 Quality: Fair	A vs. B: Age (mean): 50 vs. 49 years Female: 34% vs. 40% Non-White race: Not reported Cirrhosis: Not reported (severe fibrosis or cirrhosis 22% vs. 20%) Minimal or no fibrosis: Not reported (mild, minimal, or no fibrosis 78% vs. 80%)	100%	Alfa-2a 180 mcg	1000-1200 mg	A. 24 weeks B. 16 weeks	A. 95% B. 94%
24 Weeks vs. 12-16 Weeks Among Those With Undetectable Virus by Week 4						
Dalgard, 2008[62] Denmark, Sweden, Norway N=298 Quality: Fair	A vs. B: : Age (median): 38 vs. 38 years Female: 35% vs. 36% Non-White race: Not reported Cirrhosis: Not reported Minimal or no fibrosis: Not reported	100%	Alfa-2b 1.5 mcg/kg	800-1400 mg	A. 24 weeks B. 14 weeks	A. 91% B. 81%
Mecenate, 2010 (CLEO)[67] Italy N=143 Quality: Fair	Demographics reported overall only Age (mean): 43 years Female: 19% Non-White race: Not reported Cirrhosis: 10% (overall) Minimal or no fibrosis: Not reported	100%	Alfa-2a 180 mcg	800-1200 mg	A. 24 weeks B. 12 weeks	A. 75% B. 83%

Table 3. Trials on effects of duration with dual therapy with pegylated interferon (alfa-2a or alfa-2b) plus ribavirin[a] (continued)

Trial Country N Quality	Population Characteristics	Percent Genotype 2 or 3	Weekly Pegylated Interferon Dose	Daily Ribavirin Dose	Duration	Sustained Virologic Response Among Patients with Genotype 2 or 3 Infection
24 Weeks vs. 12-16 Weeks Among Those With Undetectable Virus by Week 4 (continued)						
von Wagner, 2005[69] Germany N=142 Quality: Fair	A vs. B: Age (mean): 39 vs. 38 Female: 42% vs. 26% Non-White race: Not reported Cirrhosis: Not reported Minimal or no fibrosis: Not reported	100%	Alfa-2a 180 mcg	800-1200 mg	A. 24 weeks B. 16 weeks	A. 80% B. 82%
Other Duration Comparisons						
Andriulli, 2009[61b] Italy N=120 Quality: Fair	A vs. B: Age (mean): 53 vs. 53 years Female: 51% vs. 41% Race: Not reported Cirrhosis: Not reported Minimal or no fibrosis: Not reported	100%	Alfa-2a 180 mcg	A. 1000-1200 mg for 12 weeks B. 1000-1200 mg for 6 weeks	12 weeks	A. 82% B. 54%
Mangia, 2005[65] Italy N=283 Quality: Fair	A vs. B: Age (mean): 47 vs. 50 years Female: 44% vs. 44% Race: Not reported Cirrhosis: Not reported (16% vs. 23% severe fibrosis or cirrhosis) Minimal or no fibrosis: Not reported	100%	Alfa-2b 1.0 mcg/kg	1000-1200 mg	A. 24 weeks B. 12-24 weeks[c]	A. 77% B. 76%

Note: Cirrhosis = METAVIR F4, Ishak 5-6, or equivalent. Minimal or no fibrosis=METAVIR F0-F1, Ishak 0-2, or equivalent.
[a] Sample sizes and results restricted to patients with genotype 2 or 3 infection.
[b] Patients who had undetectable HCV-RNA at 4 weeks randomized to 6 or 12 weeks of ribavirin.
[c]Treatment for 12 weeks if HCV RNA undetectable at 4 weeks, and for 24 weeks if detectable.

Six trials compared fixed-duration regimens of dual therapy with pegylated interferon (alfa-2a or alfa-2b) plus ribavirin in patients with genotype 2 or 3 infection.[63, 64, 66, 68, 70, 71] Two trials found no difference between 48 versus 24 weeks of dual therapy in likelihood of achieving an SVR (pooled RR 0.97, 95% CI 0.84 to 1.1, I^2=43%) (Figure 5).[63, 71] Four other trials found 24 weeks of dual therapy associated with a higher likelihood of achieving an SVR than 12 to 16 weeks of dual therapy (pooled RR 1.2, 95% CI 1.0 to 1.3; I^2=80%),[64, 66, 68, 70] but substantial statistical heterogeneity was present (I^2=80%) (Figure 6). Of the four trials, three found 12 to 16 weeks of dual therapy associated with lower likelihood of SVR compared with 24 weeks.[64, 66, 68] The fourth trial,[70] which found no difference between 16 versus 24 weeks of dual therapy (RR 1.0, 95% CI 0.93 to 1.1), used weight-based dosing of ribavirin starting at 1,000 mg (1,000-1,200 mg), compared with a flat dose of 800 mg or weight-based dosing starting at 800 mg (800-1,400 mg) in the other three trials. This trial also enrolled only patients with a genotype 2 infection, whereas the others enrolled genotype 2 or 3. It reported substantially higher overall SVR rates

(94 vs. 95 percent) than the other trials (57−62 percent vs. 67−78 percent). Excluding this trial from the meta-analysis reduced statistical heterogeneity, with no appreciable impact on the pooled estimate of effect (three trials, pooled RR 1.2, 95% CI 1.1 to 1.3, I^2=47%).[64, 66, 68] Another potential source of heterogeneity was the evaluation of pegylated interferon alfa-2b and high attrition in one of the trials.[66] However, excluding this trial did not affect the pooled estimate or reduce statistical heterogeneity (three trials, pooled RR 1.1, 95% CI 0.99 to 1.3, I^2=86%).[64, 68, 70]

Figure 5. Sustained virologic response: Dual therapy with pegylated interferon (alfa-2a or alfa-2b) plus ribavirin for 48 versus 24 weeks in patients with genotype 2 or 3 infection

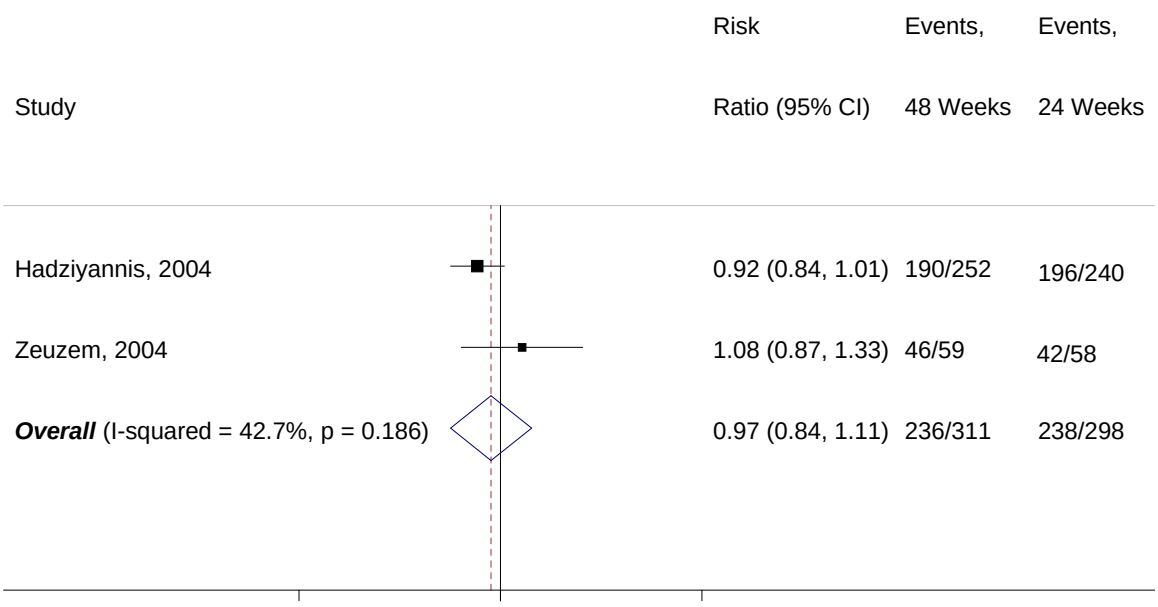
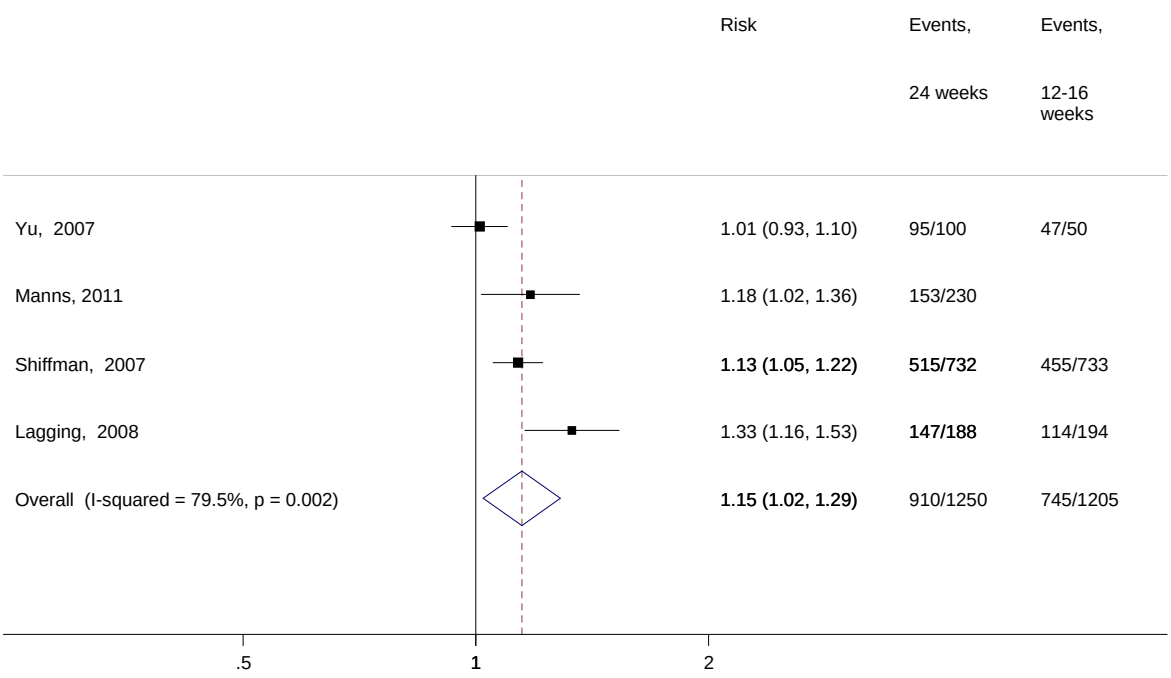
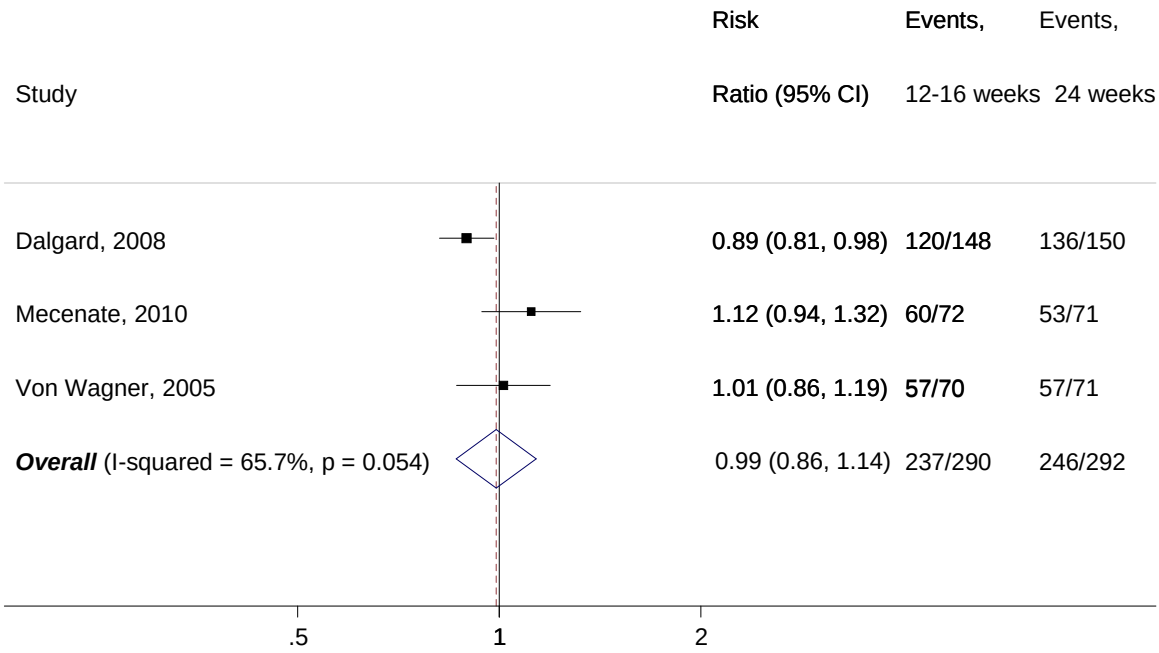


Figure 6. Sustained virologic response: Dual therapy with pegylated interferon (alfa-2a or alfa-2b) plus ribavirin for 24 weeks versus 12 to 16 weeks in patients with genotype 2 or 3 infection



Three trials of patients with genotype 2 or 3 infection who achieved a rapid virologic response (defined as undetectable HCV-RNA by week 4) found no difference between patients randomized to a total of 24 versus 12 to 16 weeks of dual therapy with pegylated interferon alfa-2a (two trials) or alfa-2b (one trial) plus ribavirin (pooled RR 0.99, 95% CI 0.86 to 1.1, I^2=66%) (Figure 7).[62, 67, 69] Although statistical heterogeneity was present, absolute differences were relatively small, ranging from 10 percentage points favoring 24 over 16 weeks of therapy[62] to 9 percentage points favoring 12 over 24 weeks of therapy.[67] One trial used the alfa-2b form of pegylated interferon and a somewhat different weight-based ribavirin dosing algorithm, which might account for some of the heterogeneity.[62]

Figure 7. Sustained virologic response: Dual therapy with pegylated interferon (alfa-2a or alfa-2b) plus ribavirin for a total of 24 versus 12 to 16 weeks in patients with genotype 2 or 3 infection with a rapid virologic response



Two other trials evaluated other comparisons related to duration of dual therapy with pegylated interferon plus ribavirin in patients with HCV genotype 2 or 3 infection.[61, 65] One trial found fixed duration therapy with low dose (1.0 mcg/kg/week) pegylated interferon alfa-2b plus ribavirin for 24 weeks associated with nearly identical likelihood of achieving an SVR versus response-guided therapy for 12 or 24 weeks, based on absence or presence of a rapid virologic response (76 vs. 77 percent).[65] A trial of patients who experienced a rapid virologic response found 12 weeks of pegylated interferon alfa-2a with early discontinuation of ribavirin after 6 weeks associated with lower likelihood of SVR than dual therapy for 12 weeks (54 vs. 82 percent; RR 0.66, 95% CI 0.51 to 0.86).[61]

Dual Therapy With Pegylated Interferon Alfa-2a or Alfa-2b Plus Ribavirin: Dose Effects of Pegylated Interferon (Alfa-2a or Alfa-2b)

Six trials of dual therapy with pegylated interferon plus ribavirin compared lower versus higher doses of pegylated interferon alfa-2b in patients with genotype 2 or 3 infection (Table 4, Appendix H: Evidence Table 7).[66, 73-77] Three trials[66, 74, 77] restricted enrollment to patients with genotype 2 or 3 infection and three trials[73, 75, 76] enrolled other genotypes but reported results in the subgroup of patients with genotype 2 or 3 infection. Sample sizes ranged from 53 to 454 people with genotype 2 or 3 infection. Two trials[66, 76] were rated poor quality and the remainder fair quality (Appendix H: Evidence Table 8). Methodologic shortcomings included open-label or inadequately described blinding procedures[66, 73-77] and unclear randomization methods.[66, 73-77] Five trials compared standard dose pegylated interferon alfa-2b (1.5 mcg/kg/week) compared with lower doses (1.0 or 0.75 mcg/kg/week).[66, 73, 74, 76, 77] The sixth trial evaluated an atypical pegylated interferon alfa-2b dosing regimen of 100-150 mcg weekly (100 mcg if <75 kg or 150 mcg if ≥75 kg) compared with 50 mcg weekly.[75]

Table 4. Dose effects of pegylated interferon, trials of with dual therapy with pegylated interferon (alfa-2a or alfa-2b) plus ribavirin[a]

Author Country N Quality	Population Characteristics	Percent Genotype 2 or 3	Weekly Pegylated Interferon Dose	Daily Ribavirin Dose	Duration	Sustained Virologic Response Among Genotype 2 or 3
Trials of Higher vs. Lower Doses of Pegylated Interferon Alfa-2b						
Abergel, 2006[73] France N=78 with genotype 2 or 3 infection N(total)=203 Quality: Fair	A vs. B Age (mean): 50 vs. 52 years Female: 36% vs. 32% Race: Not reported Cirrhosis: 46% vs. 57% Minimal or no fibrosis: Not reported	38%	A. Alfa-2b 1.5 mcg/kg B. Alfa-2b 0.75 mcg/kg	800 mg	48 weeks	A. 73% B. 73%
Kawaoka, 2009[74] Japan N=53 Quality: Fair	A vs. B Age (median): 57 vs. 55 years Female: 65% vs. 44% Race: Not reported (study conducted in Japan) Cirrhosis: None Minimal or no fibrosis: 55% vs. 48%	100%	A. Alfa-2b 1.0 mcg/kg B. Alfa-2b 1.5 mcg/kg	600-1000 mg	24 weeks	A. 39% B. 74%
Krawitt, 2006[75] U.S. N=86 with genotype 2 or 3 infection N(total) = 301 Quality: Fair	A vs. B Age >50 years: 18% vs. 19% Female: 38% vs. 36% Non-White race: 4.6% vs. 3.1% Cirrhosis: 17% vs. 10% Minimal or no fibrosis: 30% vs. 33%	29%	A. Alfa-2b 50 mcg B. Alfa-2b 100-150 mcg	1000 mg	48 weeks	A. 56% B. 65%
Meyer-Wyss, 2006[76] Switzerland N=91 with genotype 2 or 3 infection N(total)=219 Quality: Poor	A vs. B Age (median): 39 vs. 42 years Female: 43% vs. 28% Race: Not reported Cirrhosis: None Minimal or no fibrosis: 58% vs. 49%	42%	A. Alfa-2b 1.0 mcg/kg B. Alfa-2b 1.5 mcg/kg	800 mg	24-48 weeks by genotype	A. 71% B. 81%
Sood, 2008[77] India N=103 Quality: Fair	A vs. B Age (mean): 43 vs. 37 years Female: 12% vs. 22% Race: Not reported Cirrhosis: Not reported Minimal or no fibrosis: Not reported	100%	A. Alfa-2b 1.0 mcg/kg B. Alfa-2b 1.5 mcg/kg	10-12 mg/kg	24 weeks	A. 79% B. 93%
Manns, 2011[66] International N=454 (24 week) N(total)=602 Quality: Poor	A vs. B Age (Mean): 40 vs. 39 vs. years Female: 35% vs. 40% vs. Non-White race: Not reported Cirrhosis: Not reported Minimal or no fibrosis: Not reported	100%	A: Alfa-2b 1.5 mcg B: Alfa-2b 1.0 mcg	800-1400 mg	24 weeks	A. 67% B. 64%

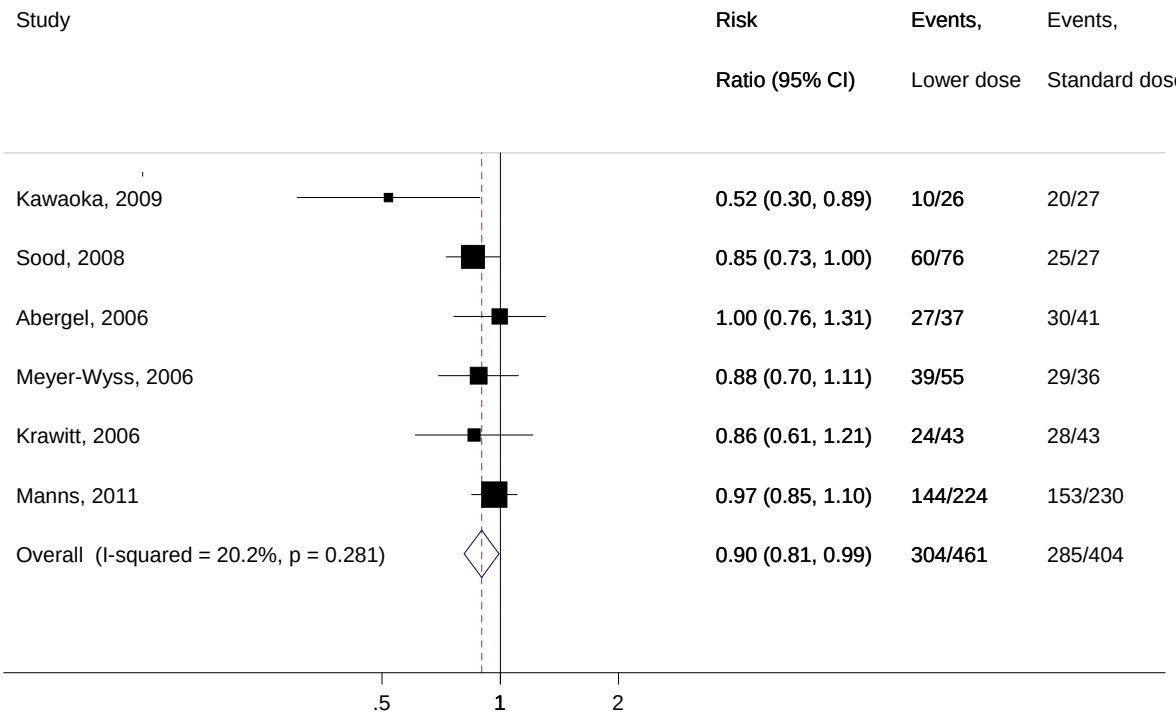
Table 4. Dose effects of pegylated interferon, trials of with dual therapy with pegylated interferon (alfa-2a or alfa-2b) plus ribavirin[a] (continued)

Author Country N Quality	Population Characteristics	Percent Genotype 2 or 3	Weekly Pegylated Interferon Dose	Daily Ribavirin Dose	Duration	Sustained Virologic Response Among Genotype 2 or 3
Trials of Induction Dosing Regimens						
Manns, 2001[78] U.S. & UK N=1530 Quality: Fair	A vs. B Age (mean): Female: Non-White race: Cirrhosis: Not reported (29% vs. 30% severe fibrosis or cirrhosis) Minimal or no fibrosis: Not reported	29%	A. Alfa-2b 1.5 mcg/kg x 4 weeks, then 0.5 mcg/kg x 44 weeks B. Alfa-2b 1.5 mcg/kg x 48 weeks	A. 1000-1200 mg B. 800 mg	48 weeks	A. 80% B. 88%
Mimidis, 2006[79] Greece N=120 Quality: Poor	A vs. B Age (mean): Not reported Female: : 49% vs. 51% Race: Not reported Cirrhosis: Not reported Minimal or no fibrosis: Not reported	51%	A. Alfa-2b 3.0 mcg/kg x 12 weeks, 1.5 mcg/kg x 36 weeks B. Alfa-2b 1.5 mcg/kg x 48 weeks	800-1200 mg	48 weeks	A. 48% B. 59%

HCV = hepatitis C virus; NA = not applicable; SD = standard deviation; U.K. = United Kingdom; U.S. = United States.
Note: Cirrhosis = METAVIR F4, Ishak 5-6, or equivalent. Minimal or no fibrosis=METAVIR F0-F1, Ishak 0-2, or equivalent.
[a] Sample sizes and results restricted to patients with genotype 2 or 3 infection.

Lower dose pegylated interferon alfa-2b as part of dual therapy with ribavirin was associated with lower likelihood of SVR than standard dose (six trials, pooled RR 0.90, 95% CI 0.81 to 0.99, I^2=20%) (Figure 8).[66, 73-77] Excluding two poor quality trials[66, 76] (four trials, pooled RR 0.85, 95% CI 0.71 to 1.0, I^2=38%) or the trial that compared atypical dosing regimens[75] (five trials, pooled RR 0.89, 95% CI 0.79 to 1.0, I^2=35%) had little effect on the pooled estimates.

Figure 8. Sustained virologic response: Dual therapy with lower dose pegylated interferon alfa-2b plus ribavirin versus higher dose pegylated interferon alfa-2b plus ribavirin in patients with genotype 2 or 3 infection



Two other trials evaluated induction regimens of pegylated interferon alfa-2b (higher initial doses followed by lower doses until completion of therapy) plus ribavirin compared with standard fixed-dose regimens of pegylated interferon alfa-2b plus ribavirin.[78, 79] One good quality trial found dual therapy with pegylated interferon alfa-2b (3.0 mcg/kg/week) plus ribavirin for 12 weeks followed by 36 weeks of standard dose pegylated interferon alfa-2b plus ribavirin associated with a nonstatistically significant trend towards decreased likelihood of SVR versus standard fixed dose dual therapy for 48 weeks (48 vs. 59 percent, $p>0.05$).[79] Another trial found no clear difference in likelihood of achieving an SVR between dual therapy with standard dose pegylated interferon alfa-2b plus ribavirin for 4 weeks followed by 0.5 mcg/kg/week for 44 weeks versus fixed dose dual therapy with standard doses of pegylated interferon alfa-2b for 48 weeks (82 vs. 80 percent), but results are difficult to interpret because ribavirin dosing was higher (1000 to 1200 mg daily) in the induction compared with the standard therapy arm (800 mg daily).[78]

Ribavirin

Four trials compared effects of dual therapy with pegylated interferon plus ribavirin with different doses of ribavirin in patients with genotype 2 or 3 infection (Table 5, Appendix H: Evidence Table 5).[63, 80-82] One trial[80] restricted enrollment to patients with genotype 2 or 3 infection and three trials[63, 81, 82] enrolled other genotypes but reported results in the subgroup of patients with genotype 2 or 3 infection. Sample sizes ranged from 60 to 1831 with genotype 2 or

3 infection. All four trials were rated fair quality (Appendix H: Evidence Table 6). Methodological shortcomings included open-label design or inadequately described blinding[63, 80-82] and high loss to followup.[63, 82] Three trials[63, 80, 81] evaluated ribavirin in combination with pegylated interferon alfa-2a and one trial in combination with pegylated interferon alfa-2b.[82]

Table 5. Dose effects of ribavirin: Trials of with dual therapy with pegylated interferon (alfa-2a or alfa-2b) plus ribavirin[a]

Author Country Study Name N Quality	Population Characteristics	Percent Genotype 2 or 3	Pegylated Interferon Dose	Ribavirin Dose	Duration	Sustained Virologic Response Among Genotype 2 or 3
Ferenci, 2008[80] Austria N= 282 Quality: Poor	A vs. B Age (mean): 37 vs. 36 years Female: 40% vs. 38% Race: Not reported Cirrhosis: Not reported Minimal or no fibrosis: Not reported	100%	Alfa-2a 180 mcg	A. 400 mg B. 800 mg	24 weeks	A. 64% B. 69%
Hadziyannis, 2004 (PEGASYS)[63] Worldwide N=492 with genotype 2 or 3 infection Quality: Fair	A vs. B vs. C vs. D: Age (mean): 41 vs. 42 vs. 43 vs. 43 years Female: 32% vs. 34% vs. 27% vs. 34% Nonwhite race: 12% vs. 9% vs. 13% vs. 10% Cirrhosis: 5% vs. 7% vs. 7% vs. 8% Minimal or no fibrosis: Not reported	38%	Alfa-2a 180 mcg	A/C. 800 mg B/D. 1000-1200 mg	A. 24 weeks B. 24 weeks C. 48 weeks D. 48 weeks	A/C. 82% B/D. 80%
Helbling, 2006[81] Switzerland N= 60 (genotype 2 or 3) N(total)=97 Quality: Fair	A vs. B Age (median): 47 vs. 47 years Female: 30% vs. 40% Race: Not reported Cirrhosis: 57% vs. 52% Minimal or no fibrosis: 6% vs. 2%	48%	Alfa-2a 180 mcg	A. 1000-1200 mg B. 600-800 mg	24-48 weeks by genotype	A. 72% B. 45%
Jacobson, 2007a (WIN-R)[82] U.S. N=1831 with genotype 2 or 3 infection N(total)=4913 Quality: Fair	A vs. B Age (mean): 46 vs. 46 years Female - 37.7% vs. 36.2% Nonwhite race: 19% vs. 21% Cirrhosis: 10% vs. 10% Minimal or no fibrosis: Not reported (mild, minimal, or no fibrosis 70% vs. 70%)	37%	Alfa-2b 1.5 mcg	A. 800 mg B. 800-1400 mg	24-48 weeks by genotype	A. 60% B. 62%

Cirrhosis = METAVIR F4, Ishak 5-6, or equivalent. Minimal or no fibrosis=METAVIR F0-F1, Ishak 0-2, or equivalent.
[a] Sample sizes and results restricted to patients with genotype 2 or 3 infection.

The trials each evaluated a different ribavirin dose comparison, precluding pooled analyses. The two largest trials found no clear differences between lower flat doses of ribavirin versus higher or weight-based doses.[63, 82] One trial (n=492 with genotype 2 or 3 infection) randomized patients to dual therapy with pegylated interferon alfa-2a 180 mcg/week plus flat-dose ribavirin, in one of four regimens: 24 weeks with ribavirin 800 mg/day, 24 weeks with ribavirin 1000–1200 mg/day, 48 weeks with ribavirin 800 mg/day, and 48 weeks with ribavirin 1000–1200 mg/day.[63] Rates of SVR were very similar in the combined 800 mg versus the combined 1200 mg arms (82 vs. 80 percent, RR 1.1, 95% CI 0.99 to 1.2). Another trial (n=1831 with genotype 2 or 3 infection) found no difference between dual therapy for 24 weeks with pegylated interferon alfa-2b 1.5 mcg/kg week and flat-dose ribavirin 800 mg versus weight-dosed ribavirin 800 to 1400 mg (60 vs. 62 percent, RR 0.96, 95% CI 0.89 to 1.0).[82] One other smaller trial (n=282) found no difference between dual therapy with pegylated interferon alfa-2a with flat doses of ribavirin 400 mg versus ribavirin 800 mg in likelihood of an SVR (64 vs. 69 percent, RR 0.92, 95% C I 0.78 to 1.1). [80]

One trial (n=60 with genotype 2 or 3 infection) of pegylated interferon alfa-2a found 600-800 mg daily of ribavirin associated with lower likelihood of SVR than 1000-1200 mg daily (45 vs. 72 percent, RR 0.62, 95% CI 0.40 to 0.98), but differed from the others in that it enrolled subjects primarily with advanced fibrosis or cirrhosis (Ishak stage F4-F6).[81]

Trials of Triple Therapy With Pegylated Interferon Alfa-2b, Ribavirin, and Boceprevir

Two randomized trials compared triple therapy with boceprevir, pegylated interferon alfa-2b and weight-based ribavirin with dual therapy with pegylated interferon alfa-2b plus ribavirin in antiviral treatment-naïve patients with chronic HCV genotype 1 infection (Table 6, Appendix H: Evidence Table 3).[30, 32] The Serine Protease Inhibitor Therapy (SPRINT-1)[30] and SPRINT-2[32] trials (n=1088 and 520, respectively) were conducted in the U.S., Canada, and Europe. In SPRINT-1,[30] 7 percent of enrolled patients had cirrhosis at baseline and in SPRINT-2[32] about 10 percent had either severe fibrosis or cirrhosis. Both trials were rated fair quality (Appendix H: Evidence Table 4). SPRINT-1 was an open label trial, and in SPRINT-2, 24 percent of patients did not complete followup. Neither trial evaluated the FDA-recommended dosing regimen for boceprevir in antiviral-naïve patients without cirrhosis at baseline (4 weeks of dual therapy lead-in with pegylated interferon alfa-2a or alfa-2b plus ribavirin, followed by triple therapy with the addition of boceprevir for either 24 or 32 weeks, based on virologic response at weeks 8 and 24),[84] although both trials evaluated the FDA-recommended dosing regimen for boceprevir in antiviral treatment-naïve patients with cirrhosis at baseline (4 weeks of dual therapy lead-in, followed by triple therapy for the final 44 weeks).

Table 6. Trials of triple therapy with pegylated interferon alfa-2b, ribavirin, and boceprevir versus dual therapy with pegylated interferon alfa-2b plus ribavirin

Trial Country Study Name N Quality	Population characteristics	Boceprevir Dose / Duration	Weekly Pegylated interferon dose	Daily Ribavirin Dose	Overall Duration of Therapy (weeks)	Sustained Virologic Response
Kwo, 2010[30] U.S., Canada, Europe Serine Protease Inhibitor Therapy 1 (SPRINT-1) Trial N(total)=520 Quality: Fair	A vs. B vs. C vs. D vs. E Age (mean): 47 vs. 46 vs. 48 vs. 48. vs. 48 years Female: 39% vs. 41% vs. 44% vs. 50% vs. 33% Nonwhite race: 16% vs. 20% vs. 17% vs. 17% vs. 20% Genotype 1: 100% Cirrhosis: 7% (overall) Minimal or no fibrosis: Not reported Elevated transaminases: Not reported	A. BCP 800 mg tid weeks 1-48 B. BCP 800 mg tid weeks 1-28 C. BCP 800 mg tid weeks 5-48[a] D. BCP 800 mg tid weeks 5-28 E. placebo	Alfa-2b 1.5 mcg/kg	800-1400 mg	A. 48 B. 28 C. 48 D. 28 E. 48	A. 67% B. 54% C. 75%[a] D. 56% E. 38%
Poordad, 2011[32] U.S. and Europe Serine Protease Inhibitor Therapy 2 (SPRINT-2) N=1,088 Quality: Fair	A vs. B vs. C Age (mean) 49 vs. 50 vs. 49 years Female: 40% vs. 38% vs. 43% Nonwhite race: 19% vs. 17% vs. 18% Genotype 1: 100% Cirrhosis: Not reported (Severe fibrosis or cirrhosis 11% vs. 9% vs. 7%) Minimal or no fibrosis: Not reported Elevated transaminases:	A. 800 mg tid weeks 5-48 B. 800 mg tid weeks 5-28 C. placebo	Alfa-2b 1.5 mcg/kg	A. 600-1400 mg weeks 5-48 B. 600-1400 mg weeks 5-28 C. 600-1400 mg	A. 48 B. 28/48[b] C. 48	A. 66%[a] B. 63% C. 38%

BCP = boceprevir; bid = twice daily; eRVR = extended rapid virologic response; TCP = telaprevir; tid = three times daily
Note: Cirrhosis=METAVIR F4, Ishak 5-6, or equivalent. Minimal or no fibrosis=METAVIR F0-F1, Ishak 0-2, or equivalent.
[a] Dosing recommended by the U.S. Food and Drug Administration for boceprevir in antiviral-naïve patients with cirrhosis at baseline.
[b] Response-guided duration: 28 weeks of pegylated interferon/ribavirin if HCV-RNA negative from week 8 through week 24. Patients not meeting these criteria continued until week 48.

SPRINT-1 randomized patients to five different antiviral regimens: (1) 4-week dual therapy lead-in with pegylated interferon alfa-2b plus ribavirin followed by the addition of boceprevir for 24 weeks (total 28 weeks); (2) 28 weeks of triple therapy with pegylated interferon alfa-2b, ribavirin, and boceprevir with no lead-in; (3) 4-week dual therapy lead-in followed by triple therapy for 44 weeks (total 48 weeks); (4) 48 weeks of triple therapy with no lead-in; or (5) dual therapy for 48 weeks.[30] SVR rates were 56 percent and 54 percent in the 28-week boceprevir treatment arms and 75 percent and 67 percent in the 48-week boceprevir treatment arms (with and without dual therapy lead- in, respectively), versus 38 percent with dual therapy ($p<0.01$ for

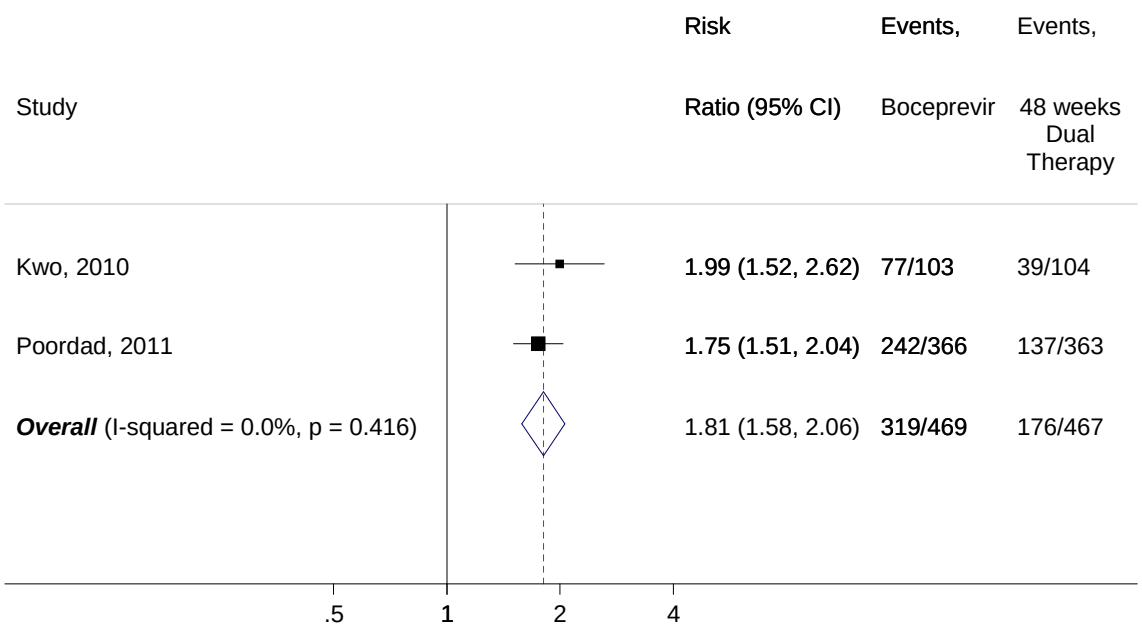
each triple therapy arm vs. dual therapy), for an absolute risk difference for triple compared with dual therapy that ranged from 19–37 percent. Versus dual therapy, the relative risk for achieving an SVR for the two 48-week triple therapy arms combined was 1.9 (95% CI 1.5 to 2.5), and for the two 28-week triple therapy arms combined was 1.5 (95% CI 1.1 to 1.9). Four-week dual therapy lead-in was associated with an increased absolute rate of achieving an SVR versus no lead-in of 2 percent for the 28-week regimens and 8 percent for the 48-week regimens.

SPRINT-2 compared a fixed duration triple therapy regimen, a response-guided triple therapy regimen, and dual therapy.[32] The fixed duration regimen consisted of four weeks of dual therapy lead-in with pegylated interferon alfa-2b plus ribavirin followed by the addition of boceprevir for 44 weeks (48 weeks total). The response-guided approach consisted of a four-week dual therapy lead-in, followed by triple therapy for 24 weeks. Patients with undetectable serum HCV-RNA from weeks 8 through 24 completed their antiviral treatment at week 28. Patients with detectable HCV-RNA at any time between weeks 8 and 24 continued dual therapy for another 20 weeks (48 weeks total). The third (control) arm consisted of dual therapy for 48 weeks. SVR rates for the three regimens were 66, 63, and 38 percent, respectively, ($p<0.001$ for either boceprevir regimen vs. dual therapy), with an absolute risk difference of 25–28 percent for triple compared with dual therapy. Compared with dual therapy, the relative risk for achieving an SVR for the two regimens with boceprevir combined was 1.7 (95% CI 1.5 to 2.0).

The only treatment regimen evaluated in both SPRINT trials was the 48-week regimen with dual therapy lead-in for the first 4 weeks and boceprevir added for the final 44 weeks. Based on data from both trials, triple therapy was associated with a higher likelihood of SVR than dual therapy (pooled RR 1.8, 95% CI 1.6 to 2.1, $I^2=0\%$), with a pooled absolute increase in SVR of 31 percentage points (95% CI 23 to 39) (Figure 9).[30, 32]

SPRINT-1 also included a separate trial of 75 patients randomized to weight-based low dose (400–1000 mg) or standard dose (800–1400 mg) ribavirin as part of 48 weeks of triple therapy with boceprevir without dual therapy lead in[30] Low dose ribavirin was associated with a non–statistically significant trend towards lower likelihood of SVR (36 vs. 50%, RR 0.71, 95% CI 0.39 to 1.3).

Figure 9. Sustained virologic response: 48 weeks of triple therapy with boceprevir (4 weeks of dual therapy lead-in with pegylated interferon alfa-2b followed by the addition of 44 weeks boceprevir) versus 48 weeks of dual therapy in patients with genotype 1 infection



Trials of Triple Therapy With Pegylated Interferon (Alfa-2a or Alfa-2b), Ribavirin, and Telaprevir

Six randomized trials compared triple therapy with telaprevir, pegylated interferon alfa-2a or alfa-2b and weight-based ribavirin compared with dual therapy with pegylated interferon alfa-2a or alfa-2b and ribavirin for antiviral treatment-naïve patients with chronic HCV genotype 1 infection (Table 7, Appendix H: Evidence Table 3).[31, 51, 59, 85-87] A seventh, small trial was excluded because it evaluated patients with HCV genotype 2 or 3 (telaprevir is only approved for use in genotype 1 infection).[88] One trial[31] was rated good quality and the remainder fair quality (Appendix H: Evidence Table 4). The proportion of patients with cirrhosis at baseline in the trials ranged from 0–10 percent. Methodological shortcomings included open-label design or unclear blinding procedures,[59, 85, 87] unclear randomization methods,[31, 85] and unclear reporting of attrition.[31, 86] Three trials (n=189 to 323) evaluated fixed duration triple compared with dual therapy regimens (12, 24, or 48 weeks).[31, 85, 86] Two other trials[51, 59] (n=161 and 1088) evaluated response-guided duration triple therapy regimens, including one trial[51] that compared the FDA-recommended telaprevir dosing regimen (12 weeks of triple therapy followed by 12 or 36 weeks of dual therapy, depending on early virologic response) with dual therapy.[84] The sixth trial (n=322) compared different durations of antiviral therapy in patients who experienced an extended rapid virologic response.[87] In all evaluated triple therapy regimens, telaprevir was administered with pegylated interferon (alfa-2a or alfa-2b) plus ribavirin for the first 8 to 12 weeks. For regimens longer than 12 weeks, dual therapy with pegylated interferon alfa-2a or alfa-2b plus ribavirin without telaprevir was continued for the remainder of the regimen.

Table 7. Trials of triple therapy with pegylated interferon alfa-2b, ribavirin, and telaprevir

Author Country Study Name N Quality	Population Characteristics	Telaprevir Dose / Duration	Weekly Pegylated interferon Dose	Daily Ribavirin Dose	Overall Duration of Therapy (weeks)	Sustained Virologic Response
Hezode, 2009[85] Europe N=323 Quality: Fair	A vs. B vs. C vs. D Age (median): 46 vs. 44 vs. 45 vs. 45 years Female: 33% vs. 40% vs. 45% vs. 44% Non White race: 7% vs. 7% vs. 1% vs. 7% Genotype 1: 100% Cirrhosis: 0% vs. 0% vs. 1% vs. 0% Minimal or no fibrosis: 43% vs. 37% vs. 40% vs. 34% Elevated transaminases: Not reported	A. 750 mg tid weeks 1-12 B. 750 mg tid weeks 1-12 C. 750 mg tid weeks 1-12 D. placebo	Alfa-2a 180 mcg	A. 1000-1200 mg B. 1000-1200 mg C. placebo D. 1000-1200 mg	A. 12 B. 24 C. 12 D. 48	A. 69% B. 60% C. 36% D. 46%
Jacobson, 2011[51] Worldwide N=1088 Quality: Good	A vs. B vs. C Age (median): 49 vs. 49 vs. 49 years Female: 41% vs. 42% vs. 42% Non White race: 10% vs. 13% vs. 12% Genotype 1: 100% Cirrhosis: 6% overall Minimal or no fibrosis: 28% overall Elevated transaminases: Not reported	A. 750 mg tid weeks 1-8 B. 750 mg tid weeks 1-12[b] C. placebo	Alfa-2a 180 mcg	1000-1200 mg	A. 24/48[a] B. 24/48[a] C. 48	A. 69% B. 75%[b] C. 44%
Kumada, 2012[86] Japan N=189 Quality: Fair	A vs. B Age (mean): 53 vs. 55 Female: 48% vs. 48% Non White: Not reported (conducted in Japan) Minimal or no fibrosis: Not reported Elevated transaminases: Not reported	A. 750 mg tid weeks 1-12 B. placebo	Alfa-2b 1.5 mcg/kg	600-1000 mg	A. 24 B. 48	A. 73% B. 49%
Marcellin, 2011[59] Europe N=161 Quality: Fair	A vs. B vs. C vs. D Age (median): 47 vs. 46 vs. 40 vs. 49 years Female: 50% vs. 52% vs. 48% vs. 51% Non White race: 10% vs. 10% vs. 10% vs. 8% Genotype 1: 100% Cirrhosis: 2.5% vs. 2.4% vs. 0 vs. 5.1% Minimal or no fibrosis: 39% overall Elevated transaminases: Not reported	A. 750 mg tid weeks 1-12 B. 750 mg tid weeks 1-12 C. 1125 mg bid weeks 1-12 D. 1125 mg bid weeks 1-12	A. Alfa-2a 180 mcg B. Alfa-2b 1.5 mcg/kg C. Alfa-2a 180 mcg D. Alfa-2a 1.5 mcg/kg	A. 1000-1200 mg B. 800-1200 mg C. 1000-1200 mg D. 800-1200 mg	24/48[c]	A. 85% B. 81% C. 83% D. 82%

Table 7. Trials of triple therapy with pegylated interferon alfa-2b, ribavirin, and telaprevir (continued)

Author Country Study Name N Quality	Population Characteristics	Telaprevir Dose / Duration	Weekly Pegylated interferon Dose	Daily Ribavirin Dose	Overall Duration of Therapy (weeks)	Sustained Virologic Response
McHutchison, 2009[31] U.S. PROVE1 N=250 Quality: Fair	A vs. B vs. C vs. D Age (median): 49 vs. 50 vs. 49 vs. 49 years Female: 32% vs. 39% vs. 29% vs. 43% Non White race: 24% vs. 24% vs. 24% vs. 21% Cirrhosis: 0% Minimal or no fibrosis: 31% (overall) Elevated transaminases: Not reported	A. 750 mg tid weeks 1-12 B. 750 mg tid weeks 1-12 C. 750 mg tid weeks 1-12 D. placebo	Alfa-2a 180 mcg	1000-1200 mg	A. 12 B. 24 C. 48 D. 48	A. 35% B. 61% C. 67% D. 41%
Sherman, 2011[87] U.S. Name: ILLUMINATE N=322[d] Quality: Fair	A vs. B Age (median): 51 vs. 50 years Female: 36% vs. 39% Non White race: 17% vs. 18% Cirrhosis: 11% vs. 8% Minimal or no fibrosis: 27% (overall) Elevated transaminases: Not reported	A. 750 mg tid weeks 1-12 B. 750 mg tid weeks 1-12	Alfa-2a 180 mcg	1000-1200 mg	A. 24 B. 48	A. 92% B. 88%

bid = two times daily; eRVR = extended rapid virologic response; HCV = hepatitis C virus; NA = not applicable; TCP = telaprevir; tid = three times daily

Note: Cirrhosis=METAVIR F4, Ishak 5-6, or equivalent. Minimal or no fibrosis=METAVIR F0-F1, Ishak 0-2, or equivalent.

[a] Response-guided duration: 24 weeks of pegylated interferon/ribavirin if HCV-RNA negative from week 4 through week 12. Patients not meeting these criteria continued until week 48.

[b] Dosing regimen recommended by the U.S. Food and Drug Administration for telaprevir.

[c] Response-guided duration: 24 weeks of pegylated interferon/ribavirin if HCV-RNA negative from week 4 through week . Patients not meeting these criteria continued until week 48.

[d] Patients with undetectable HCV RNA at week 4 and week 12 randomized to either 24 or 48 weeks of dual therapy.

Three trials found the 24-week fixed duration triple therapy with pegylated interferon alfa-2a or alfa-2b, ribavirin, and telaprevir associated with higher likelihood of achieving an SVR than 48 weeks of dual therapy (pooled RR 1.5, 95% CI 1.3 to 1.8, I^2=0%) (Figure 10).[31, 85, 86] The pooled absolute increase in SVR rates was 22 percentage points (95% CI 13 to 31). Two of the trials found no difference between the 12-week fixed duration triple therapy regimen versus 48 weeks of dual therapy (pooled RR 1.2, 95% CI 0.86 to 1.6, I^2=14%) (Figure 11).[31, 85] One of the trials also found a 48-week triple therapy regimen with telaprevir associated with similar likelihood of SVR versus a 24-week triple therapy regimen (RR 1.1, 95% CI 0.87 to 1.4).[31] The other trial also found a 12-week triple therapy regimen of telaprevir plus pegylated interferon without ribavirin associated with a non–statistically significant trend towards lower likelihood of achieving an SVR than pegylated interferon alfa-2a plus ribavirin for 48 weeks (RR 0.77, 95% CI 0.53 to 1.1).[85] One trial of 24-week fixed duration triple therapy with telaprevir was conducted in Japan,[86] while the other two were conducted in the United States and Europe. Additionally, the Japanese trial studied telaprevir with pegylated interferon alfa-2b, compared

with pegylated interferon alfa-2a in the other fixed duration trials. Excluding this trial did not change the pooled result for SVR (two trials, pooled RR 1.5, 95% CI 1.20 to 1.8, I^2=0%).[31, 85]

Figure 10. Sustained virologic response: Triple therapy with pegylated interferon alfa-2a, ribavirin, and telaprevir for 12 weeks followed by dual therapy for 12 weeks versus dual therapy with pegylated interferon alfa-2a plus ribavirin for 48 weeks in patients with genotype 1 infection

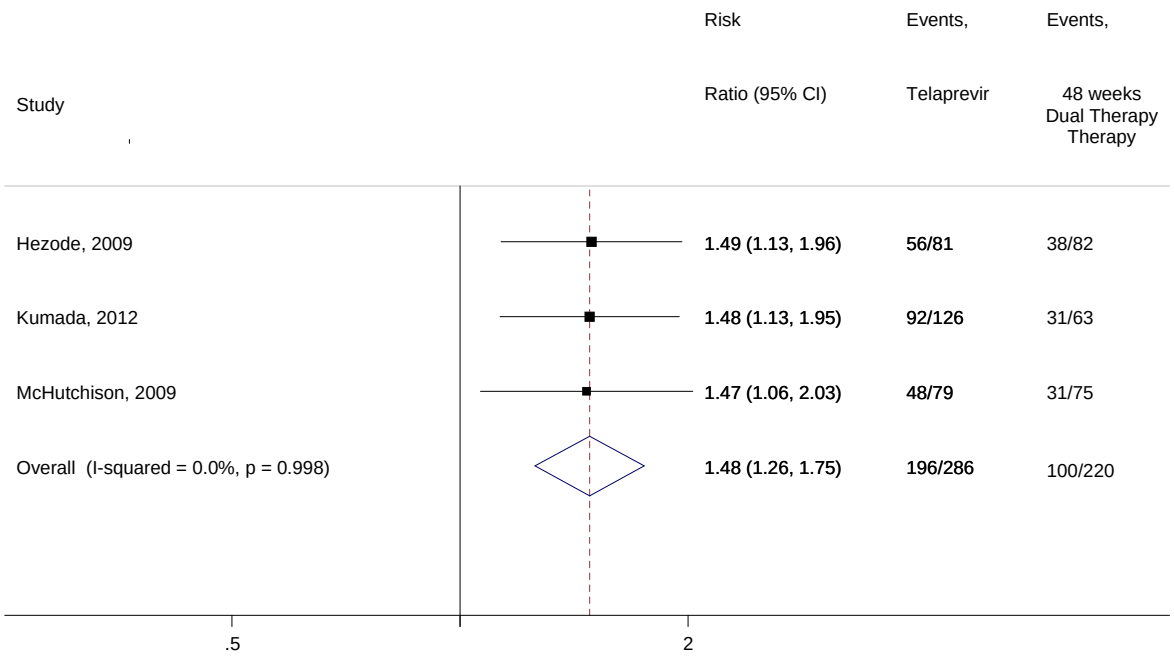
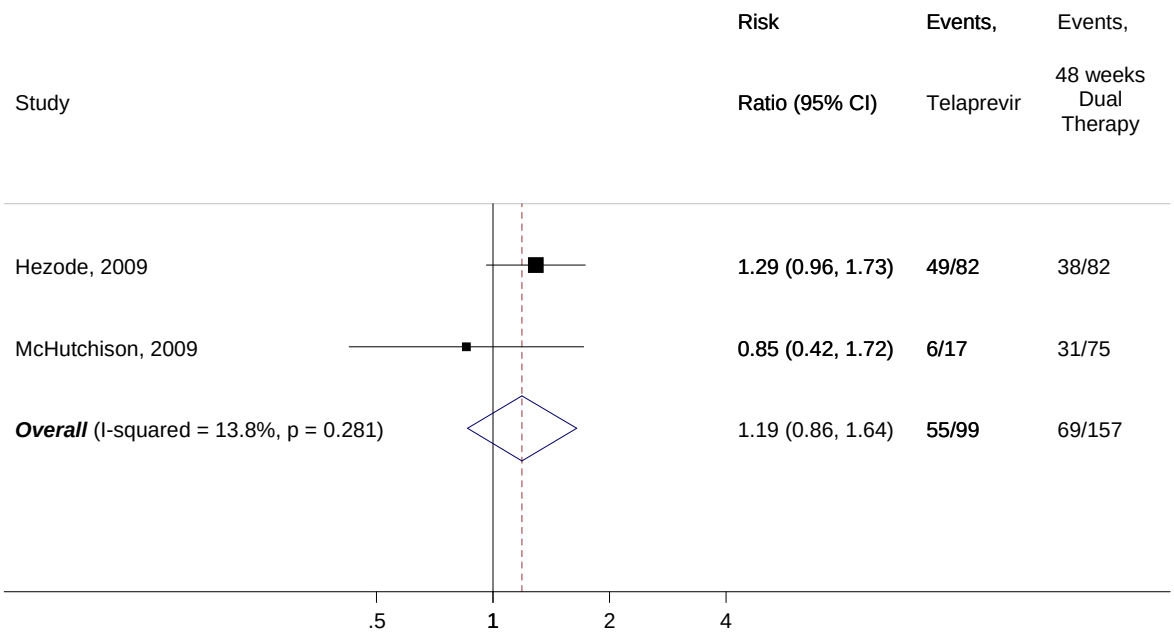


Figure 11. Sustained virologic response: Triple therapy with pegylated interferon alfa-2a, ribavirin, and telaprevir for 12 weeks versus dual therapy with pegylated interferon alfa-2a plus ribavirin for 48 weeks in patients with genotype 1 infection



One trial compared response-guided duration triple therapy with telaprevir compared with dual therapy.[51] Patients were randomized to 8 weeks of initial triple therapy with pegylated interferon alfa-2a, ribavirin, and telaprevir, 12 weeks of initial triple therapy, or dual therapy with pegylated interferon alfa-2a plus ribavirin. In the telaprevir arms, patients with an extended rapid viral response (HCV-RNA undetectable between weeks 4 and 12) continued pegylated interferon plus ribavirin for a total of 24 weeks, while those without an extended rapid viral response continued dual therapy for a total of 48 weeks. Patients randomized to dual therapy received pegylated interferon alfa-2a plus ribavirin for a fixed duration of 48 weeks. Both telaprevir treatment-guided response regimens were associated with higher SVR rates than dual therapy (69, 75, and 44 percent for 8 weeks of telaprevir, 12 weeks of telaprevir, and dual therapy, respectively; $p<0.001$ for either telaprevir regimen vs. dual therapy), with an absolute increase in SVR ranging from 25–31 percent for triple therapy compared with dual therapy. The relative risk for achieving an SVR in the combined telaprevir arms versus dual therapy was 1.6 (95% CI 1.4 to 1.9).

One trial of response-guided triple therapy with telaprevir (24 or 48 weeks, based on absence or presence of HCV-RNA from weeks 4 through 20) found similar SVR rates (81–85 percent) for regimens that varied on telaprevir dose (750 mg three times daily vs. 1,125 mg two times daily) and type of pegylated interferon (alfa-2a or alfa-2b).[59] Another trial of patients with an extended rapid virologic response to initial triple therapy with telaprevir reported similar, high (92 and 88 percent) SVR rates in patients randomized to a total of 24 or 48 weeks of therapy, meeting the study's predefined noninferiority threshold.[87]

Key Question 2b. How does the comparative effectiveness of antiviral treatment for intermediate outcomes vary according to patient subgroup characteristics, including but not limited to HCV genotype, age, race, sex, stage of disease, or genetic markers?

- The largest randomized trial (n=3070) of dual therapy with pegylated interferon alfa-2a plus ribavirin compared with dual therapy with pegylated interferon alfa-2b plus ribavirin found no clear differences in relative risk estimates for SVR in genotype 1 patients stratified by race, sex, age, baseline fibrosis stage, or baseline viral load. Characteristics associated with lower absolute SVR rates across dual therapy regimens were older age, Black race, advanced fibrosis or cirrhosis, and high baseline viral load (strength of evidence: low).
- Four randomized trials of dual therapy with pegylated interferon alfa-2a plus ribavirin versus dual therapy with pegylated interferon alfa-2b plus ribavirin found no clear differences in relative risk estimates for SVR in patients stratified by genotype. Genotype 1 infection was associated with a lower absolute SVR rate than genotypes 2 or 3 (strength of evidence: moderate).
- Two trials of triple therapy with boceprevir for 48 weeks (4 weeks of dual therapy lead-in with pegylated interferon plus ribavirin followed by 44 weeks of triple therapy with pegylated interferon, ribavirin, and boceprevir) found no difference in relative risk estimates for SVR in men versus women, and no clear difference in relative risk estimates for Black versus non-Black patients. Black race was associated with a lower absolute SVR rate than non-Black race (strength of evidence: moderate).
- Two trials found triple therapy with pegylated interferon alfa-2b, ribavirin, and boceprevir associated with higher likelihood of achieving SVR than dual therapy with pegylated interferon alfa-2b plus ribavirin in patients with high baseline HCV-RNA viral load (>600,000 or $\geq$800,000 IU/mL), but found no difference in likelihood of SVR in patients with lower viral load (strength of evidence: moderate).
- One trial of response-guided triple therapy with telaprevir (12 weeks of pegylated interferon alfa-2a, ribavirin, and telaprevir followed by response-guided dual therapy with pegylated interferon alfa-2a and ribavirin) versus dual therapy with pegylated interferon plus ribavirin for 48 weeks found no clear differences in relative risk estimates in patients stratified by age, sex, race, baseline fibrosis status, or body mass index. Characteristics associated with lower absolute rates of SVR were older age, Black race, advanced fibrosis or cirrhosis, and higher body mass index. One other trial of 24-week fixed duration triple therapy with telaprevir, pegylated interferon alfa-2b, and ribavirin versus 48 weeks of dual therapy found no differences in estimates of effect in patients stratified by sex or age (strength of evidence: moderate).
- Two trials of triple therapy with pegylated interferon (alfa-2a or alfa-2b), ribavirin, and telaprevir versus dual therapy depending reported inconsistent findings for differential relative risk estimates according baseline viral load (strength of evidence: insufficient).

Dual Therapy With Pegylated Interferon Alfa-2a Plus Ribavirin Compared With Pegylated Interferon Alfa-2b Plus Ribavirin

Five trials of dual therapy with pegylated interferon alfa-2a plus ribavirin versus pegylated interferon alfa-2b evaluated SVR rates in patients subgroups defined by demographic and clinical characteristics (Appendix H: Evidence Table 1 and Evidence Table 2).[20-23, 56] The largest study (n=3070), the IDEAL trial, which only enrolled patients with genotype 1 infection, reported no clear differences in relative risk estimates for SVR dual therapy with pegylated interferon alfa-2b plus ribavirin versus dual therapy with pegylated interferon alfa-2a plus ribavirin in patients stratified by race (RR 0.88, 95% CI 0.59 to 1.3 for Black patients and RR 0.98, 95% CI 0.84 to 1.2 for white patients), sex (RR 0.92, 95% CI 0.77 to 1.1 for males and RR 1.1, 95% CI 0.86 to 1.3 for females), age (RR 0.95, 95% CI 0.77 to 1.2 for <40 years and RR 0.99, 95% CI 0.88 to 1.1 for age >40 years), baseline fibrosis (RR 0.88, 95% CI 0.53 to 1.4 for METAVIR F3 or F4 and RR 0.97, 95% CI 0.87 to 1.1 for METAVIR F0 to F2), and baseline viral load (RR 0.99, 95% CI 0.87 to 1.1 for HCV-RNA >600,000 IU/mL and RR 0.93, 95% CI 0.79 to 1.1 for HCV-RNA ≤600,000 IU/mL).[22] However, overall absolute SVR rates across dual therapy regimens were lower in older (38 percent) versus younger (53–56 percent) patients, Black patients (23–26 percent) versus white patients (53–55 percent), patients with F3 or F4 (21–24 percent) versus F0 to F2 fibrosis (42–44 percent), and patients with high (35–36 percent) versus low viral load (61–66 percent). The relative risk estimate was somewhat lower for patients 75 to 85 kg (RR 0.80, 95% CI 0.65 to 0.98) than other weight groups (RR ranged from 0.89 to 1.1) but the confidence intervals for the estimates overlapped, and results were potentially confounded by differential ribavirin dosing according to weight.

Four smaller (n=183 to 431) trials found no clear differences in relative risk estimates in patients stratified by genotype, although rates of SVR were lower by 24–42 percent for genotype 1 infection than genotypes 2 and 3 infection.[20, 21, 23, 56] One of these trials also found no clear differences in relative risk estimates in patient groups stratified by presence or absence of cirrhosis, or high or low viral load.[20]

Two trials that compared different durations of therapy in patients with genotype 2 or 3 infection reported risk estimates for SVR stratified by patient characteristics.[68, 70] They found no differences in relative risk estimates for 16 weeks of therapy compared with 24 weeks of therapy when patients were stratified according to fibrosis stage, body mass index, sex, or age (all RR estimates close to 1). Although the pooled estimates suggested lower likelihood of SVR with 16 compared with 24 weeks of therapy in patients with HCV-RNA >800,000 IU/mL (pooled RR 0.84, 95% CI 0.77 to 0.93, I^2=0%) and no difference in those with a viral load less than 800,000 IU/mL (pooled RR 0.99, 95% CI 0.93 to 1.06, I^2=0%), the estimates were imprecise and the confidence intervals overlapped.[68, 70]

Another large trial that compared 48 weeks with 24 weeks of dual therapy with pegylated interferon alfa-2a plus ribavirin found similar rates of SVR in patients with genotype 2 or 3 infection regardless of baseline viral load.[63]

Triple Therapy With Pegylated Interferon (Alfa-2a or Alfa-2b), Ribavirin, and Boceprevir or Telaprevir

Boceprevir

Two trials (n=520 and 1097) of triple therapy with boceprevir for a total of 48 weeks (4 weeks dual therapy lead-in with pegylated interferon alfa-2b plus ribavirin followed by the addition of 44 weeks of boceprevir) versus 48 weeks of dual therapy with pegylated interferon alfa-2b plus ribavirin found no difference in relative risk estimates for SVR in men (pooled RR 1.8, 95% CI 1.6 to 2.2, I^2=0%) versus women (pooled RR 1.9, 95% CI 1.3 to 2.8, I^2=57%).[30, 32] There was also no clear difference in the relative risk estimates for Black (pooled RR 2.5, 95% CI 1.5 to 4.2, I^2=0%) and non-Black patients (pooled RR 1.7, 95% CI 1.5 to 2.0, I^2=0%), although the overall absolute SVR rate across regimens was lower in Black (53 percent) compared with non-Black (63–78 percent) patients. The relative risk estimate was higher for patients with HCV-RNA viral load >600-800,000 IU/mL at baseline (pooled RR 2.0, 95% CI 1.7 to 2.3, I^2=0%) than those with a lower viral load (pooled RR 1.3, 95% CI 1.0 to 1.5, I^2=0%), with an absolute SVR rate of 63–73 percent in individuals with a high viral load and 85–91 percent in individuals with a lower viral load. Although triple therapy with boceprevir was associated with no difference in likelihood of SVR in the subgroup of patients with advanced fibrosis or cirrhosis, the number of patients randomized to triple therapy was small (n=30) and the estimate was imprecise (pooled RR 1.1, 95% CI 0.55 to 2.1, I^2=0%).

Telaprevir

One trial (n=1088) of response-guided duration triple therapy with telaprevir (12 weeks of pegylated interferon alfa-2a, ribavirin, and telaprevir followed by response-guided duration dual therapy) versus 48 weeks of dual therapy with pegylated interferon alfa-2a plus ribavirin found no clear differences in relative risk estimates in patients stratified by age, sex, race, baseline fibrosis status, or body mass index.[51] Absolute SVR rates were higher in patients younger than 45 years versus those older (83 vs. 70 percent), white patients versus Black patients (75 vs. 62 percent), patients with no or minimal fibrosis versus those with advanced fibrosis or cirrhotics (81 vs. 62 percent), and those with body mass index <25 versus those with higher body mass index (83 vs. 69 percent). Triple therapy was more effective than dual therapy in patients with a baseline HCV-RNA viral load ≥800,000 IU/mL (RR 2.0, 95% CI 1.7 to 2.4), but there was no difference in likelihood of achieving an SVR in those with a baseline viral load <800,000 IU/mL (RR 1.1, 95% CI 0.93 to 1.3), with triple therapy associated with similar absolute SVR rates across viral load strata (78 and 74 percent). In a second trial, SVR rates were similar among men (76 percent) and women (70 percent), age less than or greater than 50 (85 vs. 67 percent), and high versus low baseline viral load (69 vs. 74 percent).[86]

Another trial of patients with an extended rapid virologic response on triple therapy with telaprevir reported similar, high (80–90 percent) SVR rates with either 12 versus 36 additional weeks of dual therapy in patients stratified by race, body mass index, or fibrosis stage.[87]

Key Question 3a. What are the comparative harms associated with antiviral treatments?

- Dual therapy with pegylated interferon alfa-2b was associated with slightly greater risk of headache (three trials, pooled RR 1.1, 95% CI 1.1 to 1.2, I^2=0%), lower risk of serious

adverse events (two trials, pooled RR 0.76, 95% CI 0. 71 to 0. 88, I^2=0%), lower risk of neutropenia (five trials, pooled RR 0.61, 95% CI 0.46 to 0.83, I^2=38%), and lower risk of rash (two trials, pooled RR 0.79, 95% CI 0.71 to 0.88, I^2=0%) than dual therapy with pegylated interferon alfa-2a plus ribavirin, with no differences in withdrawals due to adverse events (strength of evidence: moderate).

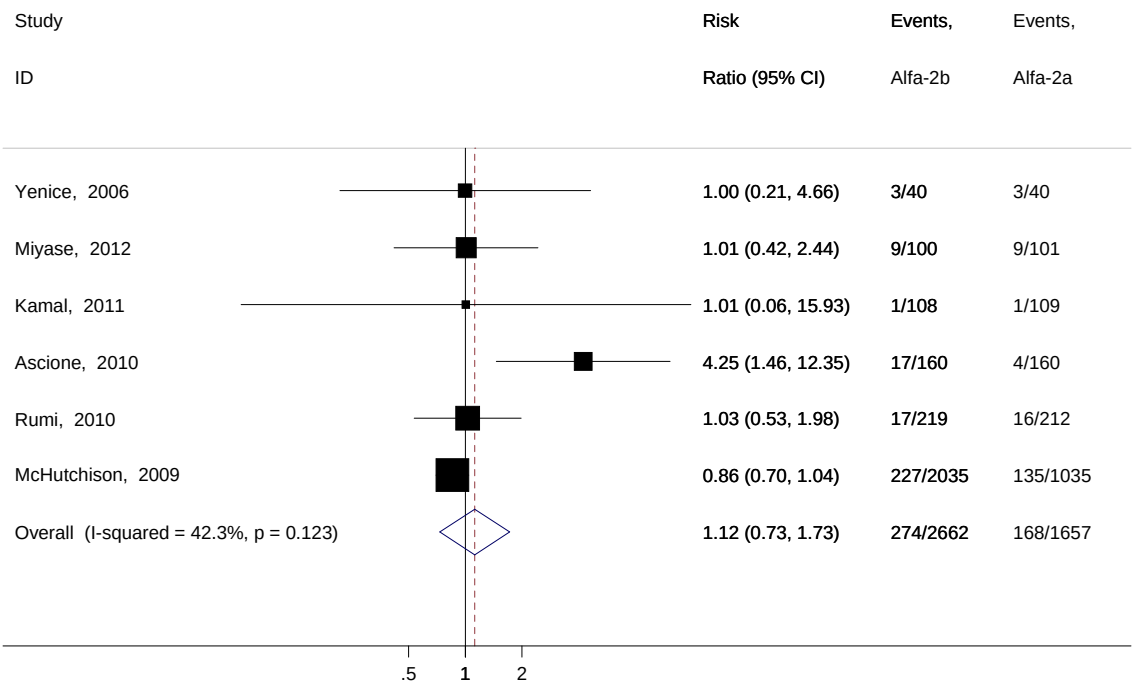
- Triple therapy with boceprevir for 48 weeks (pegylated interferon alfa-2b plus ribavirin for 4 weeks followed by addition of boceprevir for 44 weeks) was associated with increased risk of neutropenia (two trials, pooled RR 1.8, 95% CI 1.5 to 2.3, I^2=0%), dysgeusia (two trials, pooled RR 2.5, 95% CI 2.0 to 3.2, I^2=0%), anemia (two trials, pooled RR 2.0, 95% CI 1.4 to 2.8, I^2=0%), and thrombocytopenia (two trials, pooled RR 3. 2, 95% CI 1. 2 to 8.2, I^2=0%) than dual therapy with pegylated interferon alfa-2b plus ribavirin. The incidence of anemia was about 25 percent with triple therapy and the incidence of neutropenia about 33 percent, with severe anemia in 4–5 percent and severe neutropenia in 8–15 percent. There was no difference in the overall risk of withdrawal due to adverse events (strength of evidence: moderate).
- In two trials, there were no statistically significant differences between a 12-week regimen of triple therapy with pegylated interferon alfa-2a, ribavirin, and telaprevir versus dual therapy with pegylated interferon alfa-2a plus ribavirin in risk of any assessed adverse event (strength of evidence: moderate).
- In three trials, a 24-week regimen of triple therapy with telaprevir (pegylated interferon alfa-2a or alfa-2b, ribavirin, and telaprevir for 12 weeks followed by pegylated interferon alfa-2a plus ribavirin for 12 weeks) was associated with increased risk of anemia (three trials, pooled RR 1.3, 95% CI 1.1 to 1.5, I^2=0%) and rash (three trials, pooled RR 1.4, 95% CI 1.1 to 1.7, I^2=0%) versus dual therapy with pegylated interferon alfa-2a plus ribavirin for 48 weeks. Among patients randomized to the 24-week telaprevir regimen, one to two-thirds experienced rash (7–10 percent experienced severe rash) and 27–91 percent experienced anemia (4–11 percent experienced severe anemia). There was no difference in risk of withdrawal due to adverse events (strength of evidence: moderate).
- In one trial, response-guided triple therapy with telaprevir (pegylated interferon alfa-2a, ribavirin, and telaprevir for 8 or 12 weeks followed by response-guided duration pegylated interferon alfa-2a and ribavirin) was associated with increased risk of withdrawal due to adverse events (27 vs. 7.2 percent, RR 3.8, 95% CI 2.6 to 5.7), anemia (38 vs. 19 percent, RR 2.0, 95% CI 1.6 to 2.5), any rash (36 vs. 24 percent, RR 1.5 , 95% CI 1.2 to 1.8), and severe rash (5 vs. 1 percent, RR 4.6, 95% CI 1.6 to 13) versus dual therapy with pegylated interferon alfa-2a plus ribavirin for 48 weeks (strength of evidence: low).

Dual Therapy With Pegylated Interferon Alfa-2b Plus Ribavirin Compared With Dual Therapy With Pegylated Interferon Alfa-2a Plus Ribavirin

Seven head-to-head randomized trials of dual therapy with pegylated interferon alfa-2b plus ribavirin versus dual therapy with pegylated interferon alfa-2a plus ribavirin reported adverse events (Table 8, Appendix H: Evidence Table 1 and Evidence Table 2).[20-23, 53, 57, 58] Characteristics of the trials were described earlier (see Key Question 2a).

There was no difference between dual therapy with pegylated interferon alfa-2b and dual therapy with pegylated interferon alfa-2a in risk of withdrawal due to adverse events (six trials, pooled RR 1.1, 95% CI 0.73 to 1.7, I^2=42%) (Figure 12).[20, 22, 23, 53, 57, 58] In the largest study, the IDEAL trial, about 13 percent of patients randomized to dual therapy with standard doses of pegylated interferon alfa-2b or pegylated interferon alfa-2a plus ribavirin withdrew due to adverse events, versus about 10 percent in those randomized to low-dose pegylated interferon alfa-2b plus ribavirin.[22] Excluding the low-dose pegylated interferon alfa-2b arm of IDEAL from the pooled analysis resulted in a similar pooled estimate (six trials, RR 1.2, 95% CI 0.8 to 1.7, I^2=30%).[20, 22, 23, 53, 57, 58] One outlier trial found dual therapy with pegylated interferon alfa-2b associated with substantially higher risk of withdrawal due to adverse events than dual therapy with pegylated interferon alfa-2a (RR 4.2, 95% CI 1.5 to 12).[20] Excluding it eliminated statistical heterogeneity, but the association remained non–statistically significant (five trials, pooled RR 0.88, 95% CI 0.7 to 1.1, I^2=0%).[22, 23, 53, 57, 58]

Figure 12. Withdrawal due to adverse events: Dual therapy with pegylated interferon alfa-2b plus ribavirin versus dual therapy with pegylated interferon alfa-2a plus ribavirin



Two trials found dual therapy with pegylated interferon alfa-2b plus ribavirin associated with lower risk of serious adverse events than dual therapy with pegylated interferon alfa-2a plus ribavirin (pooled RR 0. 76, 95% CI 0. 61 to 0.95, I^2=0%).[22, 23] In the IDEAL trial, serious treatment-related adverse events occurred in about 4 percent of patients.[22] There were no statistically significant differences between regimens in risk of anemia, thrombocytopenia, depression, fatigue, myalgia, or flulike symptoms (Table 8). Dual therapy with pegylated interferon alfa-2b plus ribavirin was associated with slightly greater risk of headache (three trials, pooled RR 1. 1, 95% CI 1.1 to 1. 2, I^2=0%)[20, 22, 57] and slightly lower risk of rash (two trials,

pooled RR 0.79, 95% CI 0.71 to 0.88, I^2=0%)[22, 57] and neutropenia (five trials, pooled RR 0.61, 95% CI 0.46 to 0.83, I^2=38%)[20-23, 57] than dual therapy with pegylated interferon alfa-2a plus ribavirin. In the IDEAL trial, dual therapy with either pegylated interferon (alfa-2a or alfa-2b) was associated with fatigue in about 65 percent of patients, headache in about 45 percent, nausea in about 40 percent, and myalgia in about 25 percent, neutrophil count <500/mm^3 in about 5 percent, and hemoglobin <8.5 g/dL in about 3 percent.[22]

Table 8. Harms: Dual therapy with pegylated interferon alfa-2b plus ribavirin versus dual therapy with pegylated interferon alfa-2a plus ribavirin

Outcome	Relative Risk (95% CI); I^2	Number of Trials
All-cause mortality	RR 0.85 (95% CI 0.26 to 2.8)	1[22]
Serious adverse events	RR 0.76 (0. 61 to 0.95); I^2=0%	2[22, 23]
Withdrawal due to adverse events	RR 1.1 (0.73 to 1.7); I^2=42%	6[20, 22, 23, 53, 57, 58]
Neutropenia	RR 0.61 (0.46 to 0.83); I^2=38%	5[20-23, 57]
Anemia	RR 0.97 (0.72 to 1.3); I^2=64%	4[20, 22, 23, 57]
Thrombocytopenia	RR 0.87 (0.59 to 1.3); I^2=0%	3[20, 23, 57]
Depression	RR 1.1 (0.92 to 1.2); I^2=0%	3[20, 22, 57]
Fatigue	RR 1.0 (0.96 to 1.1): I^2=7%	3[20, 22, 57]
Flulike symptoms	RR 0.98 (0.85 to 1.1)	1[23]
Headache	RR 1.1 (1.1 to 1.2); I^2=0%	3[20, 22, 57]
Myalgia	RR 1.1 (0.86 to 1.5); I^2=33%	3[20, 22, 57]
Rash	RR 0.79 (0.71 to 0.88); I^2=0%	2[22, 57]

RR = relative risk

Excluding data from the IDEAL trial[22] for patients who received pegylated interferon alfa-2b at a lower dose of 1.0 mcg/kg/week had little effect on pooled results, except the pooled estimate for depression became greater and statistically significant in favor of dual therapy with pegylated interferon alfa-2a (three trials, pooled RR 1.2, 95% CI 1.0 to 1.4, I^2=0%)[20, 22, 57] There was also reduced statistical heterogeneity in the analysis of neutropenia, but the risk estimate was unchanged (five trials, pooled RR 0.64, 95% CI 0.51 to 0.80, I^2=0%).[20-23, 57] Excluding two poor-quality trials[21, 58] from the pooled analysis also had little effect on estimates.

Trials of Triple Therapy With Pegylated Interferon (Alfa-2a or Alfa-2b), Ribavirin, and Boceprevir or Telaprevir

Five trials of triple therapy with pegylated interferon (alfa-2a or alfa-2b), ribavirin, and either boceprevir or telaprevir versus dual therapy with pegylated interferon (alfa-2a or alfa-2b) plus ribavirin without a protease inhibitor in patients with genotype 1 infection reported adverse events (Appendix H: Evidence Table 3 and Evidence Table 4).[30-32, 85, 86] Characteristics of the trials were described earlier (see Key Question 2a).

Boceprevir

For boceprevir, two trials evaluated a 48-week fixed duration regimen consisting of dual therapy lead-in for 4 weeks with pegylated interferon alfa-2b plus ribavirin, with the addition of boceprevir from weeks 5 through 48.[30, 32] Triple therapy was associated with increased risk of neutropenia (two trials, pooled RR 1.8, 95% CI 1.5 to 2.3, I^2=0%), dysgeusia (two trials, pooled RR 2.5, 95% CI 2.0 to 3.2, I^2=0%), anemia (two trials, pooled RR 2.0, 95% CI 1.4 to 2.8,

I^2=0%), and thrombocytopenia (two trials, pooled RR 3.2, 95% CI 1.2 to 8.2, I^2=0%) versus dual therapy with pegylated interferon alfa-2b plus ribavirin (Table 9). About 25 percent of patients on triple therapy experienced anemia and about 33 percent neutropenia, with an incidence of severe neutropenia (neutrophil count <500 cells per μL) that ranged from 8–15 percent and an incidence of severe anemia (hemoglobin <80 or <85 g/L) of 4–5 percent. In addition, more patients randomized to boceprevir triple therapy used erythropoietin (43 and 87 percent) than those randomized to dual therapy (24 and 33 percent). One of the trials reported similar use of granulocyte stimulating agents with boceprevir triple therapy and dual therapy (8 vs. 6 percent).[32] There were no statistically significant differences between triple therapy and dual therapy in risk of withdrawal due to adverse events, serious adverse events, depression, fatigue, headache, myalgia, chills/rigors, rash, or flulike symptoms (Table 9).

Table 9. Harms: Triple therapy with boceprevir, pegylated interferon alfa-2b, and ribavirin versus dual therapy with pegylated interferon alfa-2b plus ribavirin

Outcome	Triple Therapy With Pegylated Interferon and Ribavirin for 48 Weeks With Boceprevir From Weeks 5 to 48 vs. Dual Therapy for 48 Weeks: Relative Risk (95% CI); I^2	Number of Trials
Serious adverse events	RR 1.4 (0.93 to 2.2)	1[32]
Withdrawal due to adverse events	RR 1.1 (0.77 to 1.4); I^2=0%	2[30, 32]
Neutropenia	RR 1.8 (1.5 to 2.3); I^2=0%	2[30, 32]
Anemia	RR 2.0 (1.4 to 2.8); I^2=0%	2[30, 32]
Thrombocytopenia	RR 3.2 (1.2 to 8.2); I^2=0%),	2[30, 32]
Depression	RR 0.87 (0.65 to 1.2)	1[32]
Fatigue	RR 1.1 (0.82 to 1.5); I^2=82%	2[30, 32]
Flulike symptoms	RR 0.80 (0.58 to 1.1); I^2=27%	2[30, 32]
Headache	RR 1.1 (0.96 to 1.3); I^2=0%	2[30, 32]
Myalgia	RR 0.97 (0.76 to 1.2)	1[32]
Rash	RR 1.1 (0.81 to 1.4)	1[32]
Dysgeusia	RR 2.5 (2.0 to 3.2); I^2=0%	2[30, 32]

RR = relative risk

Telaprevir

For fixed duration triple therapy with telaprevir (administered during the first 12 weeks in combination with pegylated interferon and ribavirin), we focused on 12- or 24-week regimens, as 48 week triple therapy regimens have not been shown to be more effective than 24 weeks.[31, 87] There were no differences between a 12-week regimen of triple therapy with telaprevir versus dual therapy with pegylated interferon alfa-2a plus ribavirin for 48 weeks in risk of serious adverse events, neutropenia, anemia, depression, fatigue, headache, myalgia, chills/rigors, rash, or flulike symptoms (Table 10). Rash was reported in 44–77 percent of patients randomized to 12 weeks of triple therapy with telaprevir, with 6 percent of patients reporting severe rash.[31, 85]

Table 10. Harms: Triple therapy with telaprevir, pegylated interferon (alfa-2a or alfa-2b), and ribavirin versus dual therapy with pegylated interferon (alfa-2a or alfa-2b) plus ribavirin

Outcome	12-Week Regimen With Telaprevir vs. Dual Therapy for 48 Weeks: Relative Risk (95% CI); I^2	Number of Trials	24-Week Regimen With Telaprevir vs. Dual Therapy for 48 Weeks: Relative Risk (95% CI); I^2	Number of Trials
All-cause mortality	No deaths reported	No deaths reported	No deaths reported	No deaths reported
Serious adverse events	RR 1.3 (0.68 to 2.5)	1[85]	RR 1.0, 95% CI 0.50 to 2.0)	1[85]
Withdrawal due to adverse events	RR 1.5 (0.56 to 4.0)	1[85]	RR 1.1 (0.45 to 2.6); I^2=60%	2[85, 86]
Neutropenia	RR 0.11 (0.01 to 1.8)	1[31]	RR 0.81 (0.51 to 1.3); I^2=53%	2[31, 86]
Anemia	RR 1.2 (0.72 to 1.9); I^2=0%	2[31, 85]	RR 1.3 (1.1 to 1.5); I^2=0%	3[31, 85, 86]
Thrombocytopenia	Not reported	Not reported	RR 1.8 (1.2 to 2.5)	1[86]
Depression	RR 0. 90 (0.53 to 1.5); I^2=0%	2[31, 85]	RR 1.0 (0.66 to 1.6); I^2=0%	2[31, 85]
Fatigue	RR 0.94 (0.63 to 1.4); I^2=61%	2[31, 85]	RR 0.96 (0.74 to 1.2); I^2=53%	3[31, 85]
Flulike symptoms	RR 0.76 (0.56 to 1.0); I^2=0%	2[31, 85]	RR 0.87(0.63 to 1.2); I^2=50%	3[31, 85, 86]
Headache	RR 0.87 (0.65 to 1.2); I^2=0%	2[31, 85]	RR 0.83 (0.69 to 1.0); I^2=0%	3[31, 85, 86]
Myalgia	RR 0.71 (0.40 to 1.3); I^2=0%	2[31, 85]	RR 0.76 (0.43 to 1.3); I^2=57%	3[31, 85]
Rash	RR 1.2 (0.92 to 1.7); I^2=0%	2[31, 85]	RR 1.4 (1.1 to 1.7);I^2=0%	3[31, 85, 86]

CI = confidence interval; RR = relative risk

A 24-week regimen of triple therapy with telaprevir was associated with increased risk of anemia (three trials, pooled RR 1.3, 95% CI 1.1 to 1.5, I^2=0%) and increased risk of rash (three trials, pooled RR 1.4, 95% CI 1.1 to 1.7, I^2=0%) versus dual therapy for 48 weeks, but there were no statistically significant differences in risk of serious adverse events, neutropenia, depression, fatigue, headache, chills/rigors, or flulike symptoms (Table 10).[31, 85, 86] Triple therapy was also associated with increased risk of thrombocytopenia, but this outcome was only evaluated in one trial (RR 1.8, 95% CI 1.2 to 2.5).[86] One-third to two-thirds of patients randomized to the 24-week regimen with telaprevir experienced a rash, with the incidence of severe rash ranging from 7−10 percent.[31, 85, 86] The incidence of anemia with telaprevir was 27–91 percent,[31, 85, 86] with two trials[31, 85] reporting severe anemia in 4−9 percent of patients and another trial[86] reporting grade 3 anemia (hemoglobin <8 g/dl) in 11 percent of patients. Two trials found no difference in risk of withdrawal due to adverse events (RR 1.1, 95% CI 0.45 to 2.6, I^2=60%).[85, 86] The third trial did not report withdrawal due to adverse events separately for the 24 week telaprevir regimen, but reported a similar trend towards higher risk of withdrawal due to adverse events for all telaprevir regimens combined (12, 24, or 48 weeks) versus dual therapy (21 vs. 11 percent, RR 2.0, 95% CI 0.97 to 4.1).[31]

One trial evaluated triple therapy with telaprevir for 8 or 12 weeks followed by response-guided dual therapy for 12 or 36 weeks versus dual therapy for 48 weeks.[51] Since the two telaprevir regimens were associated with similar rates of harms, results were combined. The trial found response-guided therapy with telaprevir associated with increased risk of withdrawal due to adverse events (27 vs. 7.2 percent, RR 3.8, 95% CI 2.6 to 5.7), anemia (38 vs. 19 percent, RR

2.0, 95% CI 1.6 to 2.5), any rash (36 vs. 24 percent, RR 1.5, 95% CI 1.2 to 1.8), and severe rash (5 vs. 1 percent, RR 4.6, 95% CI 1.6 to 13).

A trial of extended early virologic responders (undetectable HCV-RNA levels at weeks 4 and 12) to telaprevir triple therapy reported very similar rates of adverse events in patients randomized after 20 weeks of therapy to 4 weeks versus 28 more weeks of dual therapy.[87] The overall incidence of rash was 38 percent (severe rash 5 percent) and the incidence of anemia 42 percent (severe anemia 6 percent).

Key Question 3b. Do these harms differ according to patient subgroup characteristics, including HCV genotype, age, race, sex, stage of disease, or genetic markers?

- No trial of dual therapy with pegylated interferon alfa-2b plus ribavirin versus dual therapy with pegylated interferon alfa-2a plus ribavirin reported harms in patients stratified by factors such as HCV genotype, age, race, sex, stage of disease, or genetic markers. Three trials that restricted enrollment to patients with genotype 1 infection reported risk estimates for risk of harms that were similar to the risk estimates based on all trials (strength of evidence: insufficient).
- No trial evaluated harms associated with triple therapy with pegylated interferon, ribavirin, and boceprevir or telaprevir versus dual therapy with pegylated interferon plus ribavirin in patient subgroups. All trials evaluated patients with genotype 1 infection (strength of evidence: insufficient).

No trial of dual therapy with pegylated interferon alfa-2b plus ribavirin versus dual therapy with pegylated interferon alfa-2a plus ribavirin reported harms in patients stratified by factors such as HCV genotype, age, race, sex, stage of disease, or genetic markers. A subgroup of three trials of dual therapy with pegylated interferon alfa-2a versus pegylated interferon alfa-2b that restricted enrollment to patients with genotype 1 infection reported pooled estimates for risk of harms that were similar to the risk estimates based on all trials.[22, 58, 59] All trials of triple therapy including protease inhibitors restricted enrollment to patients with genotype 1 infection.

Key Question 4. Have improvements in intermediate outcomes (SVR, histologic changes) been shown to reduce the risk or rates of adverse health outcomes from HCV infection?

- A large Veterans Affairs (VA) study that controlled well for potential confounders found an SVR after antiviral therapy associated with lower risk of all-cause mortality versus no SVR (adjusted HR 0.71 [0.60–0.86], 0.62 [0.44–0.87] and 0.51 [0.35–0.75] for genotypes 1, 2, and 3, respectively). Eighteen other cohort studies found an SVR associated with decreased risk of all-cause mortality, liver-related mortality, HCC, and other complications of end-stage liver disease versus no SVR, with stronger effect estimates than the VA study (adjusted HRs generally ranged from around 0.10 to 0.33). However, the studies had methodological shortcomings, including inadequate handling of confounders, and 10 were conducted in Asia (strength of evidence: moderate).
- Nine studies found an SVR associated with greater improvement in measures related to quality of life (generic or disease-specific) 24 weeks after the end of antiviral treatment versus no SVR, with differences averaging less than 5 to 10 points on various SF-36 domains. All studies were poor quality and were characterized by failure to adjust for

confounders, high loss to followup, and failure to blind patients to SVR status (strength of evidence: low).

All-Cause Mortality, Liver-Related Mortality, and Complications Related to Chronic Hepatitis C Virus Infection

Nineteen cohort studies evaluated the association between achieving an SVR following interferon-based antiviral therapy and mortality (all-cause or liver-related) or complications related to chronic HCV infection, such as HCC, ascites, hepatic encephalopathy, or gastrointestinal bleeding, and these 19 studies reported risk estimates adjusted for potential confounders (Table 11, Appendix F, Appendix H: Evidence Table 9).[8, 9, 89-105] Sample sizes ranged from 105 to 16,864 subjects and duration of followup ranged from 3 to 9 years. Ten studies were conducted in Asia.[89, 95-100, 102, 104, 105] Four studies focused on patients who received pegylated interferon (alfa-2a or alfa-2b) plus ribavirin.[8, 9, 91, 94] The others evaluated patients who received nonpegylated interferon plus ribavirin, or either pegylated or nonpegylated interferon monotherapy. Ten studies[8, 89, 92, 97-101, 104, 105] evaluated general populations of HCV patients treated with antiviral therapy (baseline rate of cirrhosis ranged from 3–20 percent) and nine studies[9, 90, 91, 93-96, 102, 103] focused on patients with advanced fibrosis or cirrhosis at the time of antiviral treatment. Six studies[90, 93-96, 102] enrolled patients with cirrhosis only, and the baseline rate of cirrhosis ranged from 21–77 percent in three others.[9, 91, 103]

All studies had methodological shortcomings (Appendix H: Evidence Table 10). Eight studies[92-94, 100, 102-105] were rated poor quality and the remainder fair quality. Although all of the studies reported adjusted risk estimates, only eight[8, 89, 91, 95-98, 101] of the 19 studies evaluated five key potential confounders (age, sex, genotype, viral load, and fibrosis stage). No study clearly described assessment of outcomes blinded to SVR status and only five studies[8, 94, 97, 98, 102] reported the number of patients who met inclusion criteria but were excluded due to missing data or loss to followup.

For general populations of HCV patients treated with antiviral therapy, the largest study (n=16,864) had the fewest methodological shortcomings and was also conducted in the United States. (Appendix H: Evidence Table 11).[8] It adjusted for multiple potential confounders, including age, sex, viral load, presence of cirrhosis, multiple comorbidities, aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels, and others; and stratified results by genotype. In a predominantly male (>95 percent) population of veterans, the study found SVR after antiviral therapy associated with decreased risk of all-cause mortality versus no SVR, after a median followup of 3.8 years (adjusted HR 0.71 [0.60 to 0.86], 0.62 [0.44 to 0.87] and 0.51 [0.35 to 0.75] for genotypes 1, 2, and 3, respectively). Although point estimates showed somewhat smaller effects for genotype 1 compared with genotypes 2 or 3, the confidence intervals for the three genotypes overlapped. The very rapid (within 3 months after assessing for SVR for genotype 3) separation of mortality curves suggests possible residual confounding, given the expected duration required to observe benefits in long-term clinical outcomes. Clinical outcomes other than mortality were not assessed.

Nine other studies also evaluated the association between achieving an SVR and mortality or hepatic complications in general populations of HCV patients (Appendix H: Evidence Table 11).[89, 92, 97-101, 104, 105] One fair-quality study from Scotland found an SVR after antiviral therapy associated with decreased risk of liver-related mortality (adjusted HR 0.22, 95% CI 0.09 to 0.58) and liver-related hospital episodes (adjusted HR 0.22, 95% CI 0.15 to 0.34) versus no SVR.[98] One Australian study (poor quality) found no statistically significant association between

virologic response status (SVR, response-relapse, or nonresponse) and all-cause mortality, liver-related mortality, or HCC, although trends favored the SVR group.[92] The other seven studies (three poor quality), all conducted in Asia, each found an SVR after antiviral therapy associated with substantially lower risk of all-cause mortality, liver-related mortality, or HCC versus no SVR.[89, 97, 99-101, 104, 105] Six studies reported substantially lower risk for all-cause mortality than the U.S. study described above (adjusted HR range 0.12 to 0.39).[89, 97, 100, 101, 104, 105] For liver-related mortality, four studies[89, 97, 100, 104] reported adjusted HRs that ranged from 0.04 to 0.17 and for HCC, four studies reported adjusted HRs that ranged from of 0.12 to 0.36.[89, 99, 101, 105]

Six studies of European or North American populations (two poor quality) evaluated the association between achieving an SVR after antiviral therapy and clinical outcomes in patients with advanced fibrosis and cirrhosis prior to antiviral treatment (Appendix H: Evidence Table 11).[9, 90, 91, 93, 94, 103] One study (fair quality) found an SVR after antiviral therapy associated with decreased risk of all-cause mortality or liver transplantation versus no SVR (adjusted HR 0.17, 95% CI 0.06 to 0.46).[9] Another study (poor quality) found an SVR associated with decreased risk of all-cause mortality (adjusted HR 0.31, 95% CI 0.07 to 1.4).[103] Four studies found an SVR associated with decreased risk of liver-related mortality and HCC versus no SVR (adjusted HRs ranged from 0.12 to 0.27 and from 0.19 to 0.46, respectively).[9, 90, 91, 103] For complications of chronic HCV infection (variably defined), six studies reported adjusted HRs that ranged from 0.13 to 0.38.[9, 90, 91, 93, 94, 103] Results from three Asian studies[95, 96, 102] (one poor quality) were consistent with the North American and European studies. One study[102] found an SVR associated with lower risk of all-cause mortality versus no SVR (adjusted HR 0.07, 95% CI 0.09 to 0.56) and three studies[95, 96, 102] found an SVR associated with lower risk of HCC versus no SVR (adjusted HR range 0.18 to 0.40).

One study stratified results according to presence or absence of cirrhosis of baseline. Although effects of an SVR versus no SVR on all-cause mortality appeared more favorable in patients with cirrhosis compared with those without cirrhosis, estimates were imprecise and confidence intervals overlapped substantially, precluding strong conclusions.[104]

The only study to evaluate the association between improvement in histological outcomes and clinical outcomes did not meet inclusion criteria because it did not report adjusted risk estimates.[106] In 96 patients with chronic HCV infection and cirrhosis, it found regression of cirrhosis (defined as a decrease in METAVIR fibrosis score from 4 to $\leq$2) after interferon-based therapy associated with decreased risk of liver-related events (ascites, hepatic encephalopathy, variceal bleeding, spontaneous bacterial peritonitis, HCC, or liver transplantation) or death (0 vs. 4 events/100 patients-years, p=0.002) after a median followup of 10.5 years. Transplantation-free survival was 100 percent in patients with regression of cirrhosis compared with 74 percent in those without regression (p=0.02). In addition to failure to analyze potential confounders, the study only included patients who underwent a post-treatment biopsy, which could have resulted in selection bias, and cirrhosis regression only occurred in 13 patients, resulting in low precision.

Table 11. Sustained virologic response and clinical outcomes

Author Country N Quality	Comparison Definition of Sustained Virologic Response	Population Characteristics	Treatments	Results
Arase, 2007[89] Japan N=500 Quality: Fair	SVR vs. no SVR SVR=Undetectable HCV-RNA 6 months after completion of long-term IFN therapy	SVR (n=140) vs. no SVR (n=360) Mean age (years): 63 vs. 64 (p=0.07) Female: 41% vs. 53% (p=0.01) Race: Not reported Genotype 1b: 34% vs. 71% (p<0.0001) Viral load (kIU/ml): 172 vs. 661 (p<0.0001) Cirrhosis (Knodell F4): 9% vs. 16% (p=0.009)	Interferon-2a or Interferon-2b monotherapy: 94% Interferon plus ribavirin combination therapy: 6%	SVR vs. no SVR HCC: Adjusted HR 0.19 (0.08-0.45) All-cause mortality: Adjusted HR 0.39 (0.16-0.93) Liver-related mortality: Adjusted HR 0.13 (0.03-0.59)
Backus, 2011[8] U.S. N=16,864 Quality: Fair	SVR vs. no SVR SVR=Undetectable HCV-RNA 6 months after completion of antiviral therapy	SVR vs. no SVR (genotypes 1 [n=12,166], 2 [n=2904], and 3 [n=1794], respectively) Mean age (years): 51 vs. 52, 53 vs. 53. and 51 vs. 51 Female: 5% vs. 4%, 4% vs. 3%, and 4% vs. 3% Non-White: 40% vs. 51%, 33% vs. 31%, and 30% vs. 29% Genotype: Results stratified by genotype Viral load ≥500,000 IU/mL: 70% vs. 82%, 78% vs. 83%, and 64% vs. 68% Cirrhosis: 9% vs. 15%, 7% vs. 12%, and 12% vs. 20%	Pegylated interferon (alfa-2a or alfa-2b) plus ribavirin	SVR vs. no SVR (genotypes 1, 2, and 3, respectively) All-cause mortality: Adjusted HR 0.71 (0.60-0.86), 0.62 (0.44-0.87), and 0.51 (0.35-0.75)
Bruno, 2007[90] Italy N=883 Quality: Fair	SVR vs. no SVR SVR=Undetectable HCV-RNA 6 months after completion of antiviral therapy	SVR (n=124) vs. no SVR (n=759) Mean age (years): 53 vs. 44 (p=0.004) Female: 27% vs. 38% (p<0.001) Non White: 0 (0%) vs. 0 (0%) Race: Not reported Genotypes 1 and 4: 37% vs. 63% (p<0.001) Viral load: Not reported Cirrhosis: All (inclusion criterion)	Interferon monotherapy	SVR vs. no SVR Ascites, encephalopathy, or gastrointestinal bleeding: Not calculated, 0 events/1061 person-years vs. 107 events/5703 person-years (1.88 events/100 person-years) HCC: Adjusted HR 0.39 (0.17-0.88) Liver-related mortality: 0.14 (0.04-0.59)
Cardoso, 2010[91] France N=307 Quality: Fair	SVR vs. no SVR SVR=Undetectable HCV-RNA 6 months after completion of antiviral therapy	SVR (n=103) vs. no-SVR (n=204) Mean age (years): 55 vs. 55 (p=0.93) Female: 30% vs. 34% (p=0.51) Race: Not reported Genotype 1: 36% vs. 72% (p<0.001) Viral load (log_{10} l/ml): 5.5 vs. 5.7 (p=0.08) Cirrhosis (METAVIR F4): 53% vs. 61% (p=0.19)	Pegylated interferon (alfa-2a or alfa-2b) and ribavirin: 252 (82%) Pegylated interferon monotherapy: 22 (7%) Nonpegylated interferon with or without ribavirin: 33 (11%)	SVR vs. no SVR HCC: Adjusted HR 0.33 (0.23-0.89) Ascites or variceal bleeding: Adjusted HR 0.21 (0.05-0.92) Liver-related mortality: Adjusted HR 0.27 (0.08-0.95)

Table 11. Sustained virologic response and clinical outcomes (continued)

Author Country N Quality	Comparison Definition of Sustained Virologic Response	Population Characteristics	Treatments	Results
Coverdale, 2004[92] Australia N=343 Quality: Poor	SVR vs. response relapse vs. nonresponse SVR=Undetectable HCV-RNA on at least 2 occasions at least 2 years after completion of therapy	Demographics for all treated patients (not reported by SVR status) Median age (years): 37 Female: 33% Race: Not reported Genotype 1: 38% Viral load: Not reported Median fibrosis score (Scheuer): 2	Interferon-2a or Interferon-2b	SVR vs. response-relapse vs. nonresponse Liver-related complications (hepatic decompensation, complications of portal hypertension, HCC, liver transplantation, and liver-related mortality) at 10 years: Not statistically significant in multivariate analysis, adjusted HR not reported (p=0.06) HCC at 10 years: Not statistically significant in multivariate analysis, adjusted HR and p value not reported Liver transplant or liver-related death at 10 years: Not statistically significant in multivariate analysis, adjusted HR not reported (p=0.20)
El Braks, 2007[93] France N=113 Quality: Poor	SVR vs. no SVR SVR=Undetectable HCV-RNA 6 months after completion of antiviral therapy	SVR (n=37) vs. no SVR (n=76) Mean age (years): 51 vs. 56 (p=0.02) Female: 16% vs. 50% (p=0.0005) Race: Not reported HCV genotype 1: 36% vs. 73% (p=0.0001) Viral load: Not reported Cirrhosis: All (inclusion criterion)	Interferon monotherapy: 35/113 (31%) Interferon + ribavirin: 40/113 (35%) Pegylated interferon + ribavirin: 38/113 (34%)	SVR (n=37) vs. no SVR (n=76) Clinical events (HCC, ascites, hepatic encephalopathy, or death): Adjusted HR 0.14 (0.04-0.45)
Fernandez-Rodriguez, 2010[94] Spain N=509 Quality: Poor	SVR vs. no SVR SVR=Undetectable HCV-RNA 6 months after completion of antiviral therapy	SVR (n=174) vs. no SVR (n=394) Mean age (years): 51 vs. 52 (p=0.31) Female: 69% vs. 73%, p=0.37 Genotype 1: 24% vs. 55% (p=0.001) Race: Not reported Viral load (10^6 IU/ml): 1.7 vs. 3.1 (p=0.001) Cirrhosis: All (inclusion criterion)	Pegylated interferon-2a or 2b	SVR vs. no SVR Combined clinical endpoint (hepatic decompensation, upper gastrointestinal bleeding secondary to rupture of esophageal or gastric varices, HCC, liver transplantation, and liver-related or liver-unrelated mortality): Adjusted HR 0.38 (0.18-0.76)

Table 11. Sustained virologic response and clinical outcomes (continued)

Author Country N Quality	Comparison Definition of Sustained Virologic Response	Population Characteristics	Treatments	Results
Hasegawa, 2007[95] Japan N=105 Quality: Fair	SVR vs. no SVR SVR=Sustained undetectable HCV-RNA after completion of antiviral therapy (duration of undetectability not specified)	SVR (n=48) vs. no SVR (n=58) Age >56 years: 60% vs. 55% (p>0.05) Female: 35% vs. 34% (p>0.05) Race: Not reported Genotype 1b: 19% vs. 21% (p>0.05) Viral load ≥100 KIU/ml or ≥1 mg/mL: 25% vs. 62% (p<0.001) Cirrhosis: All (inclusion criterion)	Natural or recombinant interferon alfa: 67% Natural interferon-beta: 31% Both: 1.6%	SVR vs. no SVR HCC: Adjusted HR 0.18 (0.04-0.81)
Hung, 2006[96] Taiwan N=132 Quality: Fair	SVR vs. no SVR SVR=Undetectable HCV-RNA 6 months after completion of antiviral therapy	SVR (n=73) vs. no SVR (n=59) Mean age (years): 55 vs. 58 (p=0.07) Female: 43% vs. 54% (p=0.12) Race: Not reported Genotype 1b: 27% vs. 78% (p<0.001) Viral load ≥2 x 10^6 copies/ml: 21% vs. 51% (p<0.001) Cirrhosis: 100% (inclusion criterion)	Interferon-2b plus ribavirin	SVR vs. no SVR HCC: Adjusted HR 0.28 (0.09-0.92)
Imazeki, 2003[97] Japan N=459 Quality: Fair	SVR vs. no SVR SVR=Undetectable HCV-RNA 6 months after completion of antiviral therapy	Demographics for all treated patients (not reported by SVR status) Mean age (years): 49 Female: 36% Race: Not reported Genotype 1: 74% Viral load: Not reported Cirrhosis (Desmet F4): 13%	Interferon-2a: 84% Interferon-2b: 12% Both: 4%	SVR vs. no SVR[a] Liver-related mortality: Adjusted HR 0.11 (0.01-0.96) All-cause mortality: Adjusted HR 0.12 (0.01-1.3)
Innes, 2011[98] UK N=1,215 Quality: Fair	SVR vs. no SVR SVR=Undetectable HCV-RNA > 6 months after completion of antiviral therapy	SVR (560) vs. no SVR (655) Mean age (years): 42 overall Female: 34% vs. 28% Non-White: 10% vs. 6% Genotype 1: 19% vs. 50% Viral load: Not reported Cirrhosis: 10% vs. 18%	Pegylated interferon plus ribavirin: 61% Pegylated interferon monotherapy: 1% Interferon plus ribavirin: 21% Interferon monotherapy: 18%	SVR vs. no SVR Liver-related mortality: Adjusted HR 0.22 (0.09-0.58) Liver-related hospital episode: Adjusted HR 0.22 (0.15-0.34)

Table 11. Sustained virologic response and clinical outcomes (continued)

Author Country N Quality	Comparison Definition of Sustained Virologic Response	Population Characteristics	Treatments	Results
Izumi 2005[99] Japan N=495 Quality: Fair	SVR vs. no SVR SVR=Undetectable HCV-RNA 6 months after completion of antiviral therapy	Demographics for patients treated with interferon monotherapy and interferon plus ribavirin combination therapy, respectively (not reported by SVR status) Mean age (years): 52 and 58 Female: 43% and 44% Race: Not reported Genotype 1b: 71% and 80% Median viral load (kIU/ml): 470 and 680 Cirrhosis: 7% and 2%	Interferon monotherapy: 69% Interferon-2b plus ribavirin combination therapy: 34%	SVR vs. no SVR HCC: Adjusted HR 0.36 (0.04-0.83)
Kasahara 2004[100] Japan N=2,698 Quality: Poor	SVR vs. no SVR SVR=Undetectable HCV-RNA 6 months after completion of antiviral therapy	SVR (n=738) vs. no-SVR (n=1930) Median age (years): 51 vs. 54 (p=0.12) Female: 31% vs. 37% (p=0.32) Race: Not reported Genotype 1: Not reported Viral load: Not reported Cirrhosis (Desmet F4): 3.0% vs. 5.4% (p=0.34)	Interferon	SVR vs. no SVR Liver-related mortality: Adjusted HR 0.04 (0.005-0.30) All-cause mortality: Adjusted HR 0.14 (0.06-0.35)
Maruoka 2012[101] Japan N=577 Quality: Fair	SVR vs. no SVR SVR=Undetectable HCV-RNA >6 months after completion of antiviral therapy	For all treated patients (not reported by SVR status) Mean age (years): 50 Female: 36% Non-White: Not reported Genotype 1: 73% Viral load high (≥100 KIU, 100 kc, 1.0 Meq, 10^4/50 microL, or 30 core antigens): 69% Cirrhosis: 10%	Interferon-alfa or -beta monotherapy: 83% Interferon-alfa or -beta sequential therapy: 3.3% Interferon-alfa plus ribavirin combination therapy: 14%	SVR vs. no SVR[a] All-cause mortality: Adjusted HR 0.20 (0.08-0.54) HCC: Adjusted HR: 0.12 (0.04-0.40)

Table 11. Sustained virologic response and clinical outcomes (continued)

Author Country N Quality	Comparison Definition of Sustained Virologic Response	Population Characteristics	Treatments	Results
Morgan, 2010[9] U.S. Name: HALT-C N=526 Quality: Fair	SVR vs. no SVR SVR=Undetectable HCV-RNA 6 months after completion of antiviral therapy	SVR (n=140) vs. breakthrough/relapse (n=77) vs. no SVR (n=309) Mean age (years): 49 vs. 49 vs. 50 (p=0.23) Female: 24% vs. 26% vs. 30% (p=0.30) Non-White: 20% vs. 20% vs. 32% (p=0.001) Genotype 1: 72% vs. 86% vs. 94% (p<0.0001) Viral load: Not reported Cirrhosis (Ishak 5 or 6): 21% vs. 31% vs. 43% (p<0.0001)	Pegylated interferon-2a-180 µg/week + ribavirin 1000-12000 mg/day for 24weeks	SVR vs. no SVR All-cause mortality or liver transplantation: Adjusted HR 0.17 (0.06-0.46) Any liver-related outcome (decompensated liver disease [ascites, variceal bleeding, hepatic encephalopathy, spontaneous bacterial peritonitis], HCC, liver transplantation, liver-related mortality): Adjusted HR 0.15 (0.06-0.38) Decompensated liver disease: Adjusted HR 0.13 (0.03-0.53) HCC: Adjusted HR 0.19 (0.04-0.80) Liver-related mortality or liver transplantation: Adjusted HR 0.12 (0.03-0.48)
Shiratori, 2005[102] Japan N=271 Quality: Poor	SVR vs. no SVR SVR=Undetectable HCV-RNA 6 months after completion of antiviral therapy	For all treated patients (not reported by SVR status) Mean age (years): 57 Female: 62% Race: Not reported Genotype 1: 75% Viral load (log_{10} copies/ml): 5.8 Cirrhosis: 100% (inclusion criterion)	Interferon alfa-2a: 58% Natural interferon alfa: 42%	SVR vs. no SVR[a] HCC: Adjusted HR 0.40 (0.18-0.89) All-cause mortality: Adjusted HR 0.07 (0.01-0.56)
Veldt, 2007[103] Europe and Canada N=479 Quality: Poor	SVR vs. no SVR SVR=Undetectable HCV-RNA 6 months after completion of antiviral therapy	SVR (n=142) vs. no-SVR (n=337) Mean age (years): 48 vs. 49 (p=0.45) Female: 27% vs. 32% (p=0.23) Race: Not reported Genotype 1: 39% vs. 67% (p<0.001) Viral load ($x10^5$ IU/mL): 8.5 vs. 8.0 (p=0.75) Cirrhosis (Ishak 5 or 6): 71% vs. 77% (p=0.45)	Interferon monotherapy: 27% Interferon and ribavirin: 27% Pegylated interferon monotherapy: 2.1% Pegylated interferon and ribavirin: 43%	SVR vs. no SVR Any event (death, liver failure, and HCC): Adjusted HR 0.20 (0.07-0.58) All-cause mortality: Adjusted HR 0.31 (0.07-1.4) Liver-related mortality: Adjusted HR 0.19 (0.02-1.4) HCC: Adjusted HR 0.46 (0.12-1.70)
Yoshida, 2002[104] Japan N=459 Quality: Poor	SVR vs. no SVR SVR=Undetectable HCV-RNA 6 months after completion of antiviral therapy	SVR (817) vs. non-SVR (1613) Mean age (years): 48 vs. 51 Female: 30% vs. 40% Race: Not reported Genotype: Not reported Viral load: Not reported Cirrhosis (Desmet F4): 6.5% vs. 11%	Interferon-alfa: 84% Interferon-beta: 14% Both: 2%	SVR vs. no SVR[a] Liver-related mortality: Adjusted HR 0.13 (0.02-0.66) All-cause mortality Adjusted HR 0.32 (0.12-0.86)

Table 11. Sustained virologic response and clinical outcomes (continued)

Author Country N Quality	Comparison Definition of Sustained Virologic Response	Population Characteristics	Treatments	Results
Yu, 2006[105] Taiwan N=1,057 Quality: Poor	SVR vs. no SVR SVR=Undetectable HCV-RNA 6 months after completion of antiviral therapy	For all treated patients (not reported by SVR status) Mean age (years): 47 Female: 40% Race: Not reported Genotype 1: 46% Viral load: Not reported Cirrhosis (criteria not reported): 16%	Interferon monotherapy: 28% Interferon plus ribavirin combination therapy: 72%	SVR vs. no SVR[a] All-cause mortality: Adjusted HR 0.28 (0.08-1.0) HCC: Adjusted HR 0.25 (0.13-0.50)

HCV = hepatitis C virus; HR = hazard ratio; NA = not applicable; HCC = hepatocellular carcinoma; HCV-RNA = hepatitis C virus-ribonucleic acid; SVR = sustained virologic response

[a] Calculated from estimates of SVR compared with untreated and no SVR compared with untreated.

Quality of Life

Nine cohort studies evaluated the association between an SVR following interferon-based antiviral therapy and outcomes related to quality of life (Appendix H: Evidence Table 12).[107-115] Sample sizes ranged from 138 to 1121. Only one study[107] reported adjusted risk estimates, thus we included studies that reported unadjusted risk estimates. Eight studies[107, 108, 110-115] evaluated patients originally enrolled in randomized trials[27, 41, 116-119] of antiviral treatments. Two studies evaluated the same cohort of patients[113, 115] and one study[114] evaluated a cohort of patients included in a study[108] that reported results for three pooled cohorts. One study included patients randomized to pegylated interferon (alfa-2a or alfa-2b) plus ribavirin, although results were not stratified according to what type of antiviral therapy was received.[111] The remainder of the studies evaluated nonpegylated interferon plus ribavirin combination therapy, or nonpegylated or pegylated interferon monotherapy.

All studies were rated poor quality (Appendix H: Evidence Table 13). One study adjusted for potential confounders,[107] one study reported low loss to followup,[112] and one study reported blinding of patients to virologic outcomes.[110] Followup was at 24 weeks after treatment (typically 72 weeks from start of treatment) in all studies. No study evaluated longer term quality of life according to SVR status.

All of the studies found patients with an SVR experienced better improvement from baseline on individual SF-36 domains as well as SF-36 physical and mental component summary scores compared with those with no SVR (Appendix H: Evidence Table 14). In most studies, differences between patients with and without an SVR on various SF-36 domains were less than 5 to 10 points. Patients with an SVR also reported greater improvements from baseline on hepatitis C specific quality of life measures (health distress and limitations) and measures related to fatigue and sleep somnolence. However, results are subject to the methodological limitations of the studies.

One study also found achieving an overall response (defined as SVR plus 2-point improvement in the Histological Activity Index) associated with improved quality of life compared with those without an overall response.[113]

Discussion

The evidence reviewed in this study is summarized in Table 12. The specific domain scores used to determine the overall strength of evidence for each body of evidence are shown in Appendix G.

Antiviral therapy for chronic hepatitis C virus (HCV) infection continues to evolve. No study has evaluated comparative effectiveness of current antiviral regimens on long-term clinical outcomes such as mortality, complications of chronic HCV infection, or quality of life. Such trials would be difficult to design and carry out due to the long time required for complications of chronic HCV infection to develop in most patients. The first pegylated interferon was approved by the FDA only in 2001, and the initial major trials of pegylated interferon plus ribavirin were published in 2002. The protease inhibitors telaprevir and boceprevir were approved only in 2011. Although some trials reported short-term (prior to 1 year after the end of antiviral therapy) mortality,[22, 32, 51] few adverse events were reported, precluding reliable conclusions.

Dual Therapy Regimens With Pegylated Interferon and Ribavirin

In lieu of direct evidence on long-term clinical outcomes, sustained virologic response (SVR) rates are the primary outcome to assess comparative benefits of different antiviral regimens. In trials of treatment-naïve patients, the likelihood of achieving an SVR was slightly lower with dual therapy with pegylated interferon alfa-2b plus ribavirin compared with dual therapy with pegylated interferon alfa-2a plus ribavirin (pooled RR 0.87, 95% CI 0.80 to 0.95; I^2=27%), with a difference in absolute SVR rates of about 8 percentage points.[20-23, 53, 55, 58] Although the largest study, the IDEAL trial, found no difference in SVR rates between dual therapy with pegylated interferon alfa-2a compared with dual therapy with pegylated interferon alfa-2b, excluding the IDEAL trial from pooled analyses resulted in similar effect estimates.[22] Although there was no difference between dual therapy regimens in risk of withdrawals due to adverse events, dual therapy with pegylated interferon alfa-2b plus ribavirin was associated with a lower risk of serious adverse events than dual therapy with pegylated interferon alfa-2a plus ribavirin (pooled RR 0.76, 95% CI 0. 61 to 0.95, I^2=0%), suggesting a potential tradeoff between greater benefits and harms. However, serious adverse events were only reported in two trials;[22, 23] the rate of serious adverse events was relatively low (about 4 percent overall in IDEAL), with an absolute difference of about one percent; and adverse events with antiviral treatments generally resolve following discontinuation of therapy.

Trials found no clear differences in estimates of relative effectiveness of dual therapy with pegylated interferon alfa-2a compared with dual therapy with pegylated interferon alfa-2b in patient subgroups stratified by age, sex, race, viral load, fibrosis stage, and genotype, although absolute response rates were lower in older patients, Black patients, patients with high viral load, patients with more advanced fibrosis or cirrhosis, and genotype 1 infection.[20-23, 56] SVR rates ranged from 24–42 percent lower in patients with genotype 1 infection compared with patients with genotype 2 or 3.

In patients with genotype 2 or 3 infection, dual therapy for 12 to 16 weeks appears to be associated with lower likelihood of SVR compared with dual therapy for 24 weeks, with no differences between 24 weeks and longer courses of therapy.[63, 64, 66, 68, 70, 71] Standard doses of pegylated interferon alfa-2b were more effective than lower doses (no trials compared different

doses of pegylated interferon alfa-2a).[66, 73-77] Although trials comparing different ribavirin doses found no clear differences, with the exception of one trial that found lower doses associated with lower SVR rates in patients with advanced fibrosis,[81] they evaluated different dose comparisons, precluding firm conclusions.[63, 80, 82]

Table 12. Summary of evidence on comparative effectiveness of treatment for hepatitis C

Key Question	Outcome	Summary of Evidence	Strength of Evidence
Key Question 1a What is the comparative effectiveness of antiviral treatment in improving health outcomes in patients with HCV infection?	Long-term clinical outcomes	No evidence.	Insufficient
	Short-term mortality	Three trials that compared current antiviral regimens[a] found no differences in risk of short-term mortality, but reported very few (20 total) events.	Low
	Short-term quality of life	One open-label randomized trial of patients with genotype 4 infection found dual therapy with pegylated interferon alfa-2a plus ribavirin associated with statistically significant, slightly better short-term scores on some quality of life assessments compared with dual therapy with pegylated interferon alfa-2b plus ribavirin.	Low
Key Question 1b How does the comparative effectiveness of antiviral treatment for health outcomes vary according to patient subgroup characteristics?	Any clinical outcome	No evidence.	Insufficient
Key Question 2a What is the comparative effectiveness of antiviral treatments on intermediate outcomes?	***Dual Therapy With Pegylated Interferon Alfa-2b Plus Ribavirin vs. Dual Therapy With Pegylated Interferon Alfa-2a Plus Ribavirin***		
	Sustained virologic response	Seven trials found dual therapy with standard doses of pegylated interferon alfa-2b plus ribavirin associated with lower likelihood of achieving an SVR than pegylated interferon alfa-2a plus ribavirin (pooled RR 0.87, 95% CI 0.80 to 0.95; I^2=27%), with an absolute difference in SVR rates of 8 percentage points (95% CI 3 to 14).	Moderate

Table 12. Summary of evidence on comparative effectiveness of treatment for hepatitis C (continued)

Key Question	Outcome	Summary of Evidence	Strength of Evidence
Key Question 2a What is the comparative effectiveness of antiviral treatments on intermediate outcomes? (continued)	***Dual Therapy With Pegylated Interferon Alfa-2a or Alfa-2b Plus Ribavirin: Duration Effects***		
	Sustained virologic response	Two trials of patients with genotype 2 or 3 infection found no difference in likelihood of achieving an SVR between 48 vs. 24 weeks of dual therapy with pegylated interferon alfa-2a plus ribavirin (pooled RR 0.97, 95% CI 0.84 to 1.1; I^2=43%).	Moderate
	Sustained virologic response	Four trials of patients with genotype 2 or 3 infection found 24 weeks of dual therapy with pegylated interferon (alfa-2a or alfa-2b) more effective than 12-16 weeks for achieving an SVR (pooled RR 1.2, 95% CI 1.0 to 1.3; I^2=80%). Relative risk estimates ranged from 1.0 to 1.3 in the four trials and may have varied in part due to differences across studies in ribavirin dosing.	Moderate
	Sustained virologic response	Three trials of patients with genotype 2 or 3 infection with a rapid virologic response (undetectable HCV-RNA by week 4) found no differences between 24 vs. 12-16 weeks of dual therapy with pegylated interferon (alfa-2a or alfa-2b) plus ribavirin (pooled RR 0.99, 95% CI 0.86 to 1.1, I^2=66%). Relative risk estimates ranged from 0.89 to 1.1.	Moderate
	Dual Therapy With Pegylated Interferon Alfa-2a or Alfa-2b Plus Ribavirin: Dose Effects		
	Sustained virologic response	Six trials of patients with genotype 2 or 3 infection found lower doses of pegylated interferon alfa-2b (0.75-1.0 mcg/kg or 50 mcg) associated with lower likelihood of achieving an SVR than higher doses (1.5 mcg/kg or 100-150 mcg) (pooled RR 0.90; 95% CI 0.81 to 0.99; I^2=20%).	Moderate
	Sustained virologic response	Three trials of patients with genotype 2 or 3 infection who did not specifically have advanced fibrosis or cirrhosis found no clear difference in likelihood of SVR between lower doses of ribavirin (400 or 800 mg flat dose or 600 to 800 mg weight-based dose) vs. higher doses (800 or 1,200 mg flat dose or 800 to 1400 mg weight-based dose).	Moderate
	Sustained virologic response	One small trial of patients with genotype 2 or 3 infection (N=60) and advanced fibrosis or cirrhosis (Ishak stage 4-6) found 600 to 800 mg daily of ribavirin associated with lower likelihood of SVR than 1000 to 1200 mg daily (45 vs. 72 percent, RR 0.62, 95% C I 0.40 to 0.98).	Low

Table 12. Summary of evidence on comparative effectiveness of treatment for hepatitis C (continued)

Key Question	Outcome	Summary of Evidence	Strength of Evidence
Key Question 2a What is the comparative effectiveness of antiviral treatments on intermediate outcomes? (continued)	***Triple Therapy With Pegylated Interferon Alfa-2b, Ribavirin, and Boceprevir vs. Dual Therapy With Pegylated Interferon Alfa-2b Plus Ribavirin***		
	Sustained virologic response	Two trials of patients with genotype 1 infection found triple therapy with boceprevir (pegylated interferon alfa-2b plus ribavirin for 4 weeks, followed by the addition of boceprevir for 44 weeks) associated with higher likelihood of SVR than dual therapy with pegylated interferon alfa-2b plus ribavirin therapy for 48 weeks (pooled RR 1.8; 95% CI 1.6 to 2.1; I^2=0%), with an absolute increase in SVR rate of 31% (95% CI 23 to 39).	Moderate
	Sustained virologic response	One trial of patients with genotype 1 infection found 48 weeks of triple therapy with boceprevir using a low dose of ribavirin (400-1000 mg daily) associated with a non–statistically significant trend toward lower likelihood of SVR compared with 48 weeks of triple therapy with a standard ribavirin dose (800-1400 mg daily) (36% vs. 50%, RR 0.71, 95% CI 0.39 to 1.3).	Low
	Triple Therapy With Pegylated Interferon Alfa-2a or Alfa-2b, Ribavirin, and Telaprevir vs. Dual Therapy With Pegylated Interferon Alfa-2a or Alfa-2b Plus Ribavirin		
	Sustained virologic response	Three trials of patients with genotype 1 infection found triple therapy with telaprevir for 24 weeks (12 weeks of pegylated interferon alfa-2a, ribavirin, and telaprevir followed by 12 weeks of pegylated interferon alfa-2a plus ribavirin) associated with a higher likelihood of SVR than dual therapy with pegylated interferon alfa-2a plus ribavirin for 48 weeks (pooled RR 1.5, 95% CI 1.3 to 1.8; I^2=0%), with an absolute increase in SVR rate of 22% (95% CI 13 to 31).	Moderate
	Sustained virologic response	One trial of patients with genotype 1 infection found no difference in likelihood of SVR between triple therapy with pegylated interferon, ribavirin, and telaprevir for 12 weeks vs. dual therapy with pegylated interferon alfa-2a plus ribavirin for 48 weeks.	Moderate
	Sustained virologic response	One trial of patients with genotype 1 infection found response-guided triple therapy with telaprevir (pegylated interferon alfa-2a, ribavirin, and telaprevir for 8 or 12 weeks followed by a response-guided dual therapy with pegylated interferon alfa-2a plus ribavirin for an additional 12 or 36 weeks) associated with a higher likelihood of SVR than dual therapy with pegylated interferon alfa-2a plus ribavirin for 48 weeks (RR 1.6, 95% CI 1.4 to 1.9), with an absolute increase in SVR rate ranging from 25% to 31%. The regimen with 8 weeks of telaprevir was associated with a slightly lower SVR rate than the 12 week telaprevir regimen (69% vs. 75%).	Low

Table 12. Summary of evidence on comparative effectiveness of treatment for hepatitis C (continued)

Key Question	Outcome	Summary of Evidence	Strength of Evidence
Key Question 2a What is the comparative effectiveness of antiviral treatments on intermediate outcomes? (continued)	***Triple Therapy With Pegylated Interferon Alfa-2a or Alfa-2b, Ribavirin, and Telaprevir vs. Dual Therapy With Pegylated Interferon Alfa-2a or Alfa-2b Plus Ribavirin (continued)***		
	Sustained virologic response	One trial of patients with genotype 1 infection found no difference in likelihood of SVR between triple therapy with telaprevir for 48 weeks (12 weeks of triple therapy with pegylated interferon alfa-2a, ribavirin, and telaprevir followed by 36 weeks of dual therapy with pegylated interferon alfa-2a plus ribavirin) vs. triple therapy with telaprevir for 24 weeks (12 weeks of triple therapy followed by 12 weeks of dual therapy).	Low
	Triple Therapy With Pegylated Interferon Alfa-2a, Ribavirin, and Telaprevir: Dose Effects of Pegylated Interferon Alfa-2a vs. Alfa-2b and Duration Effects		
	Sustained virologic response	One trial of response-guided triple therapy with telaprevir (24 or 48 weeks, based on absence or presence of HCV-RNA from weeks 4 through 20) found similar SVR rates (81–85%) for regimens that varied on telaprevir dose (750 mg tid vs. 1125 mg bid) and type of pegylated interferon (alfa-2a or alfa-2b).	Low
	Sustained virologic response	One trial of patients with an extended rapid virologic response to initial triple therapy with telaprevir reported similar, high (92% and 88%) SVR rates in patients randomized to a total of 24 or 48 weeks of therapy.	Low
Key Question 2b How does the comparative effectiveness of antiviral treatment for intermediate outcomes vary according to patient subgroup characteristics?	***Dual Therapy With Pegylated Interferon Alfa-2b Plus Ribavirin vs. Dual Therapy With Pegylated Interferon Alfa-2a Plus Ribavirin***		
	Sustained virologic response	The largest randomized trial (n=3070) of dual therapy with pegylated interferon alfa-2a plus ribavirin vs. dual therapy with pegylated interferon alfa-2b plus ribavirin found no clear differences in relative risk estimates for SVR in genotype 1 patients stratified by race, sex, age, baseline fibrosis stage, or baseline viral load. Characteristics associated with lower absolute SVR rates across dual therapy regimens were older age, Black race, advanced fibrosis or cirrhosis, and high baseline viral load.	Low
	Sustained virologic response	Four randomized trials of dual therapy with pegylated interferon alfa-2a plus ribavirin vs. dual therapy with pegylated interferon alfa-2b plus ribavirin found no clear differences in relative risk estimates for SVR in patients stratified by genotype. Genotype 1 infection was associated with a lower absolute SVR rate than genotypes 2 or 3.	Moderate

Table 12. Summary of evidence on comparative effectiveness of treatment for hepatitis C (continued)

Key Question	Outcome	Summary of Evidence	Strength of Evidence
Key Question 2b How does the comparative effectiveness of antiviral treatment for intermediate outcomes vary according to patient subgroup characteristics?	***Triple Therapy With Pegylated Interferon Alfa-2b, Ribavirin, and Boceprevir vs. Dual Therapy With Pegylated Interferon Alfa-2b Plus Ribavirin***		
	Sustained virologic response	Two trials of triple therapy with boceprevir for 48 weeks (4 weeks of dual therapy lead-in with pegylated interferon plus ribavirin followed by 44 weeks of triple therapy with pegylated interferon, ribavirin, and boceprevir) found no difference in relative risk estimates for SVR in men vs. women, and no clear difference in relative risk estimates for Black vs. non-Black patients. Black race was associated with a lower absolute SVR rate than non-Black race.	Moderate
	Sustained virologic response	Two trials found triple therapy with pegylated interferon alfa-2b, ribavirin, and boceprevir associated with higher likelihood of achieving SVR than dual therapy with pegylated interferon alfa-2b plus ribavirin in patients with high baseline HCV-RNA viral load (>600,000 or ≥800,000 IU/mL), but found no difference in likelihood of SVR in patients with lower viral load.	Moderate
	Triple Therapy With Pegylated Interferon Alfa-2a or Alfa-2b, Ribavirin, and Telaprevir vs. Dual Therapy With Pegylated Interferon Alfa-2a or Alfa-2b Plus Ribavirin		
	Sustained virologic response	One trial of response-guided triple therapy with telaprevir (12 weeks of pegylated interferon alfa-2a, ribavirin, and telaprevir followed by response-guided dual therapy with pegylated interferon alfa-2a and ribavirin) vs. dual therapy with pegylated interferon plus ribavirin for 48 weeks found no clear differences in relative risk estimates in patients stratified by age, sex, race, baseline fibrosis status, or body mass index. Characteristics associated with lower absolute rates of SVR were older age, Black race, advanced fibrosis or cirrhosis, and higher body mass index. One other trial of 24-week fixed duration triple therapy with telaprevir, pegylated interferon alfa-2b, and ribavirin vs. 48 weeks of dual therapy found no differences in estimates of effect in patients stratified by sex or age.	Moderate (for age and sex) Low (for other factors)
	Sustained virologic response	Two trials of triple therapy with pegylated interferon (alfa-2a or alfa-2b), ribavirin, and telaprevir vs. dual therapy depending reported inconsistent findings for differential relative risk estimates according baseline viral load.	Insufficient

Table 12. Summary of evidence on comparative effectiveness of treatment for hepatitis C (continued)

Key Question	Outcome	Summary of Evidence	Strength of Evidence
Key Question 3a What are the comparative harms associated with antiviral treatments?	***Dual Therapy With Pegylated Interferon Alfa-2b Plus Ribavirin vs. Dual Therapy With Pegylated Interferon Alfa-2a Plus Ribavirin***		
	Harms	Dual therapy with pegylated interferon alfa-2b was associated with slightly greater risk of headache (three trials, pooled RR 1.1, 95% CI 1.1 to 1.2, I^2=0%), and a lower risk of serious adverse events (two trials, pooled RR 0.76; 95% CI 0.71 to 0.88; I^2=0%), lower risk of neutropenia (five trials, pooled RR 0.61, 95% CI 0.46 to 0.83, I^2=38%), and lower risk of rash (two trials, pooled RR 0.79, 95% CI 0.71 to 0.88, I^2=0%) than dual therapy with pegylated interferon alfa-2a plus ribavirin, with no differences in withdrawals due to adverse events.	Moderate
	Triple Therapy With Pegylated Interferon Alfa-2b, Ribavirin, and Boceprevir vs. Dual Therapy With Pegylated Interferon Alfa-2b Plus Ribavirin		
	Harms	Triple therapy with boceprevir for 48 weeks (pegylated interferon alfa-2b plus ribavirin for 4 weeks followed by addition of boceprevir for 44 weeks) was associated with increased risk of neutropenia (two trials, pooled RR 1.8, 95% CI 1.5 to 2.3, I^2=0%), dysgeusia (two trials, pooled RR 2.5, 95% CI 2.0 to 3.2, I^2=0%), anemia (two trials, pooled RR 2.0, 95% CI 1.4 to 2.8, I^2=0%), and thrombocytopenia (two trials, pooled RR 3.2, 95% CI 1.2 to 8.2; I^2=0%) than dual therapy with pegylated interferon alfa-2b plus ribavirin. The incidence of anemia was about 25% with triple therapy and the incidence of neutropenia about 33%, with severe anemia in 4–5% and severe neutropenia in 8–15%.	Moderate
	Triple Therapy With Pegylated Interferon Alfa-2a or Alfa-2b, Ribavirin, and Telaprevir vs. Dual Therapy With Pegylated Interferon Alfa-2a or Alfa-2b Plus Ribavirin		
	Harms	In two trials, there were no statistically significant differences between a 12-week regimen of triple therapy with pegylated interferon alfa-2a, ribavirin, and telaprevir vs. dual therapy with pegylated interferon alfa-2a plus ribavirin in risk of any assessed adverse event.	Moderate

Table 12. Summary of evidence on comparative effectiveness of treatment for hepatitis C (continued)

Key Question	Outcome	Summary of Evidence	Strength of Evidence
Key Question 3a What are the comparative harms associated with antiviral treatments? (continued)	***Triple Therapy With Pegylated Interferon Alfa-2a or Alfa-2b, Ribavirin, and Telaprevir vs. Dual Therapy With Pegylated Interferon Alfa-2a or Alfa-2b Plus Ribavirin (continued)***		
	Harms	In three trials, a 24-week regimen of triple therapy with telaprevir (pegylated interferon alfa-2a or alfa-2b, ribavirin, and telaprevir for 12 weeks followed by pegylated interferon alfa-2a plus ribavirin for 12 weeks) was associated with increased risk of anemia (three trials, pooled RR 1.3, 95% CI 1.1 to 1.5, I^2=0%) and rash (three trials, pooled RR 1.4, 95% CI 1.1 to 1.7; I^2=0%) vs. dual therapy with pegylated interferon alfa-2a plus ribavirin for 48 weeks. Among patients randomized to the 24-week telaprevir regimen, one to two-thirds experienced a rash (7–10% experienced severe rash) and 27–91% experienced anemia (4–11% experienced severe anemia). There was no difference in risk of withdrawal due to adverse events.	Moderate
	Harms	In one trial, response-guided triple therapy with telaprevir (pegylated interferon alfa-2a, ribavirin, and telaprevir for 8 or 12 weeks followed by response-guided duration pegylated interferon alfa-2a and ribavirin) was associated with increased risk of withdrawal due to adverse events (27% vs. 7.2%, RR 3.8, 95% CI 2.6 to 5.7), anemia (38% vs. 19%, RR 2.0, 95% CI 1.6 to 2.5), any rash (36% vs. 24%, RR 1.5 , 95% CI 1.2 to 1.8), and severe rash (5% vs. 1%, RR 4.6, 95% CI 1.6 to 13) vs. therapy with pegylated interferon alfa-2a plus ribavirin for 48 weeks.	Low
Key Question 3b Do these harms differ according to patient subgroup characteristics?	***Dual Therapy With Pegylated Interferon Alfa-2b Plus Ribavirin vs. Dual Therapy With Pegylated Interferon Alfa-2a Plus Ribavirin***		
	Harms	No trial of dual therapy with pegylated interferon alfa-2b plus ribavirin vs. dual therapy with pegylated interferon alfa-2a plus ribavirin reported harms in patients stratified by factors such as HCV genotype, age, race, sex, stage of disease, or genetic markers. Three trials that restricted enrollment to patients with genotype 1 infection reported risk estimates for risk of harms that were similar to the risk estimates based on all trials.	Insufficient
	Triple Therapy With Pegylated Interferon Alfa-2a or Alfa-2b, Ribavirin, and Telaprevir or Boceprevir vs. Dual Therapy With Pegylated Interferon Alfa-2a or Alfa-2b Plus Ribavirin		
	Harms	No trial evaluated harms associated with triple therapy with pegylated interferon, ribavirin, and boceprevir or telaprevir vs. dual therapy with pegylated interferon plus ribavirin in patient subgroups. All trials evaluated patients with genotype 1 infection.	Insufficient

Table 12. Summary of evidence on comparative effectiveness of treatment for hepatitis C (continued)

Key Question	Outcome	Summary of Evidence	Strength of Evidence
Key Question 4 Have improvements in intermediate outcomes been shown to reduce the risk or rates of adverse health outcomes from HCV infection?	Mortality and long-term hepatic complications	A large VA hospital study that controlled well for potential confounders found an SVR after antiviral therapy associated with lower risk of all-cause mortality vs. no SVR (adjusted HR 0.71 [0.60-0.86], 0.62 [0.44-0.87] and 0.51 [0.35-0.75] for genotypes 1, 2, and 3, respectively). Eighteen other cohort studies found an SVR associated with decreased risk of all-cause mortality, liver-related mortality, HCC, and other complications of ESLD compared with no SVR, with stronger effect estimates than the VA study (adjusted HRs generally ranged from around 0.10 to 0.33). However, the studies had methodological shortcomings, including inadequate handling of confounders, and 10 were conducted in Asia.	Moderate
	Short-term quality of life	Nine studies found an SVR associated with greater improvement in measures related to quality of life (generic or disease-specific) 24 weeks after the end of antiviral treatment vs. no SVR, with differences averaging less than 5 to 10 points on various SF-36 domains. All studies were poor-quality and were characterized by failure to adjust for confounders, high loss to followup, and failure to blind patients to SVR status.	Low

CI = confidence interval; ESLD = end-stage liver disease; HCC = hepatocellular carcinoma; HCV = hepatitis C virus; HCV-RNA = hepatitis C virus ribonucleic acid; HR = hazard ratio; I^2=index measures the extent of true heterogeneity in a meta-analysis, RR = relative risk; SVR = sustained virologic response

[a] "Current antiviral treatment regimen" refers to dual therapy with pegylated interferon (alfa-2a or alfa-2b) plus ribavirin, or triple therapy with pegylated interferon (alfa-2a or alfa-2b) plus ribavirin and boceprevir or telaprevir.

Triple Therapy Regimens With Pegylated Interferon, Ribavirin, and Either Boceprevir or Telaprevir

The relatively low SVR rates with pegylated interferon plus ribavirin dual therapy for genotype 1 infection (present in about three-quarters of U.S. patients with HCV infection) has led to ongoing efforts to identify more effective treatment alternatives. Recent trials found triple therapy regimens with pegylated interferon (alfa-2a or alfa-2b), ribavirin, and either boceprevir or telaprevir associated with substantially higher SVR rates than standard dual therapy with pegylated interferon (alfa-2a or alfa-2b) plus ribavirin in treatment-naïve patients with genotype 1 infection.[30-32, 51, 59, 85-87] SVR rates with triple therapy approached the 70–80 percent rates observed with dual therapy in patients with genotype 2 or 3 infection. Trials that evaluated the telaprevir regimen recommended by the FDA (12 weeks of triple therapy with telaprevir followed by response-guided duration of 12 or 36 weeks of dual therapy) reported SVR rates of 75–80 percent.[51, 59] Trials that evaluated the FDA-recommended boceprevir regimen for antiviral-naïve patients with cirrhosis (4 weeks of dual therapy lead-in followed by 44 weeks of triple therapy with boceprevir) reported SVR rates of 66–75 percent.[30, 32] Trials that evaluated other regimens in antiviral naïve patients, including fixed duration telaprevir regimens, shorter fixed duration triple therapy with boceprevir, and boceprevir without dual therapy lead-in,

reported similar or lower SVR rates. The SVR rates with various antiviral regimens or placebo are summarized in Table 13.

Table 13. Sustained virologic response rates with different antiviral regimens for hepatitis C virus infection

Regimen	Sustained Virologic Response Rate 6 Months after Treatment (%)	Approximate Number Needed To Treat To Achieve One Sustained Virologic Response Compared With Placebo	References
Placebo	<2	Not applicable	Poynard et al., 1996[12]
Interferon monotherapy	6-16	7-25	Chander, 2002[10] Kjaegard, 2000[11] Poynard, 1996[12] Shepherd., 2000[13]
Interferon plus ribavirin	33-41	2.6-3.2	Chander, 2002[10] Kjaergard, 2001[11] Shepherd, 2000[13]
Pegylated interferon plus ribavirin	54-61 overall, 42-52 in patients with genotype 1 infection	1.7-1.9 overall; 2.0-2.5 for genotype 1 infection	Shepherd, 2005[120] Sieber, 2005[121] Zaman, 2003[122]
Pegylated interferon plus ribavirin plus boceprevir or telaprevir[a]	66-80 (genotype 1 infection only)	1.3-1.6 (genotype 1 infection only)	Jacobson, 2011[51] Kwo, 2010[30] Marcellin, 2011[59] Poordad , 2011[32]

[a] Based on regimens recommended by the U.S. Food and Drug Administration evaluated in trials of antiviral-naïve patients.

The boceprevir regimen recommended by the FDA[84] for antiviral-naïve patients without baseline cirrhosis (4 weeks of dual therapy lead-in with pegylated interferon plus ribavirin followed by the addition of boceprevir for 24 weeks for virologic responders at weeks 8 to 24, or 4 weeks of dual therapy lead-in followed by the addition of boceprevir for 32 weeks and then 12 additional weeks of dual therapy for late virologic responders) has not been evaluated in a trial of antiviral-naïve patients. Rather, the FDA recommendation was based on a trial of previous partial responders to pegylated interferon plus ribavirin which found slightly higher SVR rates in late virologic responders who received 32 weeks of triple therapy followed by 12 weeks of dual therapy versus those who received 44 weeks of triple therapy, each following 4 weeks of dual therapy lead-in (SVR rates 79 vs. 73 percent).[123]

As in the head-to-head trials of dual therapy with pegylated interferon alfa-2a plus ribavirin versus pegylated interferon alfa-2b plus ribavirin, relative risk estimates were similar (or there was no clear difference) in patient subgroups based on age, sex, and race, although absolute SVR rates were lower in older patients and Black patients. Triple therapy with either boceprevir or telaprevir was no more effective than dual therapy in the subgroup of patients with lower HCV-RNA viral load (<600,000 or <800,000 IU/mL).[30, 32, 51] There was insufficient evidence to evaluate relative effectiveness of triple compared with dual therapy based on fibrosis stage.

In addition to higher likelihood of SVR, another advantage of triple therapy regimens in patients with genotype 1 infection is the potential for shorter duration (24 or 28 weeks in patients with early virologic response compared with the standard 48 weeks of dual therapy with pegylated interferon plus ribavirin). Shorter courses of treatment would probably be appealing to patients of high relevance to patients, given the high frequency of bothersome flulike symptoms associated with interferon-based therapy. Triple therapy regimens were associated with increased risk of certain harms, in particular hematological adverse events (neutropenia, anemia, and thrombocytopenia) with boceprevir and anemia and rash (including severe rash in <10 percent of

patients that could result in treatment discontinuation) with telaprevir. However, there was no clear increase in risk of serious adverse events with use of protease inhibitors, and the adverse events appear to be self-limited following drug discontinuation.

Sustained Virologic Response After Antiviral Therapy and Clinical Outcomes

The strongest evidence on the association between an SVR after antiviral therapy and improved clinical outcomes is a large VA cohort study (n=16,864) that adjusted for many confounders.[8] The VA study found decreased risk of all-cause mortality in patients who achieved an SVR compared with those who didn't achieve an SVR across groups stratified by genotype (adjusted HR 0.71 [0.60–0.86], 0.62 [0.44–0.87] and 0.51 [0.35–0.75] for genotypes 1, 2, and 3, respectively). Despite controlling for important confounders, the possibility of residual confounding is suggested by the very rapid separation of mortality curves for patients with an SVR versus those without an SVR, which was observed at three months after assessment for SVR. This is more rapid than expected given the typically prolonged natural history of HCV infection. Therefore, estimates of effects of SVR on clinical outcomes from this study may be exaggerated, though it is not possible to determine to what degree.

Eighteen other cohort studies also found an SVR after antiviral therapy associated with decreased risk of all-cause mortality and complications of chronic HCV infection, including studies specifically of patients with baseline cirrhosis, but had more methodological shortcomings. In addition, 10 of the 19 studies were conducted in Asia, where the incidence of HCC in patients with chronic HCV infection is higher than in the United States,[46] potentially limiting their generalizability. Other studies found an SVR after antiviral therapy associated with better scores on various measures of quality of life than no SVR, but those studies focused on short-term outcomes, and typically did not adjust for confounders or blind patients to SVR status when assessing outcomes.

Findings in Relationship to What Is Already Known

Our findings regarding the comparative effectiveness of dual therapy with pegylated interferon alfa-2b plus ribavirin compared with dual therapy with pegylated interferon alfa-2a plus ribavirin are consistent with recent systematic reviews that also found the former associated with a lower likelihood of SVR.[18, 124] Our findings of no clear difference in comparative effectiveness between 12 to 16 weeks compared with 24 weeks of response-guided dual therapy with pegylated interferon plus ribavirin in hepatitis C genotype 2 or 3 infection with rapid virologic response are discordant with a recent systematic review, which found a shorter duration of treatment associated with a lower likelihood of achieving an SVR.[125] The discrepancy may be explained by the inclusion in the other systematic review of a study that we excluded because it evaluated a nonstandard dose of pegylated interferon,[65] as well as its inclusion of subgroup analyses from trials of patients randomized to different fixed durations of therapy prior to assessment of rapid virologic response,[64, 68, 70] which we considered separately because they did not represent randomized comparisons of response-guided treatment.

Because telaprevir and boceprevir are so new, we are unaware of other published systematic reviews on the comparative benefits and harms of regimens including these drugs, compared with standard dual therapy. Our findings on the association between achieving an SVR and

reduced risk of mortality or complications associated with chronic HCV infection are consistent with a recent review that used some systematic methods.[126]

Applicability

The trials included in this review generally met criteria for efficacy studies, based on the exclusion of patients with common comorbidities (such as serious psychiatric conditions or recent or ongoing substance abuse) who may receive treatments in clinical practice. In addition, the trials may have overestimated efficacy compared with what would be seen in typical practice due to improved adherence as a result of closer followup, effects of trial participation, selection of patients, or other factors. A separate review funded by AHRQ will focus on issues related to adherence in the treatment of HCV infection.[127]

The severity of baseline liver disease in the patients enrolled in the trials suggests that they enrolled a broad range of patients. In trials of triple therapy with boceprevir or telaprevir, the proportion of patients with cirrhosis at enrollment ranged from <1–11 percent.[30-32, 51, 59, 85, 87] Trials that reported the proportion of patients with minimal or no fibrosis reported rates of 27–39 percent.[31, 51, 59, 87]

Evidence to evaluate potential differences in comparative benefits or harms in patient subgroups based on age, sex, race, and other clinical factors was relatively limited, precluding strong conclusions in these specific subgroups. The strongest evidence on the association between an SVR versus no SVR after antiviral therapy and reduced mortality comes from a study performed in a VA population, which might limit generalizability to other settings.[8] As described above, studies conducted in Asia on the association between an SVR after antiviral therapy and risk of clinical outcomes may be of limited applicability to U.S. populations because of a higher incidence of HCC in Asian patients with chronic HCV infection.[46] However, HCC incidence is increasing in the United States in HCV-infected patients,[128] which may attenuate such concerns regarding applicability.

The results of this CER are not applicable to populations excluded from the review, including patients previously treated with antiviral therapies and excluded populations such as patients with HIV coinfection, post-transplant patients, or hemodialysis patients. Antiviral therapy is not recommended in patients following kidney transplant, and ribavirin is not recommended in those with more severe (stage 3 to 5) kidney disease since it is cleared via renal function and associated with increased risk of hemolytic anemia in this setting. Such patients were typically excluded from randomized trials of antiviral treatment.[15]

Implications for Clinical and Policy Decisionmaking

Our review has potential implications for clinical and policy decisionmaking. For patients with genotype 1 infection, triple therapy regimens with pegylated interferon (alfa-2a or alfa-2b), ribavirin, and telaprevir or boceprevir may be considered an alternative to dual therapy with pegylated interferon alfa-2a or alfa-2b plus ribavirin as standard treatment due to substantially superior efficacy for achieving SVR compared with dual therapy with pegylated interferon alfa-2a or alfa-2b, as well as a shorter duration of treatment. Factors that may affect decisions to utilize regimens with boceprevir or telaprevir include cost and specific harms associated with use of these drugs (such as hematologic adverse events with boceprevir and anemia and rash with telaprevir). Dual therapy with pegylated interferon alfa-2a plus ribavirin appears to be associated with higher likelihood of achieving SVR compared with dual therapy with pegylated interferon alfa-2b plus ribavirin, but absolute differences were relatively small and may be offset in part by

a small increase in serious (but generally self-limited) adverse events. Therefore, decisions about which pegylated interferon to use may be affected by other considerations, such as cost, patient preferences, or other factors. For genotype 2 or 3 infection, standard doses and duration (24 weeks) of pegylated interferon as part of dual therapy are more effective than shorter regimens or lower doses, lending support to dosing guidance from the FDA and clinical practice guidelines.[15, 33, 34] Evidence on differential effects of ribavirin dose are too limited to draw strong conclusions about optimal dosing of this component of antiviral regimens, though differences appeared relatively small.

The findings that absolute SVR rates are lower in certain subgroups (such as older patients, Black patients, patients with worse baseline fibrosis, and patients with high viral load) can be used to inform individualized decisionmaking. Patients who are less likely to achieve a SVR may make different informed decisions about therapy compared to those more likely to achieve an SVR, given the adverse effects associated with treatment.

The findings of the review are also relevant to screening recommendations, which are based in part on the effectiveness of treatments in patients found through screening to have HCV infection. Important new evidence that may affect assessments regarding potential benefits of screening include stronger evidence on the link between achieving an SVR and improvement in clinical outcomes, as well as evidence showing substantially higher SVR rates with newer triple therapy regimens with boceprevir or telaprevir in patients with genotype 1 infection, the predominant type of HCV infection in the United States.

Limitations of the Comparative Effectiveness Review Process

Our review had some potential limitations. We excluded non–English-language articles, which could result in language bias, although a recent systematic review found little empirical evidence that exclusion of non–English-language articles leads to biased estimates for noncomplementary or alternative medicine interventions.[129]

We did not formally assess for publication bias with funnel plots due to small numbers (<10) of studies for all comparisons. Small numbers of studies can make interpretation of funnel plots unreliable, and experts suggest 10 studies as the minimum number of studies to perform funnel plots.[50] We included some studies which were published only as abstracts and found that their inclusion or exclusion from analyses did not change conclusions. In addition, we searched trial registries and solicited drug manufacturers for additional unpublished trials and identified none.

Another potential limitation is that we included cohort studies to evaluate the association between SVR and mortality or hepatic complications associated with chronic HCV infection. Such studies are susceptible to confounding if factors associated with SVR (such as age, race, viral load, or fibrosis stage) are also associated with these outcomes. Therefore, we only included studies that reported adjusted risk estimates, and we evaluated how well studies addressed key potential confounders as part of our quality assessment. Nonetheless, residual confounding is a possibility even in cohort studies that adjust for potential confounding.

Limitations of the Evidence Base

We identified several important limitations of the evidence base. First, studies assessing important long-term clinical outcomes associated with current antiviral treatments for chronic HCV infection are not available. In the case of antiviral regimens involving newly approved

antiviral drugs, such studies are not possible yet because of the extended followup required to adequately evaluate effects on clinical outcomes. Second, no trials directly compared regimens with boceprevir compared with regimens with telaprevir. Given the increased efficacy of these regimens in patients with genotype 1 infection, trials directly comparing their effects would be helpful for informing treatment choices between these drugs. In addition, few trials have evaluated the specifically FDA-approved regimens for these drugs, limiting confidence in conclusions regarding estimates of benefits and harms for the regimens likely to be used in clinical practice. Third, almost all of the randomized trials were funded by pharmaceutical companies. Studies have shown that such studies tend to report more favorable results for drugs produced by the funder than studies funded by governmental or other sources.[130, 131] Fourth, there was relatively limited information on effects of newer triple therapy regimens with a protease inhibitor in subgroups defined by age, body weight, baseline fibrosis stage, and other important factors. Such information would be helpful for individualizing treatment decisions with these regimens. Finally, few methodologically rigorous studies conducted in settings applicable to U.S. populations evaluated the association between achieving an SVR and improvements in clinical outcomes. Such studies would be very helpful for confirming the results of the recent, large, well-conducted VA cohort study showing an association between achieving an SVR and reduced mortality risk.[8]

Future Research

Evaluating the comparative effectiveness of current antiviral regimens on clinical outcomes in randomized trials or cohort studies is a challenge due to the long lead-time and large samples necessary to adequately assess these outcomes. This might be more feasible if the studies were to focus on populations at higher risk for complications from chronic HCV infection (e.g., patients with baseline cirrhosis, high viral load, or other risk factors for progression).

For all trials of antiviral treatments, studies that enroll broader populations with medical and psychological comorbidities, as frequently encountered in clinical practice, are needed to better understand comparative effectiveness, rather than just comparative efficacy. Studies designed using an effectiveness paradigm would also be helpful for understanding real-world effects of antiviral regimens, including effects related to the poorer treatment adherence than expected from efficacy trials. Studies that evaluate the usefulness of genomics and other methods for individualizing treatment decisions in patients with HCV infection are also needed.

Trials directly comparing triple therapy with telaprevir compared with triple therapy with boceprevir would be very helpful for understanding comparative effectiveness of these two protease inhibitors. In addition, trials evaluating the boceprevir regimen by the FDA in antiviral-naïve patients without baseline cirrhosis are needed to verify that results from studies of previously treated patients were appropriately generalized. Prolonged followup of patients exposed to telaprevir and boceprevir is needed to understand the long-term harms associated with these medications. A number of other protease inhibitors and other newer drugs for treatment of hepatitis C virus infection are currently in active development and further studies with new drugs and drug regimens are expected, including regimens without interferon.[88]

It is critical that future studies that evaluate clinical outcomes in patients with an SVR versus no SVR after antiviral therapy adequately control for other factors that influence clinical outcomes in chronic HCV infection. Studies on effects of achieving an SVR on long-term quality of life would be very helpful for understanding other potential clinical benefits of antiviral

therapy, but a significant challenge is whether it is possible to ethically blind patients to virologic status, which may have an important impact on assessments of quality of life.

References

1. Armstrong GL, Wasley A, Simard EP, et al. The prevalence of hepatitis C virus infection in the United States, 1999 through 2002. Ann Intern Med. 2006;144:705-14. PMID: 16702586.
2. Ly KN, Xing J, Klevens RM, et al. The increasing burden of mortality from viral hepatitis in the United States between 1999 and 2007. Ann Intern Med. 2012;156(4):271-8. PMID: 22351712.
3. Kim WR. The burden of hepatitis C in the United States. Hepatology. 2002;36 (5 suppl. 1): S30-S4. PMID: 12407574.
4. Davis GL, Alter MJ, El-Serag H, et al. Aging of hepatitis C virus (HCV)-infected persons in the United States: a multiple cohort model of HCV prevalence and disease progression. Gastroenterol. 2010 Feb;138(2):513-21. PMID: 19861128.
5. National Center for HIV/AIDS VH, STD & TB Prevention. Disease Burden from Viral Hepatitis A, B, and C in the United States. Centers for Disease Control and Prevention; 2011. www.cdc.gov/hepatitis/hcv/StatisticsHCV.htm. Accessed on 10/27/11.
6. Swain M, Lai MY, Shiffman ML, et al. Durability of sustained virological response (SVR) after treatment with peginterferon alfa-2A (40KD) (PEGASYS) alone or in combination with ribavirin (COPEGUS): results of an ongoing long-term follow-up study. Hepatology (Baltimore, Md.). 2004;40(4 Suppl 1):400A-1A.
7. Swain MG, Lai MY, Shiffman ML, et al. A sustained virologic response is durable in patients with chronic hepatitis C treated with peginterferon alfa-2a and ribavirin. Gastroenterol. 2010 Nov. 2010;139(5):1593-601. PMID: 20637202.
8. Backus LI, Boothroyd DB, Phillips BR, et al. A sustained virologic response reduces risk of all-cause mortality in patients with hepatitis C. Clin Gastroenterol Hepatol. 2011;9:509-16. PMID: 21397729.
9. Morgan TR, Ghany MG, Kim H-Y, et al. Outcome of sustained virological responders with histologically advanced chronic hepatitis C. Hepatology. 2010 Sep;52(3):833-44. PMID: 20564351.
10. Chander G, Sulkowski MS, Jenckes MW, et al. Treatment of chronic hepatitis C: a systematic review. Hepatology. 2002 Nov;36(5 Suppl 1):S135-44. PMID: 12407587.
11. Kjaegard LL, Krogsgaard K, Gluud C. Interferon alfa with or without ribavirin for chronic hepatitis C: systematic review of randomised trials. BMJ. 2001;323:1151-5. PMID: 11711405.
12. Poynard T, Leroy V, Cohard M, et al. Meta-analysis of interferon randomized trials in the treatment of viral hepatitis C: effects of dose and duration. Hepatology. 1996;24:778-89. PMID: 8855176.
13. Shepherd J, Waugh N, Hewitson P. Combination therapy (interferon alfa and ribavirin) in the treatment of chronic hepatitis C: a systematic review. Hepatology. 2000;36:S135-44. PMID: 11134916.
14. Anonymous. National Institutes of Health consensus development conference statement: Management of hepatitis c: 2002--June 10-12, 2002. Hepatology. 2002;36(5 (Suppl 1):S3-S20. PMID: 12407572.
15. Ghany MG, Strader DB, Thomas DL, et al. Diagnosis, management, and treatment of hepatitis C: an update. Hepatology. 2009;49(4):1335-74. PMID: 19330875.
16. Strader DB, Wright T, Thomas DL, et al. Diagnosis, management, and treatment of hepatitis C. Hepatology. 2004;2004:1147-71. PMID: 15057920.
17. Foster GR. Review article: pegylated interferons: chemical and clinical differences. Aliment Pharmacol Ther. 2004 Oct 15;20(8):825-30. PMID: 15479353.

18. Awad T, Thorlund K, Hauser G, et al. Peginterferon alpha-2a is associated with higher sustained virological response than peginterferon alfa-2b in chronic hepatitis C: Systematic review of randomized trials. Hepatology. 2010;51(4):1176-84. PMID: 20187106.

19. Chou R CS, Chan BKS. Drug Class Review on Pegylated Interferons for Chronic Hepatitis C Infection. Portland, OR: Oregon Health & Science University; 2007.

20. Ascione A, De Luca M, Tartaglione MT, et al. Peginterferon alfa-2a plus ribavirin is more effective than peginterferon alfa-2b plus ribavirin for treating chronic hepatitis C virus infection. Gastroenterol. 2010 Jan;138(1):116-22. PMID: 19852964.

21. Escudero A, Rodriguez F, Serra MA, et al. Pegylated alpha-interferon-2a plus ribavirin compared with pegylated alpha-interferon-2b plus ribavirin for initial treatment of chronic hepatitis C virus: prospective, non-randomized study. J Gastroenterol Hepatol. 2008 Jun;23(6):861-6. PMID: 18422960.

22. McHutchison JG, Lawitz EJ, Shiffman ML, et al. Peginterferon alfa-2b or alfa-2a with ribavirin for treatment of hepatitis C infection.[Erratum appears in N Engl J Med. 2009 Sep 3;361(10):1027]. N Engl J Med. 2009 Aug 6;361(6):580-93. PMID: 19625712.

23. Rumi MG, Aghemo A, Prati GM, et al. Randomized study of peginterferon-alpha2a plus ribavirin vs peginterferon-alpha2b plus ribavirin in chronic hepatitis C. Gastroenterol. 2010 Jan;138(1):108-15. PMID: 19766645.

24. Nainan OV, Alter MJ, Kruszon-Moran D, et al. Hepatitis C virus genotypes and viral concentratiosn in participants of a general population survey in the United States. Gastroenterol. 2006;131:478-84. PMID: 16890602

25. Ge D, Fellay J, Thompson AJ, et al. Genetic variation in IL28B predicts hepatitis C treatment-induced viral clearance. Nature. 2009;461(7262):399-401. PMID: 19684573.

26. Suppiah V, Moldovan M, Ahlenstiel G, et al. IL28B is associated with response to chronic hepatitis C interferon-α and ribavirin therapy. Nat Genet. 2009;41(10):1100-4. PMID: 19749758.

27. Fried MW, Shiffman ML, Reddy KR, et al. Peginterferon alfa-2a plus ribavirin for chronic hepatitis C virus infection. N Engl J Med. 2002 Sep 26;347(13):975-82. PMID: 12324553.

28. FDA. Approval of Victrelis (boceprevir) a direct acting antiviral drug (DAA) to treat hepatitis C virus (HCV). 2011. www.fda.gov/ForConsumers/ByAudience/ForPatientAdvocates/ucm255413.htm.

29. FDA. Approval of Incivek (telaprevir), a direct acting antiviral drug (DAA) to treat hepatitis C (HCV). 2011. www.fda.gov/ForConsumers/ByAudience/ForPatientAdvocates/ucm256328.htm.

30. Kwo PY, Lawitz EJ, McCone J, et al. Efficacy of boceprevir, an NS3 protease inhibitor, in combination with peginterferon alfa-2b and ribavirin in treatment-naive patients with genotype 1 hepatitis C infection (SPRINT-1): an open-label, randomised, multicentre phase 2 trial.[Erratum appears in Lancet. 2010 Oct 9;376(9748):1224 Note: SPRINT-1 investigators [added]; multiple investigator names added]. Lancet. 2010 Aug 28;376(9742):705-16. PMID: 20692693.

31. McHutchison JG, Everson GT, Gordon SC, et al. Telaprevir with peginterferon and ribavirin for chronic HCV genotype 1 infection.[Erratum appears in N Engl J Med. 2009 Oct 8;361(15):1516]. N Engl J Med. 2009 Apr 30;360(18):1827-38. PMID: 19403902.

32. Poordad F, McCone J, Jr., Bacon BR, et al. Boceprevir for untreated chronic HCV genotype 1 infection. N Engl J Med. 2011 Mar 31;364(13):1195-206. PMID: 21449783.

33. PEGASYS [package insert]. Hoffmann-La Roche Inc. Nutley, NJ; 2002.

34. PEG-Intron [package insert]. Schering Corporation. Kenilworth, NJ; 2005.

35. Chou R, Cottrell E, Wasson N, et al. Screening for Hepatitis C Virus Infection in Adults: Comparative Effectiveness Review. (Prepared by Oregon Evidence-based Practice Center under Contract No. 290-2007-10057-I). Rockville, MD: Agency for Healthcare Research and Quality; Forthcoming 2012.

36. Pembrey L, Newell M-L, Tovo P-A, et al. The management of HCV infected pregnant women and their children European paediatric HCV network. J Hepatol. 2005;43(3):515-25. PMID: 16144064.

37. Ghany M, Nelson DR, Strader DB, et al. An update on treatment of genotype 1 chronic hepatitis C virus infection: 2011 practice guidelines by the American Association for the Study of Liver Diseases. Hepatology. 2011 Oct; 54(4):1433-44. PMID: 21898493.

38. Lindsay KL. Introduction to therapy of hepatitis C. Hepatology. 2002 Nov;36(5 Suppl 1):S114-20. PMID: 12407584.

39. Civeira MP, Prieto J. Early predictors of response to treatment in patients with chronic hepatitis C. J Hepatol. 1999;31 Suppl 1:237-43. PMID: 10622595.

40. Hung CH, Lee CM, Lu SN, et al. Is delayed normalization of alanine aminotransferase a poor prognostic predictor in chronic hepatitis C patients treated with a combined interferon and ribavirin therapy? J Gastroenterol Hepatol. 2002;17(12):1307-11. PMID: 12423276.

41. Zeuzem S, Feinman S, Rasenack J, et al. Peginterferon alfa-2a in patients with chronic hepatitis C. N Engl J Med. 2000;343(23):1666-72. PMID: 11106715.

42. Basso M, Giannini EG, Torre F, et al. Elevations in alanine aminotransferase levels late in the course of antiviral therapy in hepatitis C virus RNA–negative patients are associated with virological relapse. Hepatology. 2009;49(5):1442-8. PMID: 19350657.

43. Downs SH, Black N. The feasibility of creating a checklist for the assessment of the methodological quality both of randomised and non-randomised studies of health care interventions. J Epidemiol Community Health. 1998;52(6):377-84. PMID: 9764259.

44. 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;20(3 Suppl):21-35. PMID: 11306229.

45. AHRQ. Methods Guide for Effectiveness and Comparative Effectiveness Reviews. Rockville, MD: Agency for Healthcare Research and Quality; 2011.

46. Shibuya K, Yano E. Regression analysis of trends in mortality from hepatocellular carcinoma in Japan, 1972-2001. Int J Epidemiol. 2005;34(2):397-402. PMID: 15561746.

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;4(1):38. PMID: 15615589.

48. Fu R, Gartlehner G, Grant M, et al. Conducting quantitative synthesis when comparing medical interventions: AHRQ and the effective health care program. J Clin Epidemiol. 2011 Nov;64(11):1187-97. PMID: 21477993.

49. Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. Stat Med. 2002;21(11):1539-58. PMID: 12111919.

50. Sterne JA, Sutton AJ, Ioannidis JP, et al. Recommendations for examining and interpreting funnel plot asymmetry in meta-analyses of randomised controlled trials. British Medical Journal. 2011 Jul 2011;343(1):d4002. PMID: 21784880.

51. Jacobson IM, McHutchison JG, Dusheiko G, et al. Telaprevir for previously untreated chronic hepatitis C virus infection. N Engl J Med. 2011;364(25):2405-16. PMID: 21696307.

52. Bronowicki J-P, Ouzan D, Asselah T, et al. Effect of ribavirin in genotype 1 patients with hepatitis C responding to pegylated interferon alfa-2a plus ribavirin. Gastroenterol. 2006 Oct;131(4):1040-8. PMID: 17030174.

53. Kamal SM, Ahmed A, Mahmoud S, et al. Enhanced efficacy of pegylated interferon alpha-2a over pegylated interferon and ribavirin in chronic hepatitis C genotype 4A randomized trial and quality of life analysis. Liver Int. 2011;31(3):401-11. PMID: 21281434.

54. Khan A, Awan A, Shahbuddin S, et al. Abstract # S1231: Peginterferon alfa 2a / ribavirin versus peginterferon alfa 2b / ribavirin combination therapy in chronic hepatitis C genotype 3. Gastroenterol. 2007;132(4):A200.

55. Mach TH, Ciesla A, Warunek W, et al. Efficacy of pegylated interferon alfa-2a or alfa-2b in combination with ribavirin in the treatment of chronic hepatitis caused by hepatitis C virus genotype 1b. Polskie Archiwum Medycyny Wewnetrznej. 2011;121(12):434-40.

56. Magni C NF, Argenteri B, Giorgi R, Mainini A, Pastecchia C, Ricci E, Schiavini M, Terzi R, Vivirito MC, Resta M. Abstract #883: Antiviral activity and tolerability between pegylated interferon alpha 2a and alpha 2b in naive patients with chronic hepatitis C: Results of a prospective monocentric randomized trial. Hepatology. 2009;50(S4):720A.

57. Miyase S, Haraoka K, Ouchida Y, et al. Randomized trial of peginterferon α-2a plus ribavirin versus peginterferon α-2b plus ribavirin for chronic hepatitis C in Japanese patients. J Gastroenterol. 2012:1-8. PMID: 22382633.

58. Yenice N, Mehtap O, Gumrah M, et al. The efficacy of pegylated interferon alpha 2a or 2b plus ribavirin in chronic hepatitis C patients. Turk J Gastroenterol. 2006 Jun;17(2):94-8. PMID: 16830289.

59. Marcellin P, Forns X, Goeser T, et al. Telaprevir is effective given every 8 or 12 hours with ribavirin and peginterferon alfa-2a or -2b to patients with chronic hepatitis C. Gastroenterol. 2011 Feb;140(2):459-68.e1; quiz e14. PMID: 21034744.

60. McHutchison J, Sulkowski M. Scientific rationale and study design of the individualized dosing efficacy vs flat dosing to assess optimal pegylated interferon therapy (IDEAL) trial: determining optimal dosing in patients with genotype 1 chronic hepatitis C. J Viral Hepat. 2008;15(7):475-81. PMID: 18363672.

61. Andriulli A, Cursaro C, Cozzolongo R, et al. Early discontinuation of ribavirin in HCV-2 and HCV-3 patients responding to Peg-interferon alpha-2a and ribavirin. J Viral Hepat. 2009 Jan;16(1):28-35. PMID: 18761603.

62. Dalgard O, Bjoro K, Ring-Larsen H, et al. Pegylated interferon alfa and ribavirin for 14 versus 24 weeks in patients with hepatitis C virus genotype 2 or 3 and rapid virological response. Hepatology. 2008 Jan;47(1):35-42. PMID: 17975791.

63. Hadziyannis SJ, Sette H, Jr., Morgan TR, et al. Peginterferon-alpha2a and ribavirin combination therapy in chronic hepatitis C: a randomized study of treatment duration and ribavirin dose. Ann Intern Med. 2004 Mar 2;140(5):346-55. PMID: 14996676.

64. Lagging M, Langeland N, Pedersen C, et al. Randomized comparison of 12 or 24 weeks of peginterferon alpha-2a and ribavirin in chronic hepatitis C virus genotype 2/3 infection. Hepatology. 2008 Jun;47(6):1837-45. PMID: 18454508.

65. Mangia A, Santoro R, Minerva N, et al. Peginterferon alfa-2b and ribavirin for 12 vs. 24 weeks in HCV genotype 2 or 3. N Engl J Med. 2005 Jun 23;352(25):2609-17. PMID: 15972867.

66. Manns M, Zeuzem S, Sood A, et al. Reduced dose and duration of peginterferon alfa-2b and weight-based ribavirin in patients with genotype 2 and 3 chronic hepatitis C. J Hepatol. 2011b;55(3):554-63. PMID: 21237227.

67. Mecenate F, Pellicelli AM, Barbaro G, et al. Short versus standard treatment with pegylated interferon alfa-2A plus ribavirin in patients with hepatitis C virus genotype 2 or 3: the cleo trial. BMC Gastroenterol. 2010;10:21. PMID: 20170514.

68. Shiffman ML, Suter F, Bacon BR, et al. Peginterferon alfa-2a and ribavirin for 16 or 24 weeks in HCV genotype 2 or 3. N Engl J Med. 2007 Jul 12;357(2):124-34. PMID: 17625124.

69. von Wagner M, Huber M, Berg T, et al. Peginterferon-alpha-2a (40KD) and ribavirin for 16 or 24 weeks in patients with genotype 2 or 3 chronic hepatitis C. Gastroenterol. 2005 Aug;129(2):522-7. PMID: 16083709.

70. Yu M-L, Dai C-Y, Huang J-F, et al. A randomised study of peginterferon and ribavirin for 16 versus 24 weeks in patients with genotype 2 chronic hepatitis C. Gut. 2007 Apr;56(4):553-9. PMID: 16956917.

71. Zeuzem S, Diago M, Gane E, et al. Peginterferon alfa-2a (40 kilodaltons) and ribavirin in patients with chronic hepatitis C and normal aminotransferase levels. Gastroenterol. 2004 Dec;127(6):1724-32. PMID: 15578510.

72. Lam KD, Trinh HN, Do ST, et al. Randomized controlled trial of pegylated interferon-alfa 2a and ribavirin in treatment-naive chronic hepatitis C genotype 6. Hepatology. 2010 Nov;52(5):1573-80. PMID: 21038410.

73. Abergel A, Hezode C, Leroy V, et al. Peginterferon alpha-2b plus ribavirin for treatment of chronic hepatitis C with severe fibrosis: a multicentre randomized controlled trial comparing two doses of peginterferon alpha-2b. J Viral Hepat. 2006 Dec;13(12):811-20. PMID: 17109680.

74. Kawaoka T, Kawakami Y, Tsuji K, et al. Dose comparison study of pegylated interferon-alpha-2b plus ribavirin in naive Japanese patients with hepatitis C virus genotype 2: a randomized clinical trial. J Gastroenterol Hepatol. 2009 Mar;24(3):366-71. PMID: 19032459.

75. Krawitt EL, Gordon SR, Grace ND, et al. A study of low dose peginterferon alpha-2b with ribavirin for the initial treatment of chronic hepatitis C. Am J Gastroenterol. 2006 Jun;101(6):1268-73. PMID: 16771948.

76. Meyer-Wyss B, Rich P, Egger H, et al. Comparison of two PEG-interferon alpha-2b doses (1.0 or 1.5 microg/kg) combined with ribavirin in interferon-naive patients with chronic hepatitis C and up to moderate fibrosis. J Viral Hepat. 2006 Jul;13(7):457-65. PMID: 16792539.

77. Sood A, Midha V, Hissar S, et al. Comparison of low-dose pegylated interferon versus standard high-dose pegylated interferon in combination with ribavirin in patients with chronic hepatitis C with genotype 3: an Indian experience. J Gastroenterol Hepatol. 2008 Feb;23(2):203-7. PMID: 17645472.

78. Manns MP, McHutchison JG, Gordon SC, et al. Peginterferon alfa-2b plus ribavirin compared with interferon alfa-2b plus ribavirin for initial treatment of chronic hepatitis C: a randomised trial. Lancet. 2001;358(9286):958-65. PMID: 11583749.

79. Mimidis K, Papadopoulos VP, Elefsiniotis I, et al. Hepatitis C virus survival curve analysis in naive patients treated with peginterferon alpha-2b plus ribavirin. A randomized controlled trial for induction with high doses of peginterferon and predictability of sustained viral response from early virologic data. J Gastrointestin Liver Dis. 2006 Sep;15(3):213-9. PMID: 17013444.

80. Ferenci P, Brunner H, Laferl H, et al. A randomized, prospective trial of ribavirin 400 mg/day versus 800 mg/day in combination with peginterferon alfa-2a in hepatitis C virus genotypes 2 and 3. Hepatology. 2008 Jun;47(6):1816-23. PMID: 18454510.

81. Helbling B, Jochum W, Stamenic I, et al. HCV-related advanced fibrosis/cirrhosis: randomized controlled trial of pegylated interferon alpha-2a and ribavirin. J Viral Hepat. 2006 Nov;13(11):762-9. PMID: 17052276.

82. Jacobson (a) IM, Brown RS, Jr., Freilich B, et al. Peginterferon alfa-2b and weight-based or flat-dose ribavirin in chronic hepatitis C patients: a randomized trial. Hepatology. 2007 Oct;46(4):971-81. PMID: 17894303.

83. Ferenci P, Laferl H, Scherzer T-M, et al. Peginterferon alfa-2a/ribavirin for 48 or 72 weeks in hepatitis C genotypes 1 and 4 patients with slow virologic response. [Reprint in Korean J Hepatol. 2010 Jun;16(2):201-5; PMID: 20606507]. Gastroenterol. 2010 Feb;138(2):503-12. PMID: 19909752.

84. Bocepriver [package insert] In: Merck & Co I, editor Merck & Co, Inc. Whitehouse Station, NJ; 2011.

85. Hezode C, Forestier N, Dusheiko G, et al. Telaprevir and peginterferon with or without ribavirin for chronic HCV infection. N Engl J Med. 2009 Apr 30;360(18):1839-50. PMID: 19403903.

86. Kumada H, Toyota J, Okanoue T, et al. Telaprevir with peginterferon and ribavirin for treatment-naive patients chronically infected with HCV of genotype 1 in Japan. J Hepatol. 2012;56(1):78-84. PMID: 21827730.

87. Sherman KE, Flamm SL, Afdhal NH, et al. Response-guided telaprevir combination treatment for hepatitis C virus infection. N Engl J Med. 2011;365(11):1014-24. PMID: 21916639.

88. Lok A. Preliminary study of two antiviral agents for hepatitis C genotype 1. N Engl J Med. 2012;366(3):273-5. PMID: 22256811.

89. Arase Y, Ikeda K, Suzuki F, et al. Long-term outcome after interferon therapy in elderly patients with chronic hepatitis C. Intervirology. 2007;50(1):16-23. PMID: 17164553.

90. Bruno S, Stroffolini T, Colombo M, et al. Sustained virological response to interferon-alpha is associated with improved outcome in HCV-related cirrhosis: a retrospective study. Hepatology. 2007 Mar;45(3):579-87. PMID: 17326216.

91. Cardoso A-C, Moucari R, Figueiredo-Mendes C, et al. Impact of peginterferon and ribavirin therapy on hepatocellular carcinoma: incidence and survival in hepatitis C patients with advanced fibrosis. J Hepatol. 2010 May;52(5):652-7. PMID: 20346533.

92. Coverdale SA, Khan MH, Byth K, et al. Effects of interferon treatment response on liver complications of chronic hepatitis C: 9-year follow-up study. Am J Gastroenterol. 2004 Apr;99(4):636-44. PMID: 15089895.

93. El Braks RE, Ganne-Carrie N, Fontaine H, et al. Effect of sustained virological response on long-term clinical outcome in 113 patients with compensated hepatitis C-related cirrhosis treated by interferon alpha and ribavirin. World J Gastroenterol. 2007;13(42):5648-53. PMID: 17948941.

94. Fernández-Rodríguez CM, Alonso S, Martinez SM, et al. Peginterferon plus ribavirin and sustained virological response in HCV-related cirrhosis: Outcomes and factors predicting response. Am J Gastroenterol. 2010. PMID: 20927082.

95. Hasegawa E, Kobayashi M, Kawamura Y, et al. Efficacy and anticarcinogenic activity of interferon for hepatitis C virus-related compensated cirrhosis in patients with genotype 1b low viral load or genotype 2. Hepatol Res. 2007;37(10):793-800. PMID: 17593231.

96. Hung CH, Lee CM, Lu SN, et al. Long-term effect of interferon alpha-2b plus ribavirin therapy on incidence of hepatocellular carcinoma in patients with hepatitis C virus-related cirrhosis. J Viral Hepat. 2006;13(6):409-14. PMID: 16842444.

97. Imazeki F, Yokosuka O, Fukai K, et al. Favorable prognosis of chronic hepatitis C after interferon therapy by long-term cohort study. Hepatology. 2003 Aug;38(2):493-502. PMID: 12883494.

98. Innes HA, Hutchinson SJ, Allen S, et al. Excess liver-related morbidity of chronic hepatitis C patients, who achieve a sustained viral response, and are discharged from care. Hepatology. 2011;54(5):1547-58. PMID: 22045672.

99. Izumi N, Yasuhiro A, Kurosaki M, et al. Development of hepatocellular carcinoma after interferon therapy in chronic hepatitis C. Is it possible to reduce the incidence by ribanirin and IFN combination therapy? Intervirology. 2005;48(1):59-63. PMID: 15785091.

100. Kasahara A, Tanaka H, Okanoue T, et al. Interferon treatment improves survival in chronic hepatitis C patients showing biochemical as well as virological responses by preventing liver-related death. J Viral Hepat. 2004 Mar;11(2):148-56. PMID: 14996350.

101. Maruoka D, Imazeki F, Arai M, et al. Long-term cohort study of chronic hepatitis C according to interferon efficacy. J Gastroenterol Hepatol. 2012b;27(2):291-9. PMID: 21793911.

102. Shiratori Y, Ito Y, Yokosuka O, et al. Antiviral therapy for cirrhotic hepatitis C: association with reduced hepatocellular carcinoma development and improved survival. Ann Intern Med. 2005 Jan 18;142(2):105-14. PMID: 15657158.

103. Veldt BJ, Heathcote EJ, Wedemeyer H, et al. Sustained virologic response and clinical outcomes in patients with chronic hepatitis C and advanced fibrosis. Ann Intern Med. 2007;147(10):677-84. PMID: 18025443.

104. Yoshida H, Arakawa Y, Sata M, et al. Interferon therapy prolonged life expectancy among chronic hepatitis C patients. Gastroenterol. 2002 Aug;123(2):483-91. PMID: 12145802.

105. Yu M-L, Lin S-M, Chuang W-L, et al. A sustained virological response to interferon or interferon/ribavirin reduces hepatocellular carcinoma and improves survival in chronic hepatitis C: a nationwide, multicentre study in Taiwan. Antiver Ther. 2006;11(8):985-94. PMID: 17302368.

106. Mallet V, Gilgenkrantz H, Serpaggi J, et al. Brief communication: the relationship of regression of cirrhosis to outcome in chronic hepatitis C. Ann Intern Med. 2008;149(6):399-403. PMID: 18794559.

107. Arora S, O'Brien C, Zeuzem S, et al. Treatment of chronic hepatitis C patients with persistently normal alanine aminotransferase levels with the combination of peginterferon alpha-2a (40 kDa) plus ribavirin: impact on health-related quality of life. J Gastroenterol Hepatol. 2006 Feb;21(2):406-12. PMID: 16509866.

108. Bernstein D, Kleinman L, Barker CM, et al. Relationship of health-related quality of life to treatment adherence and sustained response in chronic hepatitis C patients. Hepatology. 2002 Mar;35(3):704-8. PMID: 11870387.

109. Bini EJ, Mehandru S. Sustained virological response rates and health-related quality of life after interferon and ribavirin therapy in patients with chronic hepatitis C virus infection and persistently normal alanine aminotransferase levels. Aliment Pharmacol Ther. 2006;23(6):777-85. PMID: 16556180.

110. Bonkovsky HL, Woolley JM. Reduction of health-related quality of life in chronic hepatitis C and improvement with interferon therapy.The Consensus Interferon Study Group. Hepatology. 1999;29(1):264-70. PMID: 9862876.

111. Hassanein T, Cooksley G, Sulkowski M, et al. The impact of peginterferon alfa-2a plus ribavirin combination therapy on health-related quality of life in chronic hepatitis C. J Hepatol. 2004 Apr;40(4):675-81. PMID: 15030985.

112. McHutchison J, Manns M, Harvey J, et al. Adherence to therapy enhanges sustained response in chronic hepatitis C patients receiving PEG-Interferon alfa-2b plus Ribavirin [abstract]. J Hepatol. 2001;34(1):2-3.

113. Neary MP, Cort S, Bayliss MS, et al. Sustained virologic response is associated with improved health-related quality of life in relapsed chronic hepatitis C patients. Semin Liver Dis. 1999;19 Suppl 1:77-85. PMID: 10349695.

114. Rasenack J, Zeuzem S, Feinman SV, et al. Peginterferon alpha-2a (40kD) [Pegasys] improves HR-QOL outcomes compared with unmodified interferon alpha-2a [Roferon-A]: in patients with chronic hepatitis C.[Erratum appears in Pharmacoeconomics. 2003;21(17):1290]. Pharmacoeconomics. 2003;21(5):341-9. PMID: 12627987.

115. Ware JE, Bayliss MS, Mannocchia M, et al. Health-related quality of life in chronic hepatitis C: impact of disease and treatment response. The Interventional Therapy Group. Hepatology. 1999;30(2):550-5. PMID: 10421667.

116. Myles PS, Davis BB. "Low SVR syndrome" or SIRS after cardiac operations? Ann Thorac Surg. 1998;65(1):298. PMID: 9456150.

117. McHutchison JG, Gordon SC, Schiff ER, et al. Interferon alfa-2b alone or in combination with ribavirin as initial treatment for chronic hepatitis C. N Engl J Med. 1998;339(21):1485-92. PMID: 9819446.

118. Tong MJ, Blatt LM, McHutchison JG, et al. Prediction of response during interferon alfa 2b therapy in chronic hepatitis C patients using viral and biochemical characteristics: a comparison. Hepatology. 1997;26(6):1640-5. PMID: 9398010.

119. Zeuzem S, Hultcrantz R, Bourliere M, et al. Peginterferon alfa-2b plus ribavirin for treatment of chronic hepatitis C in previously untreated patients infected with HCV genotypes 2 or 3.[see comment][erratum appears in J Hepatol. 2005 Mar;42(3):434]. J Hepatol. 2004 Jun;40(6):993-9. PMID: 15158341.

120. Shepherd J, Brodin HFT, Cave CB, et al. Clinical- and cost-effectiveness of pegylated interferon alfa in the treatment of chronic hepatitis C: a systematic review and economic evaluation. Int J Technol Assess Health Care. 2005;21(1):47-54. PMID: 15736514.

121. Siebert U, Sroczynski G, German Hepatitis CMGEHMOG, et al. Effectiveness and cost-effectiveness of initial combination therapy with interferon/peginterferon plus ribavirin in patients with chronic hepatitis C in Germany: a health technology assessment commissioned by the German Federal Ministry of Health and Social Security. Int J Technol Assess Health Care. 2005;21(1):55-65. PMID: 15736515.

122. Zaman A, Fennerty MB, Keeffe EB. Systematic review: peginterferon vs. standard interferon in the treatment of chronic hepatitis C. Aliment Pharmacol Ther. 2003 Oct 1;18(7):661-70. PMID: 14510739.

123. Background Material for Boceprevir Advisory Committee.FDA; 2011. www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/drugs/AntiviralDrugsAdvisoryCommittee/ucm252341.pdf.

124. Singal AK, Jampana SC, Anand BS. Peginterferon alfa-2a is superior to peginterferon alfa-2b in the treatment of naïve patients with hepatitis C virus infection: meta-analysis of randomized controlled trials. Dig Dis Sci. 2011 Aug;56(8):2221-6. PMID: 21643737.

125. Singal AK, Anand BS. Tailoring treatment duration to 12 to 16 weeks in hepatitis C genotype 2 or 3 with rapid virologic response: systematic review and meta-analysis of randomized controlled trials. J Clin Gastroenterol. 2010;44(8):583-7. PMID: 20375729.

126. Pearlman BL, Traub N. Sustained virologic response to antiviral therapy for chronic hepatitis C virus infection: a cure and so much more. Clin Infect Dis. 2011;52(7):889-900. PMID: 21427396.

127. Garg V, van Heeswijk R, Eun Lee J, et al. Effect of telaprevir on the pharmacokinetics of cyclosporine and tacrolimus. Hepatology. 2011;54(1):20-7. PMID: 21618566.

128. El-Serag HB. Hepatocellular carcinoma. N Engl J Med. 2011;365(12):1118-27. PMID: 21992124.

129. Morrison A, Moulton K, Clark M, et al. English-Language Restriction When Conducting Systematic Review-based Metaanalyses: Systematic Review of Published Studies. Ottawa: Canadian Agency for Drugs and Technologies in Health; 2009.

130. Bhandari M, Busse JW, Jackowski D, et al. Association between industry funding and statistically significant pro-industry findings in medical and surgical randomized trials. CMAJ. 2004;170(4):477-80. PMID: 14970094.

131. Lexchin J, Bero LA, Djulbegovic B, et al. Pharmaceutical industry sponsorship and research outcome and quality: systematic review. BMJ. 2003 May 31;326(7400):1167-70. PMID: 12775614.

Abbreviations and Acronyms

AHRQ	Agency for Healthcare Research and Quality
ALT	Alanine aminotransferase
CER	Comparative effectiveness review
CHIP	Children's Health Insurance Program
CI	Confidence Interval
EPC	Evidence-based Practice Center
ESLD	End-stage liver disease
HCC	Hepatocellular carcinoma
HCV	Hepatitis C virus
HCV-RNA	Hepatitis C virus ribonucleic acid
HIV	Human immunodeficiency virus
HR	Hazard ratio
PCR	Polymerase chain reaction
PEG	Pegylated
PICOTS	Populations, Interventions, Comparators, Outcomes, Timing, and Setting
RR	Relative risk
SVR	Sustained virologic response
TEP	Technical Expert Panel
USPSTF	U.S. Preventive Services Task Force

Appendix A. Exact Search Strategy

The following databases have been searched for relevant information:

Database Searches: Hepatitis C: Treatment

Name	Date Limits	Platform Provider
Medline	2002 through August 2012	OvidSP
Embase	2002 through April 2012	Embase (Elsevier)
Cochrane Library: CDSR, DARE, CCRCT	2002 through August 2012	Cochrane Library
Clinical Trials.gov	2002 through August 2012	
Drugs@FDA	2002 through August 2012	
Health Canada Drug Products Database	2002 through August 2012	
European Public Assessment Reports (European Medicine Agency)	2002 through August 2012	
Scopus	2002 through August 2012	Scopus
PsycINFO	2002 through August 2012	OvidSP

Hand Search of Journals & Supplements - Topic-Specific Search Terms

Concept	Controlled Vocabulary	Keywords
Hepatitis C	Hepatitis C/ Hepatitis C,` Chronic/ Hepacivirus/ OR	hcv.mp hepacivirus$.mp
Treatment	Antiviral agents/ Interferons/ Interferon-alpha/ Interferon Alfa-2a/ Interferon Alpha-2b/ Exp Polyethylene Glycols/ Ribavirin/ Exp Protease Inhibitors/	Interferon$ interferon alpha-2a interferon alpha-2b IFNalpha2a IFNalpha2b interferon alpha 2a interferon alpha 2b pegasys Peg-intron peginterferon alpha-2a peginterferon alpha-2b peginterferon alpha 2a peginterferon alpha 2b pegylated interferon$ IFN$ PEG IFN$ Ribavirin RBV protease inhibitor$ polymerase

		inhibit$ HCV protease$ Telaprevir boceprevir
Harms - treatment	AE.fs MO.fs PO.fs TO.fs CT.fs AE=adverse effects CT=contraindications MO=mortality PO=poisoning TO=toxicity	Unsafe Safety harm$ complication$ poison$ risk$ side-effect$ side effect$ (undesirable ADJ1 effect$) (treatment ADJ1 emergent) tolerab$ toxic$ adrs (adverse ADJ2 (effect or effects or reaction or reactions or event or events or outcome or outcomes)) (undesirable ADJ1 effect$) (treatment ADJ1 emergent) tolerab$ toxic$ adrs (adverse ADJ2 (effect or effects or reaction or reactions or event or events or outcome or outcomes))

Original Search: 12/16/2011

Ovid MEDLINE(R) and Ovid OLDMEDLINE(R) 1946 to November Week 3 2011,
Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations December 15, 2011

1	Hepatitis C/ or Hepatitis C, Chronic/ or Hepacivirus/ or Hepatitis C.mp. or hepacivirus$.mp. or HCV.mp.	58901
2	Antiviral agents/ or Interferons/ or Interferon-alpha/ or Interferon Alfa-2a/ or Interferon Alpha-2b/ or Interferon$.mp. or interferon alpha-2a.mp. or interferon alpha-2b.mp. or IFNalpha2a.mp. or IFNalpha2b.mp. or interferon alpha 2a.mp. or interferon alpha 2b.mp. or exp Polyethylene Glycols/ or pegasys.mp. or Peg-intron.mp. or peginterferon alpha-2a.mp. or peginterferon alpha-2b.mp. or peginterferon alpha 2a.mp. or peginterferon alpha 2b.mp. or pegylated	379981

	interferon$.mp. or IFN$.mp. or PEG IFN$.mp. or Ribavirin/ or ribavirin.mp. or RBV.mp. or exp Protease Inhibitors/ or protease inhibitor$.mp. or polymerase inhibit$.mp. or HCV protease$.mp. or telaprevir.mp. or boceprevir.mp.	
3	1 and 2	17670
4	(randomized controlled trial or controlled clinical trial or meta analysis or review).pt. or clinical trials as topic/ or cohort studies/ or randomized.ab. or randomly.ab. or placebo.ab. or (systematic adj1 review).ti,ab.	2498350
5	3 and 4	5896
6	limit 5 to (yr="2002 -Current" and ("adult (19 to 44 years)" or "middle age (45 to 64 years)" or "all aged (65 and over)"))	1382
7	(unsafe or safety or harm$ or complication$ or poison$ or risk$).mp. or AE.fs. or MO.fs. or PO.fs. or TO.fs. or CT.fs. or side-effect$.mp. or (undesirable adj1 effect$).mp. or (treatment adj1 emergent).mp. or tolerab$.mp. or toxic$.mp. or adrs.mp. or (adverse adj2 (effect or effects or reaction or reactions or event or events or outcome or outcomes)).mp.	3892024
8	1 and 2 and 7	7401
9	4 and 8	3168
10	limit 9 to (yr="2002 -Current" and ("adult (19 to 44 years)" or "middle age (45 to 64 years)" or "all aged (65 and over)"))	885
11	Counseling/ or Sex Counseling/ or Health Education/ or Patient Education as Topic/ or Psychotherapy/ or Behavior Therapy/ or Cognitive Therapy/ or Immunization/ or Immunotherapy/ or Psychotherapy, Brief/ or Socioenvironmental Therapy/	268601
12	1 and 11	662
13	6 and (201102* or 201103* or 201104* or 201105* or 201106* or 201107* or 201108* or 201109* or 201110* or 201111* or 201112*).ed.	132
14	10 and (201102* or 201103* or 201104* or 201105* or 201106* or 201107* or 201108* or 201109* or 201110* or 201111* or 201112*).ed.	90
15	12 and (201102* or 201103* or 201104* or 201105* or 201106* or 201107* or 201108* or 201109* or 201110* or 201111* or 201112*).ed.	33

Additional Treatment Search: 2/28/2011

Ovid MEDLINE (R) and Ovid OLDMED (R) 1947 to February Week 3 2011
Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations February 28, 2011

1	Hepatitis C/ or Hepatitis C, Chronic/ or Hepacivirus/ or Hepatitis C.mp. or hepacivirus$.mp. or HCV.mp.	58837
2	Antiviral agents/ or Interferons/ or Interferon-alpha/ or Interferon Alfa-2a/ or Interferon Alpha-2b/ or Interferon$.mp. or interferon alpha-2a.mp. or interferon alpha-2b.mp. or IFNalpha2a.mp. or IFNalpha2b.mp. or interferon alpha 2a.mp. or interferon alpha 2b.mp. or exp Polyethylene Glycols/ or pegasys.mp. or Peg-intron.mp. or peginterferon alpha-2a.mp. or peginterferon alpha-2b.mp. or peginterferon alpha 2a.mp. or peginterferon alpha 2b.mp. or pegylated interferon$.mp. or IFN$.mp. or PEG IFN$.mp. or Ribavirin/ or ribavirin.mp. or RBV.mp. or exp Protease Inhibitors/ or protease inhibitor$.mp. or polymerase inhibit$.mp. or HCV protease$.mp. or telaprevir.mp. or boceprevir.mp.	379770
3	1 and 2	17643
4	(randomized controlled trial or controlled clinical trial or meta analysis or review).pt. or clinical trials as topic/ or cohort studies/ or randomized.ab. or randomly.ab. or placebo.ab. or (systematic adj1 review).ti,ab.	2497187
5	3 and 4	5889
6	limit 5 to (yr="2002 -Current" and ("adult (19 to 44 years)" or "middle age (45 to 64 years)" or "all aged (65 and over)"))	1380
7	(unsafe or safety or harm$ or complication$ or poison$ or risk$).mp. or AE.fs. or MO.fs. or PO.fs. or TO.fs. or CT.fs. or side-effect$.mp. or (undesirable adj1 effect$).mp. or (treatment adj1 emergent).mp. or tolerab$.mp. or toxic$.mp. or adrs.mp. or (adverse adj2 (effect or effects or reaction or reactions or event or events or outcome or outcomes)).mp.	3889277
8	1 and 2 and 7	7391
9	4 and 8	3164
10	limit 9 to (yr="2002 -Current" and ("adult (19 to 44 years)" or "middle age (45 to 64 years)" or "all aged (65 and over)"))	883
11	Counseling/ or Sex Counseling/ or Health Education/ or Patient Education as	268554

	Topic/ or Psychotherapy/ or Behavior Therapy/ or Cognitive Therapy/ or Immunization/ or Immunotherapy/ or Psychotherapy, Brief/ or Socioenvironmental Therapy/	
12	1 and 11	660

Updated Search after Peer Review: 4/04/2012

Ovid MEDLINE Search Strategy 1947 to February Week 3 2011 Searched February 28, 2011; Update Search April 04, 2012	
1	Hepatitis C/ or Hepatitis C, Chronic/ or Hepacivirus/ or Hepatitis C.mp. or hepacivirus$.mp. or HCV.mp.
2	Antiviral agents/ or Interferons/ or Interferon-alpha/ or Interferon Alfa-2a/ or Interferon Alpha-2b/ or Interferon$.mp. or interferon alpha-2a.mp. or interferon alpha-2b.mp. or IFNalpha2a.mp. or IFNalpha2b.mp. or interferon alpha 2a.mp. or interferon alpha 2b.mp. or exp Polyethylene Glycols/ or pegasys.mp. or Peg-intron.mp. or peginterferon alpha-2a.mp. or peginterferon alpha-2b.mp. or peginterferon alpha 2a.mp. or peginterferon alpha 2b.mp. or pegylated interferon$.mp. or IFN$.mp. or PEG IFN$.mp. or Ribavirin/ or ribavirin.mp. or RBV.mp. or exp Protease Inhibitors/ or protease inhibitor$.mp. or polymerase inhibit$.mp. or HCV protease$.mp. or telaprevir.mp. or boceprevir.mp.
3	1 and 2
4	(randomized controlled trial or controlled clinical trial or meta analysis or review).pt. or clinical trials as topic/ or cohort studies/ or randomized.ab. or randomly.ab. or placebo.ab. or (systematic adj1 review).ti,ab.
5	3 and 4
6	limit 5 to (yr="2002 -Current" and ("adult (19 to 44 years)" or "middle age (45 to 64 years)" or "all aged (65 and over)"))
7	(unsafe or safety or harm$ or complication$ or poison$ or risk$).mp. or AE.fs. or MO.fs. or PO.fs. or TO.fs. or CT.fs. or side-effect$.mp. or (undesirable adj1 effect$).mp. or (treatment adj1 emergent).mp. or tolerab$.mp. or toxic$.mp. or adrs.mp. or (adverse adj2 (effect or effects or reaction or reactions or event or events or outcome or outcomes)).mp.
8	1 and 2 and 7
9	4 and 8

10	limit 9 to (yr="2002 -Current" and ("adult (19 to 44 years)" or "middle age (45 to 64 years)" or "all aged (65 and over)"))
11	Counseling/ or Sex Counseling/ or Health Education/ or Patient Education as Topic/ or Psychotherapy/ or Behavior Therapy/ or Cognitive Therapy/ or Immunization/ or Immunotherapy/ or Psychotherapy, Brief/ or Socioenvironmental Therapy/
12	1 and 11

EMBASE Search Strategy 1976 – 2011 Searched April 11, 2011; Update Search April 4, 2012	
13	#12 AND (2002:py OR 2003:py OR 2004:py OR 2005:py OR 2006:py OR 2007:py OR 2008:py OR 2009:py OR 2010:py OR 2011:py)
12	#3 AND #11
11	#1 AND #10
10	'counseling'/exp OR 'patient guidance'/exp OR 'patient counseling'/exp OR 'sexual counseling'/exp OR 'psychotherapy'/exp OR 'cognitive therapy'/exp OR 'behavior therapy'/exp OR 'sex therapy'/exp OR 'patient education'/exp OR 'immunization'/exp OR 'virus vaccine'/exp OR 'immunotherapy'/exp OR counsel* OR 'socioenvironmental therapy'/de AND [embase]/lim
9	#8 AND (2002:py OR 2003:py OR 2004:py OR 2005:py OR 2006:py OR 2007:py OR 2008:py OR 2009:py OR 2010:py OR 2011:py)
8	#3 AND #7
7	#1 AND #2 AND #6
6	'adverse drug reaction'/exp OR 'adverse outcome'/exp OR 'toxicity'/exp OR 'drug toxicity'/exp OR 'drug tolerability'/exp OR 'drug safety'/exp OR 'patient safety'/exp OR unsafe OR 'safety'/exp OR harm* OR complication* OR poison* OR 'side effect'/exp OR 'side effects' OR undesirable NEAR/1 effect* OR treatment NEAR/1 emergen* OR tolerab* OR toxic* OR adrs OR adverse NEAR/2 (effect OR effects OR reaction OR reactions OR event OR events OR outcome OR outcomes) AND [embase]/lim
5	#4 AND (2002:py OR 2003:py OR 2004:py OR 2005:py OR 2006:py OR 2007:py OR 2008:py OR 2009:py OR 2010:py OR 2011:py)
4	#1 AND #2 AND #3
3	'cohort analysis'/exp OR 'meta analysis'/exp OR 'randomized controlled trial'/exp OR 'systematic review'/exp OR 'controlled clinical trial'/exp OR 'placebo'/exp OR 'clinical trial'/exp OR 'controlled study'/exp OR randomized.ab OR randomly.ab AND [embase]/lim
2	'antivirus agent'/exp OR 'antivirus agent' OR 'interferon'/exp OR interferon OR 'alpha interferon'/exp OR 'alpha interferon' OR 'alpha2a interferon'/exp OR 'alpha2a interferon' OR 'alpha2b interferon'/exp OR 'alpha2b interferon' OR 'macrogol derivative'/exp OR 'macrogol derivative' OR 'peginterferon'/exp OR peginterferon OR 'peginterferon alpha2a'/exp OR 'peginterferon alpha2a' OR 'peginterferon alpha2b'/exp OR 'peginterferon alpha2b' OR

	'ribavirin'/exp OR ribavirin OR 'protease inhibitor'/exp OR 'protease inhibitor' OR 'rna directed dna polymerase inhibitor'/exp OR 'rna directed dna polymerase inhibitor' OR 'rna directed rna polymerase inhibitor'/exp OR 'rna directed rna polymerase inhibitor' OR 'telaprevir'/exp OR telaprevir OR 'boceprevir'/exp OR boceprevir OR 'antiviral agent':ab,ti OR interferon*:ab,ti OR 'interferon-alpha2a':ab,ti OR 'interferon-alpha2b':ab,ti OR 'interferon alpha':ab,ti OR 'interferon alpha 2a':ab,ti OR 'interferon alpha 2b':ab,ti OR 'polyethylene glycols':ab,ti OR pegasys:ab,ti OR 'peg intron':ab,ti OR 'peginterferon alpha':ab,ti OR 'peginterferon alpha 2a':ab,ti OR 'peginterferon alpha 2b':ab,ti OR 'pegylated interferon':ab,ti OR ifn:ab,ti OR 'peg ifn':ab,ti OR 'peg ifns':ab,ti OR ribavirin:ab,ti OR rbv:ab,ti OR 'protease inhibitor':ab,ti OR 'protease inhibitors':ab,ti OR 'polymerase inhibitor':ab,ti OR 'polymerase inhibitors':ab,ti OR 'hcv protease':ab,ti OR telaprevir:ab,ti OR boceprevir:ab,ti AND [embase]/lim
1	'hepatitis c virus':de OR 'hepatitis c':de OR 'chronic active hepatitis':de OR 'hepatitis non a non b':de AND [embase]/lim

Cochrane Library: Cochrane Database of Systematic Reviews & Database of Abstracts of Reviews of Effects 2002-2011 Searched April 11, 2011, Update Search April 4, 2012
“Hepatitis C” OR Hepacivirus OR HCV (Title, Abstract, Keyword)
Limit to reviews, published 2002-2011

Cochrane Library: Cochrane Central Register of Controlled Trials 2002-2011 Searched April 11, 2011; Update Search April 04, 2012
"Interferon-alpha" OR "Interferon Alfa-2a" OR "Interferon Alpha-2b" OR "IFNalpha2a" OR "IFNalpha2b" OR "Interferon alpha 2a" OR "interferon alpha 2b" OR "Polyethylene Glycol*" OR pegasys OR Peg-intron OR "peginterferon alpha-2a" OR "peginterferon alpha-2b" OR "peginterferon alpha 2a" OR "peginterferon alpha 2b" OR "pegylated interferon*" OR IFN* OR "PEG IFN*" OR Ribavirin OR RBV OR "protease inhibitor*" OR "polymerase inhibit*" OR "HCV protease*" OR telaprevir OR boceprevir (Title, Abstract, Keyword)

SCOPUS Search Strategy 1960-2011 Searched April 11, 2011; Update Search April 04, 2012	
11	(TITLE-ABS-KEY(“hepatitis c” OR hepacivirus OR hcv)) AND (TITLE-ABS-KEY(cohort* OR "meta analysis" OR "randomized controlled trial*" OR "systematic review*" OR "controlled clinical trial*" OR "placebo" OR "clinical trial*" OR randomized OR randomly)) AND (TITLE-ABS-KEY(counseling OR “health education” OR “patient education” OR psychotherapy OR “behavior therapy” OR “cognitive therapy” OR immuniz* OR immunotherapy OR “socioenvironmental therapy” OR “cognitive behavior* therapy” OR vaccine*))

10	TITLE-ABS-KEY(counseling OR “health education” OR “patient education” OR psychotherapy OR “behavior therapy” OR “cognitive therapy” OR immuniz* OR immunotherapy OR “socioenvironmental therapy” OR “cognitive behavior* therapy” OR vaccine*)
9	(TITLE-ABS-KEY(“hepatitis c” OR hepacivirus OR hcv)) AND ((TITLE-ABS-KEY(“antiviral agent*” OR interferon* OR interferon-alpha OR “interferon alfa-2a” OR “interferon alpha-2b” OR ifnalpha2a OR ifnalpha2b OR “interferon alpha 2a” OR “interferon alpha 2b” OR “polyethylene glycols” OR pegasys OR peg-intron) OR TITLE-ABS-KEY(“peginterferon alpha-2a” OR “peginterferon alpha-2b” OR “peginterferon alpha 2a” OR “peginterferon alpha 2b” OR “pegylated interferon*” OR ifn* OR peg ifn* OR ribavirin OR rbv OR “protease inhibitor*” OR “polymerase inhibitor*” OR “hcv protease*” OR telapr))) AND (TITLE-ABS-KEY(cohort* OR "meta analysis" OR "randomized controlled trial*" OR "systematic review*" OR "controlled clinical trial*" OR "placebo" OR "clinical trial*" OR randomized OR randomly)) AND (TITLE-ABS-KEY(unsafe OR safety OR harm* OR complication* OR poison* OR risk* OR side-effect* OR “side effect*” OR “undesirable effect* OR “treatment emergent” OR tolerab* OR toxic* OR “adverse effect*” OR “adverse reaction*” OR “adverse event*” OR “adverse outcome*”)) AND (LIMIT-TO(PUBYEAR, 2011) OR LIMIT-TO(PUBYEAR, 2010) OR LIMIT-TO(PUBYEAR, 2009) OR LIMIT-TO(PUBYEAR, 2008) OR LIMIT-TO(PUBYEAR, 2007) OR LIMIT-TO(PUBYEAR, 2006) OR LIMIT-TO(PUBYEAR, 2005) OR LIMIT-TO(PUBYEAR, 2004) OR LIMIT-TO(PUBYEAR, 2003))
8	(TITLE-ABS-KEY(“hepatitis c” OR hepacivirus OR hcv)) AND ((TITLE-ABS-KEY(“antiviral agent*” OR interferon* OR interferon-alpha OR “interferon alfa-2a” OR “interferon alpha-2b” OR ifnalpha2a OR ifnalpha2b OR “interferon alpha 2a” OR “interferon alpha 2b” OR “polyethylene glycols” OR pegasys OR peg-intron) OR TITLE-ABS-KEY(“peginterferon alpha-2a” OR “peginterferon alpha-2b” OR “peginterferon alpha 2a” OR “peginterferon alpha 2b” OR “pegylated interferon*” OR ifn* OR peg ifn* OR ribavirin OR rbv OR “protease inhibitor*” OR “polymerase inhibitor*” OR “hcv protease*” OR telapr))) AND (TITLE-ABS-KEY(cohort* OR "meta analysis" OR "randomized controlled trial*" OR "systematic review*" OR "controlled clinical trial*" OR "placebo" OR "clinical trial*" OR randomized OR randomly)) AND (TITLE-ABS-KEY(unsafe OR safety OR harm* OR complication* OR poison* OR risk* OR side-effect* OR “side effect*” OR “undesirable effect* OR “treatment emergent” OR tolerab* OR toxic* OR “adverse effect*” OR “adverse reaction*” OR “adverse event*” OR “adverse outcome*”))
7	TITLE-ABS-KEY(unsafe OR safety OR harm* OR complication* OR poison* OR risk* OR side-effect* OR “side effect*” OR “undesirable effect* OR “treatment emergent” OR tolerab* OR toxic* OR “adverse effect*” OR “adverse reaction*” OR “adverse event*” OR “adverse outcome*”)
6	(TITLE-ABS-KEY(“hepatitis c” OR hepacivirus OR hcv)) AND ((TITLE-ABS-KEY(“antiviral agent*” OR interferon* OR interferon-alpha OR “interferon alfa-2a” OR “interferon alpha-2b” OR ifnalpha2a OR ifnalpha2b OR “interferon alpha 2a” OR “interferon alpha 2b” OR “polyethylene glycols” OR pegasys OR peg-intron) OR TITLE-ABS-KEY(“peginterferon alpha-2a” OR “peginterferon alpha-2b” OR “peginterferon alpha 2a” OR “peginterferon alpha 2b” OR “pegylated interferon*” OR ifn* OR peg ifn* OR ribavirin OR rbv OR “protease inhibitor*” OR “polymerase inhibitor*” OR “hcv protease*”

	OR telapr))) AND (TITLE-ABS-KEY(cohort* OR "meta analysis" OR "randomized controlled trial*" OR "systematic review*" OR "controlled clinical trial*" OR "placebo" OR "clinical trial*" OR randomized OR randomly)) AND (LIMIT-TO(PUBYEAR, 2011) OR LIMIT-TO(PUBYEAR, 2010) OR LIMIT-TO(PUBYEAR, 2009) OR LIMIT-TO(PUBYEAR, 2008) OR LIMIT-TO(PUBYEAR, 2007) OR LIMIT-TO(PUBYEAR, 2006) OR LIMIT-TO(PUBYEAR, 2005) OR LIMIT-TO(PUBYEAR, 2004) OR LIMIT-TO(PUBYEAR, 2003) OR LIMIT-TO(PUBYEAR, 2002))
5	(TITLE-ABS-KEY("hepatitis c" OR hepacivirus OR hcv)) AND ((TITLE-ABS-KEY("antiviral agent*" OR interferon* OR interferon-alpha OR "interferon alfa-2a" OR "interferon alpha-2b" OR ifnalpha2a OR ifnalpha2b OR "interferon alpha 2a" OR "interferon alpha 2b" OR "polyethylene glycols" OR pegasys OR peg-intron) OR TITLE-ABS-KEY("peginterferon alpha-2a" OR "peginterferon alpha-2b" OR "peginterferon alpha 2a" OR "peginterferon alpha 2b" OR "pegylated interferon*" OR ifn* OR peg ifn* OR ribavirin OR rbv OR "protease inhibitor*" OR "polymerase inhibitor*" OR "hcv protease*" OR telapr))) AND (TITLE-ABS-KEY(cohort* OR "meta analysis" OR "randomized controlled trial*" OR "systematic review*" OR "controlled clinical trial*" OR "placebo" OR "clinical trial*" OR randomized OR randomly))
4	(TITLE-ABS-KEY("hepatitis c" OR hepacivirus OR hcv)) AND ((TITLE-ABS-KEY("antiviral agent*" OR interferon* OR interferon-alpha OR "interferon alfa-2a" OR "interferon alpha-2b" OR ifnalpha2a OR ifnalpha2b OR "interferon alpha 2a" OR "interferon alpha 2b" OR "polyethylene glycols" OR pegasys OR peg-intron) OR TITLE-ABS-KEY("peginterferon alpha-2a" OR "peginterferon alpha-2b" OR "peginterferon alpha 2a" OR "peginterferon alpha 2b" OR "pegylated interferon*" OR ifn* OR peg ifn* OR ribavirin OR rbv OR "protease inhibitor*" OR "polymerase inhibitor*" OR "hcv protease*" OR telapr))) AND (TITLE-ABS-KEY(cohort* OR "meta analysis" OR "randomized controlled trial*" OR "systematic review*" OR "controlled clinical trial*" OR "placebo" OR "clinical trial*" OR randomized OR randomly))
3	TITLE-ABS-KEY(cohort* OR "meta analysis" OR "randomized controlled trial*" OR "systematic review*" OR "controlled clinical trial*" OR "placebo" OR "clinical trial*" OR randomized OR randomly)
2	(TITLE-ABS-KEY("antiviral agent*" OR interferon* OR interferon-alpha OR "interferon alfa-2a" OR "interferon alpha-2b" OR ifnalpha2a OR ifnalpha2b OR "interferon alpha 2a" OR "interferon alpha 2b" OR "polyethylene glycols" OR pegasys OR peg-intron) OR TITLE-ABS-KEY("peginterferon alpha-2a" OR "peginterferon alpha-2b" OR "peginterferon alpha 2a" OR "peginterferon alpha 2b" OR "pegylated interferon*" OR ifn* OR peg ifn* OR ribavirin OR rbv OR "protease inhibitor*" OR "polymerase inhibitor*" OR "hcv protease*" OR telaprevir))
1	TITLE-ABS-KEY("hepatitis c" OR hepacivirus OR hcv)

OvidSP PSYCINFO Search Strategy 1806 to February Week 4 2011 Searched April 12, 2011; Update Search April 4, 2012	
1	hepatitis/ or (Hepatitis C or hepacivirus$ or HCV).mp.

2	[exp treatment/ or exp intervention/ or exp psychotherapy/ or exp alcohol rehabilitation/ or exp counseling/ or exp support groups/ or exp rehabilitation/ or exp mental health services/ or exp community services/ or exp outreach programs/ or exp drug rehabilitation/ or exp sobriety/ or exp detoxification/ or exp drug rehabilitation/ or exp treatment outcomes/ or exp alcoholics anonymous/]
3	alcohol*.mp.
4	1 and 2 and 3

Clinicaltrials.gov Searched April 12, 2011; Update Search April 4, 2012
interferon alfa OR peginterferon OR ribavirin OR telaprevir OR boceprevir | Closed Studies | Studies With Results | hepatitis c | Adult, Senior

Updated Search: 8/28/2012

Ovid MEDLINE Search Strategy 1947 to February Week 3 2011 Searched February 28, 2011; Update Search April 04, 2012; Update Search August 28, 2012	
1	Hepatitis C/ or Hepatitis C, Chronic/ or Hepacivirus/ or Hepatitis C.mp. or hepacivirus$.mp. or HCV.mp.
2	Antiviral agents/ or Interferons/ or Interferon-alpha/ or Interferon Alfa-2a/ or Interferon Alpha-2b/ or Interferon$.mp. or interferon alpha-2a.mp. or interferon alpha-2b.mp. or IFNalpha2a.mp. or IFNalpha2b.mp. or interferon alpha 2a.mp. or interferon alpha 2b.mp. or exp Polyethylene Glycols/ or pegasys.mp. or Peg-intron.mp. or peginterferon alpha-2a.mp. or peginterferon alpha-2b.mp. or peginterferon alpha 2a.mp. or peginterferon alpha 2b.mp. or pegylated interferon$.mp. or IFN$.mp. or PEG IFN$.mp. or Ribavirin/ or ribavirin.mp. or RBV.mp. or exp Protease Inhibitors/ or protease inhibitor$.mp. or polymerase inhibit$.mp. or HCV protease$.mp. or telaprevir.mp. or boceprevir.mp.
3	1 and 2
4	(randomized controlled trial or controlled clinical trial or meta analysis or review).pt. or clinical trials as topic/ or cohort studies/ or randomized.ab. or randomly.ab. or placebo.ab. or (systematic adj1 review).ti,ab.
5	3 and 4
6	limit 5 to (yr="2002 -Current" and ("adult (19 to 44 years)" or "middle age (45 to 64 years)" or "all aged (65 and over)"))

7	(unsafe or safety or harm$ or complication$ or poison$ or risk$).mp. or AE.fs. or MO.fs. or PO.fs. or TO.fs. or CT.fs. or side-effect$.mp. or (undesirable adj1 effect$).mp. or (treatment adj1 emergent).mp. or tolerab$.mp. or toxic$.mp. or adrs.mp. or (adverse adj2 (effect or effects or reaction or reactions or event or events or outcome or outcomes)).mp.
8	1 and 2 and 7
9	4 and 8
10	limit 9 to (yr="2002 -Current" and ("adult (19 to 44 years)" or "middle age (45 to 64 years)" or "all aged (65 and over)"))
11	Counseling/ or Sex Counseling/ or Health Education/ or Patient Education as Topic/ or Psychotherapy/ or Behavior Therapy/ or Cognitive Therapy/ or Immunization/ or Immunotherapy/ or Psychotherapy, Brief/ or Socioenvironmental Therapy/
12	1 and 11

EMBASE Search Strategy 1976 – 2011 An updated search for August 28, 2012 was not conducted as Oregon Health and Sciences University no longer subscribes to this database.

Cochrane Library: Cochrane Database of Systematic Reviews & Database of Abstracts of Reviews of Effects 2002-2011 Searched April 11, 2011, Update Search April 4, 2012; Update Search August 28, 2012
"Hepatitis C" OR Hepacivirus OR HCV (Title, Abstract, Keyword)
Limit to reviews, published 2002-2011

Cochrane Library: Cochrane Central Register of Controlled Trials 2002-2011 Searched April 11, 2011; Update Search April 04, 2012; Update Search August 28, 2012
"Interferon-alpha" OR "Interferon Alfa-2a" OR "Interferon Alpha-2b" OR "IFNalpha2a" OR "IFNalpha2b" OR "Interferon alpha 2a" OR "interferon alpha 2b" OR "Polyethylene Glycol*" OR pegasys OR Peg-intron OR "peginterferon alpha-2a" OR "peginterferon alpha-2b" OR "peginterferon alpha 2a" OR "peginterferon alpha 2b" OR "pegylated interferon*" OR IFN* OR "PEG IFN*" OR Ribavirin OR RBV OR "protease inhibitor*" OR "polymerase inhibit*" OR "HCV protease*" OR telaprevir OR boceprevir (Title, Abstract, Keyword)

SCOPUS Search Strategy 1960-2011 Searched April 11, 2011; Update Search April 04, 2012; Update Search August 28, 2012	
11	(TITLE-ABS-KEY("hepatitis c" OR hepacivirus OR hcv)) AND (TITLE-ABS-KEY(cohort* OR "meta analysis" OR "randomized controlled trial*" OR "systematic review*" OR "controlled clinical trial*" OR "placebo" OR "clinical trial*" OR randomized OR randomly)) AND (TITLE-ABS-KEY(counseling OR "health education" OR "patient

	education” OR psychotherapy OR “behavior therapy” OR “cognitive therapy” OR immuniz* OR immunotherapy OR “socioenvironmental therapy” OR “cognitive behavior* therapy” OR vaccine*))
10	TITLE-ABS-KEY(counseling OR “health education” OR “patient education” OR psychotherapy OR “behavior therapy” OR “cognitive therapy” OR immuniz* OR immunotherapy OR “socioenvironmental therapy” OR “cognitive behavior* therapy” OR vaccine*)
9	(TITLE-ABS-KEY(“hepatitis c” OR hepacivirus OR hcv)) AND ((TITLE-ABS-KEY(“antiviral agent*” OR interferon* OR interferon-alpha OR “interferon alfa-2a” OR “interferon alpha-2b” OR ifnalpha2a OR ifnalpha2b OR “interferon alpha 2a” OR “interferon alpha 2b” OR “polyethylene glycols” OR pegasys OR peg-intron) OR TITLE-ABS-KEY(“peginterferon alpha-2a” OR “peginterferon alpha-2b” OR “peginterferon alpha 2a” OR “peginterferon alpha 2b” OR “pegylated interferon*” OR ifn* OR peg ifn* OR ribavirin OR rbv OR “protease inhibitor*” OR “polymerase inhibitor*” OR “hcv protease*” OR telapr))) AND (TITLE-ABS-KEY(cohort* OR "meta analysis" OR "randomized controlled trial*" OR "systematic review*" OR "controlled clinical trial*" OR "placebo" OR "clinical trial*" OR randomized OR randomly)) AND (TITLE-ABS-KEY(unsafe OR safety OR harm* OR complication* OR poison* OR risk* OR side-effect* OR “side effect*” OR “undesirable effect* OR “treatment emergent” OR tolerab* OR toxic* OR “adverse effect*” OR “adverse reaction*” OR “adverse event*” OR “adverse outcome*”)) AND (LIMIT-TO(PUBYEAR, 2011) OR LIMIT-TO(PUBYEAR, 2010) OR LIMIT-TO(PUBYEAR, 2009) OR LIMIT-TO(PUBYEAR, 2008) OR LIMIT-TO(PUBYEAR, 2007) OR LIMIT-TO(PUBYEAR, 2006) OR LIMIT-TO(PUBYEAR, 2005) OR LIMIT-TO(PUBYEAR, 2004) OR LIMIT-TO(PUBYEAR, 2003))
8	(TITLE-ABS-KEY(“hepatitis c” OR hepacivirus OR hcv)) AND ((TITLE-ABS-KEY(“antiviral agent*” OR interferon* OR interferon-alpha OR “interferon alfa-2a” OR “interferon alpha-2b” OR ifnalpha2a OR ifnalpha2b OR “interferon alpha 2a” OR “interferon alpha 2b” OR “polyethylene glycols” OR pegasys OR peg-intron) OR TITLE-ABS-KEY(“peginterferon alpha-2a” OR “peginterferon alpha-2b” OR “peginterferon alpha 2a” OR “peginterferon alpha 2b” OR “pegylated interferon*” OR ifn* OR peg ifn* OR ribavirin OR rbv OR “protease inhibitor*” OR “polymerase inhibitor*” OR “hcv protease*” OR telapr))) AND (TITLE-ABS-KEY(cohort* OR "meta analysis" OR "randomized controlled trial*" OR "systematic review*" OR "controlled clinical trial*" OR "placebo" OR "clinical trial*" OR randomized OR randomly)) AND (TITLE-ABS-KEY(unsafe OR safety OR harm* OR complication* OR poison* OR risk* OR side-effect* OR “side effect*” OR “undesirable effect* OR “treatment emergent” OR tolerab* OR toxic* OR “adverse effect*” OR “adverse reaction*” OR “adverse event*” OR “adverse outcome*”))
7	TITLE-ABS-KEY(unsafe OR safety OR harm* OR complication* OR poison* OR risk* OR side-effect* OR “side effect*” OR “undesirable effect* OR “treatment emergent” OR tolerab* OR toxic* OR “adverse effect*” OR “adverse reaction*” OR “adverse event*” OR “adverse outcome*”)
6	(TITLE-ABS-KEY(“hepatitis c” OR hepacivirus OR hcv)) AND ((TITLE-ABS-KEY(“antiviral agent*” OR interferon* OR interferon-alpha OR “interferon alfa-2a” OR “interferon alpha-2b” OR ifnalpha2a OR ifnalpha2b OR “interferon alpha 2a” OR “interferon alpha 2b” OR “polyethylene glycols” OR pegasys OR peg-intron) OR TITLE-ABS-KEY(“peginterferon alpha-2a” OR “peginterferon alpha-2b” OR “peginterferon alpha

	2a" OR "peginterferon alpha 2b" OR "pegylated interferon*" OR ifn* OR peg ifn* OR ribavirin OR rbv OR "protease inhibitor*" OR "polymerase inhibitor*" OR "hcv protease*" OR telapr))) AND (TITLE-ABS-KEY(cohort* OR "meta analysis" OR "randomized controlled trial*" OR "systematic review*" OR "controlled clinical trial*" OR "placebo" OR "clinical trial*" OR randomized OR randomly)) AND (LIMIT-TO(PUBYEAR, 2011) OR LIMIT-TO(PUBYEAR, 2010) OR LIMIT-TO(PUBYEAR, 2009) OR LIMIT-TO(PUBYEAR, 2008) OR LIMIT-TO(PUBYEAR, 2007) OR LIMIT-TO(PUBYEAR, 2006) OR LIMIT-TO(PUBYEAR, 2005) OR LIMIT-TO(PUBYEAR, 2004) OR LIMIT-TO(PUBYEAR, 2003) OR LIMIT-TO(PUBYEAR, 2002))
5	(TITLE-ABS-KEY("hepatitis c" OR hepacivirus OR hcv)) AND ((TITLE-ABS-KEY("antiviral agent*" OR interferon* OR interferon-alpha OR "interferon alfa-2a" OR "interferon alpha-2b" OR ifnalpha2a OR ifnalpha2b OR "interferon alpha 2a" OR "interferon alpha 2b" OR "polyethylene glycols" OR pegasys OR peg-intron) OR TITLE-ABS-KEY("peginterferon alpha-2a" OR "peginterferon alpha-2b" OR "peginterferon alpha 2a" OR "peginterferon alpha 2b" OR "pegylated interferon*" OR ifn* OR peg ifn* OR ribavirin OR rbv OR "protease inhibitor*" OR "polymerase inhibitor*" OR "hcv protease*" OR telapr))) AND (TITLE-ABS-KEY(cohort* OR "meta analysis" OR "randomized controlled trial*" OR "systematic review*" OR "controlled clinical trial*" OR "placebo" OR "clinical trial*" OR randomized OR randomly))
4	(TITLE-ABS-KEY("hepatitis c" OR hepacivirus OR hcv)) AND ((TITLE-ABS-KEY("antiviral agent*" OR interferon* OR interferon-alpha OR "interferon alfa-2a" OR "interferon alpha-2b" OR ifnalpha2a OR ifnalpha2b OR "interferon alpha 2a" OR "interferon alpha 2b" OR "polyethylene glycols" OR pegasys OR peg-intron) OR TITLE-ABS-KEY("peginterferon alpha-2a" OR "peginterferon alpha-2b" OR "peginterferon alpha 2a" OR "peginterferon alpha 2b" OR "pegylated interferon*" OR ifn* OR peg ifn* OR ribavirin OR rbv OR "protease inhibitor*" OR "polymerase inhibitor*" OR "hcv protease*" OR telapr))) AND (TITLE-ABS-KEY(cohort* OR "meta analysis" OR "randomized controlled trial*" OR "systematic review*" OR "controlled clinical trial*" OR "placebo" OR "clinical trial*" OR randomized OR randomly))
3	TITLE-ABS-KEY(cohort* OR "meta analysis" OR "randomized controlled trial*" OR "systematic review*" OR "controlled clinical trial*" OR "placebo" OR "clinical trial*" OR randomized OR randomly)
2	(TITLE-ABS-KEY("antiviral agent*" OR interferon* OR interferon-alpha OR "interferon alfa-2a" OR "interferon alpha-2b" OR ifnalpha2a OR ifnalpha2b OR "interferon alpha 2a" OR "interferon alpha 2b" OR "polyethylene glycols" OR pegasys OR peg-intron) OR TITLE-ABS-KEY("peginterferon alpha-2a" OR "peginterferon alpha-2b" OR "peginterferon alpha 2a" OR "peginterferon alpha 2b" OR "pegylated interferon*" OR ifn* OR peg ifn* OR ribavirin OR rbv OR "protease inhibitor*" OR "polymerase inhibitor*" OR "hcv protease*" OR telaprevir))
1	TITLE-ABS-KEY("hepatitis c" OR hepacivirus OR hcv)

OvidSP PSYCINFO Search Strategy 1806 to February Week 4 2011 Searched April 12, 2011; Update Search April 4, 2012; Update Search August 28, 2012	
1	hepatitis/ or (Hepatitis C or hepacivirus$ or HCV).mp.

2	[exp treatment/ or exp intervention/ or exp psychotherapy/ or exp alcohol rehabilitation/ or exp counseling/ or exp support groups/ or exp rehabilitation/ or exp mental health services/ or exp community services/ or exp outreach programs/ or exp drug rehabilitation/ or exp sobriety/ or exp detoxification/ or exp drug rehabilitation/ or exp treatment outcomes/ or exp alcoholics anonymous/]
3	alcohol*.mp.
4	1 and 2 and 3

Clinicaltrials.gov Searched April 12, 2011; Update Search April 4, 2012, Update Search August 28, 2012
interferon alfa OR peginterferon OR ribavirin OR telaprevir OR boceprevir | Closed Studies | Studies With Results | hepatitis c | Adult, Senior

Appendix B. Hepatitis C Treatment: Inclusion Criteria by Key Question

	Inclusion Criteria
Populations	Asymptomatic adults with chronic hepatitis C virus infection who have not received antiviral drug treatment previously Subgroups include: HCV genotype, race, sex, stage of disease, viral load, weight, and others (e.g. genetic markers) • Excluded: Pregnant women, HIV co-infected, transplant recipients, patients with renal failure
Interventions	**KQ 1a and b:** **1a.** What is the comparative effectiveness of antiviral treatment in improving health outcomes in patients with HCV infection? **1b.** How does the comparative effectiveness of antiviral treatment for health outcomes vary according to patient subgroup characteristics, including but not limited to HCV genotype, race, sex, disease severity or genetic markers? **KQ 2a and b:** **2.** What is the comparative effectiveness of antiviral treatments in improving intermediate outcomes, such as the rate of viremia, aminotransaminase levels, and histologic changes? **2a.** How does the comparative effectiveness of antiviral treatment for intermediate outcomes vary according to patient subgroup characteristics, including but not limited to HCV genotype, race, sex, disease severity or genetic markers? **KQ 3a and b:** **3a.** What are the comparative harms (including intolerance to treatment) associated with antiviral treatment? **3b.** Do these harms differ according to patient subgroup characteristics, including HCV genotype, race, sex, disease severity or genetic markers? **KQ 4:** Have improvements in intermediate outcomes (viremia, liver function tests, histologic changes) been shown to reduce the risk or rates of health outcomes from HCV infection?

	Inclusion Criteria
Comparisons	**KQ 1a and b:** **1a.** What is the comparative effectiveness of antiviral treatment in improving health outcomes in patients with HCV infection? **1b.** How does the comparative effectiveness of antiviral treatment for health outcomes vary according to patient subgroup characteristics, including but not limited to HCV genotype, race, sex, disease severity or genetic markers? **KQ 2a and b:** **2a.** What is the comparative effectiveness of antiviral treatments in improving intermediate outcomes, such as the rate of viremia, aminotransaminase levels, and histologic changes? **2b.** How does the comparative effectiveness of antiviral treatment for intermediate outcomes vary according to patient subgroup characteristics, including but not limited to HCV genotype, race, sex, disease severity or genetic markers? **KQ 3a and b:** **3.** What are the comparative harms (including intolerance to treatment) associated with antiviral treatment? **3a.** Do these harms differ according to patient subgroup characteristics, including HCV genotype, race, sex, disease severity or genetic markers? **KQ 4:** Have improvements in intermediate outcomes (viremia, liver function tests, histologic changes) been shown to reduce the risk or rates of health outcomes from HCV infection?
Outcomes	Clinical outcomes • Mortality (all-cause or hepatic) • Cirrhosis • Hepatic decompensation • Hepatocellular carcinoma • Need for liver transplantation • Quality of life • Harms from antiviral treatments (including withdrawals due to adverse events, neutropenia, anemia, psychological adverse events, flu-like symptoms, rash) Intermediate outcomes • Sustained virological response • Improvement in liver histology
Settings	All settings (including primary care and specialty settings) and locales, though focus on studies conducted in the U.S. and other developed countries.
Study designs	**KQ 3a and b:** **3a.** What are the comparative harms (including intolerance to treatment) associated with antiviral treatment? **3b.** Do these harms differ according to patient subgroup characteristics, including HCV genotype, race, sex, disease severity or genetic markers? **KQ 4:** Have improvements in intermediate outcomes (viremia, liver function tests, histologic changes) been shown to reduce the risk or rates of health outcomes from HCV infection?

Appendix C. Included Studies List

Key Question 1: Not Applicable

Key Questions 2 and 3:

Abergel A, Hezode C, Leroy V, et al. Peginterferon alpha-2b plus ribavirin for treatment of chronic hepatitis C with severe fibrosis: a multicentre randomized controlled trial comparing two doses of peginterferon alpha-2b. Journal of Viral Hepatitis. 2006 Dec;13(12):811-20. PMID: 17109680

Andriulli A, Cursaro C, Cozzolongo R, et al. Early discontinuation of ribavirin in HCV-2 and HCV-3 patients responding to Peg-interferon alpha-2a and ribavirin. Journal of Viral Hepatitis. 2009 Jan;16(1):28-35. PMID: 18761603

Ascione A, De Luca M, Tartaglione MT, et al. Peginterferon alfa-2a plus ribavirin is more effective than peginterferon alfa-2b plus ribavirin for treating chronic hepatitis C virus infection. Gastroenterology. 2010 Jan;138(1):116-22. PMID: 19852964

Berg T, von Wagner M, Nasser S, et al. Extended treatment duration for hepatitis C virus type 1: comparing 48 versus 72 weeks of peginterferon-alfa-2a plus ribavirin. Gastroenterology. 2006 Apr;130(4):1086-97. PMID: 16618403

Berg T, Weich V, Teuber G, et al. Individualized treatment strategy according to early viral kinetics in hepatitis C virus type 1-infected patients. Hepatology. 2009 Aug;50(2):369-77. PMID: 19575366

Brady DE, Torres DM, An JW, et al. Induction pegylated interferon alfa-2b in combination with ribavirin in patients with genotypes 1 and 4 chronic hepatitis C: a prospective, randomized, multicenter, open-label study. Clinical Gastroenterology & Hepatology. 2010 Jan;8(1):66-71. PMID: 19747986

Brandao C, Barone A, Carrilho F, et al. The results of a randomized trial looking at 24 weeks vs 48 weeks of treatment with peginterferon alpha-2a (40 kDa) and ribavirin combination therapy in patients with chronic hepatitis C genotype 1. Journal of Viral Hepatitis. 2006 Aug;13(8):552-9. PMID: 16901286

Bronowicki J-P, Ouzan D, Asselah T, et al. Effect of ribavirin in genotype 1 patients with hepatitis C responding to pegylated interferon alfa-2a plus ribavirin. Gastroenterology. 2006 Oct;131(4):1040-8. PMID: 17030174

Bruno R, Sacchi P, Ciappina V, et al. Viral dynamics and pharmacokinetics of peginterferon alpha-2a and peginterferon alpha-2b in naive patients with chronic hepatitis c: a randomized, controlled study. Antiviral Therapy. 2004;9(4):491-7. PMID: 15456079.

Buti M, Lurie Y, Zakharova NG, et al. Randomized trial of peginterferon alfa-2b and ribavirin for 48 or 72 weeks in patients with hepatitis C virus genotype 1 and slow virologic response. Hepatology. 2010 Oct;52(4):1201-7. PMID: 20683847

Dalgard O, Bjoro K, Ring-Larsen H, et al. Pegylated interferon alfa and ribavirin for 14 versus 24 weeks in patients with hepatitis C virus genotype 2 or 3 and rapid virological response. Hepatology. 2008 Jan;47(1):35-42. PMID: 17975791

Di Bisceglie AM, Ghalib RH, Hamzeh FM, et al. Early virologic response after peginterferon alpha-2a plus ribavirin or peginterferon alpha-2b plus ribavirin treatment in patients with chronic hepatitis C.Journal of Viral Hepatitis. 2007 Oct;14(10):721-9. PMID: 17875007.

Escudero A, Rodriguez F, Serra MA, et al. Pegylated alpha-interferon-2a plus ribavirin compared with pegylated alpha-interferon-2b plus ribavirin for initial treatment of chronic hepatitis C virus: prospective, non-randomized study. Journal of Gastroenterology & Hepatology. 2008 Jun;23(6):861-6. PMID: 18422960

Ferenci P, Laferl H, Scherzer T-M, et al. Peginterferon alfa-2a/ribavirin for 48 or 72 weeks in hepatitis C genotypes 1 and 4 patients with slow virologic response.[Reprint in Korean J Hepatol. 2010 Jun;16(2):201-5; PMID: 20606507]. Gastroenterology. 2010 Feb;138(2):503-12. PMID: 19909752

Ferenci P, Brunner H, Laferl H, et al. A randomized, prospective trial of ribavirin 400 mg/day versus 800 mg/day in combination with peginterferon alfa-2a in hepatitis C virus genotypes 2 and 3. Hepatology. 2008 Jun;47(6):1816-23. PMID: 18454510.

Fried MW, Jensen DM, Rodriguez-Torres M, et al. Improved outcomes in patients with hepatitis C with difficult-to-treat characteristics: randomized study of higher doses of peginterferon alpha-2a and ribavirin. Hepatology. 2008 Oct;48(4):1033-43. PMID: 18697207

Hadziyannis SJ, Sette H, Jr., Morgan TR, et al. Peginterferon-alpha2a and ribavirin combination therapy in chronic hepatitis C: a randomized study of treatment duration and ribavirin dose. Annals of Internal Medicine. 2004 Mar 2;140(5):346-55. PMID: 14996676

Helbling B, Jochum W, Stamenic I, et al. HCV-related advanced fibrosis/cirrhosis: randomized controlled trial of pegylated interferon alpha-2a and ribavirin. Journal of Viral Hepatitis. 2006 Nov;13(11):762-9. PMID: 17052276

Hezode C, Forestier N, Dusheiko G, et al. Telaprevir and peginterferon with or without ribavirin for chronic HCV infection. New England Journal of Medicine. 2009 Apr 30;360(18):1839-50. PMID: 19403903

Ide T, Hino T, Ogata K, et al. A randomized study of extended treatment with peginterferon alpha-2b plus ribavirin based on time to HCV RNA negative-status in patients with genotype 1b chronic hepatitis C. American Journal of Gastroenterology. 2009 Jan;104(1):70-5. PMID: 19098852

Jacobson (a) IM, Brown RS, Jr., Freilich B, et al. Peginterferon alfa-2b and weight-based or flat-dose ribavirin in chronic hepatitis C patients: a randomized trial. Hepatology. 2007 Oct;46(4):971-81. PMID: 17894303

Jacobson (b) IM, Brown RS, Jr., McCone J, et al. Impact of weight-based ribavirin with peginterferon alfa-2b in African Americans with hepatitis C virus genotype 1. Hepatology. 2007 Oct;46(4):982-90. PMID: 17894323

Jacobson IM, McHutchison JG, Dusheiko G, et al. Telaprevir for Previously Untreated Chronic Hepatitis C Virus Infection. New England Journal of Medicine. 2011;364(25):2405-16. PMID: 21696307

Kamal SM, Ahmed A, Mahmoud S, et al. Enhanced efficacy of pegylated interferon alpha-2a over pegylated interferon and ribavirin in chronic hepatitis C genotype 4A randomized trial and quality of life analysis. Liver Int. 2011;31(3):401-11. PMID: 21281434

Kamal SM, El Tawil AA, Nakano T, et al. Peginterferon {alpha}-2b and ribavirin therapy in chronic hepatitis C genotype 4: impact of treatment duration and viral kinetics on sustained virological response. Gut. 2005 Jun;54(6):858-66. PMID: 15888797

Kawaoka T, Kawakami Y, Tsuji K, et al. Dose comparison study of pegylated interferon-alpha-2b plus ribavirin in naive Japanese patients with hepatitis C virus genotype 2: a randomized clinical trial. Journal of Gastroenterology & Hepatology. 2009 Mar;24(3):366-71. PMID: 19032459

Khan AQ AA, Shahbuddin S, Iqbal Q. Abstract # S1231: Peginterferon Alfa 2a / Ribavirin versus Peginterferon Alfa 2b / Ribavirin combination therapy in Chronic Hepatitis C Genotype 3. Gastroenterology. 2007;132(4):A200.

Krawitt EL, Gordon SR, Grace ND, et al. A study of low dose peginterferon alpha-2b with ribavirin for the initial treatment of chronic hepatitis C. American Journal of Gastroenterology. 2006 Jun;101(6):1268-73. PMID: 16771948

Kumada H, Toyota J, Okanoue T, et al. Telaprevir with peginterferon and ribavirin for treatment-naive patients chronically infected with HCV of genotype 1 in Japan. Journal of Hepatology. 2012;56(1):78-84. PMID: 21827730.

Kwo PY, Lawitz EJ, McCone J, et al. Efficacy of boceprevir, an NS3 protease inhibitor, in combination with peginterferon alfa-2b and ribavirin in treatment-naive patients with genotype 1 hepatitis C infection (SPRINT-1): an open-label, randomised, multicentre phase 2 trial.[Erratum appears in Lancet. 2010 Oct 9;376(9748):1224 Note: SPRINT-1 investigators [added]; multiple investigator names added]. Lancet. 2010 Aug 28;376(9742):705-16. PMID: 20692693

Lagging M, Langeland N, Pedersen C, et al. Randomized comparison of 12 or 24 weeks of peginterferon alpha-2a and ribavirin in chronic hepatitis C virus genotype 2/3 infection. Hepatology. 2008 Jun;47(6):1837-45. PMID: 18454508

Lam KD, Trinh HN, Do ST, et al. Randomized controlled trial of pegylated interferon-alfa 2a and ribavirin in treatment-naive chronic hepatitis C genotype 6. Hepatology. 2010 Nov;52(5):1573-80. PMID: 21038410.

Liu C-H, Liu C-J, Lin C-L, et al. Pegylated interferon-alpha-2a plus ribavirin for treatment-naive Asian patients with hepatitis C virus genotype 1 infection: a multicenter, randomized controlled trial. Clinical Infectious Diseases. 2008 Nov 15;47(10):1260-9. PMID: 18834319

Mach TH, Ciesla A, Warunek W, et al. Efficacy of pegylated interferon alfa-2a or alfa-2b in combination with ribavirin in the treatment of chronic hepatitis caused by hepatitis C virus genotype 1b. Polskie Archiwum Medycyny Wewnetrznej; 2011. p. 434-40. PMID:22157768

Magni C NF, Argenteri B, Giorgi R, et al. Abstract #883: Antiviral activity and tolerability between pegylated interferon alpha 2a and alpha 2b in naive patients with chronic hepatitis C: Results of a prospective monocentric randomized trial. Hepatology. 2009;50(S4):720A.

Mangia A, Santoro R, Minerva N, et al. Peginterferon alfa-2b and ribavirin for 12 vs. 24 weeks in HCV genotype 2 or 3. New England Journal of Medicine. 2005 Jun 23;352(25):2609-17. PMID: 15972867

Manns MP, McHutchison JG, Gordon SC, et al. Peginterferon alfa-2b plus ribavirin compared with interferon alfa-2b plus ribavirin for initial treatment of chronic hepatitis C: a randomised trial. Lancet. 2001;358(9286):958-65. PMID: 11583749

Manns M, Zeuzem S, Sood A, et al. Reduced dose and duration of peginterferon alfa-2b and weight-based ribavirin in patients with genotype 2 and 3 chronic hepatitis C. Journal of Hepatology. 2011; 55(3):554-63. PMID: 21237227

Marcellin P, Forns X, Goeser T, et al. Telaprevir is effective given every 8 or 12 hours with ribavirin and peginterferon alfa-2a or -2b to patients with chronic hepatitis C. Gastroenterology. 2011 Feb;140(2):459-68. PMID: 21034744

McHutchison JG, Everson GT, Gordon SC, et al. Telaprevir with peginterferon and ribavirin for chronic HCV genotype 1 infection.[Erratum appears in N Engl J Med. 2009 Oct 8;361(15):1516]. New England Journal of Medicine. 2009 Apr 30;360(18):1827-38. PMID: 19403902

McHutchison JG, Lawitz EJ, Shiffman ML, et al. Peginterferon alfa-2b or alfa-2a with ribavirin for treatment of hepatitis C infection.[Erratum appears in N Engl J Med. 2009 Sep 3;361(10):1027]. New England Journal of Medicine. 2009 Aug 6;361(6):580-93. PMID: 19625712

Mecenate F, Pellicelli AM, Barbaro G, et al. Short versus standard treatment with pegylated interferon alfa-2A plus ribavirin in patients with hepatitis C virus genotype 2 or 3: the cleo trial. BMC Gastroenterology. 2010;10:21. PMID: 20170514

Meyer-Wyss B, Rich P, Egger H, et al. Comparison of two PEG-interferon alpha-2b doses (1.0 or 1.5 microg/kg) combined with ribavirin in interferon-naive patients with chronic hepatitis C and up to moderate fibrosis. Journal of Viral Hepatitis. 2006 Jul;13(7):457-65. PMID: 16792539

Mimidis K, Papadopoulos VP, Elefsiniotis I, et al. Hepatitis C virus survival curve analysis in naive patients treated with peginterferon alpha-2b plus ribavirin. A randomized controlled trial for induction with high doses of peginterferon and predictability of sustained viral response from early virologic data. Journal of Gastrointestinal & Liver Diseases. 2006 Sep;15(3):213-9. PMID: 17013444

Miyase S. Randomized trial of peginterferon α--2a plus ribavirin versus peginterferon α--2b plus ribavirin for chronic hepatitis C in Japanese patients. Journal of Gastroenterology. 2012: 1-8. PMID 22382633

Pearlman BL, Ehleben C, Saifee S. Treatment extension to 72 weeks of peginterferon and ribavirin in hepatitis c genotype 1-infected slow responders. Hepatology. 2007 Dec;46(6):1688-94. PMID: 18046717

Poordad F, McCone J, Jr., Bacon BR, et al. Boceprevir for untreated chronic HCV genotype 1 infection. New England Journal of Medicine. 2011 Mar 31;364(13):1195-206. PMID: 21449783

Reddy KR, Shiffman ML, Rodriguez-Torres M, et al. Induction pegylated interferon alfa-2a and high dose ribavirin do not increase SVR in heavy patients with HCV genotype 1 and high viral loads. Gastroenterology. 2010 Dec;139(6):1972-83. PMID: 20816836

Roberts SK, Weltman MD, Crawford DHG, et al. Impact of high-dose peginterferon alfa-2A on virological response rates in patients with hepatitis C genotype 1: a randomized controlled trial. Hepatology. 2009 Oct;50(4):1045-55. PMID: 19676125

Rumi MG, Aghemo A, Prati GM, et al. Randomized study of peginterferon-alpha2a plus ribavirin vs peginterferon-alpha2b plus ribavirin in chronic hepatitis C. Gastroenterology. 2010 Jan;138(1):108-15. PMID: 19766645

Sanchez-Tapias JM, Diago M, Escartin P, et al. Peginterferon-alfa2a plus ribavirin for 48 versus 72 weeks in patients with detectable hepatitis C virus RNA at week 4 of treatment.[Erratum appears in Gastroenterology. 2006 Oct;131(4):1363]. Gastroenterology. 2006 Aug;131(2):451-60. PMID: 16890599

Sherman KE, Flamm SL, Afdhal NH, et al. Response-guided telaprevir combination treatment for hepatitis C virus infection. New England Journal of Medicine. 2011;365(11):1014-24. PMID: 21916639

Shiffman ML, Suter F, Bacon BR, et al. Peginterferon alfa-2a and ribavirin for 16 or 24 weeks in HCV genotype 2 or 3. New England Journal of Medicine. 2007 Jul 12;357(2):124-34. PMID: 17625124

Silva M, Poo JL, Wagner F, et al. A randomised trial to compare the pharmacokinetic, pharmacodynamic, and antiviral effects of peginterferon alfa-2b and peginterferon alfa-2a in patients with chronic hepatitis C (COMPARE). Journal of Hepatology.. 2006;45(2):204-13. PMID: 16780997

Sood A, Midha V, Hissar S, et al. Comparison of low-dose pegylated interferon versus standard high-dose pegylated interferon in combination with ribavirin in patients with chronic hepatitis C with genotype 3: an Indian experience. Journal of Gastroenterology & Hepatology. 2008 Feb;23(2):203-7. PMID: 17645472

von Wagner M, Huber M, Berg T, et al. Peginterferon-alpha-2a (40KD) and ribavirin for 16 or 24 weeks in patients with genotype 2 or 3 chronic hepatitis C. Gastroenterology. 2005 Aug;129(2):522-7. PMID: 16083709

Yenice N, Mehtap O, Gumrah M, et al. The efficacy of pegylated interferon alpha 2a or 2b plus ribavirin in chronic hepatitis C patients. Turkish Journal of Gastroenterology. 2006 Jun;17(2):94-8. PMID: 16830289

Yu M-L, Dai C-Y, Huang J-F, et al. Rapid virological response and treatment duration for chronic hepatitis C genotype 1 patients: a randomized trial. Hepatology. 2008 Jun;47(6):1884-93. PMID: 18508296

Yu M-L, Dai C-Y, Huang J-F, et al. A randomised study of peginterferon and ribavirin for 16 versus 24 weeks in patients with genotype 2 chronic hepatitis C. Gut. 2007 Apr;56(4):553-9. PMID: 16956917

Yu M-L, Dai C-Y, Lin Z-Y, et al. A randomized trial of 24- vs. 48-week courses of PEG interferon alpha-2b plus ribavirin for genotype-1b-infected chronic hepatitis C patients: a pilot study in Taiwan. Liver International. 2006 Feb;26(1):73-81. PMID: 16420512

Zeuzem S, Diago M, Gane E, et al. Peginterferon alfa-2a (40 kilodaltons) and ribavirin in patients with chronic hepatitis C and normal aminotransferase levels. Gastroenterology. 2004 Dec;127(6):1724-32. PMID: 15578510

Key Question 4:

Arase Y, Ikeda K, Suzuki F, et al. Long-term outcome after interferon therapy in elderly patients with chronic hepatitis C. Intervirology. 2007;50(1):16-23. PMID: 17164553

Arora S, O'Brien C, Zeuzem S, et al. Treatment of chronic hepatitis C patients with persistently normal alanine aminotransferase levels with the combination of peginterferon alpha-2a (40 kDa) plus ribavirin: impact on health-related quality of life. Journal of Gastroenterology & Hepatology. 2006 Feb;21(2):406-12. PMID: 16509866

Backus LI, Boothroyd DB, Phillips BR, et al. A sustained virologic response reduces risk of all-cause mortality in patients with hepatitis C. Clinical Gastroenterology & Hepatology. 2011;9:509-16. PMID: 21397729

Bernstein D, Kleinman L, Barker CM, et al. Relationship of health-related quality of life to treatment adherence and sustained response in chronic hepatitis C patients. Hepatology. 2002 Mar;35(3):704-8. PMID: 11870387

Bini EJ, Mehandru S. Sustained virological response rates and health-related quality of life after interferon and ribavirin therapy in patients with chronic hepatitis C virus infection and persistently normal alanine aminotransferase levels. **Alimentary Pharmacology & Therapeutics**. 2006;23(6):777-85. PMID: 16556180

Bonkovsky HL, Woolley JM. Reduction of health-related quality of life in chronic hepatitis C and improvement with interferon therapy.The Consensus Interferon Study Group. Hepatology. 1999;29(1):264-70. PMID: 9862876

Bruno S, Stroffolini T, Colombo M, et al. Sustained virological response to interferon-alpha is associated with improved outcome in HCV-related cirrhosis: a retrospective study. Hepatology. 2007 Mar;45(3):579-87. PMID: 17326216

Cardoso A-C, Moucari R, Figueiredo-Mendes C, et al. Impact of peginterferon and ribavirin therapy on hepatocellular carcinoma: incidence and survival in hepatitis C patients with advanced fibrosis. Journal of Hepatology. 2010 May;52(5):652-7. PMID: 20346533

Coverdale SA, Khan MH, Byth K, et al. Effects of interferon treatment response on liver complications of chronic hepatitis C: 9-year follow-up study. American Journal of Gastroenterology. 2004 Apr;99(4):636-44. PMID: 15089895.

El Braks RE, Ganne-Carrie N, Fontaine H, et al. Effect of sustained virological response on long-term clinical outcome in 113 patients with compensated hepatitis C-related cirrhosis treated by interferon alpha and ribavirin. **World Journal** of Gastroenterology. 2007;13(42):5648-53. PMID: 17948941

Fernández-Rodríguez CM, Alonso S, Martinez SM, et al. Peginterferon Plus Ribavirin and Sustained Virological Response in HCV-Related Cirrhosis: Outcomes and Factors Predicting Response. American Journal of Gastroenterology. 2010; 105(10): 2164-72. PMID: 20927082

Hasegawa E, Kobayashi M, Kawamura Y, et al. Efficacy and anticarcinogenic activity of interferon for hepatitis C virus-related compensated cirrhosis in patients with genotype 1b low viral load or genotype 2. Hepatology Research. 2007;37(10):793-800. PMID: 17593231

Hassanein T, Cooksley G, Sulkowski M, et al. The impact of peginterferon alfa-2a plus ribavirin combination therapy on health-related quality of life in chronic hepatitis C. Journal of Hepatology. 2004;40(4):675-81. PMID: 15030985

Hung CH, Lee CM, Lu SN, et al. Long-term effect of interferon alpha-2b plus ribavirin therapy on incidence of hepatocellular carcinoma in patients with hepatitis C virus-related cirrhosis. Journal of **Viral Hepatitis**. 2006;13(6):409-14. PMID: 16842444

Imazeki F, Yokosuka O, Fukai K, et al. Favorable prognosis of chronic hepatitis C after interferon therapy by long-term cohort study. Hepatology. 2003 Aug;38(2):493-502. PMID: 12883494

Innes HA, Hutchinson SJ, Allen S, et al. Excess liver-related morbidity of chronic hepatitis C patients, who achieve a sustained viral response, and are discharged from care. Hepatology. 2011; 54(5):1547-58. PMID:22045672

Izumi N, Yasuhiro A, Kurosaki M, et al. Development of hepatocellular carcinoma after interferon therapy in chronic hepatitis C. Is it possible to reduce the incidence by ribanirin and IFN combination therapy? Intervirology. 2005;48(1):59-63. PMID: 15785091

Kasahara A, Tanaka H, Okanoue T, et al. Interferon treatment improves survival in chronic hepatitis C patients showing biochemical as well as virological responses by preventing liver-related death. Journal of Viral Hepatitis. 2004 Mar;11(2):148-56. PMID: 14996350

Maruoka D, Imazeki F, Arai M, et al. Long-term cohort study of chronic hepatitis C according to interferon efficacy. Journal of Gastroenterology and Hepatology; 2012;27(2):291-99. PMID: 21793911

McHutchison J, Manns M, Harvey J, et al. Adherence to therapy enhanges sustained response in chronic hepatitis C patients receiving PEG-Interferon alfa-2b plus Ribavirin[abstract]. Journal of Hepatology. 2001;34(1):2-3.

McHutchison J, Sulkowski M. Scientific rationale and study design of the individualized dosing efficacy vs flat dosing to assess optimal pegylated interferon therapy (IDEAL) trial: determining optimal dosing in patients with genotype 1 chronic hepatitis C. Journal of **Viral Hepatitis**. 2008;1

Morgan TR, Ghany MG, Kim H-Y, et al. Outcome of sustained virological responders with histologically advanced chronic hepatitis C. Hepatology. 2010 Sep;52(3):833-44. PMID: 20564351

Neary MP, Cort S, Bayliss MS, et al. Sustained virologic response is associated with improved health-related quality of life in relapsed chronic hepatitis C patients. Seminars in Liver Disease. 1999;19(1):77-85. PMID: 10349695

Rasenack J, Zeuzem S, Feinman SV, et al. Peginterferon alpha-2a (40kD) [Pegasys] improves HR-QOL outcomes compared with unmodified interferon alpha-2a [Roferon-A]: in patients with chronic hepatitis C.[Erratum appears in Pharmacoeconomics. 2003;21(17):1290]. Pharmacoeconomics. 2003;21(5):341-9. PMID: 12627987

Shiratori Y, Ito Y, Yokosuka O, et al. Antiviral therapy for cirrhotic hepatitis C: association with reduced hepatocellular carcinoma development and improved survival. Annals of Internal Medicine. 2005 Jan 18;142(2):105-14. PMID: 15657158

Veldt BJ, Heathcote EJ, Wedemeyer H, et al. Sustained virologic response and clinical outcomes in patients with chronic hepatitis C and advanced fibrosis. Annals of Internal Medicine. 2007;147(10):677-84. PMID: 18025443

Ware JE, Bayliss MS, Mannocchia M, et al. Health-related quality of life in chronic hepatitis C: impact of disease and treatment response. The Interventional Therapy Group. Hepatology. 1999;30(2):550-5. PMID: 10421667

Yoshida H, Arakawa Y, Sata M, et al. Interferon therapy prolonged life expectancy among chronic hepatitis C patients. Gastroenterology. 2002 Aug;123(2):483-91. PMID: 12145802

Yu M-L, Lin S-M, Chuang W-L, et al. A sustained virological response to interferon or interferon/ribavirin reduces hepatocellular carcinoma and improves survival in chronic hepatitis C: a nationwide, multicentre study in Taiwan. Antiviral Therapy. 2006;11(8):985-94. PMID: 17302368

Appendix D. Excluded Studies List

Abergel A, Achim A, Kain I, et al. Efficacy of interferon (standard or pegylated) plus ribavirin in naive patients with hepatitis C virus genotype 5. A french multicenter study. Hepatology; 2011: 817A. **Exclusion Reason -**Wrong Population

Adherence in Patients Receiving PegIntron Pen/Rebetol for Hepatitis C in Conjunction With a Patient Assistance Program (Study P04281)(COMPLETED). **Exclusion Reason -**Wrong Population

Adherence in Patients Receiving PegIntron/Rebetol for Hepatitis C in Conjunction With a Psychotherapy Support Program (Study P04252)(COMPLETED). **Exclusion Reason -** Wrong Population

Adiwijaya BS, Hare B, Caron PR, et al. Rapid decrease of wild-type hepatitis C virus on telaprevir treatment. Antiviral Therapy. 2009;14(4):591-5. PMID: 19578245**. Exclusion Reason -**Wrong Study Design

Adiwijaya B, Herrmann E ,Hare B , et al. A Multi-Variant, Viral Dynamic Model of Genotype 1 HCV to Assess the *in vivo* Evolution of Protease-Inhibitor Resistant Variants. PLoS Comput Biol. 2010;6(4):e1000745. PMID: 20419154**. Exclusion Reason -**Not Relevant

Adiwijaya BS, Kieffer TL, Henshaw J, et al. A Viral Dynamic Model for Treatment Regimens with Direct-acting Antivirals for Chronic Hepatitis C Infection. PLoS Comput Biol. 2012;8(1):e1002339-e1002339. PMID: 22241977**. Exclusion Reason -**Not Relevant

Adiwijaya BS, Kieffer TL, Henshaw J, et al. A viral dynamic model for treatment regimens with direct-acting antivirals for chronic hepatitis c infection. PLoS Computational Biology. 2012;8(1). **Exclusion Reason -** Background

Afdhal NH, Dieterich DT, Pockros PJ, et al., Epoetin alfa maintains ribavirin dose in HCV-infected patients: a prospective, double-blind, randomized controlled study. Gastroenterology. 2004 May;126(5):1302-11. PMID: 15131791**. Exclusion Reason -**Not Relevant

Ahn & Flamm..Boceprevir versus telaprevir: A new era of directly acting antiviral therapy. Current Hepatitis Reports. 2012;11(1):23-33. **Exclusion Reason** – Background

Akuta N, Suzuki F, Hirakawa M, et al. Amino acid substitution in hepatitis C virus core region and genetic variation near the interleukin 28B gene predict viral response to telaprevir with peginterferon and ribavirin. Hepatology. 2010;52(2):421-429. PMID: 20648473**. Exclusion Reason -**Wrong Study Design

Akuta N, Suzuki F, Hirakawa M, et al. Amino acid substitutions in the hepatitis C virus core region of genotype 1b affect very early viral dynamics during treatment with telaprevir, peginterferon, and ribavirin. Journal of Medical Virology. 2010;82(4):575-582. PMID: 20166188**. Exclusion Reason -**Wrong Study Design

Akuta N, Suzuki F, Suzuki Y, et al. Long-term follow-up of interferon monotherapy in 454 consecutive naive patients infected with hepatitis C virus: multi-course interferon therapy may reduce the risk of hepatocellular carcinoma and increase survival. Scandinavian Journal of Gastroenterology. 2005 Jun;40(6):688-96. PMID: 16036529**. Exclusion Reason -**Wrong Drug

Alavian SM, Behnava B, Tabatabaei SV., et al. Comparative efficacy and overall safety of different doses of consensus interferon for treatment of chronic HCV infection: a systematic review and meta-analysis. Pharmacol Clin. 2010;66(11):1071-1071. PMID: 20857094**. Exclusion Reason -**Wrong Drug

Alavian SM, Jabbari, H, Daryani, NE ,Hepatitis C virus the rising concerns and growing hopes, report from the HCV symposium, fourth Tehran Hepatitis Congress, November 2011, Tehran, Iran. Hepatitis Monthly. 2012;12(7):107-113. **Exclusion Reason -** Background

Alsiö A, Rembeck K, Askarieh G, et al.Impact of obesity on the bioavailability of peginterferon-α2a and ribavirin and treatment outcome for chronic hepatitis c genotype 2 or 3. PLoS ONE [Electronic Resource]. 2012;7(5). **Exclusion Reason –** Background

Alvarez-Uria G, Day JN, Nasir AJ, et al. Factors associated with treatment failure of patients with psychiatric diseases and injecting drug users in the treatment of genotype 2 or 3 hepatitis C chronic infection. Liver International. 2009 Aug;29(7):1051-5. PMID: 19580634**. Exclusion Reason -**Not Relevant

Amarapurkar DN, Patel ND, Rane P, et al. Do different hepatitis C virus genotypes behave differently? Tropical Gastroenterology. 2007 Jul-Sep;28(3):99-104. PMID: 18383996**. Exclusion Reason -**Not Relevant

Andersen ES, Moessner BK, Christensen PB, et al. Lower liver stiffness in patients with sustained virological response 4 years after treatment for chronic hepatitis C. European Journal of Gastroenterology & Hepatology. 2011 Jan;23(1):41-4. PMID: 21079513**. Exclusion Reason -**Not Relevant

Angelico M, Koehler-Horst B, Piccolo P, et al. Peginterferon alpha-2a and ribavirin versus peginterferon alpha-2a monotherapy in early virological responders and peginterferon alpha-2a and ribavirin versus peginterferon alpha-2a, ribavirin and amantadine triple therapy in early virological nonresponders: the SMIEC II trial in naive patients with chronic hepatitis C. European Journal of Gastroenterology & Hepatology. 2008 Jul;20(7):680-7. PMID: 18679072**. Exclusion Reason** -Not Relevant

Angelico M, Petrolati A, Lionetti R, et al. A randomized study on Peg-interferon alfa-2a with or without ribavirin in liver transplant recipients with recurrent hepatitis C. Journal of Hepatology. 2007 Jun;46(6):1009-17. PMID: 17328985**. Exclusion Reason -**Not Relevant

Arase Y, Suzuki F, Akuta N, et al. Combination therapy of peginterferon and ribavirin for chronic hepatitis C patients with genotype 1b and low-virus load. Internal Medicine. 2009;48(5):253-8. PMID: 19252344**. Exclusion Reason** -Not Relevant

Arase Y, Suzuki F, Sezaki H, et al. Efficacy in patients with dose reduction in combination therapy of peginterferon and ribavirin for chronic hepatitis C. Intervirology. 2008;51(1):1-6. PMID: 18309242**. Exclusion Reason -**Not Relevant

Arase Y, Suzuki F, Suzuki Y, et al. Side effects of combination therapy of peginterferon and ribavirin for chronic hepatitis-C. Internal Medicine. 2007;46(22):1827-32. PMID: 18025763**. Exclusion Reason -**Not Relevant

Asahina Y, Tsuchiya K, Tamaki N, et al. Effect of aging on risk for hepatocellular carcinoma in chronic hepatitis C virus infection. Hepatology. 2010 Aug;52(2):518-27. PMID: 20683951**. Exclusion Reason -**Not Relevant

Asselah T. A revolution in HCV treatment with direct-acting antivirals: From non-response to eradication. Journal of Hepatology. 2012;57(2):455-457. **Exclusion Reason -** Background

Awad T, Brok J, Thorlund K, et al. Pegylated interferon plus ribavirin versus non-pegylated interferon plus ribavirin for chronic hepatitis C. Cochrane Database of Systematic Reviews. 2009(1). **Exclusion Reason –** Background

Awad T, Thorlund K, Hauser G, et al. Pegylated interferon alpha 2a versus pegylated interferon alpha 2b for chronic hepatitis C. Cochrane Database of Systematic Reviews. 2009(1). **Exclusion Reason -** Background

Awad T, Thorlund K, Hauser G, et al. Peginterferon alpha-2a is associated with higher sustained virological response than peginterferon alfa-2b in chronic hepatitis C: Systematic review of randomized trials. Hepatology. 2010;51(4):1176-1184. PMID: 20187106**. Exclusion Reason** -Not Relevant

Ayaz C, Celen MK, Yuce UN, et al. Efficacy and safety of pegylated-interferon alpha-2a in hemodialysis patients with chronic hepatitis C. World Journal of Gastroenterology. 2008 Jan 14;14(2):255-9. PMID: 18186564**. Exclusion Reason -**Wrong Population

Backus LI, Boothroyd DB, Phillips BR, et al. Pretreatment assessment and predictors of hepatitis C virus treatment in US veterans coinfected with HIV and hepatitis C virus. Journal of Viral Hepatitis. 2006 Dec;13(12):799-810. PMID: 17109679**. Exclusion Reason -**Wrong Outcome

Bacon BR, Khalid O. Triple therapy with boceprevir for HCV genotype 1 infection: Phase III results in relapsers and nonresponders. Liver International. 2012;32(SUPPL. 1):51-53. **Exclusion Reason -** Background

Bain VG, Lee SS, Peltekian K, et al. Clinical trial: exposure to ribavirin predicts EVR and SVR in patients with HCV genotype 1 infection treated with peginterferon alpha-2a plus ribavirin. Alimentary Pharmacology & Therapeutics. 2008 Jul;28(1):43-50. PMID: 18397386**. Exclusion Reason -**Not Relevant

Balon R. Clinical factor 2011. Psychotherapy and Psychosomatics. 2012;81(4):199-205. **Exclusion Reason -** Background

Barbotte L, Ahmed-Belkacem A, Chevaliez S, et al. Characterization of V36C, a Novel Amino Acid Substitution Conferring Hepatitis C Virus (HCV) Resistance to Telaprevir, a Potent Peptidomimetic Inhibitor of HCV Protease. Antimicrobial Agents and Chemotherapy. 2010 June 2010;54(6):2681-2683. PMID: 20368394**. Exclusion Reason -**Wrong Outcomes

Barritt Iv AS, Fried MW. Maximizing opportunities and avoiding mistakes in triple therapy for hepatitis C virus. Gastroenterology. 2012;142(6):1314-1323.e1. **Exclusion Reason -** Background

Bartels DJ, Zhou Y, Zhang EZ, et al. Natural Prevalence of Hepatitis C Virus Variants with Decreased Sensitivity to NS3·4A Protease Inhibitors in Treatment-Naive Subjects. Journal of Infectious Diseases. 2008 September 15, 2008;198(6):800-807. PMID: 18637752**. Exclusion Reason -**Wrong Study Design

Berak. Randomized, open label trial comparing efficacy and safety of pegylated interferon alfa 2a vs alfa 2b treatment of patients with chronic hepatitis C infected with non 2/3 genotypes – 12 week virological response analysis. Hepatology. 2005;42(Suppl 1):1. **Exclusion Reason -**Wrong Drug

Boceprevir (SCH 503034) Plus Peg-Intron, With and Without Added Ribavirin, in Patients With Chronic Hepatitis C, Genotype 1, Who Did Not Respond to Previous Treatment With Peginterferon Alfa Plus Ribavirin.. **Exclusion Reason -**Wrong Population

Bognar F. Boceprevir in addition to standard of care enhanced SVR in hepatitis C virus (HCV) genotype-1 with advanced fibrosis/cirrhosis: Subgroup analysis of SPRINT-2 and RESPOND-2 Studies. Journal of Gastroenterology and Hepatology. 2011; 26:93. **Exclusion Reason -**Wrong Population

Bognar F. IL28B polymorphism predicts virologic response in patients with hepatitis C genotype 1 treated with boceprevir (BOC) combination therapy. Journal of Gastroenterology and Hepatology. 2011; 19-20. **Exclusion Reason -**Wrong Population

Bognar F. Projecting the clinical impact of therapeutic regimens including boceprevir in previously untreated adult subjects with chronic hepatitis C genotype 1. Journal of Gastroenterology and Hepatology. 2011; 19. **Exclusion Reason -**Wrong Population

Bonner, JB, Barret AS, Fried FW, et al. Tangible resources for preparing patients for antiviral therapy for chronic hepatitis C. Digestive Diseases & Sciences. 2012 Jun;57(6):1439-44. PMID: 22488633. **Exclusion Reason -** Background

Bonkovsky HL, Snow KK, Malet PF, et al. Health-related quality of life in patients with chronic hepatitis C and advanced fibrosis. Journal of Hepatology. 2007 Mar;46(3):420-31. PMID: 17196293**. Exclusion Reason -**Not Relevant

Bonkovsky HL, Tice AD, Yapp RG, et al. Efficacy and safety of peginterferon alfa-2a/ribavirin in methadone maintenance patients: randomized comparison of direct observed therapy and self-administration. American Journal of Gastroenterology. 2008 Nov;103(11):2757-65. PMID: 18684176**. Exclusion Reason -**Not Relevant

Borroni G, Andreoletti M, Casiraghi MA, et al. Effectiveness of pegylated interferon/ribavirin combination in 'real world' patients with chronic hepatitis C virus infection. Alimentary Pharmacology & Therapeutics. 2008 May;27(9):790-7. PMID: 18298638**. Exclusion Reason** -Not Relevant

Bourlière, M, Ouzan D, Rosenheim M, et al. Pegylated interferon-α2a plus ribavirin for chronic hepatitis C in a real-life setting: The Hepatys French cohort (2003-2007). Antiviral Therapy. 2012;17(1):101-110. **Exclusion Reason –** Background

Brandman, D, Bacchetti P, Ayala CE, et al. Impact of insulin resistance on HCV treatment response and impact of HCV treatment on insulin sensitivity using direct measurements of insulin action. Diabetes Care. 2012;35(5):1090-1094. **Exclusion Reason –** Background

Brennan, BJ, Morcos PN, Wang K, et al. The pharmacokinetics of peginterferon alfa-2a and ribavirin in African American, Hispanic and Caucasian patients with chronic hepatitis C. Alimentary Pharmacology & Therapeutics. 2012 May;35(10):1209-20. PMID: 22469033. **Exclusion Reason -** Wrong Outcomes

Brok J, Gluud LL, Gluud C, et al. Ribavirin monotherapy for chronic hepatitis C. Cochrane Database of Systematic Reviews. 2009(1). **Exclusion Reason –** Background

Brok J, Gluud LL, Gluud C, et al. Ribavirin plus interferon versus interferon for chronic hepatitis C. Cochrane Database of Systematic Reviews. 2010(5). **Exclusion Reason -** Background

Bruno R, Sacchi P, Ciappina V, et al. Viral dynamics and pharmacokinetics of peginterferon alpha-2a and peginterferon alpha-2b in naive patients with chronic hepatitis c: a randomized, controlled study. Antiviral Therapy. 2004;9(4):491-497. PMID: 15456079**. Exclusion Reason -**Wrong Outcome

Bruno R, Sacchi P, Cima S, et al. Comparison of peginterferon pharmacokinetic and pharmacodynamic profiles. Journal of Viral Hepatitis. 2012;19(1):33-36. **Exclusion Reason -** Wrong Outcomes

Bühler S, Bartenschlager R. New targets for antiviral therapy of chronic hepatitis C. Liver International. 2012;32(1):9-16. **Exclusion Reason –** Background

Burton, MJ, Passarella MJ, McGuire BM. Telaprevir and boceprevir in African Americans with genotype 1 chronic hepatitis C: Implications for patients and providers. Southern Medical Journal. 2012;105(8):431-436. **Exclusion Reason -** Wrong Study Design

Calès P, Zarski JP, Marc Chapplain J, et al. Fibrosis progression under maintenance interferon in hepatitis C is better detected by blood test than liver morphometry. Journal of Viral Hepatitis. 2012;19(2):e143-e153. **Exclusion Reason –** Background

Carruthers SJ. Hepatitis C treatment and injecting drug users in Perth, Western Australia: Knowledge of personal status and eligibility criteria for treatment. Journal of Substance Use. 2012 Feb;17(1):32-40. PMID: Peer Reviewed Journal: 2012-00263-003. **Exclusion Reason –** Background

Casey LC, Lee W.M. Hepatitis C therapy update. Current Opinion in Gastroenterology. 2012;28(3):188-192. **Exclusion Reason - Background**

Chak E, Talal AH, Sherman KE, et al. Hepatitis C virus infection in USA: an estimate of true prevalence. Liver Int; 2011. 31(8):1090-101 **Exclusion Reason –** Background

Chang CH, Chen KY, Lai MY, et al. Meta-analysis: ribavirin-induced haemolytic anaemia in patients with chronic hepatitis C. Alimentary Pharmacology & Therapeutics. 2002 Sep;16(9):1623-32. PMID: 12197841**. Exclusion Reason -**Not Relevant

Charlebois A, Lee L, Cooper E, et al. Factors associated with HCV antiviral treatment uptake among participants of a community-based HCV programme for marginalized patients. Journal of Viral Hepatitis. 2012. **Exclusion Reason -** Background

Chavalitdhamrong D, Tanwandee T. Long-term outcomes of chronic hepatitis C patients with sustained virological response at 6 months after the end of treatment. World Journal of Gastroenterology. 2006 Sep 14;12(34):5532-5. PMID: 17006994**. Exclusion Reason -**Wrong Drug

Chayama K, Hayes CN, Abe H, et al. IL28B But Not ITPA Polymorphism Is Predictive of Response to Pegylated Interferon, Ribavirin, and Telaprevir Triple Therapy in Patients With Genotype 1 Hepatitis C. Journal of Infectious Diseases. 2011 July 1, 2011;204(1):84-93. PMID: 21628662**. Exclusion Reason -**Wrong Outcomes

Chen L-j, Li M-h, Xie Y, et al. [Effect of hepatitis C virus serotype on the response of patients with chronic hepatitis C to interferon treatment]. Chinese Journal of Experimental & Clinical Virology. 2007 Jun;21(2):117-9. PMID: 17653309**. Exclusion Reason -**Not Relevant

Chen T-M, Huang P-T, Lin C-H, et al. Feasibility of individualized treatment for hepatitis C patients in the real world. Journal of Gastroenterology & Hepatology. 2010 Jan;25(1):61-9. PMID: 19780879**. Exclusion Reason -**Not Relevant

Chen W-l, Chen X-p, Chen X-f, et al. [Individualized respond guidance treatment of chronic hepatitis C with combination of peginterferon -2a and ribavirin]. Chung Hua Kan Tsang Ping Tsa Chih. 2010 Aug;18(8):585-9. PMID: 20825712**. Exclusion Reason -**Not Relevant

Cheng WSC, Roberts SK, McCaughan G, et al. Low virological response and high relapse rates in hepatitis C genotype 1 patients with advanced fibrosis despite adequate therapeutic dosing. Journal of Hepatology. 2010 Oct;53(4):616-23. PMID: 20619475**. Exclusion Reason -**Not Relevant

Chevaliez, S, Hézode C,, Pawlotsky, JM. Antiviral strategies in hepatitis C infection. Stratégies antivirales dans l'hépatite chronique C. 2012;14(2):78-88. **Exclusion Reason –** Background

Chu TW, Kulkarni R, Gane EJ,,et al. Effect of IL28B genotype on early viral kinetics during interferon-free treatment of patients with chronic hepatitis C. Gastroenterology. 2012;142(4):790-795. **Exclusion Reason -** Background

Ciancio A, Picciotto A, Giordanino C, et al. A randomized trial of pegylated-interferon-alpha2a plus ribavirin with or without amantadine in the re-treatment of patients with chronic hepatitis C not responding to standard interferon and ribavirin. Alimentary Pharmacology & Therapeutics. 2006 Oct 1;24(7):1079-86. PMID: 16984502**. Exclusion Reason -**Not Relevant

Comparison of Safety and Resulting Blood Level Profiles After Administration of a New Boceprevir Tablet Versus Its Current Capsule Formulation for Treatment of Chronic Hepatitis C. 2010. **Exclusion Reason -** Background

Dalgard O, Bjoro K, Hellum KB, et al. Treatment with pegylated interferon and ribavarin in HCV infection with genotype 2 or 3 for 14 weeks: a pilot study. Hepatology. 2004 Dec;40(6):1260-5. PMID: 15558712**. Exclusion Reason -**Not Relevant

Dalgard O, Bjoro K, Ring-Larsen H, et al. In patients with HCV genotype 2 or 3 infection and RVR 14 weeks treatment is noninferior to 24 weeks. Pooled analysis of two Scandinavian trials. European Journal of Gastroenterology & Hepatology. 2010 May;22(5):552-6. PMID: 20154627**. Exclusion Reason -**Not Relevant

Dan AA, Crone C, Wise TN, et al.Anger experiences among hepatitis C patients: relationship to depressive symptoms and health-related quality of life. Psychosomatics. 2007 May-Jun;48(3):223-9. PMID: 17478591**. Exclusion Reason -**Not Relevant

Daw MA , Dau AA. Hepatitis C virus in Arab world: A state of concern. The Scientific World Journal. 2012;2012. **Exclusion Reason –** Background

De Azevedo FKSF, de Azevedo CCSF, Souto FJD. Souto. Assessment of the treatment of chronic hepatitis C in the state of mato grosso, central Brazil. Memorias do Instituto Oswaldo Cruz. 2012;107(2):117-123. **Exclusion Reason -** Background

de Bruijne J, Bergmann JF, Reesink HW, et al. Antiviral activity of narlaprevir combined with ritonavir and pegylated interferon in chronic hepatitis C patients. Hepatology. 2010 Nov;52(5):1590-9. PMID: 20938912**. Exclusion Reason -**Not Relevant

De Bruijne J, Van Vliet A, Weegink CJ, et al. Rapid decline of viral RNA in chronic hepatitis C patients treated once daily with IDX320: A novel macrocyclic HCV protease inhibitor. Antiviral Therapy. 2012;17(4):633-642. **Exclusion Reason -** Background

De Rosa FG, Bargiacchi O, Audagnotto S, et al.. Dose-dependent and genotype-independent sustained virological response of a 12 week pegylated interferon alpha-2b treatment for acute hepatitis C. Journal of Antimicrobial Chemotherapy. 2006 Feb;57(2):360-3. PMID: 16396921**. Exclusion Reason -**Not Relevant

De-Rueda PM, Ruiz-Extremera A, Candel JM, et al. Plasma Ribavirin trough concentrations during treatment of chronic hepatitis C in genotype-1 patients. Journal of Clinical Gastroenterology. 2012;46(4):328-333. **Exclusion Reason -** Background

Derbala MF, Al Kaabi SR, El Dweik NZ, et al. Treatment of hepatitis C virus genotype 4 with peginterferon alfa-2a: impact of bilharziasis and fibrosis stage. World Journal of Gastroenterology. 2006 Sep 21;12(35):5692-8. PMID: 17007024**. Exclusion Reason** -Not Relevant

Desai, TK, Bortman J, Al-Sibae R, et al. The role of iron in hepatitis C infection. Current Hepatitis Reports. 2012;11(1):41-47. **Exclusion Reason** - Background

Di Bisceglie AM, Ghalib RH, Hamzeh FM, et al. Early virologic response after peginterferon alpha-2a plus ribavirin or peginterferon alpha-2b plus ribavirin treatment in patients with chronic hepatitis C. Journal of Viral Hepatitis. 2007 Oct;14(10):721-9. PMID: 17875007**. Exclusion Reason** -Not Relevant

Di Bisceglie AM, Shiffman ML, Everson GT, et al. Prolonged therapy of advanced chronic hepatitis C with low-dose peginterferon. New England Journal of Medicine. 2008 Dec 4;359(23):2429-41. PMID: 19052125**. Exclusion Reason** -Wrong Outcomes

Di Bisceglie AM, Dusheiko GM, Muir AJ, et al. Telaprevir in combination with peginterferon alfa-2a and ribavirin: Analyses of pre-defined subpopulations in the phase 3 advance trial. Gastroenterology; 2011a. p. S908. **Exclusion Reason** -Wrong Population

Diago M, Olveira A, Sola R, et al. Treatment of chronic he1patitis C genotype 1 with peginterferon-alpha2a (40 kDa) plus ribavirin under routine clinical practice in Spain: early prediction of sustained virological response rate. Alimentary Pharmacology & Therapeutics. 2007 Apr 15;25(8):899-906. PMID: 17402993**. Exclusion Reason** -Not Relevant

Diago M, Shiffman ML, Bronowicki J-P, et al. Identifying hepatitis C virus genotype 2/3 patients who can receive a 16-week abbreviated course of peginterferon alfa-2a (40KD) plus ribavirin. Hepatology. 2010 Jun;51(6):1897-903. PMID: 20196118**. Exclusion Reason** -Not Relevant

Dieterich DT, Wasserman R, Brau N, et al. Once-weekly epoetin alfa improves anemia and facilitates maintenance of ribavirin dosing in hepatitis C virus-infected patients receiving ribavirin plus interferon alfa. American Journal of Gastroenterology. 2003 Nov;98(11):2491-9. PMID: 14638354**. Exclusion Reason** -Not Relevant

Druyts E, Mills EJ, Nachega J, et al. Differences in clinical outcomes among hepatitis C genotype 1-infected patients treated with peginterferon alpha-2a or peginterferon alpha-2b plus ribavirin: A meta-analysis. Clinical and Experimental Gastroenterology. 2012; 5(1): 11-21. PMID:22427726 **Exclusion Reason** - Wrong Population

Ebner N, Wanner C, Winklbaur B, et al. Retention rate and side effects in a prospective trial on hepatitis C treatment with pegylated interferon alpha-2a and ribavirin in opioid-dependent patients. Addiction Biology. 2009 Apr;14(2):227-37. PMID: 19291011**. Exclusion Reason** -Not Relevant

Effects of 48 Weeks Versus 24 Weeks of Therapy With Peg-Intron/Ribavirin in Patients With Chronic Hepatitis C, Genotype 3 (Study P04143)(TERMINATED). **Exclusion Reason** -Wrong Population

Efficacy and Safety of 24 vs 48 Weeks of Pegetron® (Peginterferon Alfa-2b + Ribavirin) in Naïve Genotype 1 Hepatitis C (Study P05016)(TERMINATED). **Exclusion Reason** -Wrong Population

Efficacy and Safety of Peginterferon Alfa-2b and Ribavirin Therapy in Subjects With Type C Compensated Liver Cirrhosis (Study P05116). **Exclusion Reason** -Wrong Population

El-Serag HB, Mason AC. Rising Incidence of Hepatocellular Carcinoma in the United States. New England Journal of Medicine. 1999; 340(10): 745-50. **Exclusion Reason –** Background

El-Serag HB, Mason AC. Risk factors for the rising rates of primary liver cancer in the United States. Archives of Internal Medicine. 2000; 160(21):3227-30. **Exclusion Reason -** Background

El-Serag HB, Davila JA, Petersen NJ, et al. The continuing increase in the incidence of hepatocellular carcinoma in the United States: an update. Annals of Internal Medecine. 2003; 139(10): 817-23. **Exclusion Reason –** Background

El-Zayadi AR, Attia M, Barakat EM, et al. Response of hepatitis C genotype-4 naive patients to 24 weeks of Peg-interferon-alpha2b/ribavirin or induction-dose interferon-alpha2b/ribavirin/amantadine: a non-randomized controlled study. American Journal of Gastroenterology. 2005 Nov;100(11):2447-52. PMID: 16279899**. Exclusion Reason** -Not Relevant

Everhart JE, Lok AS, Kim H-Y, et al. Weight-related effects on disease progression in the hepatitis C antiviral long-term treatment against cirrhosis trial. Gastroenterology. 2009 Aug;137(2):549-57. PMID: 19445938**. Exclusion Reason** -Not Relevant

Everson GT, Balart L, Lee SS, et al. Histological benefits of virological response to peginterferon alfa-2a monotherapy in patients with hepatitis C and advanced fibrosis or compensated cirrhosis. Alimentary Pharmacology & Therapeutics. 2008 Apr 1;27(7):542-51. PMID: 18208570**. Exclusion Reason** -Wrong Outcomes

Everson GT, Shiffman ML, Hoefs JC, et al. Quantitative tests of liver function measure hepatic improvement after sustained virological response: results from the HALT-C trial. Alimentary Pharmacology & Therapeutics. 2009 Mar 1;29(5):589-601. PMID: 19053983**. Exclusion Reason** -Not Relevant

Extended Treatment With PEG-Intron® and Rebetol® in Patients With Genotype 1 Chronic Hepatitis C and Slow Virologic Response (Study P03685AM3)(COMPLETED). **Exclusion Reason** - Wrong Population

Fabrizi F, Dixit V, Messa P,,et al. Interferon therapy of acute hepatitis c in dialysis patients: Meta-analysis. Journal of Viral Hepatitis. 2012. **Exclusion Reason –** Background

Fabrizi F, Dixit V, Messa P, et al. Hepatitis C-related liver disease in dialysis patients. 2012;176:42-53. **Exclusion Reason -** Background

Falasca K, Mancino P, Ucciferri C, et al. Quality of life, depression, and cytokine patterns in patients with chronic hepatitis C treated with antiviral therapy. Clinical & Investigative Medicine - Medecine Clinique et Experimentale. 2009;32(3):E212-8. PMID: 19480737**. Exclusion Reason** -Not Relevant

Fartoux L, Degos F, Trepo C, et al. Effect of prolonged interferon therapy on the outcome of hepatitis C virus-related cirrhosis: a randomized trial. Clinical Gastroenterology & Hepatology. 2007 Apr;5(4):502-7. PMID: 17261383**. Exclusion Reason** -Not Relevant

Feld JJ. Is there a role for ribavirin in the era of hepatitis C virus direct-acting antivirals? Gastroenterology. 2012;142(6):1356-1359. **Exclusion Reason -** Background

Ferenci P, Laferl H, Scherzer T-M, et al. Peginterferon alfa-2a and ribavirin for 24 weeks in hepatitis C type 1 and 4 patients with rapid virological response. Gastroenterology. 2008 Aug;135(2):451-8. PMID: 18503773**. Exclusion Reason** -Not Relevant

Ferenci P. Optimal treatment duration for patients with HCV genotype 1 infection. Journal of Viral Hepatitis. 2012;19(SUPPL. 1):7-13. **Exclusion Reason –** Background

Ferenci P. Treatment of chronic hepatitis C - are interferons really necessary? Liver International. 2012;32(SUPPL. 1):108-112. **Exclusion Reason -** Background

Fernández-Rodríguez CM, Alonso S, Martinez SM, et al. Peginterferon plus ribavirin and sustained virological response in HCV-related cirrhosis: outcomes and factors predicting response.[Erratum appears in Am J Gastroenterol. 2010 Oct;105(10):2308]. American Journal of Gastroenterology. 2010 Oct;105(10):2164-72; quiz 2173. PMID: 20700116**. Exclusion Reason** -Not Relevant

Feuerstadt P, Bunim AL, Garcia H, et al. Effectiveness of hepatitis C treatment with pegylated interferon and ribavirin in urban minority patients. Hepatology. 2010 Apr;51(4):1137-43. PMID: 20049907**. Exclusion Reason** -Not Relevant

Flamm S, Lawitz ., Jacobson I, et al. High Sustained Virologic Response Among Genotype 1 Previous Non-responders and Relapsers to Peginterferon/Ribavirin when Re-treated With Boceprevir Plus Peginterferon Alfa-2a/Ribavirin . 2011. **Exclusion Reason -** Wrong Population

Floreani, et al. Pegylated interferon alpha-2b plus ribavirin for naive patients with HCV-related cirrhosis. Journal of Clinical Gastroenterology. 2008 Jul;42(6):734-7. PMID: 18285717**. Exclusion Reason** -Not Relevant

Fonseca-Coronado S, Escobar-Gutierrez A, Ruiz-Tovar K, et al. Specific Detection of Naturally Occurring Telaprevir and Boceprevir (Protease Inhibitors) HCV Resistant Mutants among Treatment Naïve Infected Individuals. Journal of Clinical Microbiology. 2011 November 23, 2011PMID: 22116161**. Exclusion Reason** -Wrong Outcomes

Fontana RJ, Bieliauskas LA, Back-Madruga C, et al. Cognitive function does not worsen during long-term low-dose peginterferon therapy in patients with chronic hepatitis C. American Journal of Gastroenterology. 2010 Jul;105(7):1551-60. PMID: 20104219**. Exclusion Reason** -Not Relevant

Fontana RJ, Bieliauskas LA, Lindsay KL, et al. Cognitive function does not worsen during pegylated interferon and ribavirin retreatment of chronic hepatitis C. Hepatology. 2007 May;45(5):1154-63. PMID: 17465000**. Exclusion Reason** -Not Relevant

Fontana RJ, Sanyal AJ, Ghany MG, et al. Factors that determine the development and progression of gastroesophageal varices in patients with chronic hepatitis C. Gastroenterology. 2010 2010 Jun;138(7):2321-31. PMID: 20211180**. Exclusion Reason** -Not Relevant

Fontanges T, Beorchia S, Douvin C, et al. Safety and efficacy of combination therapy with peginterferon alfa-2a (40kD) and ribavirin in the outpatient setting: prospective analysis of 197 patients with chronic hepatitis C viral infection. Gastroenterologie Clinique et Biologique. 2007 Jun-Jul;31(6-7):566-72. PMID: 17646782**. Exclusion Reason** -Not Relevant

Ford N, Kirby C, Singh K, et al. Chronic hepatitis C treatment outcomes in low- and middle-income countries: A systematic review and meta-analysis. Bulletin of the World Health Organization. 2012;90(7):540-550. **Exclusion Reason -** Background

Forestier N, Reesink HW, Weegink CJ, et al. Antiviral activity of telaprevir (VX-950) and peginterferon alfa-2a in patients with hepatitis C. Hepatology. 2007 Sep;46(3):640-8. PMID: 17879366**. Exclusion Reason -**Not Relevant

Forestier N , Zeuzem S. Telaprevir for the treatment of hepatitis C. Expert Opinion on Pharmacotherapy. 2012;13(4):593-606. **Exclusion Reason -** Background

Formann E, Jessner W, Bennett L, et al. Twice-weekly administration of peginterferon-alpha-2b improves viral kinetics in patients with chronic hepatitis C genotype 1. Journal of Viral Hepatitis. 2003 Jul;10(4):271-6. PMID: 12823593**. Exclusion Reason -**Not Relevant

Foster GR, Fried MW, Hadziyannis SJ, et al. Prediction of sustained virological response in chronic hepatitis C patients treated with peginterferon alfa-2a (40KD) and ribavirin. Scandinavian Journal of Gastroenterology. 2007 Feb;42(2):247-55. PMID: 17327945**. Exclusion Reason -**Not Relevant

Foster GR, Hezode C, Bronowicki J, et al. Telaprevir Alone or With Peginterferon and Ribavirin Reduces HCV RNA in Patients With Chronic Genotype 2 but Not Genotype 3 Infections. Gastroenterology. 2011;141(3):881-889.e1. PMID: 21699786**. Exclusion Reason -**Wrong Outcomes

Fuster D, Planas R, Gonzalez J, et al. Results of a study of prolonging treatment with pegylated interferon-alpha2a plus ribavirin in HIV/HCV-coinfected patients with no early virological response.[Erratum appears in Antivir Ther. 2006;11(5):667]. Antiviral Therapy. 2006;11(4):473-82. PMID: 16856621**. Exclusion Reason -**Not Relevant

Gaetano, JN, Desai AP, Reau Net al. The era of direct-acting antivirals: The evolving role of interferon and ribavirin for the treatment of chronic hepatitis C. Clinical Medicine Insights: Therapeutics. 2012;4:39-56. **Exclusion Reason -** Background

Gane EJ, Roberts SK, Stedman CAM, et al. Oral combination therapy with a nucleoside polymerase inhibitor (RG7128) and danoprevir for chronic hepatitis C genotype 1 infection (INFORM-1): a randomised, double-blind, placebo-controlled, dose-escalation trial. Lancet. 2010 Oct 30;376(9751):1467-75. PMID: 20951424**. Exclusion Reason -**Not Relevant

Garg V, Chandorkar G, Farmer HF, et al. Effect of Telaprevir on the Pharmacokinetics of Midazolam and Digoxin. The Journal of Clinical Pharmacology. 2011 December 12, 2011PMID: 22162542**. Exclusion Reason -**Wrong Study Design

Garg V, van Heeswijk R, Eun Lee J, et al. Effect of telaprevir on the pharmacokinetics of cyclosporine and tacrolimus. Hepatology. 2011;54(1):20-27. PMID: 21618566**. Exclusion Reason -**Wrong Study Design

Garg V, van Heeswijk R, Yang Y, et al. The Pharmacokinetic Interaction Between an Oral Contraceptive Containing Ethinyl Estradiol and Norethindrone and the HCV Protease Inhibitor Telaprevir. J Clin Pharmacol. 2011PMID: 22039291**. Exclusion Reason -**Wrong Study Design

Geitmann M, Dahl G, Danielson UH. Mechanistic and kinetic characterization of hepatitis C virus NS3 protein interactions with NS4A and protease inhibitors. Journal of Molecular Recognition. 2011;24(1):60-70. PMID: 21194118**. Exclusion Reason -**Not Relevant

Gheorghe L, Iacob S, Sporea I, et al. Efficacy, tolerability and predictive factors for early and sustained virologic response in patients treated with weight-based dosing regimen of PegIFN alpha-2b ribavirin in real-life healthcare setting. Journal of Gastrointestinal & Liver Diseases. 2007 Mar;16(1):23-9. PMID: 17410285**. Exclusion Reason -**Not Relevant

Giannini E, Fasoli A, Botta F, et al. Long-term follow up of chronic hepatitis C patients after α-interferon treatment: A functional study. Journal of Gastroenterology and Hepatology. 2001;16(4):399-405. PMID: 11354278**. Exclusion Reason -**Wrong Drug

Giannini EG, Marenco S, Fazio V, et al. Peripheral blood cytopaenia limiting initiation of treatment in chronic hepatitis C patients otherwise eligible for antiviral therapy. Liver International. 2012;32(7):1113-1119. **Exclusion Reason -** Background

Girolomoni G, Altomare G, Ayala F, et al. Safety of anti-TNFα agents in the treatment of psoriasis and psoriatic arthritis. Immunopharmacology and Immunotoxicology. 2012;34(4):548-560. **Exclusion Reason -** Background

Gish RG, Arora S, Rajender Reddy K, et al. Virological response and safety outcomes in therapy-nai ve patients treated for chronic hepatitis C with taribavirin or ribavirin in combination with pegylated interferon alfa-2a: a randomized, phase 2 study. Journal of Hepatology. 2007 Jul;47(1):51-9. PMID: 17470380**. Exclusion Reason -**Not Relevant

Gluud LL, Krogsgaard K, Gluud C. Ribavirin with or without alpha interferon for chronic hepatitis C. Cochrane Database of Systematic Reviews. 2009(1). **Exclusion Reason -** Background

Gonçalves,CBT, Amaral KM, Sander GB, et al. Effectiveness of alpha interferon (+ ribavirin) in the treatment of chronic viral hepatitis C genotypes 2 and 3 in a brazilian sample. Efetividade da alfainterferona (+ribavirina) no tratamento da hepatite viral crônica C genótipos 2 e 3 em amostra brasileira. 2012;49(2):150-156. **Exclusion Reason -** Background

Goodman ZD, Stoddard AM, Bonkovsky HL, et al. Fibrosis progression in chronic hepatitis C: morphometric image analysis in the HALT-C trial. Hepatology. 2009 Dec;50(6):1738-49. PMID: 19824074**. Exclusion Reason -**Not Relevant

Gramenzi A, Cursaro C, Margotti M, et al. Ketoprofen, peginterferon 2a and ribavirin for genotype 1 chronic hepatitis C: a phase II study. World Journal of Gastroenterology. 2009 Dec 21;15(47):5946-52. PMID: 20014458**. Exclusion Reason -**Not Relevant

Grebely J, Raffa JD, Meagher C, et al. Directly observed therapy for the treatment of hepatitis C virus infection in current and former injection drug users. Journal of Gastroenterology & Hepatology. 2007 Sep;22(9):1519-25. PMID: 17645460**. Exclusion Reason -**Not Relevant

Grebely J, Pham ST, Matthews GV, et al. White. Hepatitis C virus reinfection and superinfection among treated and untreated participants with recent infection. Hepatology. 2012;55(4):1058-1069. **Exclusion Reason -** Background

Guedj J & Perelson A. Second-phase hepatitis C virus RNA decline during telaprevir-based therapy increases with drug effectiveness: implications for treatment duration. Hepatology (Baltimore, Md.). 2011;53(6):1801-8. PMID: 21384401**. Exclusion Reason -**Wrong Outcomes

Gupta, R, Kim S, Taylor MW, et al. Suppression of ribosomal protein synthesis and protein translation factors by Peg-interferon alpha/ribavirin in HCV patients blood mononuclear cells (PBMC). Journal of Translational Medicine. 2012;10(1). **Exclusion Reason -** Background

Han Q, Liu Z, Kang W, et al. Interferon beta 1a versus interferon beta 1a plus ribavirin for the treatment of chronic hepatitis C in Chinese patients: a randomized, placebo-controlled trial. Digestive Diseases & Sciences. 2008 Aug;53(8):2238-45. PMID: 18080763**. Exclusion Reason -**Not Relevant

Harrington PR, Zeng W, Naeger LK, et al. Clinical relevance of detectable but not quantifiable hepatitis C virus RNA during boceprevir or telaprevir treatment. Hepatology. 2011. PMID: 22095516**. Exclusion Reason -**Wrong Outcomes

Harrison SA, Hamzeh FM, Han J, et al. Chronic hepatitis C genotype 1 patients with insulin resistance treated with pioglitazone and peginterferon alpha-2a plus ribavirin. Hepatology. 2012;56(2):464-473. **Exclusion Reason -** Background

Hayashi K, Kumada T, Nakano S, et al. Incidence of hepatocellular carcinoma in chronic hepatitis C after interferon therapy. Hepatogastroenterology. 2002;49(44):508-512. PMID: 11995484**. Exclusion Reason -**Wrong Population

Helbling B, Stamenic I, Viani F, et al. Interferon and amantadine in naive chronic hepatitis C: a double-blind, randomized, placebo-controlled trial. Hepatology. 2002 Feb;35(2):447-54. PMID: 11826422**. Exclusion Reason -**Not Relevant

Helsper CWa, Hellinga, H.L.a, van Essen, G.A.a, et al. Real-life costs of hepatitis C treatment. Netherlands Journal of Medicine. 2012;70(3):145-153. **Exclusion Reason -** Background

Hinrichsen H, Benhamou Y, Wedemeyer H, et al. Short-term antiviral efficacy of BILN 2061, a hepatitis C virus serine protease inhibitor, in hepatitis C genotype 1 patients. Gastroenterology. 2004 Nov;127(5):1347-55. PMID: 15521004**. Exclusion Reason -**Not Relevant

Ho RJY, Chien JY. Drug delivery trends in clinical trials and translational medicine: Growth in biologic molecule development and impact on rheumatoid arthritis, crohn's disease, and colitis. Journal of Pharmaceutical Sciences. 2012;101(8):2668-2674. **Exclusion Reason –** Background

Hofmann WP, Zeuzem S. Hepatitis C in 2011: A new standard of care and the race towards IFN-free therapy. Nature Reviews Gastroenterology and Hepatology. 2012;9(2):67-68. **Exclusion Reason -** Background

Horsmans Y, Colle I, Van Vlierberghe H, et al. Weekly pegylated interferon alpha-2b vs daily interferon a-2b versus standard regimen of interferon a-2b in the treatment of patients with chronic hepatitis C virus infection. Acta Gastroenterologica Belgica. 2008 Jul-Sep;71(3):293-7. PMID: 19198574**. Exclusion Reason -**Not Relevant

Hotho DM, De Bruijne J, O'Farrell AM, et al. Pharmacokinetics and antiviral activity of PHX1766, a novel HCV protease inhibitor, using an accelerated Phase I study design. Antiviral Therapy. 2012;17(2):365-375. **Exclusion Reason -** Background

Iacobellis A, Siciliano M, Perri F, et al. Peginterferon alfa-2b and ribavirin in patients with hepatitis C virus and decompensated cirrhosis: a controlled study. Journal of Hepatology. 2007 Feb;46(2):206-12. PMID: 17125876**. Exclusion Reason -**Not Relevant

Iacobellis A, Perri F, Valvano MR, et al. Long-Term Outcome After Antiviral Therapy of Patients With Hepatitis C Virus Infection and Decompensated Cirrhosis. Clinical Gastroenterology and Hepatology. 2011; 9(3):. 249-53. PMID: 21092761 **Exclusion Reason -**Wrong Population

Ikeda K, Arase Y, Kobayashi M, et al. A Long-Term Glycyrrhizin Injection Therapy Reduces Hepatocellular Carcinogenesis Rate in Patients with Interferon-Resistant Active Chronic Hepatitis C: A Cohort Study of 1249 Patients. Digestive Diseases and Sciences. 2006;51(3):603-609. PMID: 16614974**. Exclusion Reason -**Wrong Drug

Imai Y, Kasahara A, Tanaka H, et al. Interferon therapy for aged patients with chronic hepatitis C: improved survival in patients exhibiting a biochemical response. Journal of Gastroenterology. 2004 Nov;39(11):1069-77. PMID: 15580400**. Exclusion Reason -**Not Relevant

Imhof I, Simmonds P.Genotype differences in susceptibility and resistance development of hepatitis C virus to protease inhibitors telaprevir (VX-950) and danoprevir (ITMN-191). Hepatology. 2011;53(4):1090-1099. PMID: 21480315**. Exclusion Reason -**Wrong Outcomes

Innes H, Hutchinson S, Allen S,, et al. the Hepatitis C Clinical Database Monitoring Committee. Ranking predictors of a sustained viral response for patients with chronic hepatitis C treated with pegylated interferon and ribavirin in Scotland. European Journal of Gastroenterology & Hepatology. 2012 Jun;24(6):646-55. PMID: 22433796. **Exclusion Reason -** Wrong Study Design

Jacobson IM, Ahmed F, Russo MW, et al. Interferon alfa-2b [correction of alpha-2b]and ribavirin for patients with chronic hepatitis C and normal ALT.[Erratum appears in Am J Gastroenterol. 2004 Oct;99(10):2075]. American Journal of Gastroenterology. 2004 Sep;99(9):1700-5. PMID: 15330905**. Exclusion Reason -**Not Relevant

Jafferbhoy H, Miller MH, Dunbar JK, et al. Intravenous drug use: Not a barrier to achieving a sustained virological response in HCV infection. Journal of Viral Hepatitis. 2012;19(2):112-119. **Exclusion Reason -** Background

Jee Eun JEL, Rolf RvH, Katia KA, et al. Effect of the hepatitis C virus protease inhibitor telaprevir on the pharmacokinetics of amlodipine and atorvastatin. CORD Conference Proceedings. 2011;55(10):4569-4574. PMID: 21825288**. Exclusion Reason -**Not Relevant

Jeong S, Kawakami Y, Kitamoto M, et al. Prospective study of short-term peginterferon-alpha-2a monotherapy in patients who had a virological response at 2 weeks after initiation of interferon therapy. Journal of Gastroenterology & Hepatology. 2008 Apr;23(4):541-5. PMID: 18397484**. Exclusion Reason -**Not Relevant

Kabbaj N, Guedira MM, El Atmani H, et al. Thyroid disorders during interferon alpha therapy in 625 patients with chronic hepatitis C: a prospective cohort study. Annales d Endocrinologie. 2006 Sep;67(4):343-7. PMID: 17072240**. Exclusion Reason -**Not Relevant

Kagawa T, Kojima SI, Shiraishi K, et al. Weight-based high- and low-dose ribavirin in combination with peginterferon α-2b therapy for genotype 2 chronic hepatitis C: A randomized trial. Hepatology Research. 2012;42(4):351-358. **Exclusion Reason -** Background

Kaito M, Yasui-Kawamura N, Iwasa M, et al. Twice-a-day versus once-a-day interferon-beta therapy in chronic hepatitis C. Hepato-Gastroenterology. 2003 May-Jun;50(51):775-8. PMID: 12828083**. Exclusion Reason -**Not Relevant

Kamal SM, El Kamary SS, Shardell MD, et al. Pegylated interferon alpha-2b plus ribavirin in patients with genotype 4 chronic hepatitis C: The role of rapid and early virologic response. Hepatology. 2007 Dec;46(6):1732-40. PMID: 17943989**. Exclusion Reason -**Not Relevant

Kashiwagi K, Furusyo N, Kubo N, et al. A prospective comparison of the effect of interferon-alpha and interferon-beta treatment in patients with chronic hepatitis C on the incidence of hepatocellular carcinoma development. Journal of Infection and Chemotherapy. 2003;9(4):333-340. **Exclusion Reason -**Wrong Drug

Khattab M, Emad M, Abdelaleem A, et al. Pioglitazone improves virological response to peginterferon alpha-2b/ribavirin combination therapy in hepatitis C genotype 4 patients with insulin resistance. Liver International. 2010 Mar;30(3):447-54. PMID: 19919569**. Exclusion Reason -**Not Relevant

Kim JH, Han KH, Lee KS, et al. Efficacy and long-term follow up of combination therapy with interferon alpha and ribavirin for chronic hepatitis C in Korea. Yonsei Med J. 2006;47(6):793-798. PMID: 17191307**. Exclusion Reason -**Wrong Drug

Kim KI, Sasase N, Taniguchi M, et al. Prediction of Efficacy of Interferon Treatment of Chronic Hepatitis C and Occurrence of HCC after Interferon Treatment by a New Classification. Intervirology. 2005;48(1):52-58. **Exclusion Reason -**Wrong Drug

Kim TH, Kim KA, Lim YS, et al. Prediction of treatment outcome in chronic hepatitis C patients based on early viral dynamics during high-dose induction interferon and ribavirin therapy. Intervirology. 2005;48(4):230-8. PMID: 15920347**. Exclusion Reason -**Not Relevant

Kiser JJ, Burton JR, Anderson PL, et al. Review and management of drug interactions with boceprevir and telaprevir. Hepatology. 2012;55(5):1620-1628. **Exclusion Reason –** Background

Klibanov OM, Vickery SB, Olin JL, et al. Boceprevir: A novel NS3/4 protease inhibitor for the treatment of hepatitis C. Pharmacotherapy. 2012;32(2):173-190. **Exclusion Reason -** Background

Ko W-S, Guo C-H, Hsu G-SW, et al. The effect of zinc supplementation on the treatment of chronic hepatitis C patients with interferon and ribavirin. Clinical Biochemistry. 2005 Jul;38(7):614-20. PMID: 15904908**. Exclusion Reason** -Not Relevant

Kobayashi S, Takeda T, Enomoto M, et al. Development of hepatocellular carcinoma in patients with chronic hepatitis C who had a sustained virological response to interferon therapy: a multicenter, retrospective cohort study of 1124 patients. Liver International. 2007 Mar;27(2):186-91. PMID: 17311612**. Exclusion Reason** -Wrong Outcomes

Köse S, Senger SS, Ersan G, et al. Virological responses of pegylated interferon alpha-2a treatment in hemodialysis patients infected with hepatitis C. Clinical and Experimental Nephrology. 2012:1-5. **Exclusion Reason** - Wrong study design

Kozielewicz, D, Halota W, Dybowska D, et al.. Efficacy of triple therapy in patients with chronic hepatitis C not treated and patients previously treated ineffectively. Skuteczność terapii trójlekowej u chorych przewlekle zakazonych HCV, nieleczonych i z nieskuteczna wcześniejsza terapia. 2012;66(1):49-54. **Exclusion Reason** - Background

Kramer JR, Davila JA, Duan Z, et al. Antiviral treatment for hepatitis C virus is associated with a reduced risk of hepatocellular carcinoma in a national cohort of U.S. veterans. Gastroenterology. 2011; 140(5):899. **Exclusion Reason** -Wrong Population

Kramer JR, Kanwal F, Richardson P, et al. Gaps in the achievement of effectiveness of HCV treatment in national VA practice. Journal of Hepatology. 2012;56(2):320-325. **Exclusion Reason** - Background

Kraus MR, Schafer A, Faller H, et al. Psychiatric symptoms in patients with chronic hepatitis C receiving interferon alfa-2b therapy. Journal of Clinical Psychiatry. 2003 Jun;64(6):708-14. PMID: 12823087**. Exclusion Reason** -Not Relevant

Kronenberger B, Berg T, Herrmann E, et al. Efficacy of amantadine on quality of life in patients with chronic hepatitis C treated with interferon-alpha and ribavirin: results from a randomized, placebo-controlled, double-blind trial. European Journal of Gastroenterology & Hepatology. 2007 Aug;19(8):639-46. PMID: 17625432**. Exclusion Reason** -Not Relevant

Kronenberger B , Zeuzem, S. Advances in the treatment of hepatitis C virus infection. Gastroenterology and Hepatology. 2012;8(2):91-101. **Exclusion Reason –** Background

Kronenberger B , Zeuzem, S. New developments in HCV therapy. Journal of Viral Hepatitis. 2012;19(SUPPL. 1):48-51. **Exclusion Reason** - Background

Kuboki M, Iino S, Okuno T, et al. Peginterferon alpha-2a (40 KD) plus ribavirin for the treatment of chronic hepatitis C in Japanese patients.[Erratum appears in J Gastroenterol Hepatol. 2007 May;22(5):768]. Journal of Gastroenterology & Hepatology. 2007 May;22(5):645-52. PMID: 17444850**. Exclusion Reason** -Not Relevant

Kunzler-Heule PPE. Hepatitis C! Experience in diagnosis and medical treatment. A literature review. Pflege. 2012 Jun;25(3):185-95. PMID: 22661065. **Exclusion Reason** - Background

Kurosaki M, Hiramatsu N, Sakamoto M, et al. Age and total ribavirin dose are independent predictors of relapse after interferon therapy in chronic hepatitis C revealed by data mining analysis. Antiviral Therapy. 2012;17(1):35-43. E**xclusion Reason** - Background

Kwo. PY.Boceprevir: A novel nonstructural 3 (NS3) protease inhibitor for the treatment of chronic hepatitis C infection. Therapeutic Advances in Gastroenterology. 2012;5(3):179-188. **Exclusion Reason** - Background

Kwo. PY. Phase III results in Genotype 1 naïve patients: Predictors of response with boceprevir and telaprevir combined with pegylated interferon and ribavirin. Liver International. 2012;32(SUPPL. 1):39-43. **Exclusion Reason** - No Original Data

Kwong AD, Kauffman RS, Hurter P, et al. Discovery and development of telaprevir: an NS3-4A protease inhibitor for treating genotype 1 chronic hepatitis C virus. Nat Biotech. 2011;29(11):993-1003. PMID: 22068541**. Exclusion Reason** -Background

Laguno M, Cifuentes C, Murillas J, et al. Randomized trial comparing pegylated interferon α-2b versus pegylated interferon α-2a, both plus ribavirin, to treat chronic hepatitis C in human immunodeficiency virus patients. Hepatology. 2009;49(1):22-31. PMID: 19085908**. Exclusion Reason** -Wrong Outcome

Lam KD, Trinh HN, Do ST, et al. Randomized controlled trial of pegylated interferon-alfa 2a and ribavirin in treatment-naive chronic hepatitis C genotype 6. Hepatology. 2010 Nov;52(5):1573-80. PMID: 21038410 **Exclusion Reason** -Wrong Population

Lang, et al. Pegylated interferon-alpha2b plus ribavirin therapy in patients with hepatitis C and psychiatric disorders: results of a cohort study. Antiviral Therapy. 2010;15(4):599-606. PMID: 20587853**. Exclusion Reason** -Not Relevant

Lange CM, Susser S, Herrmann E, et al. HVR-1 heterogeneity during treatment with telaprevir with or without pegylated interferon alfa-2a. Scandinavian Journal of Gastroenterology. 2011;46(11):1362-1368. PMID: 21815864**. Exclusion Reason** -Wrong Outcomes

Langlet P, D'Heygere F, Henrion J, et al. Clinical trial: a randomized trial of pegylated-interferon-alpha-2a plus ribavirin with or without amantadine in treatment-naive or relapsing chronic hepatitis C patients. Alimentary Pharmacology & Therapeutics. 2009 Aug 15;30(4):352-63. PMID: 19485978**. Exclusion Reason -**Not Relevant

Lau DT, Kleiner DE, Ghany MG, et al. 10-year follow-up after interferon-α therapy for chronic hepatitis C. Hepatology. 1998;28(4):1121-1127. PMID: 9755252 Exclusion reason - Wrong Drug

Lawitz E, Rodriguez-Torres M, Muir AJ, et al. Antiviral effects and safety of telaprevir, peginterferon alfa-2a, and ribavirin for 28 days in hepatitis C patients. Journal of Hepatology. 2008;49(2):163-169. PMID: 18486984**. Exclusion Reason -**Wrong Outcomes

Lee SS, Sherman M, Ramji A, et al. Randomised clinical trial: The efficacy of treatment, guided by a shorter duration of response, using peginterferon alfa-2a plus ribavirin for hepatitis C virus other than genotypes 2 or 3. Alimentary Pharmacology and Therapeutics; 2012. p. 37-47. PMID:22050141 **Exclusion Reason -**Wrong Population

Le Lan C, Guillygomarc'H A, Danielou H, et al. A multi-disciplinary approach to treating hepatitis C with interferon and ribavirin in alcohol-dependent patients with ongoing abuse. Journal of Hepatology. 2012;56(2):334-340. **Exclusion Reason -** Background

Lee LY, Tong CYW, Wong, T, et al. New therapies for chronic hepatitis C infection: A systematic review of evidence from clinical trials. International Journal of Clinical Practice. 2012;66(4):342-355. **Exclusion Reason -** Background

Lee SS, Roberts SK, Berak H, et al. Safety of peginterferon alfa-2a plus ribavirin in a large multinational cohort of chronic hepatitis C patients. Liver International. 2012. **Exclusion Reason -** Wrong Study Design

Lindenburg CEA, Lambers FAE, Urbanus AT, et al. Hepatitis C testing and treatment among active drug users in Amsterdam: results from the DUTCH-C project. European Journal of Gastroenterology & Hepatology. 2011 Jan;23(1):23-31. PMID: 21042221**. Exclusion Reason -**Not Relevant

Liu CH, Liang CC, Liu CJ, et al. Peginterferon plus ribavirin for 48 or 72 weeks in asian hepatitis C virus genotype 1 patients without rapid virologic response. Hepatology International. 2011; 5(1): 268. **Exclusion Reason -**Wrong Population

Livingston SE, Townshend-Bulson LJ, Bruden DL, et al.Treatment eligibility in Alaska Native and American Indian persons with hepatitis C virus infection. International Journal of Circumpolar Health. 2012;71(1). **Rxclusion Reason -** Wrong design

Lodato F, Azzaroli F, Brillanti S, et al. Higher doses of peginterferon alpha-2b administered twice weekly improve sustained virological response in difficult-to-treat patients with chronic hepatitis C: results of a pilot randomized study.[Erratum appears in J Viral Hepat. 2005 Nov;12(6):663]. Journal of Viral Hepatitis. 2005 Sep;12(5):536-42. PMID: 16108771**. Exclusion Reason -** Not Relevant

Lok A. Preliminary study of two antiviral agents for hepatitis C genotype 1. The New England journal of medicine. 2012;366(3):273-5. PMID: 22256811**. Exclusion Reason -**Wrong Outcomes

Lok ASF, Ghany MG, Goodman ZD, et al. Predicting cirrhosis in patients with hepatitis C based on standard laboratory tests: results of the HALT-C cohort. Hepatology. 2005 Aug;42(2):282-92. PMID: 15986415**. Exclusion Reason -**Wrong Population

Lok ASF, Pawlotsky, J.-M.. Viral hepatitis at a crossroad. Gastroenterology. 2012;142(6):1261-1263. **Exclusion Reason -** Background

Louie KS, St Laurent S, Forssen UM, et al. The high comorbidity burden of the hepatitis C virus infected population in the United States. BMC Infectious Diseases. 2012;12. **Exclusion Reason -** Background

Lurie Y, Rouzier-Panis R, Webster GJM, et al. Optimal dosing frequency of pegylated interferon alfa-2b monotherapy for chronic hepatitis C virus infection. Clinical Gastroenterology & Hepatology. 2005 Jun;3(6):610-5. PMID: 15952104**. Exclusion Reason -**Wrong Drug

Ma L-n, Chen X-y, Chen J, et al. [Efficacy, influencing factors and safety of PEG-INF alpha-2a (PEG-INF-2a) in the treatment of chronic hepatitis C: analysis of 89 patients]. Chinese Journal of Experimental & Clinical Virology. 2006 Jun;20(2):42-5. PMID: 16816861**. Exclusion Reason -**Not Relevant

Makiyama A, Itoh Y, Kasahara A, et al. Characteristics of patients with chronic hepatitis C who develop hepatocellular carcinoma after a sustained response to interferon therapy. Cancer. 2004 Oct 1;101(7):1616-22. PMID: 15378504**. Exclusion Reason -**Wrong Outcomes

Maruoka D, Imazeki F, Arai M, et al. Longitudinal changes of the laboratory data of chronic hepatitis C patients with sustained virological response on long-term follow-up. Journal of Viral Hepatitis. 2012;19(2):e97-e104. **Exclusion Reason –** Background

Mauss, S, Berger F, Vogel M, et al.Treatment results of chronic hepatitis C genotype 5 and 6 infections in Germany. Zeitschrift fur Gastroenterologie. 2012;50(5):441-444. **Exclusion Reason -** Wrong population

Mallet V, Gilgenkrantz H, Serpaggi J, et al. Brief communication: the relationship of regression of cirrhosis to outcome in chronic hepatitis C. Ann Intern Med. 2008;149(6):399-403. PMID: 18794559**. Exclusion Reason -**Wrong Drug

Mangia A, Bandiera F, Montalto G, et al. Individualized treatment with combination of Peg-interferon alpha 2b and ribavirin in patients infected with HCV genotype 3. Journal of Hepatology. 2010 Dec;53(6):1000-5. PMID: 20843575**. Exclusion Reason -**Not Relevant

Mangia A, Dalgard O, Minerva N, et al. Ribavirin dosage in patients with HCV genotypes 2 and 3 who completed short therapy with peg-interferon alpha-2b and ribavirin. Alimentary Pharmacology & Therapeutics. 2010 Jun;31(12):1346-53. PMID: 20222909**. Exclusion Reason** -Not Relevant

Mangia A, Minerva N, Bacca D, et al. Individualized treatment duration for hepatitis C genotype 1 patients: A randomized controlled trial. Hepatology. 2008 Jan;47(1):43-50. PMID: 18069698**. Exclusion Reason** -Not Relevant

Manns MP, Markova AA, Serrano BC, et al. Phase III results of Boceprevir in treatment naive patients with chronic hepatitis C genotype 1. Liver International. 2012; 27-31. PMID:22212568 **Exclusion Reason -** Wrong Population

Marcellin P, Gish RG, Gitlin N, et al.Safety and efficacy of viramidine versus ribavirin in ViSER2: randomized, double-blind study in therapy-naive hepatitis C patients. Journal of Hepatology. 2010 Jan;52(1):32-8. PMID: 19913323**. Exclusion Reason** -Not Relevant

Marcellin P, Jacobson IM, Zeuzem S, et al. Telaprevir in combination with peginterferon alfa-2a and ribavirin: Analyses of pre-defined subpopulations in the phase 3 advance trial. Journal of Hepatology. 2011;54 :183-S4. **Exclusion Reason -**Wrong Population

Marcellin P, Forns X, Goeser T, et al. Telaprevir is effective given every 8 or 12 hours with ribavirin and peginterferon alfa-2a or -2b to patients with chronic hepatitis C. Gastroenterology; 2011d. p. 459-68.e1; quiz e14. PMID:21034744 **Exclusion Reason -**Wrong Population

Maylin S, Laouénan C, Martinot-Peignoux M, et al. Role of hepatic HCV-RNA level on the severity of chronic hepatitis C and response to antiviral therapy. Journal of Clinical Virology. 2012;53(1):43-47. **Exclusion Reason -** Background

McLaren M, Garber G, Cooper C. Barriers to hepatitis C virus treatment in a Canadian HIV-hepatitis C virus coinfection tertiary care clinic. Canadian Journal of Gastroenterology. 2008 Feb;22(2):133-7. PMID: 18299730**. Exclusion Reason** -Not Relevant

Mendez-Navarro J, Chirino RA, Corey KE, et al. A randomized controlled trial of double versus triple therapy with amantadine for genotype 1 chronic hepatitis C in Latino patients.[Erratum appears in Dig Dis Sci. 2010 Oct;55(10):3010 Note: Juarez, Jesus A [added]]. Digestive Diseases & Sciences. 2010 Sep;55(9):2629-35. PMID: 19960257**. Exclusion Reason -**Not Relevant

Michielsen Pa, Ho E, Francque S, et al Does antiviral therapy reduce the risk of hepatocellular carcinoma in patients with chronic hepatitis C? Minerva Gastroenterologica e Dietologica. 2012;58(1):65-79. **Exclusion Reason -** Background

Milazzo L, Meroni L, Galazzi M, et al. Does fluvastatin favour HCV replication in vivo? A pilot study on HIV-HCV coinfected patients. Journal of Viral Hepatitis. 2009 Jul;16(7):479-84. PMID: 19215577**. Exclusion Reason** -Not Relevant

Milazzo L, Foschi A, Antinori S. Rapid virological response: Is it four or eight weeks? Hepatology. 2012;55(3):979. **Exclusion Reason -** Background

Milla P, Dosio F, Cattel L. PEGylation of proteins and liposomes: A powerful and flexible strategy to improve the drug delivery. Current Drug Metabolism. 2012;13(1):105-119. **Exclusion Reason –** Background

Miller ER, McNally, S., Wallace, J., Schlichthorst, M.The ongoing impacts of hepatitis c - a systematic narrative review of the literature. BMC Public Health. 2012:672. **Exclusion Reason -** Background

Minami T, Kishikawa T, Sato M, et al. Meta-analysis: mortality and serious adverse events of peginterferon plus ribavirin therapy for chronic hepatitis C. Journal of Gastroenterology. 2012:1-15. **Exclusion Reason –** Background

Mirza S, Siddiqui AR, Hamid S, et al. Extent of liver inflammation in predicting response to interferon alpha & Ribavirin in chronic hepatitis C patients: A cohort study. BMC Gastroenterology. 2012:71. **Exclusion Reason -** Background

Miyajima I. The incidence of hepatocellular carcinoma in patients with chronic hepatitis C after interferon treatment. Oncology Reports. 1998;5(1):201-204. **Exclusion Reason -**Wrong Population

Mizui M, Tanaka J, Katayama K, et al. Liver disease in hepatitis C virus carriers identified at blood donation and their outcomes with or without interferon treatment: Study on 1019 carriers followed for 5–10 years. Hepatology Research. 2007;37(12):994-1001. **Exclusion Reason -**Wrong Drug

Morishima C, Di Bisceglie AM, Rothman AL, et al. Antigen-specific T lymphocyte proliferation decreases over time in advanced chronic hepatitis C. Journal of Viral Hepatitis. 2012;19(6):404-413. **Exclusion Reason –** Background

Morishima C, Shiffman, ML, Dienstag JL,, et al. Reduction in Hepatic Inflammation Is Associated With Less Fibrosis Progression and Fewer Clinical Outcomes in Advanced Hepatitis C. American Journal of Gastroenterology. 2012. **Exclusion Reason -** Background

Moriyama M, Matsumura H, Aoki H, et al. Decreased risk of hepatocellular carcinoma in patients with chronic hepatitis C whose serum alanine aminotransferase levels became less than twice the upper limit of normal following interferon therapy. Liver International. 2005;25(1):85-90. **Exclusion Reason -**Wrong Drug

Muir AJ, Poordad FF, McHutchison JG, et al. Retreatment with telaprevir combination therapy in hepatitis C patients with well-characterized prior treatment response. Hepatology. 2011;54(5):1538-1546. PMID: 22045671**. Exclusion Reason -**Wrong Outcomes

Muir AJ, Shiffman ML, Zaman A, et al. Phase 1b study of pegylated interferon lambda 1 with or without ribavirin in patients with chronic genotype 1 hepatitis C virus infection. Hepatology. 2010 Sep;52(3):822-32. PMID: 20564352**. Exclusion Reason -**Wrong Population

Myers,RP, Regimbeau C, Thevenot T, et al.Interferon for interferon naive patients with chronic hepatitis C. Cochrane Database of Systematic Reviews. 2009(1). **Exclusion Reason –** Background

Myers RP, Regimbeau C, Thevenot T, et al. Interferon for acute hepatitis C. Cochrane Database of Systematic Reviews. 2010(4). **Exclusion Reason -** Background

Nagaki M, Shimizu M, Sugihara JI, et al. Clinical trial: extended treatment duration of peginterferon-alpha2b plus ribavirin for 72 and 96 weeks in hepatitis C genotype 1-infected late responders. Alimentary Pharmacology & Therapeutics. 2009 Aug 15;30(4):343-51. PMID: 19485982**. Exclusion Reason -**Not Relevant

Napoli N, Giannelli G, Antonaci A, et al. The use of different Peg-interferon alpha-2b regimens plus ribavirin in HCV-1b-infected patients after rapid virological response does not affect the achievement of sustained virological response. Journal of Viral Hepatitis. 2008 Apr;15(4):300-4. PMID: 18307592**. Exclusion Reason -**Not Relevant

Negro F. Steatosis and insulin resistance in response to treatment of chronic hepatitis C. Journal of Viral Hepatitis. 2012;19(SUPPL. 1):42-47. **Exclusion Reason -** Background

Nelson DR, Benhamou Y, Chuang W-L, et al. Albinterferon Alfa-2b was not inferior to pegylated interferon- in a randomized trial of patients with chronic hepatitis C virus genotype 2 or 3. Gastroenterology. 2010 Oct;139(4):1267-76. PMID: 20600017**. Exclusion Reason -**Not Relevant

Neukam K, Mira JA, Gilabert I, et al.Efficacy of chronic hepatitis C therapy with pegylated interferon and ribavirin in patients on methadone maintenance treatment. European journal of clinical microbiology & infectious diseases : official publication of the European Society of Clinical Microbiology. 2012;31(6):1225-1232. **Exclusion Reason -** Wrong Population

Neumann AU, Pianko S, Zeuzem S, et al. Positive and negative prediction of sustained virologic response at weeks 2 and 4 of treatment with albinterferon alfa-2b or peginterferon alfa-2a in treatment-naive patients with genotype 1, chronic hepatitis C. Journal of Hepatology. 2009 Jul;51(1):21-8. PMID: 19447518**. Exclusion Reason -**Not Relevant

Nevens E, Van Vlierberghe H, D'Heygere E, et al. A randomized, open-label, multicenter study evaluating the efficacy of peginterferon alfa-2a versus interferon alfa-2a, in combination with ribavirin, in naive and relapsed chronic hepatitis C patients. Acta Gastroenterologica Belgica. 2010 Apr-Jun;73(2):223-8. PMID: 20690560**. Exclusion Reason -**Wrong Population

Niederau C. Chronic hepatitis C: treat or wait? Medical decision making in clinical practice. World Journal of Gastroenterology. 2012 Mar 28;18(12):1339-47. PMID: 22493547. **Exclusion Reason -** Background

Nishiguchi S, Kuroki T, Nakatani S, et al. Randomised trial of effects of interferon-α on incidence of hepatocellular carcinoma in chronic active hepatitis C with cirrhosis. Lancet. 1995;346(8982):1051-1055. **Exclusion Reason -**Wrong Drug

Omata M, Kanda T, Yu M, et al. APASL consensus statements and management algorithms for hepatitis C virus infection. Hepatology International. 2012;6(2):409-435. **Exclusion Reason –** Background

O'Shaughnessy MM, O'Regan JA, Murray FE, et al..Re-infection following sustained virological response with a different hepatitis C virus genotype: Implications for infection control policy. CKJ: Clinical Kidney Journal. 2012;5(3):250-253. **Exclusion Reason -** Background

Oze T, Hiramatsu N, Song C, et al.Reducing peg-IFN doses causes later virologic response or no response in HCV genotype 1 patients treated with Peg-IFN alfa-2b plus ribavirin. Journal of Gastroenterology. 2012;47(3):334-342. **Exclusion Reason -** Background

Ozeki I, Akaike J, Karino Y, et al. Antiviral effects of peginterferon alpha-2b and ribavirin following 24-week monotherapy of telaprevir in Japanese hepatitis C patients. Journal of Gastroenterology. 2011;46(7):929-937. PMID: 21556829**. Exclusion Reason -**Wrong Outcomes

Palmer. The future of hepatitis C beyond protease inhibitors-will hepatitis C be a disease of the past? Practical Gastroenterology. 2012;36(1):13-22. Exclusion Reason – Background

Palmer M, Rubin R, Rustgi V, et al. Randomised clinical trial: Pre-dosing with taribavirin before starting pegylated interferon vs. standard combination regimen in treatment-naïve patients with chronic hepatitis C genotype 1. Alimentary Pharmacology and Therapeutics. 2012;36(4):370-378. **Exclusion Reason –** Background

Papafragkakis H, Rao, MS, Moehlen, M, et al. Depression and pegylated interferon-based hepatitis C treatment. International Journal of Interferon, Cytokine and Mediator Research. 2012;4(1):25-35. **Exclusion Reason -** Background

Papastergiou V, Dimitroulopoulos D, Skorda L, et al. Predictors of sustained virological response in Greek and Egyptian patients with hepatitis C genotype 4: Does ethnicity matter? Journal of Medical Virology. 2012;84(8):1217-1223. **Exclusion Reason -** Wrong Study Design

Patel K, Benhamou Y, Yoshida EM, et al. An independent and prospective comparison of two commercial fibrosis marker panels (HCV FibroSURE and FIBROSpect II) during albinterferon alfa-2b combination therapy for chronic hepatitis C. Journal of Viral Hepatitis. 2009 Mar;16(3):178-86. PMID: 19175870**. Exclusion Reason -**Wrong Outcome

Pawelczyk T, Pawelczyk A, Strzelecki D, et al. Pegylated interferon alpha and ribavirin therapy may induce working memory disturbances in chronic hepatitis C patients. General Hospital Psychiatry. 2008 Nov-Dec;30(6):501-8. PMID: 19061675**. Exclusion Reason -**Not Relevant

Pawlotsky. The Results of Phase III Clinical Trial With Telaprevir and Boceprevir Presented at the Liver Meeting 2010: A New Standard of Care for Hepatitis C Virus Genotype 1 Infection, But With Issues Still Pending. Gastroenterology. 2011. PMID: 21255572**. Exclusion Reason -**Wrong Outcomes

Pawlotsky. New antiviral agents for hepatitis C. F1000 Biology Reports. 2012;4(1). **Exclusion Reason -** Background

Peese. HCV protease inhibitor telaprevir: phase II clinical results. Drug Discovery Today. 2010;15(9–10):406. **Exclusion Reason –**Background

Peg-Intron/Ribavirin in G 1 HCV for Non-Extended Versus 24 Week Extended Treatment After 24 Weeks (Study P04144)(COMPLETED). **Exclusion Reason -** Wrong Population

Perry. Telaprevir: A review of its use in the management of genotype 1 chronic hepatitis C. Drugs. 2012;72(5):619-641. **Exclusion Reason** - Background

A Phase 3 Study of Telaprevir in Combination With Pegasys® and Copegus® in Treatment-Naive Subjects With Genotype 1 HCV. **Exclusion Reason -**Wrong Population

Pockros P, Zeuzem S, Lawitz EJ, et al. Telaprevir-based regimen in genotype 1 hepatitis C virus-infected patients with prior null response, partial response or relapse to peginterferon/ribavirin: REALIZE trial final results. Gastroenterology. 2011;140(5) : S898. **Exclusion Reason -**Wrong Population

Poordad F, Lawitz E, Shiffman ML, et al. Virologic response rates of weight-based taribavirin versus ribavirin in treatment-naive patients with genotype 1 chronic hepatitis C. Hepatology. 2010 Oct;52(4):1208-15. PMID: 20721883**. Exclusion Reason -**Not Relevant

Poordad F, Bronowicki J, Gordon SC, et al. Factors That Predict Response of Patients With Hepatitis C Virus Infection to Boceprevir. Gastroenterology. 2012. **Exclusion Reason - Background**

Potthoff A, Wedemeyer H, Boecher WO, et al. The HEP-NET B/C co-infection trial: A prospective multicenter study to investigate the efficacy of pegylated interferon-alpha2b and ribavirin in patients with HBV/HCV co-infection. Journal of Hepatology. 2008 Nov;49(5):688-94. PMID: 18490077**. Exclusion Reason -**Not Relevant

Powis J, Peltekian KM, Lee SS, et al. Exploring differences in response to treatment with peginterferon alpha 2a (40kD) and ribavirin in chronic hepatitis C between genotypes 2 and 3. Journal of Viral Hepatitis. 2008 Jan;15(1):52-7. PMID: 18088245**. Exclusion Reason -**Not Relevant

Poynard T, Imbert-Bismut F, Ratziu V, et al. Biochemical markers of liver fibrosis in patients infected by hepatitis C virus: longitudinal validation in a randomized trial. Journal of Viral Hepatitis. 2002 Mar;9(2):128-33. PMID: 11876795**. Exclusion Reason -**Not Relevant

Poynard T, Myers RP.Interferon for interferon nonresponding and relapsing patients with chronic hepatitis C. Cochrane Database of Systematic Reviews. 2009(1). **Exclusion Reason -** Background

Poynard T, McHutchison J, Manns M, et al. Impact of pegylated interferon alfa-2b and ribavirin on liver fibrosis in patients with chronic hepatitis C. Gastroenterology. 2002 May;122(5):1303-13. PMID: 11984517**. Exclusion Reason -**Not Relevant

Pradat P, Tillmann HL, Sauleda S, et al. Long-term follow-up of the hepatitis C HENCORE cohort: response to therapy and occurrence of liver-related complications. Journal of Viral Hepatitis. 2007;14(8):556-563. **Exclusion Reason -**Wrong Population

Qu LS, Chen H, Kuai XL, et al. Effects of interferon therapy on development of hepatocellular carcinoma in patients with hepatitis C-related cirrhosis: A meta-analysis of randomized controlled trials. Hepatology Research. 2012;42(8):782-789. **Exclusion Reason –** Background

Ramachandran P, Fraser A, Agarwal K,,,et al. UK consensus guidelines for the use of the protease inhibitors boceprevir and telaprevir in genotype 1 chronic hepatitis C infected patients. Alimentary Pharmacology and Therapeutics. 2012;35(6):647-662. **Exclusion Reason -** Background

Randomized Trial of 24 or 48 Weeks of Peginterferon Alfa-2a Plus Ribavirin for HCV Genotype 1-infected Patients. **Exclusion Reason -**Wrong Population

Rate and Predictors of Relapse in the Treatment of Hepatitis C (Study P05181). 2011. **Exclusion Reason -** Background

Re VL, Teal V, Localio R, et al. Adherence to hepatitis C virus therapy: Relationship with virologic outcomes and change in adherence over time. Journal of the International Association of Physicians in AIDS Care. 2011;10(3) :195-6. **Exclusion Reason -**Wrong Population

Reddy KR, Messinger D, Popescu M, et al. Peginterferon alpha-2a (40 kDa) and ribavirin: comparable rates of sustained virological response in sub-sets of older and younger HCV genotype 1 patients. Journal of Viral Hepatitis. 2009 Oct;16(10):724-31. PMID: 19486469**. Exclusion Reason -**Not Relevant

Reddy KR, Lin F, Zoulim F, et al. Response-guided and -unguided treatment of chronic hepatitis C. Liver International. 2012;32(SUPPL. 1):64-73. **Exclusion Reason –** Background

Relapse Rate in Hepatitis C Patients Treated With Peginterferon Alfa-2b Plus Ribavirin in Common Clinical Practice in France (P05484)(Completed). 2011. **Exclusion Reason -** Background

Reesink HW, Fanning GC, Farha KA, et al. Rapid HCV-RNA decline with once daily TMC435: a phase I study in healthy volunteers and hepatitis C patients. Gastroenterology. 2010 Mar;138(3):913-21. PMID: 19852962**. Exclusion Reason -**Wrong Outcome

Reesink HW, Zeuzem S, Weegink CJ, et al. Rapid decline of viral RNA in hepatitis C patients treated with VX-950: a phase Ib, placebo-controlled, randomized study. Gastroenterology. 2006 Oct;131(4):997-1002. PMID: 17030169**. Exclusion Reason -**Wrong Drug

Roberts SK, Cooksley G, Dore GJ, et al.Robust antiviral activity of R1626, a novel nucleoside analog: a randomized, placebo-controlled study in patients with chronic hepatitis C. Hepatology. 2008 Aug;48(2):398-406. PMID: 18553458**. Exclusion Reason -**Not Relevant

Rodis JL, Kibbe P. Evaluation of medication adherence and quality of life in patients with hepatitis C virus receiving combination therapy. Gastroenterology Nursing. 2010 Sep-Oct;33(5):368-73. PMID: 20890160**. Exclusion Reason -**Not Relevant

Rodríguez-Torres M, Burguera J, Hallman D, et al.Hepatitis C viral kinetics in Latino patients: A comparison to African American and Caucasian patients. Annals of Hepatology. 2012;11(4):450-463. **Exclusion Reason -** Background

Roffi L, Colloredo G, Pioltelli P, et al. Pegylated interferon-alpha2b plus ribavirin: an efficacious and well-tolerated treatment regimen for patients with hepatitis C virus related histologically proven cirrhosis. Antiviral Therapy. 2008;13(5):663-73. PMID: 18771050**. Exclusion Reason -**Not Relevant

Roomer R, Hansen BE, Janssen HLA, et al.. Thrombocytopenia and the risk of bleeding during treatment with peginterferon alfa and ribavirin for chronic hepatitis C. Journal of Hepatology. 2010 Sep;53(3):455-9. PMID: 20561709**. Exclusion Reason -**Not Relevant

Roomer R, Hansen BE, Janssen HLA, et al. Risk factors for infection during treatment with peginterferon alfa and ribavirin for chronic hepatitis C. Hepatology. 2010 Oct;52(4):1225-31. PMID: 20830784**. Exclusion Reason -**Not Relevant

Roomer R, Bergmann JF, Boonstra A, et al.Continuous interferon-α,2b infusion in combination with ribavirin for chronic hepatitis C in treatment-experienced patients. Antiviral Therapy. 2012;17(3):509-517. **Exclusion Reason -** Background

Rousseau CM, Ioannou GN, Todd-Stenberg JA, et al. Racial differences in the evaluation and treatment of hepatitis C among veterans: a retrospective cohort study. American Journal of Public Health. 2008 May;98(5):846-52. PMID: 18382007**. Exclusion Reason -**Not Relevant

Rumi M, Aghemo A, Prati GM, et al. Comparative trials of peginterferon α2a and peginterferon α2b for chronic hepatitis C. Journal of Viral Hepatitis. 2012;19(SUPPL. 1):37-41. **Exclusion Reason –** Background

Saez V, Ramón J, Peniche C, et al. Microencapsulation of alpha interferons in biodegradable microspheres. Journal of Interferon and Cytokine Research. 2012;32(7):299-311. **Exclusion Reason** – Background

Salloum, Sa T, AW et al. Treating hepatitis C infection by targeting the host. Translational Research. 2012;159(6):421-429. **Exclusion Reason –** Background

Santos C, Reis A, dos Santos CV, et al. The use of real-time PCR to detect hepatitis C virus RNA in dried blood spots from Brazilian patients infected chronically. Journal of Virological Methods. 2012;179(1):17-20. **Exclusion Reason -** Background

Sarwar S, Ryan EJ, Iqbal M, et al. Rapid, early and sustained virological responses in a cohort of Irish patients treated with pegylated interferon and ribavirin for chronic hepatitis C virus infection. Irish Journal of Medical Science. 2012;181(1):53-58. **Exclusion Reason –** Background

Schaefer EAK, Chung RT. Anti-hepatitis C virus drugs in development. Gastroenterology. 2012;142(6):1340-1350.e1. **Exclusion Reason -** Background

Schneider MD,, Sarrazin C. Hepatitis C triple therapy with boceprevir and telaprevir. Triple-Therapie der Hepatitis C mit Boceprevir und Telaprevir. 2012;30(1):23-34. **Exclusion Reason –** Background

Scotto G, Fazio V, Fornabaio C, et al. Peg-Interferon Alpha-2a versus Peg-Interferon Alpha-2b in Nonresponders with HCV Active Chronic Hepatitis: A Pilot Study. Journal of Interferon & Cytokine Research. 2008;28(10):623-630. PMID: 18778199**. Exclusion Reason -**Wrong Outcome

Sharvadze L, Karchava M, Bolokadze N, et al. Safety and efficacy of systematic administration of Filgrastim to prevent neutropenia and infections in patient with hepatitis C. Georgian Medical News. 2009 Oct(175):32-5. PMID: 19893121**. Exclusion Reason -** Not Relevant

Sharvadze L, Tsertsvadze T, Gochitashvili N, et al. Ifn/Rbv treatment induced anemia and its correction with epoetin alpha in patients with hepatitis C. Georgian Medical News. 2006 Aug(137):62-5. PMID: 16980747**. Exclusion Reason -**Not Relevant

ShenY.. A critical evaluation of the preventive effect of antiviral therapy on the development of hepatocellular carcinoma in patients with chronic hepatitis C or B: a novel approach by using meta-regression. Oncology. 2012;82(5):275-89. PMID: 22555181. **Exclusion Reason** - Background

Shiffman ML, Diago M, Tran A, et al. Chronic hepatitis C in patients with persistently normal alanine transaminase levels.[Erratum appears in Clin Gastroenterol Hepatol. 2006 Aug;4(8):1072]. Clinical Gastroenterology & Hepatology. 2006 May;4(5):645-52. PMID: 16630770**. Exclusion Reason -**Not Relevant

Shiffman ML, Ghany MG, Morgan TR, et al. Impact of reducing peginterferon alfa-2a and ribavirin dose during retreatment in patients with chronic hepatitis C. Gastroenterology. 2007 Jan;132(1):103-12. PMID: 17241864**. Exclusion Reason -**Wrong Population

Shiffman ML, Morishima C, Dienstag JL, et al. Effect of HCV RNA suppression during peginterferon alfa-2a maintenance therapy on clinical outcomes in the HALT-C trial.[Erratum appears in Gastroenterology. 2010 Mar;138(3):1215]. Gastroenterology. 2009 Dec;137(6):1986-94. PMID: 19747918**. Exclusion Reason -**Wrong Drug

Shiffman ML, Salvatore J, Hubbard S, et al. Treatment of chronic hepatitis C virus genotype 1 with peginterferon, ribavirin, and epoetin alpha. Hepatology. 2007 Aug;46(2):371-9. PMID: 17559152**. Exclusion Reason -**Not Relevant

Shiffman ML, Esteban R. Triple therapy for HCV genotype 1 infection: Telaprevir or boceprevir? Liver International. 2012;32(SUPPL. 1):54-60. **Exclusion Reason -** Background

Shindo M, Hamada K, Oda Y, et al. Long-term follow-up study of sustained biochemical responders with interferon therapy. Hepatology. 2001;33(5):1299-1302. **Exclusion Reason -**Wrong Drug

Silva M, Poo JL, Wagner F, et al. A randomised trial to compare the pharmacokinetic, pharmacodynamic, and antiviral effects of peginterferon alfa-2b and peginterferon alfa-2a in patients with chronic hepatitis C (COMPARE). Journal of Hepatology. 2006;45(2):204-213. **Exclusion Reason -**Wrong Outcome

Simin M, Myers RP, Stimac D, et al. Pegylated interferon for acute hepatitis C. Cochrane Database of Systematic Reviews. 2009(1). **Exclusion Reason -** Background

Simonetti RG, Gluud C, Pagliaro L. Interferon for hepatocellular carcinoma. Cochrane Database of Systematic Reviews. 2009(1). **Exclusion Reason -** Background

Singal AK, Anand BS. Tailoring treatment duration to 12 to 16 weeks in hepatitis C genotype 2 or 3 with rapid virologic response: systematic review and meta-analysis of randomized controlled trials. J Clin Gastroenterol. 2010;44(8):583-587**. Exclusion Reason -**Wrong Drug

Sinha S. A randomized prospective clinical trial comparing pegylated interferon alpha 2a/ribavirin versus pegylated interferon alpha 2b/ribavirin in the treatment of chronic hepatitis C. American Journal of Gastroenterology. 2004 October 2004;99(10 (Suppl)):S77-8. **Exclusion Reason -**Wrong Drug

Sjogren MH, Sjogren R, Jr., Lyons MF, et al. Antiviral response of HCV genotype 1 to consensus interferon and ribavirin versus pegylated interferon and ribavirin. Digestive Diseases & Sciences. 2007 Jun;52(6):1540-7. PMID: 17406822**. Exclusion Reason -**Not Relevant

Slavenburg S, Weggelaar I, van Oijen MGH, et al. Optimal length of antiviral therapy in patients with hepatitis C virus genotypes 2 and 3: a meta-analysis. Antiviral Therapy. 2009;14(8):1139-48. PMID: 20032543**. Exclusion Reason** -Not Relevant

Smith LS, Nelson M, Naik S, et al. Telaprevir: An NS3/4A Protease Inhibitor for the Treatment of Chronic Hepatitis C. The Annals of Pharmacotherapy. 2011 May 1, 2011;45(5):639-648. PMID: 21558488**. Exclusion Reason** -Background

Snoeck E, Wade JR, Duff F, et al. Predicting sustained virological response and anaemia in chronic hepatitis C patients treated with peginterferon alfa-2a (40KD) plus ribavirin. British Journal of Clinical Pharmacology. 2006 Dec;62(6):699-709. PMID: 17118125**. Exclusion Reason** -Not Relevant

Snow KK, Bonkovsky HL, Fontana RJ, et al. Changes in quality of life and sexual health are associated with low-dose peginterferon therapy and disease progression in patients with chronic hepatitis C. Alimentary Pharmacology & Therapeutics. 2010 Apr;31(7):719-34. PMID: 20070284**. Exclusion Reason** -Wrong Population

Soga K, Shibasaki K, Aoyagi Y. Effect of interferon on incidence of hepatocellular carcinoma in patients with chronic hepatitis C. Hepato-Gastroenterology. 2005 Jul-Aug;52(64):1154-8. PMID: 16001651**. Exclusion Reason** -Wrong Drug

Sood A, Sobti P, Midha V, et al. Efficacy and safety of pegylated IFN alfa 2b alone or in combination with ribavirin in thalassemia major with chronic hepatitis C. Indian Journal of Gastroenterology. 2010 Mar;29(2):62-5. PMID: 20443101**. Exclusion Reason** -Not Relevant

Sporea I, Danila M, Sirli R, et al. Comparative study concerning the efficacy of Peg-IFN alpha-2a versus Peg-IFN alpha-2b on the early virological response (EVR) in patients with chronic viral C hepatitis. Journal of Gastrointestinal & Liver Diseases. 2006 Jun;15(2):125-30. PMID: 16802006**. Exclusion Reason** -Wrong Outcome

Sroczynski G, Esteban E, Conrads-Frank A, et al. Long-term effectiveness and cost-effectiveness of screening for Hepatitis C virus infection. Eur J Public Health; 2009. p. 245-53. **Exclusion Reason –** Wrong Design

Strayer DR, Carter WA. Recombinant and natural human interferons: Analysis of the incidence and clinical impact of neutralizing antibodies. Journal of Interferon and Cytokine Research. 2012;32(3):95-102. **Exclusion Reason -** Background

A Study of Induction Dosing With PEGASYS (Peginterferon Alfa-2a 40KD) Plus Copegus in Treatment-Naive Patients With Chronic Hepatitis C. **Exclusion Reason -** Wrong Population

Su KP. Inflammation in psychopathology of depression: Clinical, biological, and therapeutic implications. BioMedicine (Netherlands). 2012;2(2):68-74. **Exclusion Reason -** Background

Susser S, Vermehren J, Forestier N, et al. Analysis of long-term persistence of resistance mutations within the hepatitis C virus NS3 protease after treatment with telaprevir or boceprevir. Journal of Clinical Virology. 2011;52(4):321-327. PMID: 21924672**. Exclusion Reason** -Not Relevant

Suzuki F, Akuta N, Suzuki Y, et al. Rapid loss of hepatitis C virus genotype 1b from serum in patients receiving a triple treatment with telaprevir (MP-424), pegylated interferon and ribavirin for 12 weeks. Hepatology Research. 2009;39(11):1056-1063. PMID: 19619256**. Exclusion Reason** -Wrong Outcomes

Suzuki F, Suzuki Y, Akuta N, et al. Influence of ITPA polymorphisms on decreases of hemoglobin during treatment with pegylated interferon, ribavirin, and telaprevir. Hepatology. 2010:n-a. PMID: 21246582**. Exclusion Reason** -Not Relevant

Suzuki K, Ohkoshi S, Yano M, et al. Sustained biochemical remission after interferon treatment may closely be related to the end of treatment biochemical response and associated with a lower incidence of hepatocarcinogenesis. Liver International. 2003;23(3):143-147. **Exclusion Reason** -Wrong Population

Takaki S, Kawakami Y, Imamura M, et al. Eicosapentaenoic acid could permit maintenance of the original ribavirin dose in chronic hepatitis C virus patients during the first 12 weeks of combination therapy with pegylated interferon-alpha and ribavirin. A prospective randomized controlled trial. Intervirology. 2007;50(6):439-46. PMID: 18253048**. Exclusion Reason** -Not Relevant

Tanaka K, Sata M, Uchimura Y, et al. Long-term evaluation of interferon therapy in hepatitis C virus-associated cirrhosis: does IFN prevent development of hepatocellular carcinoma? Oncol Rep. 1998;5(1):205-208. **Exclusion Reason** -Wrong Population

Tang KH, Herrmann E, Pachiadakis I, et al. Clinical trial: individualized treatment duration for hepatitis C virus genotype 1 with peginterferon-alpha 2a plus ribavirin. Alimentary Pharmacology & Therapeutics. 2008 May;27(9):810-9. PMID: 18221408**. Exclusion Reason** -Not Relevant

Tangkijvanich P, Komolmit P, Mahachai V, et al. Response-guided therapy for patients with hepatitis C virus genotype 6 infection: A pilot study. Journal of Viral Hepatitis. 2012;19(6):423-430. **Exclusion Reason** - Wrong Study Design

Testino G, Ansaldi F, Andorno E, et al. Interferon therapy does not prevent hepatocellular carcinoma in HCV compensated cirrhosis. Hepato-Gastroenterology. 2002 Nov-Dec;49(48):1636-8. PMID: 12397752**. Exclusion Reason** -Not Relevant

Testino G, Icardi G. Hepatocellular carcinoma and interferon therapy in HCV compensated cirrhosis: evaluation in relation to virological response. Hepato-Gastroenterology. 2005 May-Jun;52(63):4 p preceding table of contents. PMID: 15966175**. Exclusion Reason -**Wrong Drug

Thompson AJ, Clark PJ, Muir AJ,et al. Reply to "iL28B polymorphism and hepatitis C: A genetic marker of peginterferon-α sensitivity devoid from classical interferon-α side effects?". Journal of Hepatology. 2012;56(3):742-743. **Exclusion Reason -** Background

Thu Thuy PT, Bunchorntavakul C, Tan Dat H, et al. A randomized trial of 48 versus 24 weeks of combination pegylated interferon and ribavirin therapy in genotype 6 chronic hepatitis C. Journal of Hepatology. 2012;56(5):1012-1018. **Exclusion Reason -** Wrong Population

Toyoda H, Kumada T, Kiriyama S, et al. Eight-week regimen of antiviral combination therapy with peginterferon and ribavirin for patients with chronic hepatitis C with hepatitis C virus genotype 2 and a rapid virological response. Liver International. 2009 Jan;29(1):120-5. PMID: 18384519**. Exclusion Reason** -Not Relevant

Tran HA, Attia JR, Jones TL, et al. Pegylated interferon-alpha2beta in combination with ribavirin does not aggravate thyroid dysfunction in comparison to regular interferon-alpha2beta in a hepatitis C population: meta-analysis. Journal of Gastroenterology & Hepatology. 2007 Apr;22(4):472-6. PMID: 17376035**. Exclusion Reason -**Not Relevant

Tran HA, Malcolm Reeves GE, Gibson R, et al. Development of thyroid diseases in the treatment of chronic hepatitis C with alpha-interferon may be a good prognosticator in achieving a sustained virological response: a meta-analysis. Journal of Gastroenterology & Hepatology. 2009 Jul;24(7):1163-8. PMID: 19682190**. Exclusion Reason -**Not Relevant

Treatment of Chronic Hepatitis C With Pegylated Interferon and Ribavirin in Participants With/Without Substitution Therapy (P05255). 2011. **Exclusion Reason -** Background

Tsubota A, Satoh K-i, Aizawa M, et al. Four-week pegylated interferon alpha-2a monotherapy for chronic hepatitis C with genotype 2 and low viral load: a pilot, randomized study. World Journal of Gastroenterology. 2008 Dec 21;14(47):7220-4. PMID: 19084937**. Exclusion Reason -**Not Relevant

van Soest H, van der Schaar PJ, Koek GH, et al. No beneficial effects of amantadine in treatment of chronic hepatitis C patients. Digestive & Liver Disease. 2010 Jul;42(7):496-502. PMID: 20018575**. Exclusion Reason -**Not Relevant

Van Vlerken LG, Huisman EJ, Van Soest H, et al. Ribavirin rather than PEG-interferon pharmacodynamics predict nonresponse to antiviral therapy in naive chronic hepatitis C patients. Journal of Viral Hepatitis. 2012;19(1):39-46. **Exclusion Reason -** Wrong design

Villa E, Cammà C, Di Leo A, et al.Peginterferon-A-2B plus ribavirin is more effective than peginterferon-A-2A plus ribavirin in menopausal women with chronic hepatitis C. Journal of Viral Hepatitis. 2012;19(9):640-649. **Exclusion Reason -** Wrong Study Design

Voelker R. Birth cohort screening may help find hepatitis C cases. JAMA - Journal of the American Medical Association. 2012;307(12):1242. **Exclusion Reason -** Background

von Wagner M, Hofmann WP, Teuber G, et al. Placebo-controlled trial of 400 mg amantadine combined with peginterferon alfa-2a and ribavirin for 48 weeks in chronic hepatitis C virus-1 infection. Hepatology. 2008 Nov;48(5):1404-11. PMID: 18846541**. Exclusion Reason -**Not Relevant

Weiss JJ, Alcorn MC, Rabkin JG, et al.The critical role of medication adherence in the success of boceprevir and telaprevir in clinical practice. Journal of Hepatology. 2012;56(2):503-504. **Exclusion Reason –** Background

Welsch C, Jesudian, A, Zeuzem S,. et al.New direct-acting antiviral agents for the treatment of hepatitis C virus infection and perspectives. Gut. 2012;61(SUPPL. 1):i36-i46. **Exclusion Reason –** Background

Wilby K, Partovi N, Ford J, et al. Review of boceprevir and telaprevir for the treatment of chronic hepatitis C. Canadian Journal of Gastroenterology. 2012;26(4):205-210. **Exclusion Reason -** Background

Willson RA. Visual side effects of pegylated interferon during therapy for chronic hepatitis C infection. Journal of Clinical Gastroenterology. 2004 Sep;38(8):717-22. PMID: 15319658**. Exclusion Reason -**Not Relevant

Witthoeft T, Hueppe D, John C, et al. Efficacy and tolerability of peginterferon alfa-2a or alfa-2b plus ribavirin in the daily routine treatment of patients with chronic hepatitis C in Germany: the PRACTICE study. Journal of Viral Hepatitis. 2010 Jul;17(7):459-68. PMID: 20158603**. Exclusion Reason -**Not Relevant

Wójciak RW, Mojs E, Kowalska J, et al. The assessment of trace elements nutritional habits in patients with HCV with or without interferon therapy. Trace Elements and Electrolytes. 2012;29(3):189-193. **Exclusion Reason -** Background

Wright M, Forton D, Main J, et al. Treatment of histologically mild hepatitis C virus infection with interferon and ribavirin: a multicentre randomized controlled trial. Journal of Viral Hepatitis. 2005 Jan;12(1):58-66. PMID: 15655049**. Exclusion Reason** -Not Relevant

Wright M, Grieve R, Roberts J, et al. Health benefits of antiviral therapy for mild chronic hepatitis C: randomised controlled trial and economic evaluation. Health Technology Assessment (Winchester, England). 2006 2006 Jul;10(21):1-113. PMID: 16750059**. Exclusion Reason** -Not Relevant

Xie Y, Xu D-Z, Lu Z-M, et al. Impact of virus genotype on interferon treatment of patients with chronic hepatitis C: a multicenter controlled study. Hepatobiliary & Pancreatic Diseases International. 2004 Aug;3(3):369-74. PMID: 15313671**. Exclusion Reason -**Not Relevant

Xie Y, Xu D-Z, Lu Z-M, et al. Predictive factors for sustained response to interferon treatment in patients with chronic hepatitis C: a randomized, open, and multi-center controlled trial. Hepatobiliary & Pancreatic Diseases International. 2005 May;4(2):213-9. PMID: 15908318**. Exclusion Reason** -Not Relevant

Yabuuchi I, Imai Y, Kawata S, et al. Long-term responders without eradication of hepatitis C virus after interferon therapy: characterization of clinical profiles and incidence of hepatocellular carcinoma. Liver. 2000;20(4):290-295. PMID: 10959807 **Exclusion Reason -** Wrong Population

Yamada I, Suzuki F, Kamiya N, et al. Safety, pharmacokinetics and resistant variants of telaprevir alone for 12 weeks in hepatitis C virus genotype 1b infection. Journal of Viral Hepatitis. 2012; 19(2):112-9. PMID:22239508 **Exclusion Reason -**Wrong Population

Yoneyama K, Yamaguchi M, Kiuchi Y, et al. Analysis of Background Factors Influencing Long-Term Prognosis of Patients with Chronic Hepatitis C Treated with Interferon. Intervirology. 2002;45(1):11-19. PMID: 11937766. **Exclusion Reason** - Wrong Drug

Younossi ZM, Lawitz EJ, Krastev Z, et al. SELECT-2 clinical trial assessing the efficacy and saftey of controlled- release interferon alpha-2B (CR2b)+ribavirin (RBV) versus pegylated interferon alpha-2B (Peg2b)+RBV in treatment-NaiVE genotype-1 (G1) hepatitis C. Gastroenterology. 2011;140(5):S942. **Exclusion Reason -**Wrong Population

Zarski J-P, Sturm N, Desmorat H, et al. Non-invasive assessment of liver fibrosis progression in hepatitis C patients retreated for 96 weeks with antiviral therapy: a randomized study. Liver International. 2010 Aug;30(7):1049-58. PMID: 20492512**. Exclusion Reason -**Wrong Population

Zeuzem S, Pawlotsky JM, Lukasiewicz E, et al. International, multicenter, randomized, controlled study comparing dynamically individualized versus standard treatment in patients with chronic hepatitis C. Journal of Hepatology. 2005 Aug;43(2):250-7. PMID: 16082736**. Exclusion Reason -**Not Relevant

Zeuzem S, Sulkowski MS, Lawitz EJ, et al. Albinterferon Alfa-2b was not inferior to pegylated interferon- in a randomized trial of patients with chronic hepatitis C virus genotype 1. Gastroenterology. 2010 Oct;139(4):1257-66. PMID: 20600013**. Exclusion Reason -**Not Relevant

Zeuzem S, Yoshida EM, Benhamou Y, et al. Albinterferon alfa-2b dosed every two or four weeks in interferon-naive patients with genotype 1 chronic hepatitis C. Hepatology. 2008 Aug;48(2):407-17. PMID: 18666223**. Exclusion Reason -**Not Relevant

Zhao S, Cheng D, Liu E, et al. Peginterferon vs. interferon in the treatment of different HCV genotype infections in HIV patients. European Journal of Clinical Microbiology & Infectious Diseases. 2008 Dec;27(12):1183-92. PMID: 18560911**. Exclusion Reason -**Wrong Population

Zhao S, Liu E, Wei K, et al. Treatment with peginterferon versus interferon in Chinese patients with chronic hepatitis C. European Journal of Clinical Microbiology & Infectious Diseases. 2011 Jan;30(1):51-7. PMID: 20827497**. Exclusion Reason** -Not Relevant

Zhao SH, Chu YL, Cheng DX, et al. Treatment with peginterferon plus ribavirin vs. interferon plus ribavirin for 48 weeks in Chinese patients with chronic hepatitis C. International Journal of Clinical Practice. 2009 Sep;63(9):1334-9. PMID: 19691617**. Exclusion Reason** - Not Relevant

Appendix E. Quality Assessment Methods

Individual studies were rated as "good," "fair" or "poor" as defined below[1]:

For Controlled Trials:

Each criterion was give an assessment of yes, no, or unclear.

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 alternation, case record numbers, birth dates or week days
   - Randomization reported, but method not stated
   - Not clear or not reported
   - Not randomized
2. Was the treatment allocation concealed?
   - Adequate approaches to concealment of randomization:
     - Centralized or pharmacy-controlled randomization (randomization performed without knowledge of patient characteristics).
     - Serially-numbered identical containers
     - On-site computer based system with a randomization sequence that is not readable until allocation
     - Sealed opaque envelopes
   - Inferior approaches to concealment of randomization:
     - Use of alternation, case record numbers, birth dates or week days
     - Open random numbers lists
     - Serially numbered non- opaque envelopes
     - Not clear or not reported
3. Were the groups similar at baseline in terms of prognostic factors?
4. Were the eligibility criteria specified?
5. Were outcome assessors and/or data analysts 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?

For Cohort Studies:

Each criterion was give an assessment of yes, no, or unclear.

1. Did the study attempt to enroll all (or a random sample of) patients meeting inclusion criteria, or a random sample (inception cohort)?
2. Were the groups comparable at baseline on key prognostic factors (e.g., by restriction or matching)?
3. Did the study use accurate methods for ascertaining exposures, potential confounders, and outcomes?
4. Were outcome assessors and/or data analysts blinded to treatment?
5. Did the article report attrition?
6. Did the study perform appropriate statistical analyses on potential confounders?
7. Is there important differential loss to followup or overall high loss to followup?
8. Were outcomes pre-specified and defined, and ascertained using accurate methods?

Appendix F. Sustained Virologic Response and Quality of Life

Author, Year Country Quality	Comparison Definition of Sustained Virologic Response	Population Characteristics	Treatments	Results (by clinical outcome)
Arora , 2006[1] Australia, Europe, New Zealand, North America, and South America Quality: Poor	SVR vs. no SVR SVR=No detectable HCV RNA at end of followup (72 weeks)	Not reported by SVR status Mean age: 43 years Female: 60% Race: Non-white: 14% Advanced fibrosis: 10% Genotype 1: 68% Viral load: 1.1-1.2 x 10^6 copies/ml IVDU: 30% HIV positive: excluded	Pegylated interferon alfa-2a (24 or 48 weeks)	SVR vs. no SVR, mean difference in change from baseline SF-36 physical function: +4.7 ($p<0.05$) SF-36 role limitations-physical: +13 ($p<0.05$) SF-36 bodily pain: +11 ($p<0.0001$) SF-36 general health: +10 ($p<0.0001$) SF-36 vitality: +9.3 ($p<0.0001$) SF-36 social function: +5.1 ($p>0.05$) SF-36 role limitations-emotional: +7.3 ($p>0.05$) SF-36 mental health: +3.1 ($p>0.05$) SF-36 physical component summary: +4.9 ($p<0.0001$) SF-36 mental component summary: +2.0 ($p>0.05$) Fatigue Severity Scale, total score: -4.4 ($p<0.01$) Fatigue Severity Scale, VAS: -10 ($p<0.01$)

Author, Year Country Quality	Comparison Definition of Sustained Virologic Response	Population Characteristics	Treatments	Results (by clinical outcome)
Bernstein , 2002[2] Australia, North America, Europe, Taiwan, New Zealand Quality: Poor	SVR vs. no SVR SVR=No detectable HCV RNA 24 weeks after completion of antiviral therapy	Not reported by SVR status Mean age <=40 years: 41% Female: 32% Race: Non-white: 14% Cirrhosis: 32% Genotype, viral load, HIV infection, IV drug use not reported	Pegylated interferon alfa-2a or interferon alfa-2a	SVR vs. no SVR, mean difference in change from baseline SF-36 physical function: +4.6 (p<0.001) SF-36 role limitations-physical: +9.8 (p<0.001) SF-36 bodily pain: +2.9 (p<0.01) SF-36 general health: +9.1 (p<0.001) SF-36 vitality: +9.6 (p<0.001) SF-36 social function: +6.2 (p<0.001) SF-36 role limitations-emotional: +8.4 (p<0.01) SF-36 mental health: +4.6 (p<0.001) SF-36 physical component summary: +2.8 (p<0.001) SF-36 mental component summary: +3.0 (p<0.001) Fatigue Severity Scale, total score: -0.5 (p<0.001) Fatigue Severity Scale, VAS: -11.5 (p<0.001)

Author, Year Country Quality	Comparison Definition of Sustained Virologic Response	Population Characteristics	Treatments	Results (by clinical outcome)
Bini, 2006[3] USA Quality: Poor	SVR vs. no SVR SVR=No detectable HCV RNA 24 weeks after completion of antiviral therapy	Normal ALT and elevated ALT groups, respectively (not reported by SVR status) Mean age: 50 and 49 years Female: 11% and 8% Race: Non-white: 59% and 66% Normal ALT and elevated ALT groups, respectively (not reported by SVR status) Cirrhosis: 11% and 11% Genotype 1: 78% and 78% Viral load >2 x 10^6 copies/ml: 44% and 44% IVDU: 67% and 65% HIV positive: excluded	Interferon alfa-2b + ribavirin	SVR vs. no SVR, mean difference in change from baseline (normal ALT and elevated ALT subgroups, respectively; p values not reported) SF-36 physical function: +18 and +15 SF-36 role limitations-physical: +22 and +27 SF-36 bodily pain: +3.4 and +9.3 SF-36 general health: +3.0 and +9.9 SF-36 vitality: +12 and +12 SF-36 social function: +9.5 and +11 SF-36 role limitations-emotional: +20 and +18 SF-36 mental health: +14 and +18 SF-36 physical component summary: +3.8 and +7.1 SF-36 mental component summary: +6.0 and +2.1 Positive well being: +14 and -3.1 Sleep somnolence: +11 and +5.4 Health distress: +9.3 and +11 Hepatitis-specific health distress: +5.4 and +2.6 Hepatitis-specific limitations: +13 and +3.8
Bonkovsky , 1999[4] USA and Canada Quality: Poor	SVR vs. no SVR SVR=No detectable HCV RNA 24 weeks after completion of antiviral therapy	Not reported by SVR status Mean age: 43 years Female: 27% Race: Non-white: 23% Cirrhosis: 16% Genotype 1: 68% Viral load: Not reported IVDU: 41% HIV positive: excluded	Consensus interferon or interferon alfa-2b	SVR vs. no SVR, mean difference in change from baseline (values estimated from graph) SF-36 physical function: +6.0 ($p<0.05$) SF-36 role limitations-physical: +22 ($p<0.01$) SF-36 bodily pain: -0.5 ($p>0.05$) SF-36 general health: +7.5 ($p<0.01$) SF-36 vitality: +9.5 ($p<0.05$) SF-36 social function: +10 ($p<0.05$) SF-36 role limitations-emotional: +11 ($p>0.05$) SF-36 mental health: +4.0 ($p>0.05$)

Author, Year Country Quality	Comparison Definition of Sustained Virologic Response	Population Characteristics	Treatments	Results (by clinical outcome)
Hassanein , 2004[5] Australia, North America, Europe, Taiwan, Brazil, Mexico Quality: Poor	SVR vs. no SVR SVR=No detectable HCV RNA 24 weeks after completion of antiviral therapy	Not reported by SVR status Mean age: 43 years Female: 29% Race: Non-white: 16% Cirrhosis: 13% Genotype 1: 63% Viral load: 5.9 to 6.0 x 10^6 copies/ml IVDU: Not reported HIV positive: excluded	Pegylated interferon alfa-2a, pegylated interferon alf-2a +ribavirin, or interferon alfa-2b + ribavirin	SVR vs. no SVR, mean difference in change from baseline SF-36 physical function: +5.5 (p<0.01) SF-36 role limitations-physical: +5.7 (p<0.05) SF-36 bodily pain: +4.1 (p<0.05) SF-36 general health: +8.6 (p<0.01) SF-36 vitality: +6.3 (p >0.05) SF-36 social function: +5.8 (p<0.01) SF-36 role limitations-emotional: +9.3 (p<0.01) SF-36 mental health: +5.0 (p<0.01) SF-36 physical component summary: +2.2 (p<0.01) SF-36 mental component summary: +2.6 (p<0.01) Total fatigue: +3.3 (p<0.01) Fatigue severity: +7.4 (p<0.01)
McHutchison , 2001[6] USA Quality: Poor	SVR vs. relapse vs. non-responder SVR=No detectable HCV RNA 24 weeks after completion of antiviral therapy Relapse: Not defined	Mean age: 43 vs. 44 years Female: 42% vs. 32% Race: Non-white: 8% vs. 12% Cirrhosis: Not reported Genotype 1: 43% vs. 81% Viral load >2 million copies/ml: 58% vs. 74% IVDU: Not reported HIV positive: excluded	Interferon alfa-2a for 24 or 48 weeks, with or without ribavirin	SVR and relapse, mean difference in change from baseline vs. non-responder (p not reported, values estimated from graph) SF-36 physical function: +2.4 and +0.8 SF-36 role limitations-physical: +5.2 and +3.2 SF-36 bodily pain: +1.6 and +1.7 SF-36 general health: +5.2 and +1.5 SF-36 vitality: +4.7 and +2.0 SF-36 social function: +3.1 and +0.4 SF-36 role limitations-emotional: +3.0 and +1.2 SF-36 mental health: +2.0 and 0.0 Sleep somnolence: +3.4 and +2.3 Health distress: +5.4 and +1.2 Hepatitis-related health distress: +5.7 and +1.1 Hepatitis-related limitations: +4.6 and +2.1

Author, Year Country Quality	Comparison Definition of Sustained Virologic Response	Population Characteristics	Treatments	Results (by clinical outcome)
Neary , 1999[7] USA, Europe, Australia Quality: Poor	SVR vs. no SVR and overall response versus no overall response SVR=No detectable HCV RNA 24 weeks after completion of antiviral therapy Overall response=SVR plus >=2-point improvement in Knodell HAI score	Not reported by SVR or overall response status Mean age: 43 years Female: 35% Race: Non-white: 6.4% Not reported by SVR or overall response status Bridging fibrosis or cirrhosis: 17% Genotype 1: 56% Viral load >2 million copies/ml: 75% IVDU: 40% HIV positive: excluded	Interferon alfa-2b with or without ribavirin	SVR and relapse. mean difference in change from baseline vs. non-responder (estimated from graph) (p values not reported) SF-36 physical function: +8.0 and +3.8 SF-36 role limitations-physical: +7.6 and +4.9 SF-36 bodily pain: +2.4 and +2.7 SF-36 general health: +9.4 and +5.6 SF-36 vitality: +7.8 and +5.6 SF-36 social function: +9.4 and +4.1 SF-36 role limitations-emotional: +6.0 and +12 SF-36 mental health: +2.8 and +1.8 Sleep somnolence: +2.1 and +3.8 Health distress: +8.9 and +1.6 Hepatitis-related health distress: +11 and -0.8 Hepatitis-related limitations: +6.7 and +2.6 Mental health-18: +3.4 and +2.3 Overall response vs. no response (estimated from graph) SF-36 physical function: +8.3 (p<0.05) SF-36 role limitations-physical: +10 (p>0.05) SF-36 bodily pain: +3.7 (p>0-.05) SF-36 general health: +6.9 (p<0.05) SF-36 vitality: +5.8 (p<0.05) SF-36 social function: +9.2 (p<0.05) SF-36 role limitations-emotional: +3.6 (p>0.05) SF-36 mental health: +1.3 (p>0.05) Sleep somnolence: +1.5 (p>0.05) Health distress: +6.4 (p<0.05) Hepatitis-related health distress: +12 (p<0.05) Hepatitis-related limitations: +7.8 (p<0.05) Mental health-18: +1.5 (p>0.05)

Author, Year Country Quality	Comparison Definition of Sustained Virologic Response	Population Characteristics	Treatments	Results (by clinical outcome)
Rasenack , 2003[8] Germany, Canada, New Zealand, Spain Quality: Poor	SVR vs. no SVR SVR=No detectable HCV RNA 24 weeks after completion of antiviral therapy	Not reported by SVR status Mean age: 41 years Female: 33% Race: Non-white: 15% Bridging fibrosis/cirrhosis: 13% Injection drug use: 37% Viral load: 7.4 to 8.2 x 10^6 copies/ml HIV positive: Not reported Genotype: Not reported	Pegylated interferon alfa-2a or interferon alfa-2a	SVR vs. no SVR, mean difference in change from baseline SF-36 physical function: +5.0 (p=0.001) SF-36 role limitations-physical: +14 (p<0.001) SF-36 bodily pain: +5.2 (p=0.014) SF-36 general health: 12 (p<0.001) SF-36 vitality: +9.4 (p<0.001) SF-36 social function: +5.8 (p=0.005) SF-36 role limitations-emotional: +8.4 (p=0.02) SF-36 mental health: +5.3 (p=0.001) SF-36 physical component summary: +3.2 (p<0.001) SF-36 mental component summary: +2.9 (p=0.005) Fatigue Severity Scale, total score: -0.5 (p=0.001) Fatigue Severity Scale, VAS: -8.4 (p<0.001)
Ware , 1999[9] Australia, North America, and Europe Quality: Poor	SVR vs. no SVR SVR=No detectable HCV RNA 24 weeks after completion of antiviral therapy Overall response vs. no overall response Overall response=SVR + Knodell histology activity index inflammation score improved by 2 U or more	Not reported by response status Mean age: 43 years Female: 35% Race: Non-white: 6.4% Bridging fibrosis/cirrhosis: 18% Injection drug use: 40% Viral load: 4.8 to 5.2 x 10^6 copies/ml HIV positive: Excluded Genotype 1: 56%	Interferon alfa-2b or interferon alfa-2b + ribavirin	SVR vs. no SVR and overall response vs. no overall response, mean difference in change from baseline (p values not reported) SF-36 physical function: +2.6 and +3.5 SF-36 role limitations-physical: +1.5 and +3.1 SF-36 bodily pain: +0.45 and +1.6 SF-36 general health: +3.3 and +3.5 SF-36 vitality: +2.2 and +2.8 SF-36 social function: +3.4 and +4.3 SF-36 role limitations-emotional: -0.02 and +1.1 SF-36 mental health: +1.3 and +0.62 Sleep: +0.02 and +1.2 Health distress: +7.6 and +6.2 Chronic hepatitis C health distress: +11.5 and +11.3 Chronic hepatitis C limitations: +5.3 and +7.5

Abbreviations: ALT, alanine aminotransferase; HCV, hepatitis C virus; SVR, sustained virologic response.

Appendix F References

1. Arora S, O'Brien C, Zeuzem S, et al. Treatment of chronic hepatitis C patients with persistently normal alanine aminotransferase levels with the combination of peginterferon alpha-2a (40 kDa) plus ribavirin: impact on health-related quality of life. Journal of Gastroenterology & Hepatology. 2006 Feb;21(2):406-12. PMID: 16509866.

2. Bernstein D, Kleinman L, Barker CM, et al. Relationship of health-related quality of life to treatment adherence and sustained response in chronic hepatitis C patients. Hepatology. 2002 Mar;35(3):704-8. PMID: 11870387.

3. Bini EJ, Mehandru S. Sustained virological response rates and health-related quality of life after interferon and ribavirin therapy in patients with chronic hepatitis C virus infection and persistently normal alanine aminotransferase levels. Aliment Pharmacol Ther. 2006;23(6):777-85. PMID: 16556180.

4. Bonkovsky HL, Woolley JM. Reduction of health-related quality of life in chronic hepatitis C and improvement with interferon therapy.The Consensus Interferon Study Group. Hepatology. 1999;29(1):264-70. PMID: 9862876.

5. Hassanein T, Cooksley G, Sulkowski M, et al. The impact of peginterferon alfa-2a plus ribavirin combination therapy on health-related quality of life in chronic hepatitis C. Journal of Hepatology. 2004;40(4):675-81. PMID: 15030985.

6. McHutchison J, Manns M, Harvey J, et al. Adherence to therapy enhanges sustained response in chronic hepatitis C patients receiving PEG-Interferon alfa-2b plus Ribavirin[abstract]. Journal of Hepatology. 2001;34(1):2-3.

7. Neary MP, Cort S, Bayliss MS, et al. Sustained virologic response is associated with improved health-related quality of life in relapsed chronic hepatitis C patients. Semin Liver Dis. 1999;19 Suppl 1:77-85. PMID: 10349695.

8. Rasenack J, Zeuzem S, Feinman SV, et al. Peginterferon alpha-2a (40kD) [Pegasys] improves HR-QOL outcomes compared with unmodified interferon alpha-2a [Roferon-A]: in patients with chronic hepatitis C.[Erratum appears in Pharmacoeconomics. 2003;21(17):1290]. Pharmacoeconomics. 2003;21(5):341-9. PMID: 12627987.

9. Ware JE, Bayliss MS, Mannocchia M, et al. Health-related quality of life in chronic hepatitis C: impact of disease and treatment response. The Interventional Therapy Group. Hepatology. 1999;30(2):550-5. PMID: 10421667

Appendix G. Overall Strength of Evidence

Key Question	Number of Studies	Quality (Good, Fair, Poor)	Consistency (High, Moderate, Low)	Directness (Direct or Indirect)	Precision (High, Moderate, Low)	Number of Subjects	Strength of Evidence
1a. What is the comparative effectiveness of antiviral treatment in improving health outcomes in patients with HCV infection?							
Long-term clinical outcomes	**No studies**	No studies	Unknown (no studies)	No studies	No studies	No subjects	Insufficient
Short-term mortality	**3 randomized trials**	Fair	High	Direct	Low	N = 5,255	Low
Short-term quality of life	**1 randomized trial**	Fair	Unknown (one study)	Direct	Low	N = 516	Low
1b. How does the comparative effectiveness of antiviral treatment for health outcomes vary according to patient subgroup characteristics, including but not limited to HCV genotype, race, sex, disease severity or genetic markers?							
Any clinical outcome	**No studies**	No studies	No studies	No studies	No studies	No subjects	Insufficient
2a. What is the comparative effectiveness of antiviral treatments in improving intermediate outcomes, such as the rate of viremia, aminotransaminase levels, and histologic changes?							
SVR: Dual therapy with pegylated interferon alfa-2a plus ribavirin vs. pegylated interferon alfa-2b plus ribavirin	**7 randomized trials**	Fair	High	Direct	High	N = 4,660	Moderate

Key Question	Number of Studies	Quality (Good, Fair, Poor)	Consistency (High, Moderate, Low)	Directness (Direct or Indirect)	Precision (High, Moderate, Low)	Number of Subjects	Strength of Evidence
Duration effects, dual therapy with pegylated interferon plus ribavirin (genotype 2 or 3)							
SVR: 48 vs. 24 weeks	**2 randomized trials**	Fair	High	Direct	Moderate	N = 609	Moderate
SVR: 24 vs. 12-16 weeks	**4 randomized trials**	Fair	High	Direct	Moderate	N = 2,599	Moderate
SVR: 24 vs. 12-16 weeks in patients with rapid virological response	**3 randomized trials**	Fair	High	Direct	Moderate	N = 583	Moderate
Dose effects, dual therapy with pegylated interferon plus ribavirin (genotype 2 or 3)							
SVR: Lower vs. higher dose pegylated interferon	**6 randomized trials**	Fair	High	Direct	Moderate	N = 865	Moderate
SVR: Lower vs. higher dose ribavirin	**3 randomized trials**	Fair	Moderate	Direct	Moderate	N = 2,605	Moderate
SVR: Lower vs. higher dose ribavirin, patients with advanced fibrosis or cirrhosis	**1 randomized trial**	Fair	Unknown (one study)	Direct	Low	N = 60	Low
Triple therapy with boceprevir							
SVR: Triple therapy with boceprevir vs. dual therapy	**2 randomized trials**	Fair	High	Direct	Moderate	N = 1608	Moderate
SVR: Lower vs. higher dose ribavirin	**1 randomized trial**	Fair	Unknown (one study)	Direct	Low	N = 75	Low
Triple therapy with telaprevir							
SVR: 24 weeks fixed duration triple therapy with telaprevir vs. 48 weeks dual therapy	**3 randomized trials**	Fair	High	Direct	Moderate	N= 506	Moderate
SVR: 12 weeks fixed duration triple therapy with telaprevir vs. 48 weeks dual therapy	**1 randomized trial**	Fair	Unknown (one study)	Direct	Low	N = 209	Low
SVR: 48 weeks fixed duration triple therapy with telaprevir vs. 24 weeks triple therapy	**1 randomized trial**	Fair	Unknown (one study)	Direct	Low	N = 189	Low

Key Question	Number of Studies	Quality (Good, Fair, Poor)	Consistency (High, Moderate, Low)	Directness (Direct or Indirect)	Precision (High, Moderate, Low)	Number of Subjects	Strength of Evidence
SVR: Response-guided triple therapy with telaprevir vs. dual therapy	**1 randomized trial**	Fair	Unknown (one study)	Direct	Low	N = 1,088	Low
SVR: Triple therapy with telaprevir, lower versus higher telaprevir dose and pegylated interferon alfa-2a vs. alfa-2b	**1 randomized trial**	Fair	Unknown (one study)	Direct	Low	N = 161	Low
SVR: 48 vs. 24 weeks in patients with an extended rapid virological response	**1 randomized trial**	Fair	Unknown (one study)	Direct	Low	N = 540	Low
2b. How does the comparative effectiveness of antiviral treatment for intermediate outcomes vary according to patient subgroup characteristics, including but not limited to HCV genotype, race, sex, disease severity or genetic markers?							
SVR: Dual therapy with pegylated interferon alfa-2a plus ribavirin vs. dual therapy with pegylated interferon alfa-2b plus ribavirin: effects of race, sex, age, baseline fibrosis stage, or baseline viral load	**1 randomized trial**	Fair	Unknown (one study)	Direct	Moderate	N = 3070	Low
SVR: Dual therapy with pegylated interferon alfa-2a plus ribavirin vs. dual therapy with pegylated interferon alfa-2b plus ribavirin: effects of genotype	**4 randomized trials**	Fair	High	Direct	High	N = 1,152	Moderate
SVR: Triple therapy with boceprevir vs. dual therapy: effects of sex and race	**2 randomized trials**	Fair	High	Direct	Moderate	N = 1,617	Moderate
SVR: Triple therapy with boceprevir vs. dual therapy: effects of baseline viral load	**2 randomized trials**	Fair	High	Direct	Moderate	N = 1,617	Moderate
SVR: Triple therapy with telaprevir vs. dual therapy: effects of age, sex, race, baseline fibrosis, and body weight	**1 randomized trial**	Fair	Unknown (1 study)	Direct	Moderate	N = 1,088	Moderate (for age and sex) to low (for other factors)

Key Question	Number of Studies	Quality (Good, Fair, Poor)	Consistency (High, Moderate, Low)	Directness (Direct or Indirect)	Precision (High, Moderate, Low)	Number of Subjects	Strength of Evidence
SVR: Triple therapy with telaprevir vs. dual therapy: effects of baseline viral load	**2 randomized trials**	Fair	Low	Direct	Moderate	N = 729	Insufficient
3a. What are the comparative harms (including intolerance to treatment) associated with antiviral treatment?							
Harms: Dual therapy with pegylated interferon alfa-2b plus ribavirin vs. pegylated interferon alfa-2a plus ribavirin	**5 randomized trials, depending on specific harm**	Fair	High	Direct	Moderate	N = 4,047	Moderate
Harms: Triple therapy with boceprevir	**2 randomized trials**	Fair	High	Direct	Moderate	N = 3,501	Moderate
Harms: 24 weeks fixed duration triple therapy with telaprevir vs. 48 weeks dual therapy	**3 randomized trials**	Fair	High	Direct	Moderate	N = 3,591	Moderate
Harms: 12 weeks fixed duration triple therapy with telaprevir vs. 48 weeks dual therapy	**2 randomized trials**	Fair	High	Direct	Moderate	N = 573	Moderate
Harms: Response-guided triple therapy with telaprevir vs. dual therapy	**1 randomized trial**	Fair	Unknown (one study)	Direct	Low	N = 189	Low
3b. Do these harms differ according to patient subgroup characteristics, including HCV genotype, race, sex, disease severity or genetic markers?							
Dual therapy with pegylated interferon alfa-2b plus ribavirin vs. pegylated interferon alfa-2a plus ribavirin	**3 randomized trials**	Fair	High	Indirect (no study stratified harms by patient subgroups, 3 trials evaluated only genotype 1 patients)	Moderate	N = 3,305	Insufficient
Triple therapy with pegylated interferon, ribavirin, and telaprevir or boceprevir	**No studies**	No studies	Unknown (no studies)	No studies	No studies	No subjects	Insufficient

Key Question	Number of Studies	Quality (Good, Fair, Poor)	Consistency (High, Moderate, Low)	Directness (Direct or Indirect)	Precision (High, Moderate, Low)	Number of Subjects	Strength of Evidence
4. Have improvements in intermediate outcomes (viremia, liver function tests, histologic changes) been shown to reduce the risk or rates of health outcomes from HCV infection?							
Mortality and long-term hepatic complications	**19 cohort studies**	Fair	High	Direct	High	N = 27,992	Moderate
Short-term quality of life	**9 cohort studies**	Poor	High	Direct	High	N = 4,981	Low

Note: HCV=hepatitis C virus, SVR=sustained virologic response.

Appendix H. Evidence Tables and Quality Ratings
Key Questions 2a - 3b

Evidence Table 1. Trials of dual therapy with pegylated interferon alpha-2a plus ribavirin compared with pegylated interferon alfa-2b plus ribavirin

Author, Year **Country** **Study Name** **Quality**	**Interferon Regimen**	**Ribavirin Regimen**	**Protease Inhibitor Regimen**	**Eligibility**	**Exclusion**	**Number Screened/ Eligible/ Enrolled/ Analyzed**	**Age** **Sex** **Race**
Ascione, 2010[1] Liver Unit of Cardarelli Hospital - Napoli, Italy Pegylated Interferon alfa-2a plus Ribavirin is more effective than Pegylated Interferon alfa-2b plus Ribavirin for treating chronic HCV Infection Overall Quality: Fair	A: Pegylated interferon alpha-2a 180 µg/week for 24 or 48 weeks (genotype 2/3 and 1/4 respectively) B: Genotype 2/3: Pegylated interferon alpha-2b 1.5 µg/kg/week for 24 or 48 weeks (genotype 2/3 and 1/4 respectively)	A: 800-1200 mg daily for 24 or 48 weeks (genotype 2/3 and 1/4 respectively) B: 800-1200 mg daily for 24 or 48 weeks (genotype 2/3 and 1/4 respectively)	None	Detectable serum HCV RNA level ALT level 1.5x the upper limit of normal for 6 months Liver biopsy within 12 months of starting treatment graded according to Scheuer's criteria (2002) Negative pregnancy test result/using Contraceptive methods during therapy and for 6 months after the end of treatment No alcohol use 6 months pre-enrollment Cirrhosis on basis of clinical/lab testing liver-spleen ultrasonography Upper gastrointestinal endoscopy for patients who did not have a biopsy	Hemoglobin level <120 g/L Neutrophil count <1.5x10^9/L or a platelet count <70x10^9/L Abnormal serum creatinine level; Hepatitis B surface antigen positive HIV+ Any other cause of liver disease History of liver decompensation Clinically relevant depression or any other Psychiatric disease Cancer Severe cardiac/pulmonary/renal disease Uncontrolled diabetes or severe hypertension with vascular complications including Retinopathy	408/322/320/320	A vs. B Age (mean): 51 vs. 49 years Female: 49% vs. 61% Race: Not reported **Cirrhosis: 21% vs. 16%4% (overall)** **Minimal or no fibrosis: Not reported** **Elevated transaminases: 100% (mean ALT 2.4 vs. 2.4 upper limit of normal)**

Author, Year Country Study Name Quality	Genotype Severity of Liver Disease Proportion Treatment-Naïve	Duration of Followup	Outcome	Subgroup Analyses	Subgroup Analyses	Histologic Response	Adverse Events	Funding Source
Ascione, 2010[1] Liver Unit of Cardarelli Hospital – Napoli, Italy Continued	A vs. B Genotype 1/4 - 93/160(58%) vs. 93/160(58%) Genotype 2/3 - 67/160(42%) vs. 67/160(42%) Severity by liver biopsy graded via "simple system" (Scheuer et al 2002): Chronic Hepatitis: 127/160(79.4%) vs. 134/160(83.7%) Cirrhosis (with biopsy): 33/160(20.6%) vs. 26/160(16.3%) Cirrhosis (without biopsy): 12/160(7.5%) vs. 7/160(4.4%) Treatment-naïve: 100%	Followup at 3 and 6 months post-treatment (12 and 24 weeks)	A vs. B ETR: 134/160(83.8%) vs. 103/160(64.4%), p≤0.0001 SVR: 110/160(68.8%) vs. 87/160(54.4%), p=0.008	NR	A vs. B Genotype 1/4 - 51/93(54.8%) vs. 37/93(39.8%), p=0.04 Genotype 2/3 - 59/67(88.1%) vs. 50/67(74.6%), p=0.046 Genotype 2 - 45/49(91.8%) vs. 38/50(76.0%), p=0.062 Genotype 3 - 14/18(77.8%) vs. 12/17(70.6%), p=0.92 Chronic hepatitis - 96/127(75.6%) vs. 75/134(55.9%), p=0.005 Cirrhosis - 14/33(42.4%) vs. 12/26(46.1%), p=0.774 SVR by baseline Genotype RNA level in serum, no./total (%): <500,000 IU/mL - 52/76(68.4%) vs. 44/67(65.7%), p=0.727 >500,000 IU/mL - 58/84(69.0%) vs. 43/93(46.2%), p=0.002	NR	A vs. B Overall Withdrawals: 4/160(3%) vs. 22/160(14%) Withdrawals due to adverse events; 4/160 (3%) vs. 17/160 (11%) Deaths: none Severe Adverse Events: none Fatigue - 93/160(58%) vs. 86/160(54%) Arthralgia - 48/160(30%) vs. 66/160(41%) Irritability - 53/160(33%) vs. 49/160(31%) Decreased appetite - 30/160(19%) vs. 34/160(21%) Fever - 30/160(19%) vs. 75/160(47%) Pruritus - 27/160(17%) vs. 24/160(15%) Headache - 25/160(16%) vs. 28/160(18%) Cough - 20/160(13%) vs. 20/160(13%) Myalgia - 23/160(14%) vs. 30/160(19%) Dermatitis - 19/160(12%) vs. 9/160(6%) Nausea - 14/160(9%) vs. 15/160(9%)	Carderelli Hospital, Napoli, Italy

Author, Year Country Study Name Quality	Genotype Severity of Liver Disease Proportion Treatment-Naïve	Duration of Followup	Outcome	Subgroup Analyses	Subgroup Analyses	Histologic Response	Adverse Events	Funding Source
Ascione, 2010[1] Liver Unit of Cardarelli Hospital - Napoli, Italy Continued							Dyspnea - 13/160(8%) vs. 19/160(12%) Thyroid - 12/160(8%) vs. 9/160(6%) Insomnia - 11/160(7%) vs. 17/160(11%) Alopecia - 9/160(6%) vs. 22/160(14%) Depression - 11/160(7%) vs. 9/160(6%) Dose modification due to: Anemia - 30/160(19%) vs. 30/160(19%) Neutropenia - 4/160(3%) vs. 4/160(3%) Thrombocytopenia - 7/160(4%) vs. 6/160(4%)	

Author, Year **Country** **Study Name** **Quality**	**Interferon Regimen**	**Ribavirin Regimen**	**Protease Inhibitor Regimen**	**Eligibility**	**Exclusion**	**Number Screened/ Eligible/ Enrolled/ Analyzed**	**Age** **Sex** **Race**
Bruno, 2004[2] Italy Viral dynamics and pharmacokinetics of Pegylated interferon alpha-2a and Pegylated interferon alpha-2b in naïve patients with chronic hepatitis C; a randomized, controlled study Overall Quality: Poor	A. Pegylated interferon alpha-2a 180 mcg/week for 12 weeks B. Pegylated interferon alpha-2b 1.0 mcg/week for 12 weeks	A. 1000-1200mg mg/day depending of body weight for 12 weeks (≤75 kg / >75 kg) B. 1000-1200mg mg/day depending of body weight for 12 weeks (<75 kg / >75 kg)	None	Treatment-naïve HCV-RNA ≥ 2000 / mL ALT > upper limit of normal within 6 months of study Liver biopsy consistent with chronic hepatitis	Neutrophils <1500/ mL3 Platelet count < 90K mL3 Hemoglobin <12 g/dL in women and <13 g/dL in men Creatinine level >1.5 times upper limit of normal Co infection with HIV Decompensated liver disease Poorly controlled psychiatric disease Alcohol or drug abuse within year Substantial coexisting medical conditions	NR/NR/22/22	A vs. B Age mean: 47 vs. 40 Female: 30% vs. 25% Non White: 10% vs. 0%

Author, Year Country Study Name Quality	Genotype Severity of Liver Disease Proportion Treatment-Naïve	Duration of Followup	Outcome	Subgroup Analyses	Subgroup Analyses	Histologic Response	Adverse Events	Funding Source
Bruno, 2004[2] Italy Continued	A vs. B Genotype 1: 70% vs. 50% Cirrhosis/transition to cirrhosis: 20% vs. 16% HCV-RNA mean (log): 5.8 vs. 5.6 Treatment-naïve: 100%	12 weeks	NA	NA	NA	NA	NR	Hoffman-LaRoche

Author, Year **Country** **Study Name** **Quality**	**Interferon Regimen**	**Ribavirin Regimen**	**Protease Inhibitor Regimen**	**Eligibility**	**Exclusion**	**Number Screened/ Eligible/ Enrolled/ Analyzed**	**Age** **Sex** **Race**
DiBisceglie, 2007[3] United States Early virologic response after Pegylated interferon alpha-2a plus ribavirin or Pegylated interferon alpha-2b plus ribavirin treatment in patients with chronic hepatitis C Overall Quality: Fair	A. Pegylated interferon alpha-2a 180 mcg weekly for 12 weeks B. Pegylated interferon alpha-2b 1.5 mcg/kg weekly for 12 weeks	A. 1000-1200mg mg/day depending of body weight for 12 weeks (≤75 kg / >75 kg) B. 1000-1200mg mg/day depending of body weight for 12 weeks (<75 kg / >75 kg)	None	Treatment-naïve patients Chronic HCV genotype 1 infection Age 18 years or older HCV RNA >800K IU/mL	HBV HIV co infection History of other chronic liver disease Decompensated liver disease or Child-Pugh score >6 Alcohol or drug abuse within year Pregnant or breastfeeding women and male partners Neutrophils <1500/mL3 Platelet count <90K /mL3 Hemoglobin <12 g/dL in women and <13 g/dL in men Creatinine >1.5 times upper limit of normal History of server psychiatric, immunologically mediated, cardiac, or chronic pulmonary disease	NR/NR/385/380	A vs. B Age mean: 47 vs. 48 Female: 36% vs. 29% Non White: 31% vs. 28%

Author, Year Country Study Name Quality	Genotype Severity of Liver Disease Proportion Treatment-Naïve	Duration of Followup	Outcome	Subgroup Analyses	Subgroup Analyses	Histologic Response	Adverse Events	Funding Source
DiBisceglie, 2007[3] United States Continued	A vs. B Genotype 1: all Cirrhotic: 14.8% vs. 15.2% HCV RNA mean (log): 6.5 vs. 6.5 Treatment-naïve: 100%	12 weeks	NA	NA	NA	NA	A vs. B Overall withdrawals: 18/189 (10%) vs. 27/191 (14%); p=NS Withdrawals for adverse events: 2/189 (1%) vs. 11/191 (6%); p=NS Serious adverse events: NR Deaths: NR Fatigue: 132/187 (71%) vs. 137/190 (72%); p=NS Headache: 105/187 (56%) vs. 112/190 (59%); p=NS Nausea: 77/187 (41%) vs. 85/190 (45%); p=NS Chills: 46/187 (25%) vs. 79/190 (42%); p<0.001 Irritability: 58/187 (31%) vs. 57/190 (30%); p=NS Fever: 38/187 (20%) vs. 62/190 (33%); p=NS Depression: 46/187 (25%) vs. 46/190 (24%); p=NS Arthralgia: 45/187 (24%) vs. 44/190 (23%); p=NS Dizziness: 39/187 (21%) vs. 48/190 (25%); p=NS Influenza-like illness: 34/187 (18%) vs. 44/190 (23%); p=NS Diarrhea: 33/18 (18%) vs. 39/190 (21%); p=NS Decreased appetite: 28/187 (15%) vs. 40/190 (21%); p=NS	Roche

Author, Year Country Study Name Quality	Genotype Severity of Liver Disease Proportion Treatment-Naïve	Duration of Followup	Outcome	Subgroup Analyses	Subgroup Analyses	Histologic Response	Adverse Events	Funding Source
DiBisceglie, 2007[3] United States Continued							Rash: 27/187 (14%) vs. 39/190 (21%); p=NS Myalgia: 31/187 (17%) vs. 34/190 (18%); p=NS Vomiting: 26/187 (14%) vs. 38/190 (20%); p=NS Injection-site erythema: 25/187 (13%) vs. 38/190 (20%); p=NS Anemia: 20/187 (11%) vs. 22/190 (12%); p=NS Dysgeusia: 17/187 (9%) vs. 21/190 (11%); p=NS	

Author, Year Country Study Name Quality	Interferon Regimen	Ribavirin Regimen	Protease Inhibitor Regimen	Eligibility	Exclusion	Number Screened/ Eligible/ Enrolled/ Analyzed	Age Sex Race
Escudero, 2008[4] Valencia, Spain (outpatient clinic - Service of Hepatology of University Hospital Clinic) Pegylated alpha-interferon-2a plus ribavirin compared with pegylated alpha-interferon-2b plus ribavirin for initial treatment of chronic HCV: prospective, nonrandomized study Overall Quality: Poor	A: Pegylated interferon alpha-2a 180 µg/week for 24 or 48 weeks (genotype 2/3 and 1/4 respectively) B: Genotype 2/3: Pegylated interferon alpha-2b 1.5 µg/kg/week for 24 or 48 weeks (genotype 2/3 and 1/4 respectively)	A: 800-1200 mg daily for 24 or 48 weeks (genotype 2/3 and 1/4 respectively) B: 800-1200 mg daily for 24 or 48 weeks (genotype 2/3 and 1/4 respectively)	None	Treatment naïve patients 18 years and older Sero-positive Genotype-RNA Evidence of Genotype 1,2,3 or 4 infection Serum Genotype RNA concentration > 30 IU/mL ALT above upper limit of normal Diagnostic liver biopsy done within 6 months prior to enrollment	HIV infection, Hepatitis B infection Autoimmune disease Autoimmune hepatitis, decompensated Liver disease hematological conditions Decompensated diabetes Thyroid disease (poorly controlled) History of Severe Psychiatric Disease, Alcohol or Drug dependence within 1 year prior to entry into study Subjects recruited in actual conditions of daily practice in outpatient clinic	NR/NR/183/183	A vs. B Age: mean (SD): 44.4(9.34) vs. 43.6(9.62) years Male - 64/91(70%) vs. 56/92 (61%) Race: NR

Author, Year Country Study Name Quality	Genotype Severity of Liver Disease Proportion Treatment-Naïve	Duration of Followup	Outcome	Subgroup Analyses	Subgroup Analyses	Histologic Response	Adverse Events	Funding Source
Escudero, 2008[4] Valencia, Spain (outpatient clinic - Service of Hepatology of University Hospital Clinic) Continued	A vs. B Genotype 1- 59/91(65%) vs. 58/92(64%) Genotype 2- 5/91(6%) vs. 4/92(4%) Genotype 3- 13/91(14%) vs. 23/92(25%) Genotype 4- 12/91(13%) vs. 6/92(7%) Genotype 5- 2/91(2%) vs. 1/92(1%) Scale by Batts & Ludwig, 1995: Grade - mean (SD): 2.1(.81) vs. 2.1(.91) Stage - mean (SD): 2.1(.98) vs. 2.0(1.07) Steatosis - 30/91(34%) vs. 43/92(46.7%) HCVRNA mean(log IU/mL): 5.9 vs. 5.8 Treatment-naïve: 100%	Followup at 24 weeks post-treatment	A vs. B ETR: NR SVR: 60/91(65.9%) vs. 57/92(62%)	NR	A vs. B Variables significantly associated with response to antiviral therapy: Genotype (odds ratio [OR] = 0.076, 95% confidence interval [CI] 0.029 – 0.198, P = 0.000) Presence of steatosis in the liver biopsy (OR = 2.799, 95% CI 1.362–5.755, p=0.005). Genotype 1: steatosis was the only variable significantly associated with response to antiviral treatment: (OR = 2.450, 95% CI 1.126–5.332, p=0.024) SVR: Genotype 1 - 30/59 (50.8%) vs. 27/58(46.6%) Genotype 2/3 - 17/18 (95%) vs. 24/27(89.3%) Genotype 4 - 11/12 (91.7%) vs. 5/6(83.3%)	NR	A vs. B Overall withdrawals - 22/91(24%) vs. 28/92(30%) Deaths - NR Dermatological symptoms: 5/183(3%) Severe neutropenia (<0.5 x 109 cells/L): 3/183(2%) Depression-related events: 2/183(1%) Anemia (hemoglobin, <10.0 g/dL): 2/183(1%) Thrombocytopenia (<50 x 109 cells/L): 2/183(2%) Hypothyroidism: 2/183(1%) Tachyarrhythmia: 1/183(0.5%) Poor tolerability with various adverse events: 5/183(3%) Dose modifications because of neutropenia: 8/91(8%) vs. 7/92(8%)	Internal funding

Author, Year **Country** **Study Name** **Quality**	**Interferon Regimen**	**Ribavirin Regimen**	**Protease Inhibitor Regimen**	**Eligibility**	**Exclusion**	**Number Screened/ Eligible/ Enrolled/ Analyzed**	**Age** **Sex** **Race**
Kamal, 2011[5] Egypt Enhanced efficacy of pegylated interferon alpha-2a over pegylated interferon and ribavirin in chronic hepatitis C genotype 4A randomized trial and quality of life analysis Overall Quality: Fair	A. Pegylated interferon alfa-2a 180 mcg/week for 48 weeks B. Pegylated interferon alfa-2b 1.5 mcg/kg/week for 48 weeks	A. Ribavirin 1000-1200 mg daily (<75 kg / >75 kg) for 48 weeks B. Ribavirin 1000-1200 mg daily(<75 kg / >75 kg) for 48 weeks	None	Treatment naïve Age 18-60 years HCV genotype 4 ALT at least twice the upper limit of normal during the 6 months prior Detectable anti-HCV antibodies Detectable HCV RNA Histologic evidence of chronic hepatitis C in liver biopsy within preceding year	Evidence of other liver disease Co-infection with HIV, hepatitis A, B, or schistosomiasis Leucocytes <3000/mm3 Neutrophils <1500/mm3 Hemoglobin <12 g/dl for women or <13 g/dl for men Thrombocytopenia <90K/mm3 Creatinine >1.5x upper limit of normal Organ transplantation Cancer Severe cardiac or pulmonary disease Unstable thyroid dysfunction Severe depression or psychiatric disorder Active substance abuse Pregnancy Breast feeding BMI>30Kg/m2 Known sensitivity to drugs tested Determined by investigators to be unreliable or noncompliant	226/217/217/217	A vs. B Age: 42 vs. 41 Female: 46% vs. 56% Race: NR (Egyptian centers)

Author, Year Country Study Name Quality	Genotype Severity of Liver Disease Proportion Treatment-Naïve	Duration of Followup	Outcome	Subgroup Analyses	Subgroup Analyses	Histologic Response	Adverse Events	Funding Source
Kamal, 2011[5] Egypt Continued	A vs. B Genotype 1: 0% Genotype 4: 100% Grade 3 Steatosis: 38% vs. 37% Treatment-naïve: NR	24 weeks after treatment completion	A vs. B SVR: 77/109 (70.6%) vs. 59/108 (54.6%); p=0.0172 SF-6D (During Treatment): 0.735 vs. 0.730; p=0.8067 SF-6D (after treatment): 0.769 vs. 0.737; =0.04 Chronic Liver Disease Health Survey Questionnaire (CLDQ) (during treatment): 5.3 vs. 5.0; p=0.16 CLDQ (after treatment): 5.9 vs. 5.5; p=0.02	NR	NR	NR	A vs. B Overall withdrawals: 2/109 (2%) vs. 1/108 (1%); p=NS Withdrawals for adverse events: 1/109 (1%) vs. 1/108 (1%); p=NS Mild adverse events: 54/109 (50%) vs. 40/108 (37%); p=NS Moderate adverse events; 18/109 (17%) vs. 12/108 (11%); p=NS Severe adverse events; 4/109 (4%) vs. 3/108 (3%); p=NS	Ain Shams University

Author, Year Country Study Name Quality	Interferon Regimen	Ribavirin Regimen	Protease Inhibitor Regimen	Eligibility	Exclusion	Number Screened/ Eligible/ Enrolled/ Analyzed	Age Sex Race
Khan, 2007[6] Pakistan Pegylated interferon alfa-2a ribavirin vs. Pegylated interferon alfa-2b/ribavirin combination therapy in chronic hepatitis C genotype 3 Overall Quality: Not Assessed	A: Pegylated interferon alfa-2a 180 mcg/week for 24 weeks B: Pegylated interferon alfa-2b 1.0 mcg/week for 24 weeks	A: 800 mg/day for 24 weeks B: 800 mg/day for 24 weeks	None	NR	NR	NR/NR/NR/66	NR

Author, Year Country Study Name Quality	Genotype Severity of Liver Disease Proportion Treatment-Naïve	Duration of Followup	Outcome	Subgroup Analyses	Subgroup Analyses	Histologic Response	Adverse Events	Funding Source
Khan, 2007[6] Pakistan Continued	Genotype 1: 0% Genotype 4: 100%	24 weeks after end of treatment	A vs. B SVR: 26/33 (79%) vs. 27/33 (82%), p=NS	NR	NR	NR	A vs. B Overall withdrawals: 1/33 (3%) vs. 1/33 (3%)	NR

Author, Year Country Study Name Quality	Interferon Regimen	Ribavirin Regimen	Protease Inhibitor Regimen	Eligibility	Exclusion	Number Screened/ Eligible/ Enrolled/ Analyzed	Age Sex Race
Mach 2011[7] Poland Efficacy of pegylated interferon alfa-2a or alfa-2b in combination with ribavirin in the treatment of chronic hepatitis caused by hepatitis C virus genotype 1b Overall Quality: Fair	A: Pegylated interferon alfa-2a - 180 μg subcutaneously once a week B: Pegylated interferon alfa-2b - 1.5 mg/kg of body weight once a week	A: Ribavirin 1.0–1.2 g oral daily B: Ribavirin 1–1.2 g oral daily	None	Patients with anti-HCV and HCV-RNA in serum and elevated alanine aminotransferase (ALT) levels at least 6 months before the inclusion, chronic hepatitis confirmed by histological examination, body mass index (BMI) below 30 kg/m^2.	Patients with decompensated liver cirrhosis, autoimmune liver disease, alcohol abuse, liver cancer, hepatitis B virus or HIV coinfection, any severe chronic disease, diabetes, dyslipidemia, metabolic syndrome, hemochromatosis, and immunosuppressive therapy.	NR/NR/260/260	A vs. B Age: 44 vs. 45.2 years Female: 37.7% vs. 42% Race: NR (Polish centers)

Author, Year Country Study Name Quality	Genotype Severity of Liver Disease Proportion Treatment-Naïve	Duration of Followup	Outcome	Subgroup Analyses	Subgroup Analyses	Histologic Response	Adverse Events	Funding Source
Mach 2011[7] Poland Continued	A vs. B Genotype 1b: 100% Liver fibrosis: F0-2 – 78.1% vs. 72.9% F3-4 – 21.95% vs. 27.1% Treatment-naïve: NR	24 weeks after end of treatment	A vs. B: ETR:71.7% vs. 60.7%, p=NR SVR: 49.3% vs. 44.3%, p=NS	NR	NR	NR	NR	Polish National Health Fund

Author, Year Country Study Name Quality	Interferon Regimen	Ribavirin Regimen	Protease Inhibitor Regimen	Eligibility	Exclusion	Number Screened/ Eligible/ Enrolled/ Analyzed	Age Sex Race
Magni, 2009[8] Italy Antiviral activity and tolerability between pegylated interferon alfa-2a and alfa-2b in naïve patients with chronic hepatitis C: results of a prospective monocentric randomized trial Overall Quality: Not Assessed	A: Pegylated interferon alfa-2a 180 mcg/week for 24-48 weeks based on genotype B: Pegylated interferon alfa-2b 1.0 mcg/week for 24-48 weeks based on genotype	A: 10.5 mg/kg for 24-48 weeks based on genotype B: 10.5 mg/kg for 24-48 weeks based on genotype	None	NR	NR	NR/NR/NR/218	NR

Author, Year Country Study Name Quality	Genotype Severity of Liver Disease Proportion Treatment-Naïve	Duration of Followup	Outcome	Subgroup Analyses	Subgroup Analyses	Histologic Response	Adverse Events	Funding Source
Magni, 2009[8] Italy Continued	A vs. B Genotype 1/4: 61% vs. 51% Genotype 2/3: 39% vs. 49% Treatment-naïve: NR	24 weeks after end of treatment	A vs. B SVR: 68/100 (68%) vs. 79/118 (67%); p=NS	NR	A vs. B Genotype 1/4: 36/58 (62%) vs. 34/55 (62%); p=NS Genotype 2/3: 32/37 (87%) vs. 45/52 (87%); p=NS	NR	A vs. B Withdrawals due to adverse events: 5% vs. 6.8%; p=NS	NR

Author, Year Country Study Name Quality	Interferon Regimen	Ribavirin Regimen	Protease Inhibitor Regimen	Eligibility	Exclusion	Number Screened/ Eligible/ Enrolled/ Analyzed	Age Sex Race
McHutchison, 2008[9] US Individualized Dosing Efficacy vs. Flat Dosing to Assess Optimal Pegylated Interferon Therapy (IDEAL) Overall Quality: Fair	A. Pegylated interferon alfa-2b 1.0 mcg/kg/week for 48 weeks. B. Pegylated interferon alfa-2b 1.5 cg/kg/week for 48 weeks. C. Pegylated interferon alfa-2a 180 mcg/week for 48 weeks. Discontinued if HCV RNA detectable and not decreased by 2 log IU from baseline at 12 weeks or HCV RNA detectable at 24 weeks	A. Weight-based 800-1400 mg daily for 48 weeks B. Weight-based 800-1400 mg daily for 48 weeks C. 1000 mg (<75 kg) - 1200 mg (≥75 kg) daily for 48 weeks Weight-based dosing ≤ 65 kg: 800 mg daily 66 - 85kg: 1000 mg daily 86-105kg: 1200 mg daily 106 -125kg: 1400 mg daily Discontinued if HCV RNA detectable and not decreased by 2 log IU from baseline at 12 weeks or HCV RNA detectable at 24 weeks	None	Treatment-naïve Ages 18 years or older Chronic HCV genotype 1 infection Detectable HCV RNA level Neutrophil count ≥ 1500 /mm3 Platelets ≥ 80,000 /mm3 Hemoglobin ≥ 12 g/dL for women or 13 g/dL for men	HIV HBV Other liver disease Poorly controlled diabetes Weight >125 kg Severe depression Severe psychiatric disorder Active substance abuse	4469/3431/3083/3070	A vs. B vs. C Age mean: 48 vs. 48 vs. 48 Female: 40% vs. 40% vs. 41% Non White: 29% vs. 28% vs. 29%

Author, Year Country Study Name Quality	Genotype Severity of Liver Disease Proportion Treatment-Naïve	Duration of Followup	Outcome	Subgroup Analyses	Subgroup Analyses	Histologic Response	Adverse Events	Funding Source
McHutchison, 2008[9] US Continued	A vs. B vs. C Genotype 1: 100% Metavir fibrosis score 3 or 4: 11% vs. 11% vs. 11% HCV-RNA≥600K: 82% vs. 82% vs. 82% Treatment-naïve: 100%	24 weeks after treatment completion	A vs. B vs. C ETR: 500/1016 (49%) vs. 542/1016 (53%) vs. 667/1035 (64%); (p=0.04 for A vs. B, p<0.001 for B vs. C) SVR: 386/1016 (38%) vs. 406/1019 (40%) vs. 423/1035 (41%); (p=0.20 for A vs. B, p=0.57 for B vs. C)	A vs. B vs. C (p-values from interaction models given) Black: 31/187 (17%) vs. 42/183 (23%) vs. 52/200 (26%); White: 316/362 (36%) vs. 319/732 (44%) vs. 324/733 (44%); (p=0.18 for A vs. B, p=0.62 for B vs. C) Female: 147/409 (36%) vs. 180/406 (44%) vs. 177/422 (42%) Male: 239/607 (39%) vs. 226/613 (37%) vs. 246/613 (40%); (p=0.01 for A vs. B, p=0.20 for B vs. C)	A vs. B vs. C Metavir fibrosis score F3 or F4: 32/107 (30%) vs. 23/111 (21%) vs. 26/110 (24%) Metavir fibrosis score F0-F2: 335/864 (39%) vs. 366/869 (42%) vs. 376/862 (44%); (p=0.06 for A vs. B, p=0.75 for B vs. C) Baseline HCV RNA >600K IU/mL: 277/830 (33%) vs. 295/836 (35%) vs. 303/852 (36%) Baseline HCV RNA<600K IU/mL: 109/186 (59%) vs. 111/183 (61%) vs. 120/183 (66%); (p=0.99 for A vs. B, p=0.41 for B vs. C) Weight <75 kg: 211/555 (38%) vs. 219/564 (39%) vs. 264/605 (44%) Weight >75 kg: 175/461 (38%) vs. 187/455 (41%) vs. 159/430 (37%); (weight in kg as continuous variable p=0.94 for A vs. B; p=0.39 for B vs. C)	NR	A vs. B vs. C Overall withdrawals: 523/1016 (52%) vs. 479/1019 (47%) vs. 414/1035 (40%); (p=0.04 for A vs. B, p=0.001 for B vs. C, p<0.001 for A vs. C) Withdrawals for adverse events: 98/1016 (10%) vs. 129/1019 (13%) vs. 135/1035 (13%); (p=0.03 for A vs. B, p=0.80 for B vs. C, p<0.001 for A vs. C) Deaths: 1/1016 (<1%) vs. 5/1019 (<1%) vs. 6/1035 (<1%); (p=NS) Serious adverse event: 94/1016 (9%) vs. 88/1019 (9%) vs. 121/1035 (12%); (p=0.63 for A vs. B, p=0.02 for B vs. C, p=0.07 for A vs. C) Fatigue: 676/1016 (67%) vs. 672/1016 (66%) vs. 656/1035 (63%); (p=NS) Headache: 486/1016 (48%) vs. 508/1019 (50%) vs. 438/1035 (42%); (p=0.36 for A vs. B, p=0.001 for B vs. C, p=0.01 for A vs. C) Nausea: 377/1016 (37%) vs. 433/1019 (43%) vs. 377/1035 (36%); (p=0.01 for A vs. B, p=0.005 for B vs. C, p=0.75 for A vs. C)	Schering-Plough

Author, Year Country Study Name Quality	Genotype Severity of Liver Disease Proportion Treatment-Naïve	Duration of Followup	Outcome	Subgroup Analyses	Subgroup Analyses	Histologic Response	Adverse Events	Funding Source
McHutchison, 2008[9] US Continued				Age ≤40: 72/154 (47%) vs. 74/140 (53%) vs. 91/163 (56%) Age >40: 314/862 (36%) vs. 332/879 (38%) vs. 332/872 (38%); (p=0.46 for A vs. B, p=0.67 for B vs. C)			Pyrexia: 311/1016 (33%) vs. 356/1019 (35%) vs. 237/1035 (23%); (p=0.26 for A vs. B, p<0.001 for B vs. C, p<0.001 for A vs. C) Myalgia: 270/1016 (27%) vs. 274/1019 (27%) vs. 233/1035 (23%); (p=0.87 for A vs. B, p=0.02 for B vs. C, p=0.03 for A vs. C) Depression: 197/1016 (19%) vs. 260/1019 (26%) vs. 217/1035 (21%); (p=0.001 for A vs. B, p=0.02 for B vs. C, p=0.37 for A vs. C) Neutropenia: 188/1016 (19%) vs. 263/1019 (26%) vs. 326/1035 (32%); (p<0.001 for A vs. B, p=0.004 for B vs. C, p<0.001 for A vs. C) Anemia: 293/1016 (29%) vs. 345/1016 (34%) vs. 348/1035 (34%); (p=0.02 for A vs. B, p=0.91 for B vs. C, p=0.02 for A vs. C) Neutrophils <750/mm3: 147/1008 (15%) vs. 222/1000 (22%) vs. 279/1034 (27%); (p<0.001 for A vs. B, p=0.01 for B vs. C, p<0.001 for A vs. C) Hemoglobin <10 g/dl: 255/1008 (25%) vs. 307/1000 (31%) vs. 306/1034 (30%); (p=0.007 for A vs. B, p=0.59 for B vs. C, p=0.03 for A vs. C)	

Author, Year Country Study Name Quality	Interferon Regimen	Ribavirin Regimen	Protease Inhibitor Regimen	Eligibility	Exclusion	Number Screened/ Eligible/ Enrolled/ Analyzed	Age Sex Race
Miyase, 2012[10] Japan Randomized trial of peginterferon alpha-2a plus ribavirin versus peginterferon alpha-2b plus ribavirin for chronic hepatitis C in Japanese patients Overall Quality: Good	A: Pegylated interferon alpha-2a at a dosage of 180 mcg once weekly. B: Pegylated interferon alpha-2b at a dosage of 60-150 mcg/kg (weight-based) once weekly. 35–45 kg - 60 mcg 46–60 kg, - 80 mcg 61–75 kg - 100 mcg 76–90 kg, - 120 mcg 91–120 kg - 150 mcg	A: RBV(weight-based) 600 mg/day ≤60 kg - 800 mg/day 60–80 kg - 1000 mg/day B: RBV(weight-based) 600 mg/day ≤60 kg - 800 mg/day 60–80 kg - 1000 mg/day	None	Consecutive PEG IFN-naïve adults (C18 years of age) who were infected with HCV genotype 1 were eligible for enrollment. The inclusion criteria were a serum HCV RNA level [5.0 log IU/mL, a liver biopsy performed within 6 months of starting treatment, and use of contraceptive methods during therapy and for 6 months after the end of treatment.	hemoglobin level \10 g/dL; white blood cell count\1.8x 10^3/mm3 or platelet count<7.0 x10^4/mm3; abnormal serum creatinine level; hepatitis B surface antigen positivity; human immune deficiency virus positivity; other cause of liver disease; history of liver decompensation; clinically relevant depression or any other psychiatric disease; cancer; severe cardiac, pulmonary, or renal disease; uncontrolled diabetes; or severe hypertension with vascular complications, including retinopathy.	N/NR/206/201	A vs. B Age mean: 59.2 vs. 58.9 years Female: 61.4% vs. 60% Non White: NR

Author, Year Country Study Name Quality	Genotype Severity of Liver Disease Proportion Treatment-Naïve	Duration of Followup	Outcome	Subgroup Analyses	Subgroup Analyses	Histologic Response	Adverse Events	Funding Source
Miyase, 2012[10] Japan Continued	A vs. B Genotype 1: 100% HCV RNA (log IU/mL) - 6.3 ± 0.6 vs. 6.2 ± 0.7, p= 0.151 Cirrhosis: 20% vs. 17% Treatment-naïve: 100%	24 weeks after end of treatment	A vs. B ETR: NR SVR: 66/101(65.3%) vs. 51/100(51%), p=0.039	A vs B Age: <60 years- 33/52 (63.5%) vs. 31/49 (63.3%), p=0.984 ≥60 years - 33/49 (67.3%) vs. 20/51 (39.2%),p=0.005 Female: 38/62 (61.3) vs. 26/60 (43.3), p=0.047 Weight (kg) ≥60 kg - 39/61 (63.9%) vs. 28/64 (43.8%), p= 0.024 ≤60 kg - 27/40 (67.5%) 23/36 vs. (63.9%), p= 0.740	A vs. B Non cirrhosis - 55/81 (67.9%) vs. 46/83 (55.4%), p=0.100 Cirrhosis - 11/20 (55.0%) vs. 5/17 (29.4%), p=0.117 HCV RNA: ≤6 log IU/mL - 22/28 (78.6%) vs. 28/39 (71.8%), p=0.530 >6 log IU/mL - 44/73 (60.3%) vs. 23/61 (37.7%), p=0.009		Overall withdrawals - 17(16.8%) vs. 26(26.0%) 0.124 Neutropenia - 43(42.6%) vs. 29(29.0%), p=0.056 Anemia - 62(61.4%) vs. 63(63.0%), p=0.885 Thrombocytopenia - 30(29.7%) vs. 27(27.0%), p=0.755 Dose modification - 13(12.9%) vs. 19(19.0%), p=0.253 Fever - 41(40.6%) vs. 76(76.0%), p<0.001 Dermatitis, itching - 71(70.3%) vs. 56(56.0%), p=0.041 Fatigue - 47(46.5%) vs. 42(42.0%), p=0.571 Decreased appetite - 43(42.6%) vs. 56(56.0%), p=0.067 Insomnia - 34(33.7%) vs. 39(39.0%), p=0.465 Headache - 28(27.7%) vs. 24(24.0%), p=0.630 Stomatitis - 15(14.9%) vs. 22(22.0%), p=0.207 Nausea - 13(12.9%) vs. 19(19.0%), p=0.253 Arthralgia -15(14.9%) vs. 9(9.0%), p=0.277 Irritability - 12(11.9%) vs. 8(8.0%), p=0.481 Depression - 9(8.9%) vs. 8(8.0%), p=1.000 Cough - 6(5.9%) vs. 3(3.0%), p=0.498	NR

Author, Year Country Study Name Quality	Interferon Regimen	Ribavirin Regimen	Protease Inhibitor Regimen	Eligibility	Exclusion	Number Screened/ Eligible/ Enrolled/ Analyzed	Age Sex Race
Rumi, 2010[11] University of Milan, Italy Clinical Advances in Liver, Pancreas, and Biliary Tract (MIST Study) - Randomized Study of Pegylated interferon-alpha-2a Plus Ribavirin vs. Pegylated interferon-alpha-2b plus Ribavirin in Chronic Hepatitis C Overall Quality: Fair	Genotype 1/4: A. Pegylated interferon alfa-2a 180 mcg/week for 48 weeks B. Pegylated interferon alfa-2b 1.5 mcg/kg/week for 48 weeks Genotype 2/3: A. Pegylated interferon alfa-2a 180 mcg/week for 24 weeks B. Pegylated interferon alfa-2b 1.5 mcg/kg/week for 24 weeks	Genotype 1/4: A. 1000-1200 mg/day for 48 weeks B. 800-1200 mg/day for 48 weeks Genotype 2/3: A. 800 mg/day for 24 weeks B. 800-1200 mg/day for 24 weeks	None	Treatment naïve patients 18-70 years old with serum HCV-RNA Higher than normal ALT activity, and Diagnostic Liver Biopsy done within 24 months prior to enrollment	Persistently normal ALT Hemoglobin ≤ 12g/dL in women and ≤13g/dL in men White Blood Cell count <= 2.5x103 /mm3 Neutrophil <= 1.5x103 /mm3 Platelet count<= 75x103 /mm3 Serum creatinine level >1.5x upper limit of normal Liver disease (any other) HIV co infection Autoimmune diseases Contraindications to Interferon and Ribavirin	473/447/447/431	A vs. B Age: Mean (SD): 51.6(12.0) vs. 52.8(12.0) years Male - 128/212 (60.4%) vs. 120/219 (54.8%) Race: NR

Author, Year Country Study Name Quality	Genotype Severity of Liver Disease Proportion Treatment-Naïve	Duration of Followup	Outcome	Subgroup Analyses	Subgroup Analyses	Histologic Response	Adverse Events	Funding Source
Rumi, 2010[11] University of Milan, Italy Continued	A vs. B Genotype 1- 91/212 (42.9%) vs. 87/219 (39.7%) Genotype 2- 69/212 (32.5%) vs. 74/219 (33.8%) Genotype 3- 34/212 (16.0%) vs. 32/219 (14.6%) Genotype 4- 18/212 (08.5%) vs. 26/219 (11.9%) Ishak score of S5, 6: Overall: 81/212(38%) vs. 39/219(18%) HCV-RNA >600K IU/L: 53% vs. 55% Treatment-naïve: 100%	Followup at 24 weeks post-treatment	A vs. B ETR: 166/212 (78%) vs. 146/219 (67%), p=0.009 SVR: 140/212 (66%) vs. 119/219 (54%), p=0.02	NR	A vs. B ETR: Genotype 1: 59/91 (65%) vs. 38/87 (44%), p=0.007 Genotype 2: 66/69 (96%) vs. 69/74 (93%), p=0.09 Genotype 3: 32/34 (94%) vs. 29/32 (91%), p=0.09 Genotype 4: NR ("sound comparison of treatment efficacy compromised by small sample size") SVR: Genotype 1: 44/91 (48%) vs. 28/87 (32%), p=0.04 Genotype 2: 66/69 (96%) vs. 61/74 (82%), p=0.01 Genotype 3: 22/34 (65%) vs. 22/32 (69%), p=0.09 Genotype 4: NR ("sound comparison of treatment efficacy compromised by small sample size")	NR	A vs. B Discontinuation due to adverse events: 16/212(8%) vs. 17/219(8%) Overall Withdrawals (including loss to followup and "other"): 46/212(22%) vs. 73/219(33%) Deaths: NR Serious Adverse Events: 2/212 (1%) vs. 2/219(1%) Adverse Events: Grade 2 anemia: 35/212(16%) vs. 50/219(23%) Grade 3 anemia: 2/212(1%) vs. 2/219(1%) Grade 3 neutropenia: 46/212(22%) vs. 34/219(16%) Grades 2 or 3/thrombocytopenia: 5/212 (2%) vs. 3/219(1%) Treated with GCSF: 21/212(10%) vs. 15/219(7%) Treated with erythropoietin: 30/212(14%) vs. 27/219(12%) Depression: 19/212(9%) vs. 15/219 (7%)	Schering-Plough (now Merck), Roche, Novartis, Vertex

Author, Year Country Study Name Quality	Genotype Severity of Liver Disease Proportion Treatment-Naïve	Duration of Followup	Outcome	Subgroup Analyses	Subgroup Analyses	Histologic Response	Adverse Events	Funding Source
Rumi, 2008[11] University of Milan, Italy Continued							Influenza-like syndrome: 134/212(63%) vs. 136/219(62%) Gastrointestinal symptoms: 8/212(4%) vs. 12/219(5%) Psychiatric symptoms: 79/212(37%) vs. 70/219(32%) Coughing and dyspnea: 22/212(10%) vs. 25/219(11%) Dermatologic symptoms: 99/212(47%) vs. 91/219(42%)	

Author, Year **Country** **Study Name** **Quality**	**Interferon Regimen**	**Ribavirin Regimen**	**Protease Inhibitor Regimen**	**Eligibility**	**Exclusion**	**Number Screened/ Eligible/ Enrolled/ Analyzed**	**Age** **Sex** **Race**
Silva, 2006[12] Argentina, Mexico, Germany A randomized trial to compare the pharmacokinetics, pharmacodynamic, and antiviral effects of pegylated interferon alfa-2b and Pegylated interferon alfa-2b in patients with chronic hepatitis C Overall Quality: Poor	A. Pegylated interferon alfa-2a 180 mcg/week for 8 weeks B. Pegylated interferon alfa-2b 1.5 mcg/kg/week for 8 weeks After study patients were offered full course of weight-based pegylated interferon alfa-2b and ribavirin	A. 13 mcg/kg in divided dose (bid) after 4th week B. 13 mcg/kg in divided dose (bid) after 4th week	None	Treatment-naïve patients Genotype 1a or 1b Ages 18-65 years HCV-RNA >$6x10^5$ IU/mL ALT/AST $\leq$ 10x the upper limit of normal Normal hemoglobin White-blood cells $\geq$ cells/mcg L, Neutrophils $\geq$1500 /mcg L Platelets $\geq$100K/mcg L	Liver disease of other cause HIV Hemoglobinopathy Hemophilia Severe psychiatric disease Poorly controlled diabetes mellitus Significant ischemic heart disease Chronic obstructive pulmonary disease Active immune disease	NR/NR/32/32	A vs. B Age mean: 46 vs. 48 Female: 50% vs. 44% Non White: 11% vs. 22%

Author, Year Country Study Name Quality	Genotype Severity of Liver Disease Proportion Treatment-Naïve	Duration of Followup	Outcome	Subgroup Analyses	Subgroup Analyses	Histologic Response	Adverse Events	Funding Source
Silva, 2006[12] Argentina, Mexico, Germany Continued	A vs. B Genotype 1: all Fibrosis stage: NR HCV-RNA mean (x10^6 IU/mL): 1.8 vs. 1.8 Treatment-naïve: 100%	8 weeks	NA	NA	NA	NA	A vs. B Overall withdrawals: NR Withdrawals for adverse events: 2/18 (11.1%) vs. 4/18 (22.2%); p=NS Serious adverse events: NR Deaths: NR Fatigue: 4/18 (22%) vs. 6/18 (33%); p=NS Fever: 1/18 (6%) vs. 10/18 (56%); p=0.001 Headache: 16/18 (89%) vs. 16/18 (89%); p=NS Influenza-like symptoms: 3/18 (17%) vs. 5/18 (28%); p=NS Anemia: 9/18 (50%) vs. 10/18 (56%); p=NS Hematocrit decrease: 9/18 (50%) vs. 5/18 (28%); p=NS Hemoglobin decrease: 12/18 (67%) vs. 6/18 (33%); p=0.05 Leukopenia: 14/18 (78%) vs. 9/18 (50%); p=NS Neutropenia: 12/18 (67%) vs. 10/18 (56%); p=NS Myalgia: 7/18 (39%) vs. 11/18 (61%); p=NS Platelet count decrease: 5/18 (28%) vs. 5/18 (28%); p=NS Thrombocytopenia: 5/18 (28%) vs. 3/18 (17%); p=NS	Schering Plough

Author, Year Country Study Name Quality	Interferon Regimen	Ribavirin Regimen	Protease Inhibitor Regimen	Eligibility	Exclusion	Number Screened/ Eligible/ Enrolled/ Analyzed	Age Sex Race

Author, Year Country Study Name Quality	Interferon Regimen	Ribavirin Regimen	Protease Inhibitor Regimen	Eligibility	Exclusion	Number Screened/ Eligible/ Enrolled/ Analyzed	Age Sex Race
Yenice, 2006[13] Okmeydani Research & Training Hospital (Istanbul, Turkey) The efficacy of pegylated interferon alpha 2a or 2b plus ribavirin in chronic hepatitis C patients Overall Quality: Poor	A: Pegylated interferon alpha-2a 180µg/week for 48 weeks B: Pegylated-interferon alpha-2b1.5µg/kg for 48 weeks	A: 800-1200 mg daily for 48 weeks B: 800-1200 mg daily for 48 weeks	None	Anti HCV+, normal and/or elevated serum transaminase levels HCV+ RNA At least stage 1 fibrosis according to Knodell Scoring System on liver biopsy Hemoglobin 12 g/dl for women and 13 g/dl for men Leukocyte $3x10^3/mm^3$ Neutrophils $1.5x10^3/mm^3$ Platelets $100x10^3/mm^3$ Normal range: bilirubin, albumin, and creatinine No positive test results for hepatitis B, hepatitis D, or human immunodeficiency virus antibodies or antigens.	Abdominal ascites History of bleeding from esophageal varicosities Hepatocellular carcinoma (HCC) or other malignant disorders Use of antidepressants or tranquilizing agents for more than 3 months History of depression, psychosis or suicide attempt Significant cardiac or pulmonary problems Hepatitis B or D Human Immunodeficiency Virus or antibodies (HIV)	NR/80/80/74	A vs. B Age - Mean: 48.2 vs. 50.8 Male - 24/37(65%) vs. 27/37(73%) Race: NR

Author, Year Country Study Name Quality	Genotype Severity of Liver Disease Proportion Treatment-Naïve	Duration of Followup	Outcome	Subgroup Analyses	Subgroup Analyses	Histologic Response	Adverse Events	Funding Source
Yenice, 2006[13] Okmeydani Research & Training Hospital (Istanbul, Turkey) Continued	A vs. B Genotype 1 - 100% of subjects including 3 subtypes: Genotype 1a: 7/37 (18.9%) vs. 2/37(5.5%) Genotype 1b: 28/37(75.6%) vs. 35/37(94.6%) Genotype 1c: 2/37(5.5%) vs. 0/37(0%) 100% of subjects included had at least Stage 1 fibrosis (Knodell scale) Treatment-naïve: 100%	Followup at 24 weeks post-treatment Most patients refused a followup biopsy at the end of treatment; therefore, histological improvement was not assessed in this study due to the low number of followup biopsies.	A vs. B ETR: 28/37(75.7%) vs. 27/37(73%), p=0.79 SVR: 18/37(48.6%) vs. 13/37(35.1%), p=0.239	NR	NR	NR	A vs. B Discontinuation: 3/37(8%) vs. 3/37(8%) Overall Withdrawals: 3/37(8%) vs. 3/37(8%) Deaths: NR Serious Adverse Events: NR	Okmeydani Research and Training Hospital

Evidence Table 2. Quality rating: Trials of dual therapy with pegylated interferon alpha-2a plus ribavirin compared with pegylated interferon alfa-2b plus ribavirin

Author, Year	Randomization adequate?	Allocation concealment adequate?	Groups similar at baseline?	Eligibility criteria specified?	Outcome assessors masked?	Care provider masked?	Patient masked?	Attrition and withdrawals reported?	Loss to followup: differential/high?	Intention-to-treat analysis	Quality	Funding
Ascione, 2010[1]	Yes	Yes	Yes	Yes	No	No	No	Yes	Yes	Yes	Fair	Carderelli Hospital, Napoli, Italy
Escudero, 2008[4]	No	No	Yes	Yes	No	No	No	No	Unclear	Yes	Poor	Hoffman-LaRoche
Kamal, 2011[5]	Yes	Yes	Yes	Yes	No - open label	No - open label	No - open label	Yes	No	Yes	Fair	NR
Mach 2011[7]	Unclear	Unclear	Yes	Yes	No - open label	No - open label	No - open label	No	Unclear	No	Fair	Polish National Health Fund
McHutchison 2008[9]	Yes	Yes	Unclear	Unclear	Unclear	Yes	Unclear	Yes	No	Yes	Fair	Vertex Pharmaceuticals
Miyase, 2012[10]	Unclear	Unclear	Yes	Yes	No - open label	No - open label	No - open label	Yes	Unclear	Yes	Fair	NR
Rumi, 2010[11]	Yes	Unclear	Yes	Yes	No	No	No	Yes	Unclear	Yes	Fair	Roche
Yenice, 2006[13]	Unclear	Unclear	Yes	Yes	Unclear	Unclear	Unclear	Yes	No	No	Poor	Okmeydani Research and Training Hospital

Evidence Table 3. Trials of protease inhibitors plus pegylated interferon and ribavirin

Author, Year **Country** **Study Name** **Quality**	**Interferon Regimen**	**Ribavirin Regimen**	**Protease Inhibitor Regimen**	**Eligibility**	**Exclusion**	**Number Screened/ Eligible/ Enrolled/ Analyzed**	**Age** **Sex** **Race**	**Genotype** **Severity of Liver Disease** **Proportion Treatment-Naïve**
Hezode, 2009[14] Europe Protease Inhibition for Viral Evaluation 2 (PROVE2) Overall Quality: Fair	A. Pegylated interferon alfa-2a 180 mcg weekly for 24 weeks B. Pegylated interferon alfa-2a 180 mcg weekly for 12 weeks C. Pegylated interferon alfa-2a 180 mcg weekly for 12 weeks D. Pegylated interferon alfa-2a 180 mcg weekly for 48 weeks	A. Ribavirin1000-1200 mg daily for 24 weeks B. Ribavirin1000-1200 mg daily for 12 weeks C. Placebo D. Ribavirin1000-1200 mg daily for 48 weeks 1000 mg daily for patients <75 kg 1200 mg daily for patients ≥ 75 kg	A. Telaprevir 750 mg tid for 12 weeks B. Telaprevir 750 mg tid for 12 weeks C. Telaprevir 750 mg tid for 12 weeks D. placebo On day 1, patients received telaprevir 1250 mg	Treatment naïve patients ages 18-65 years Genotype 1 with detectable HCV RNA	histologic evidence of cirrhosis within 2 years of enrollment	388/ 334/ 334/ 323	A vs. B vs. C vs. D Age median: 46 vs. 44 vs. 45 vs. 45 Female: 33% vs. 40% vs. 45% vs. 44% Non White: 7% vs. 7% vs. 1% vs. 7%	A vs. B vs. C vs. D Genotype 1: all Cirrhosis: 0% vs. 0% vs. 1% vs. 0% Minimal or no Fibrosis: 43% vs. 37% vs. 40% vs. 34% Treatment-naïve: 100%

Author, Year Country Study Name Quality	Duration of Followup	Outcome	Subgroup Analyses	Subgroup Analyses	Histologic Response	Adverse Events	Funding Source
Hezode, 2009[14] Europe Continued	Up to 48 weeks following treatment completion	A vs. B vs. C vs. D ETR: 57/81 (70%) vs. 66/82 (80%) vs. 48/78 (62%) vs. 45/82 (55%); (A,B,C vs. D p<0.05) SVR: 56/81 (69%) vs. 49/82 (60%) vs. 28/78 (36%) vs. 38/82 (46%); (A vs. D p<0.01; B, C vs. D p=NS)	Not reported multivariate predictors of SVR presented in supplementary table (variables included treatment arm HCV geno-subtype, baseline HCV RNA, age): Baseline HCV RNA <800K IU/ml adjusted odds ratio 4.69 (95% 2.22-9.88) Age ≤45 years adjusted odds ratio 1.59 (0.99-2.57)	NR	NR	A vs. B vs. C vs. D Overall withdrawals: 20/81 (25%) vs. 10/82 (12%) vs. 8/78 (10%) vs. 32/82 (39%); (p=0.05 for A vs. D, p<0.01 for B, C vs. D) Withdrawals due to adverse events: 11/81 (14%) vs. 9/82 (11%) vs. 7/78 (9%) vs. 6/82 (7%); (p=NS for A, B, C vs. D) Serious adverse event: 13/81 (16%) vs. 17/82 (21%) vs. 10/78 (13%) vs13/82 (16%); (p=NS for A, B, C vs. D) Asthenia: 37/81 (46%) vs. 43/82 (52%) vs. 30/78 (38%) vs. 26/82 (32%); (p<0.05 A, B vs. D, p=0.37 for C vs. D) Influenza-like illness: 32/81 (40%) vs. 32/82 (39%) vs. 28/78 (36%) vs. 43/82 (52%); (p=NS for A, B vs. D, p=0.04 for C vs. D) Fatigue: 21/81 (26%) vs. 23/82 (28%) vs. 26/78 (33%) vs. 30/82 (37%); (p=NS for A, B, C vs. D) Pyrexia: 14/81 (17%) vs. 15/82 (18%) vs. 15/78 (19%) vs. 19/82 (23%); (p=NS for A, B, C vs. D) Pruritus: 41/81 (51%) vs. 52/82 (63%) vs. 46/78 (59%) vs. 29/82 (35%); (p<0.05 for A, B, C vs. D) Any rash: 40/81 (49%) vs. 36/82 (44%) vs. 37/78 (47%) vs. 29/82 (35%); (p=NS for A, B, C vs. D) Nausea: 39/81 (48%) vs. 39/82 (48%) vs. 24/78 (31%) vs. 33/82 (40%); (p=NS for A, B, C vs. D) Headache: 36/81 (44%) vs. 32/82 (39%) vs. 37/78 (47%) vs. 37/82 (45%); (p=NS for A, B, C vs. D) Depression: 16/81 (20%) vs. 18/82 (22%) vs. 17/78 (22%) vs. 19/82 (23%); (p=NS for A, B, C vs. D) Myalgia: 11/81 (14%) vs. 12/82 (15%) vs. 12/78 (15%) vs. 17/82 (21%); (p=NS for A, B, C vs. D) Arthralgia: 8/81 (10%) vs. 8/82 (10%) vs. 20/78 (26%) vs. 14/82 (17%); (p=NS for A, B, C vs. D) Anemia: 22/81 (27%) vs. 15/82 (18%) vs. 7/78 (9%) vs. 14/82 (17%); (p=NS for A, B, C vs. D)	Vertex Pharmaceuticals

Author, Year **Country** **Study Name** **Quality**	**Interferon Regimen**	**Ribavirin Regimen**	**Protease Inhibitor Regimen**	**Eligibility**	**Exclusion**	**Number Screened/ Eligible/ Enrolled/ Analyzed**	**Age** **Sex** **Race**	**Genotype** **Severity of Liver Disease** **Proportion Treatment-Naïve**
Jacobson, 2011[15] International Telaprevir for previously untreated chronic hepatitis C virus infection Overall Quality: Good	A. Pegylated interferon alfa-2a 180 mcg/week for 24 or 48 weeks (Response guided: if HCV RNA undetectable at weeks 4 and 12 then 24 total weeks, 48 weeks otherwise) B. Pegylated interferon alfa-2a 180 mcg/week for 24 or 48 weeks (Response guided: if HCV RNA undetectable at weeks 4 and 12 then 24 total weeks, 48 weeks otherwise) C. Pegylated interferon alfa-2a 180 mcg/week for 48 weeks	A. 1000-1200 mg/day for 24 or 48 weeks (Response guided: if HCV RNA undetectable at weeks 4 and 12 then 24 total weeks, 48 weeks otherwise) B. 1000-1200 mg/day for 24 or 48 weeks (Response guided: if HCV RNA undetectable at weeks 4 and 12 then 24 total weeks, 48 weeks otherwise) C. 1000-1200 mg/day for 48 weeks	A. Telaprevir 750 mg tid for 12 weeks B. Telaprevir 750 mg tid for 8 weeks C. Placebo for 12 weeks	Treatment naïve Ages 18-70 years of age HCV genotype 1 infection HCV virus confirmed with liver biopsy in the previous year Neutrophil count $\geq$ 1500 /mm^3 Platelets $\geq$ 90,000 / mm^3 Hemoglobin $\geq$ 12 g/dL in women and $\geq$ 13 g/dL in men	Decompensated liver disease Hepatocellular carcinoma HBV HIV	NR/ NR/ 1095/ 1088	A vs. B vs. C Age median: 49 vs. 49 vs. 49 Female: 41% vs. 42% vs. 42% Non White: 10% vs. 13% vs. 12%	A vs. B vs. C Genotype 1: all Proportion treatment-naïve: 100% Cirrhosis: 6% overall Minimal or no fibrosis: 28% Elevated transaminases: NR HCV RNA $\geq$ 800,000: 77% vs. 77% vs. 77%

Author, Year Country Study Name Quality	Duration of Followup	Outcome	Subgroup Analyses	Subgroup Analyses	Histologic Response	Adverse Events	Funding Source
Jacobson, 2011[15] International Continued	Up to week 72	A vs. B vs. C ETR: 314/363 (87%) vs. 295/364 (81%) vs. 229/361 (63%); p<0.001 for A or B vs. C SVR: 271/363 (75%) vs. 250/364 (69%) vs. 158/361 (44%); p<0.001 for A or B vs. C	A vs. B vs. C Male: 159/214 (74%) vs. 147/211 (70%) vs. 94/211 (45%); A or B vs. C p<0.001 Female: 112/149 (75%) vs. 103/153 (67%) vs. 64/150 (43%): A or B vs. C p<0.001 Age <45 years: 118/142 (83%) vs. 102/139 (73%) vs. 74/143 (52%); A or B vs. C p<0.001 Age >45 to <65 years: 150/214 (70%) vs. 145/222 (65%) vs. 82/216 (38%); A or B vs. C p<0.001 White: 244/325 (75%) vs. 220/315 (70%) vs. 147/318 (46%); A or B vs. C p<0.001 Black: 16/26 (62%) vs. 23/40 (58%) vs. 7/28 (25%); A vs. C p=0.05; B vs. C p=0.04 BMI <25: 129/155 (83%) vs. 104/145 (72%) vs. 57/130 (44%); A or B vs. C p<0.001	A vs. B vs. C HCV genotype 1a: 138/210 (66%) vs. 152/213 (71%) vs. 85/208 (41%); A or B vs. C p<0.001 HCV genotype 1b: 111/151 (74%) vs. 118/149 (79%) vs. 73/151 (48%); A or B vs. C p<0.001 Baseline HCV RNA <800K IU/ml: 67/85 (79%) vs. 64/82 (78%) vs. 57/82 (70%); A vs. C p=0.16; B vs. C p=0.19 Baseline HCV RNA >800K IU/ml: 183/279 (66%) vs. 207/281 (74%) vs. 101/279 (36%); A or B vs. C p<0.001 No or minimal fibrosis: 101/128 (79%) vs. 109/134 (81%) vs. 67/147 (46%); A or B vs. C p<0.001	NR	A vs. B vs. C Overall withdrawals: 95/363 (26%) vs. 104/364 (29%) vs. 159/361 (44%); A or B vs. C p<0.001 Withdrawals for adverse events: 36/363 (10%) vs. 37/364 (10%) vs. 26/361 (7%); p=NS Serious adverse events: 33/363 (9%) vs. 31/364 (9%) vs. 24/361 (7%); p=NS Deaths: 0 vs. 0 vs. 1 (<1%); p=NS Fatigue: 207/363 (57%) vs. 211/364 (58%) vs. 206/361 (57%); p=NS Influenza-like illness 102/363 (28%) vs. 105/364 (29%) vs. 101/361 (28%); p=NS Pyrexia: 95/363 (26%) vs. 108/364 (30%) vs. 87/361 (24%); p=NS Pruritus: 181/363 (50%) vs. 165/364 (45%) vs. 131/361 (36%); p=NS Rash: 133/363 (37%) vs. 129/364 (35%) vs. 88/361 (24%); A or B vs. C p<0.01 Anemia: 135/363 (37%) vs. 141/364 (39%) vs. 70/361 (19%); A or B vs. C p<0.001 Neutropenia: 51/363 (14%) vs. 62/364 (17%) vs. 68/361 (19%); p=NS Depression: 66/363 (18%) vs. 61/364 (17%) vs. 79/361 (22%); p=NS Myalgia: 54/363 (15%) vs. 76/364 (21%) vs. 77/361 (21%); p=NS Arthralgia: 49/363 (13%) vs. 56/364 (15%) vs. 68/361 (19%); p=NS	Vertex, Tibotec

Author, Year Country Study Name Quality	Duration of Followup	Outcome	Subgroup Analyses	Subgroup Analyses	Histologic Response	Adverse Events	Funding Source
Jacobson, 2011[15] International Continued			BMI >25 and <30: 87/129 (67%) vs. 92/131 (70%) vs. 65/144 (45%); A or B vs. C p<0.001 BMI >30: 55/77 (71%) vs. 53/86 (62%) vs. 36/87 (41%); A vs. C p<0.001, B vs. C p=0.02	Portal fibrosis: 104/151 (69%) vs. 117/156 (75%) vs. 67/141 (48%); A or B vs. C p<0.001 Bridging fibrosis: 34/59 (58%) vs. 32/52 (62%) vs. 17/52 (33%); A vs. C p=0.02, B vs. C p=0.01 Cirrhosis: 11/26 (42%) vs. 13/21 (62%) vs. 7/21 (33%); A vs. C p=0.04; B vs. C p=0.15			

Author, Year Country Study Name Quality	Interferon Regimen	Ribavirin Regimen	Protease Inhibitor Regimen	Eligibility	Exclusion	Number Screened/ Eligible/ Enrolled/ Analyzed	Age Sex Race	Genotype Severity of Liver Disease Proportion Treatment-Naïve
Kumada 2011[16] Japan Telaprevir with peginterferon and ribavirin for treatment-naive patients chronically infected with HCV of genotype 1 in Japan Overall Quality: Fair	A: Pegylated interferon alpha 2b 1.5 mcg/kg one time per week for 12 weeks, followed by an additional 12 weeks (24 weeks) B: Pegylated interferon alpha 2b 1.5 mcg/kg one time per week for 12 weeks, followed by an additional 12 weeks (24 weeks)	A: Ribavirin 200 – 600 mg/kg (weight-based) twice a day for 12 weeks, followed by an additional 12 weeks (24 weeks) <60 kg – 800 mg ≥60 - ≤80kg – 800 mg >80kg - 1000 mg B: Ribavirin 200 – 600 mg/kg (weight-based) twice a day for 12 weeks, followed by an additional 12 weeks (24 weeks) <60 kg – 800 mg ≥60 - ≤80kg – 800 mg >80kg - 1000 mg	A: Telaprevir 750 mg three times day at 8 hour intervals (q8h) one time a week simultaneously with interferon B: None	Diagnosis with chronic hepatitis C, and had not received antiviral treatments before, infected with HCV-1 confirmed by the sequence analysis in the NS5B region, had HCV RNA levels P5.0 log10 IU/ml determined by the COBAS TaqMan HCV test, Japanese aged from 20 to 65 years at the entry, had the body weight between >40 and 6120 kg, were not pregnant and capable of contraception until 24 weeks after the treatment. and agreed on the admission for 15 days since the treatment start	Patients with decompensated liver cirrhosis, hepatitis B surface antigen, hepatocellular carcinoma or other malignancy, or its history, autoimmune hepatitis, alcoholic liver disease, hemochromatosis or chronic liver disease other than chronic hepatitis C, depression or schizophrenia, or its history, or history of suicide attempts, chronic renal disease or creatinine clearance 650 ml/min at the baseline, hemoglobin <12 g/dl, neutrophil counts <1500/mm3 or platelet counts <100,000/mm3 at the baseline; and (h) pregnancy in progress or planned during the study period of either partner.	NR/ NR/ 220/ 189	A vs B: Age (mean): 53 vs 55 years Female: 48% vs 48% Non White: Not reported (conducted in Japan)	A vs. B: Genotype 1a: 1.6 % vs. 0% Genotype 1b: 98.4% vs. 100% Proportion treatment-naïve: 100% Cirrhosis: NR Elevated transaminases: NR HCV RNA ($\log_{10}$ IU/ml) 6.7 vs. 6.9

Author, Year Country Study Name Quality	Duration of Followup	Outcome	Subgroup Analyses	Subgroup Analyses	Histologic Response	Adverse Events	Funding Source
Kumada 2011[16] Japan Continued	>_24 weeks after treatment	A vs. B: ETR: NR SVR: 73% vs. 49.2%, p=0.002	A vs. B: ETR; NR SVR: Male: 50/66 (75.8%) vs. 18/33 (54.5%), p=0.0400 Female: 42/60 (70.0%) 13/30 (43.3%), p0.0214 Age: <49 years - 35/41 (85.4%) vs. 13/21 (61.9%), p= 0.0543 >50 years - 57/85 (67.1%) vs. 18/42 (42.9%), p= 0.0125 HCV RNA (log10 IU/ml): >7 - 18/26 (69.2%) vs. 5/18 (27.8%), p= 0.0132 <7 - 74/100 (74.0%) vs. 26/45 (57.8%), p= 0.0556	NR	NR	A vs. B: Overall withdrawals: NR Withdrawals for adverse events: NR Serious adverse events: NR Deaths: NR Anemia - 115/126(91.3%) vs. 46/63(73.0%) Pyrexia - 98/126(77.8%) vs. 46/63(73.0%) Leukocytopenia - 86/126(68.3%) vs. 46/63(73.0%) Thrombocytopenia - 81/126(64.3%) vs. 23/63(36.5%) Malaise - 73/126(57.9%) vs. 30/63(47.6%) Serum uric acid increased - 65/126(51.6%) vs. 5/63(7.9%) Serum hyaluronic acid increased - 64/126(50.8%) vs. 25/63(39.7%) Alopecia - 51/126(40.5%) vs. 29/63(46.0%) Headache - 48/126(38.1%) vs. 32/63(50.8%) Skin rashes - 48/126(38.1%) vs. 18/63(28.6%) Anorexia - 42/126(33.3%) vs. 17/63(27.0%) Insomnia - 40/126(31.7%) vs. 17/63(27.0%) Vomiting - 37/126(29.4%) vs. 9/63(14.3%) Drug eruption - 37/126(29.4%) vs. 2/63(3.2%) Arthralgia - 36/126(28.6%) vs. 15/63(23.8%) Serum triglycerides increased - 36/126(28.6%) vs. 11/63(17.5%) Dysgeusia - 34/126(27.0%) vs. 10/63(15.9%) Diarrhea - 34/126(27.0%) vs. 19/63(30.2%) Nausea - 32/126(25.4%) vs. 7/63(11.1%) Serum creatinine increased - 32/126(25.4%) vs.0 Erythema at the injection site - 33(26.2%) vs. 21/63(33.3%) Reactions at the injection site - 29/126(23.0%) vs.16/63(25.4%) Stomatitis - 24/126(19.0%) vs. 12/63(19.0%) Abdominal discomfort - 23/126(18.3%) vs.12/63(19.0%) Pruritus - 23/126(18.3%) vs.13/63(20.6%) Nasopharyngitis - 23/126(18.3%) 18/63(28.6%) Influenza-like symptoms - 22/126(17.5%) vs. 16/63(25.4%)	NR

Author, Year Country Study Name Quality	Duration of Followup	Outcome	Subgroup Analyses	Subgroup Analyses	Histologic Response	Adverse Events	Funding Source
Kumada 2011[16] Japan Continued						Serum bilirubin increased - 22/126(17.5%) vs. 13/63(20.6%) Back pain - 21/126(16.7%) vs. 12/63(19.0%) Hyperuricemia - 20/126(15.9%) vs. 2/63(3.2%) Serum phosphorus decreased - 16/126(12.7%) vs. 13/63(20.6%) Constipation - 14/126(11.1%) vs. 13/63(20.6%) Erythema - 9/126(7.1%) vs. 13/63(20.6%)	

Author, Year Country Study Name Quality	Interferon Regimen	Ribavirin Regimen	Protease Inhibitor Regimen	Eligibility	Exclusion	Number Screened/ Eligible/ Enrolled/ Analyzed	Age Sex Race	Genotype Severity of Liver Disease Proportion Treatment-Naïve
Kwo, 2010[17] US, Canada, Europe Efficacy of boceprevir, an Ns3 protease inhibitor, in combination with Pegylated interferon alfa-2b and ribavirin in treatment-naïve patients with genotype 1 hepatitis C infection (SPRINT-1): an open-label, randomized, multicentre phase 2 trial Overall Quality: Fair	A. Pegylated interferon alfa-2b 1.5 mcg/kg weekly for 48 weeks B. Pegylated interferon alfa-2b 1.5 mcg/kg weekly for 28 weeks C. Pegylated interferon alfa-2b 1.5 mcg/kg weekly for 48 weeks D. Pegylated interferon alfa-2b 1.5 mcg/kg weekly for 28 weeks E. Pegylated interferon alfa-2b 1.5 mcg/kg weekly for 48 weeks	A. 800-1400 mg daily for 48 weeks B. 800-1400 mg daily for 28 weeks C. 800-1400 mg daily for 48 weeks D. 800-1400 mg daily for 28 weeks E. 800-1400 mg daily for 48 weeks ≤ 65 kg: 400 mg bid 66-80 kg: 400 mg every morning, 600 mg every evening 81-105 kg: 600 mg bid >105 kg: 600 mg every morning, 800 mg every evening	A. Boceprevir 800 mg tid for 48 weeks B. Boceprevir 800 mg tid for 28 weeks C. Boceprevir 800 mg tid for weeks 5 through 48 (44 weeks total) D. Boceprevir 800 mg tid for weeks 5 through weeks 28 (24 weeks total) E. Placebo	Treatment naïve patients with genotype 1 Ages 18-60 years Liver biopsy consistent with chronic HCV infection within 5 years of enrollment Hemoglobin ≥ 130 g/L in men ≥ 120 g/L in women Neutrophils ≥ 1500/mm^3 Platelets ≥ 100K / mm^3 Normal bilirubin, albumin, and creatinine	History of decompensated cirrhosis HIV infection Previous organ transplantation Other causes of liver disease Pre-existing psychiatric disease Seizure disorder Cardiovascular disease Hemoglobinopathies Hemophilia Poorly controlled diabetes Autoimmune disease	765/ 642/ 520/ 520	A vs. B vs. C vs. D vs. E Age: mean 47 vs. 46 vs. 48 vs. 48 vs. 48 Female: 39% vs.41% vs. 44% vs. 50% vs. 33% Non White: 16% vs. 20% vs. 17% vs. 17% vs. 20%	A vs. B vs. C vs. D vs. E Genotype 1: 100% Cirrhosis: 9% vs. 7% vs. 6% vs. 7% vs. 8% Minimal or no fibrosis: NR Elevated transaminases: NR Treatment-naïve: 100% HCV-RNA ≥600K IU/mL: 91% vs. 92% vs. 90% vs. 87% vs. 90%

Author, Year Country Study Name Quality	Duration of Followup	Outcome	Subgroup Analyses	Subgroup Analyses	Histologic Response	Adverse Events	Funding Source
Kwo, 2010[17] US, Canada, Europe Continued	24 weeks after end of treatment	A vs. B vs. C vs. D vs. E ETR: 76/103 (74%) vs. 84/107 (79%) vs. 81/103 (79%) vs. 79/103 (77%) vs. 53/104 (51%) (A, B, C, D vs. E p<0.01) SVR: 69/103 (67%) vs. 58/107 (54%) vs. 77/103 (75%) vs. 58/103 (56%) vs. 39/104 (38%); (A, B, C, D vs. E p<0.01)	A vs. B vs. C vs. D vs. E Black: 4/14 (29%) vs. 7/18 (39%) vs. 8/15 (53%) vs. 6/15 (40%) vs. 2/16 (13%); (A, B, D vs. E p=NS, C vs. E p<0.05) Non black 65/89 (73%) vs. 51/89 (57%) vs. 69/88 (78%) vs. 52/88 (59%) vs. 37/88 (42%) (A, B, C, D vs. E p<0.05) Male: 40/63 (64%) vs. 33/63 (52%) vs. 41/58 (71%) vs. 33/51 (65%) 28/70 (40%); (A, C, D vs. E p<0.01; B vs. E p=0.15) Female: 29/40 (73%) vs. 25/44 (59%) vs. 36/45 (80%) vs. 25/52 (48%) vs. 11/34 (32%) (A, B, C vs. E p<0.05, D vs. E p=0.15)	A vs. B vs. C vs. D vs. E Cirrhosis: 7/9 (78%) vs. 4/7 (57%) vs. 3/6 (50%) vs. 4/7 (57%) vs. 2/8 (25%) (A vs. E p=0.04; B, C, D vs. E p=NS) non Cirrhosis: 62/97 (66%) vs. 54/100 (54%) vs. 74/97 (76%) vs. 54/96 (56%) vs. 37/96 (39%) (A, B, C, D vs. E p<0.05) Baseline HCV-RNA >600K IU/mL: 63/97 (67%) vs. 52/99 (53%) vs. 67/92 (73%) vs. 48/89 (54%) vs. 30/93 (32%) (A, B C, D vs. E p<0.01) Baseline HCV-RNA < 600K IU/mL: 6/9 (67%) vs. 6/8 (75%) vs. 10/11 (91%) vs. 10/14 (71%) vs. 9/11 (89%) (A, B, C, D vs. E p=NS) HCV genotype 1a: 32/55 (58%) vs. 34/67 (51%) vs. 43/60 (72%) vs. 27/53 (51%) vs. 16/53 (30%) (A, B, C, D vs. E p<0.05) HCV genotype 1b: 30/36 (83%) vs. 21/30 (70%) vs. 29/35 (83%) vs. 22/37 (60%) vs. 17/42 (41%) (A, B, C vs. E p<0.05, D vs. E p=0.09)	NR	A vs. B vs. C vs. D vs. E Overall Withdrawals: 40/103 (39%) vs. 30/107 (28%) vs. 27/103 (26%) vs. 27/103 (26%) vs. 16/104 (15%); (A, B vs. E p<0.05; C, D vs. E p=0.055) Withdrawals due to adverse events: 20/103 (19%) vs. 12/107 (11%) vs. 9/103 (9%) vs. 15/103 (15%) vs. 8/104 (8%); (A vs. E p=0.01, B vs. E p=0.38, C vs. E p= 0.78, Dives E p=0.12) Influenza-like illness: 19/103 (18%) vs. 24/107 (22%) vs. 15/103 (15%) vs. 21/103 (20%) vs. 25/104 (24%); p=NS for all comparisons Fatigue: 51/103 (50%) vs. 65/107 (61%) vs. 73/103 vs. 70/103 (68%) vs. 57/104 (55%); (A vs. E p = 0.45; B vs. E p=0.38, C vs. E p=0.02, D vs. E p=0.05) Headache: 44/103 (43%) vs. 52/107 (49%) vs. 54/103 (52%) vs. 41/103 (40%) vs. 45/104 (43%); (A, B, C, D vs. E p=NS) Nausea: 56/103 (103%) vs. 41/107 (38%) vs. 48/103 (47%) vs. 42/103 (41%) vs. 45/104 (43%); (A, B, C, D vs. E p=NS) Pyrexia: 41/103 (40%) vs. 28/107 (26%) vs. 35/103 (34%) vs. 27/103 (26%) vs. 35/104 (34%); (A, B, C, D vs. E p=NS) Chills: 33/103 (32%) vs. 31/107 (29%) vs. 35/103 (34%) vs. 31/103 (30%) vs. 35/104 (34%); (A, B, C, D vs. E p=NS) Dysgeusia: 33/103 (32%) vs. 23/107 (21%) vs. 28/103 (27%) vs. 27/103 (26%) vs. 9/104 (9%); (A, B, C, D vs. E p<0.01) Influenza-like illness: 19/103 (18%) vs. 24/107 (22%) vs. 15/103 (15%) vs. 21/103 (20%) vs. 25/104 (24%); (A, B, C, D vs. E p=NS) Arthralgia: 21/103 (20%) vs. 14/107 (13%) vs. 19/103 (18%) vs. 22/103 (21%) vs. 21/104 (20%); (A, B, C, D vs. E p=NS)	Merck

Author, Year Country Study Name Quality	Duration of Followup	Outcome	Subgroup Analyses	Subgroup Analyses	Histologic Response	Adverse Events	Funding Source
Kwo, 2010[17] US, Canada, Europe Continued						Neutrophils <750: 38/103 (37%) vs. 36/107 (34%) vs. 37/103 (36%) vs. 21/103 (20%) vs. 18/104 (17%); (A, B, C vs. E p<0.01, D vs. E p=0.52) Hemoglobin <100 g/L: 48/103 (47%) vs. 57/107 (53%) vs. 48/103 (47%) vs. 51/103 (50%) vs. 25/104 (24%); (A, B, C, D vs. E p<0.01) Platelets <50K / mm3: 1/103 (1%) vs. 4/107 (4%) vs. 4/103 (4%) vs. 2/103 (2%) vs. 0/104 (0%); (A, B, C, D vs. E p=NS)	

Author, Year Country Study Name Quality	Interferon Regimen	Ribavirin Regimen	Protease Inhibitor Regimen	Eligibility	Exclusion	Number Screened/ Eligible/ Enrolled/ Analyzed	Age Sex Race	Genotype Severity of Liver Disease Proportion Treatment-Naïve
Marcellin, 2011[18] Europe Telaprevir is effective given every 8 or 12 Hours with ribavirin and Pegylated interferon alfa-2a or 2b to patients with chronic hepatitis C Overall Quality: Fair	A. Pegylated interferon alfa-2a 180 mcg/week for 24 or 48 weeks B. Pegylated interferon alfa-2b 1.5 mcg/kg/week for 24 or 48 weeks C. Pegylated interferon alfa-2a 180 mcg/week for 24 or 48 weeks D. Pegylated interferon alfa-2b 1.5 mcg/kg/week for 24 or 48 weeks Response guided: 24 weeks total if HCV RNA undetectable from weeks 4 through 20, 48 weeks total otherwise	A. 1000-1200 mg/day for 24 or 48 weeks B. 800-1200 mg/day for 24 or 48 weeks C. 1000-1200 mg/day for 24 or 48 weeks D. 800-1200 mg/day for 24 or 48 weeks Response guided: 24 weeks total if HCV RNA undetectable from weeks 4 through 20, 48 weeks total otherwise	A. Telaprevir 750 mg tid for 12 weeks B. Telaprevir 750 mg tid for 12 weeks C. Telaprevir 1125 mg bid for 12 weeks D. Telaprevir 1125 mg bid for 12 weeks	Treatment-naïve Ages 18-65 years Chronic HCV genotype 1 infection HCV RNA >10,000 IU/mL Neutrophil count $\geq$ 1500 mm^3 Platelets $\geq$ 100,000 mm^3 Liver fibrosis status documented within 18 months	Contraindication to pegylated interferon or ribavirin History of drug use Documented cirrhosis Hepatitis B Hepatocellular cancer HIV History or suspicion of alcohol abuse	176/ 170/ 166/ 161	A vs. B vs. C vs. D Age median: 47 vs. 46 vs. 40 vs. 49 Female: 50% vs. 52% vs. 48% vs. 51 Non White: 10% vs. 10% vs. 10% vs. 8%	A vs. B vs. C vs. D Genotype 1: all Cirrhosis: 2.5% vs. 2.4% vs. 0 vs. 5.1% Minimal or no fibrosis: 39% overall Elevated transaminases: NR Proportion treatment-naïve: all HCV-RNA $\geq$ 800K IU/mL: 75% vs. 81% vs. 83% vs. 87%

Author, Year Country Study Name Quality	Duration of Followup	Outcome	Subgroup Analyses	Subgroup Analyses	Histologic Response	Adverse Events	Funding Source
Marcellin, 2011[18] Europe Continued	24 weeks after end of treatment	A vs. B vs. C vs. D ETR: 37/40 (93%) vs. 37/42 (88%) vs. 37/40 (93%) vs. 34/39 (87%); Pooled A+B (TID telaprevir) vs. C+D (BID telaprevir) p=NS Pooled A+C (alpha-2a) vs. B + D (alpha-2b) p=NS SVR: 34/40 (85%) vs. 34/42 (81%) vs. 33/40 (83%) vs. 32/39 (82%) Pooled A+B (TID telaprevir) vs. C+D (BID telaprevir) p=NS Pooled A+C (alpha-2a) vs. B + D (alpha-2b) p=NS	NR	NR	NR	A vs. B vs. C vs. D vs. E Overall withdrawals: 10/40 (25%) vs. 8/42 (19%) vs. 11/40 (28%) vs. 17/39 (44%); Withdrawals due to adverse events: 3/40 (7.5%) vs. 2/42 (5%) vs. 4/40 (10%) vs. 4/39 (10%) Nausea: 18/40 (45%) vs. 14/42 (33%0 vs. 16/40 (40%) vs. 23/39 (59%) Fatigue: 15/40 (38%) vs. 15/42 (36%) vs. 16/40 (40%) vs. 15/39 (39%) Influenza-like illness: 16/40 (40%) vs. 19/42 (45%) vs. 11/40 (28%) vs. 20/39 (51%) Pyrexia: 9/40 (23%) vs. 15/42 (36%) vs. 9/40 (23%) vs. 12/39 (31%) Depression: 7/40 (18%) vs. 9/42 (21%) vs. 4/40 (10%) vs. 9/39 (23%) Pruritus: 19/40 (48%) vs. 23/42 (55%) vs. 20/40 (50%) vs. 25/39 (64%) Rash: 29/40 (73%) vs. 23/42 (55%0 vs. 20/40 (50%) vs. 25/39 (64%) Anemia: 18/40 (45%) vs. 14/ 42 (33%) vs. 18/40 (45%) vs. 20/39 (51%) Leukopenia: 9/40 (23%) vs. 9/42 (21%) vs. 9/40 (23%) vs. 10/39 (26%) Pooled A+C (alpha-2a) vs. B + D (alpha-2b) - all comparisons p=NS Pooled A+B (TID telaprevir) vs. C+D (BID telaprevir) - all comparisons p=NS	Janssen, Vertex Pharma-ceuticals

Author, Year Country Study Name Quality	Interferon Regimen	Ribavirin Regimen	Protease Inhibitor Regimen	Eligibility	Exclusion	Number Screened/ Eligible/ Enrolled/ Analyzed	Age Sex Race	Genotype Severity of Liver Disease Proportion Treatment-Naïve
McHutchison, 2009[19] US Protease Inhibition for Viral Evaluation 1 (PROVE1)	A. Peg interferon alfa-2a 180 mcg weekly for 24 weeks B. Pegylated interferon alfa-2a 180 mcg weekly for 48 weeks C. Pegylated interferon alfa-2a 180 mcg weekly for 12 weeks D. Pegylated interferon alfa-2a 180 mcg weekly for 48 weeks	A. Ribavirin1000-1200 mg daily for 24 weeks B. Ribavirin 800-1400 mg daily for 48 weeks C. Ribavirin 800-1400 mg daily for 12 weeks D. Ribavirin1000-1200 mg daily for 48 weeks 1000 mg daily for patients <75 kg 1200 mg daily for patients ≥ 75 kg	A. Telaprevir 750 mg tid for 12 weeks B. Telaprevir 750 mg tid for 12 weeks C. Telaprevir 750 mg tid for 12 weeks D. Placebo On day 1, patients received telaprevir 1250 mg	Treatment naïve patients ages 18-65 years, neutrophils ≥ 1500 / mm3, platelets ≥ 90K / mm3, normal hemoglobin	decompensated liver disease, hepatocellular carcinoma, cirrhosis (liver biopsy within 2 years)	329/ 263/ 263/ 250	Age: median 49 vs. 50 vs. 49 vs. 49 Female: 32% vs. 39% vs. 29% vs. 43% non White: 24% vs. 24% vs. 24% vs. 21%	Genotype 1: all Portal or Bridging fibrosis: 70% vs. 57% vs. 76% vs. 75% Treatment-naïve: all

Author, Year Country Study Name Quality	Duration of Followup	Outcome	Subgroup Analyses	Subgroup Analyses	Histologic Response	Adverse Events	Funding Source
McHutchison, 2009[19] US Continued	Up to 24 weeks following treatment completion	A vs. B vs. C vs. D ETR: 45/79 (57%) vs. 51/79 (65%) vs. 12/17 (71%) vs. 35/75 (47%) (A, C vs. D p=NS, B vs. D p=0.03) SVR: 48/79 (61%) vs. 53/79 (67%) vs. 6/17 (35%) vs. 31/75 (41%); (A vs. D p=0.02, B vs. D p=0.002, C vs. D p=NS)	NR	NR	NR	A vs. B vs. C vs. D Overall withdrawals: 26/79 (33%) vs. 25/79 (32%) vs. 4/17 (24%) vs. 17/75 (23%) Withdrawals due to adverse events (telaprevir regimens A+B+C vs. D): 37/175 (21%) vs. 8/75 (11%) Fatigue: 70% vs. 73% vs. 82% vs. 76% Nausea: 56% vs. 48% vs. 65% vs. 29% Influenza-like illness: 49% vs. 40% vs. 24% vs. 23% Pruritus: 48% vs. 40% vs. 24% vs. 23% Headache: 47% vs. 43% vs. 53% vs. 60% Rash: 60% vs. 61% vs. 53% vs. 41% Vomiting: 24% vs. 20% vs. 18% vs. 12% Arthralgia: 17% vs. 22% vs. 24% vs. 21% Myalgia: 11% vs. 19% vs. 18% vs. 24% Chills: 10% vs. 23% vs. 18% vs. 19% Anemia: 37% vs. 29% vs. 35% vs. 27% Neutropenia: 14% vs. 24% vs. 0% vs. 24%	Vertex Pharmaceuticals

Author, Year Country Study Name Quality	Interferon Regimen	Ribavirin Regimen	Protease Inhibitor Regimen	Eligibility	Exclusion	Number Screened/ Eligible/ Enrolled/ Analyzed	Age Sex Race	Genotype Severity of Liver Disease Proportion Treatment-Naïve
Poordad , 2011[20] USA and Europe Serine Protease Inhibitor Therapy 2 (SPRINT-2) Overall Quality: Fair	A: Pegylated interferon alfa-2b 1.5 µg/kg/week for 48 weeks B: Pegylated interferon alfa-2b 1.5 µg/kg 1x/week for 48 weeks -if HCV RNA undetectable from week 8 through 24 treatment completed -if HCV RNA detectable at any point from week 8 through 23 Pegylated interferon continued through week 48 C: Pegylated interferon alfa-2b 1.5 µg/kg 1x/week for 48 weeks	A: 600-1400 mg (weight-based) daily for 48 weeks B: 600-1400 mg (weight-based) daily for 48 weeks -if HCV RNA undetectable from week 8 through 24 treatment completed -if HCV RNA detectable at any point from week 8 through 23 ribavirin continued through week 48 C: 600-1400 mg (weight-based) daily for 48 weeks *<51 kg: 600mg/day 51-65 kg: 800mg/day 66 - 75 kg: 1000mg/day 76 - 105 kg: 1200mg/day >105 kg: 1400mg/day	A: Boceprevir 800 mg by mouth tid from weeks 5 to 28 (24 weeks total) B: Boceprevir 800 mg by mouth tid from weeks 5 to 48 (44 weeks total) C: Placebo	No previous treatment for HCV infection Age 18 years or older Weight 40 to 125 kg Chronic infection with HCV genotype 1 Plasma HCV RNA level >=10,000 IU/mL	Liver disease of other cause Decompensated cirrhosis Renal insufficiency HIV or hepatitis B infection Pregnancy or current breast-feeding Active cancer	1472/NR/1099 /1097	A vs. B vs. C Age: Mean 49 vs. 50 vs. 49 years Female: 40% vs. 38% vs. 43% Non White: 19% vs. 17% vs. 18%	A vs. B vs. C Genotype 1: 100% Cirrhosis (METAVIR fibrosis score 3 or 4): 11% vs. 9% vs. 7% Treatment-naïve: 100%

Author, Year Country Study Name Quality	Duration of Followup	Outcome	Subgroup Analyses	Subgroup Analyses	Histologic Response	Adverse Events	Funding Source
Poordad, 2011[20] USA and Europe Continued	72 weeks (24 weeks after treatment end)	A vs. B vs. C ETR: 277/366 (76%) vs. 261/368 (71%) vs. 191/363 (53%) (p<0.001 for A or B vs. C) SVR: 242/366 (66%) vs. 233/368 (63%) vs. 137/363 (38%) (p<0.001 for A or B vs. C)	A vs. B vs. C Black: 29/55 (53%) vs. 22/52 (42%) vs. 12/52 (23%) (p=0.004 for A vs. C, p=0.04 for B vs. C) Non black: 197/313 (63%) vs. 192/314 (61%) vs. 102/308 (33%) (p<0.001 for A or B vs. C) Male: 145/221 (66%) vs. 149/229 (65%) vs. 72/206 (35%) (p<0.001 for A or B vs. C) Female: 97/145 (67%) vs. 84/139 (60%) vs. 65/157 (41%) (p<0.001 for A or B vs. C) Age <=40 years: 41/59 (69%) vs. 37/51 (73%) vs. 35/67 (52%) (p<0.001 for A or B vs. C) Age >40 years: 201/307 (65%) vs. 196/317 (62%) vs. 102/296 (34%) (p<0.001 for A or B vs. C) Weight <75 kg: 83/131 (63%) vs. 82/131 (63%) vs. 67/146 (46%) (p<0.001 for A or B vs. C) Weight >=75 kg): 159/235 (68%) vs. 151/237 (64%) vs. 70/217 (32%) (p<0.001 for A or B vs. C)	A vs. B vs. C METAVIR score 0, 1, or 2: 211/313 (67%) vs. 213/319 (67%) vs. 123/328 (38%) (p<0.001 for A or B vs. C) METAVIR score 3 or 4: 22/42 (52%) vs. 14/34 (41%) vs. 9/24 (38%) (p=0.31 for A vs. C and p=1.0 for B vs. C) Low viral load (<=800,000 IU/mL): 45/53 (85%) vs. 41/54 (76%) vs. 35/55 (64%) High viral load: 197/313 (63%) vs. 192/314 (61%) vs. 102/308 (33%) (p<0.001 for A or B vs. C) Genotype 1a: 118/187 (63%) vs. 106/179 (59%) vs. 62/177 (35%) (p<0.001 for A or B vs. C) Genotype 1b: 93/133 (70%) vs. 89/134 (66%) vs. 51/128 (40%) (p<0.001 for A or B vs. C) Cirrhosis: 10/24 (42%) vs. 5/16 (31%) vs. 6/13 (46%); p=NS for A or B vs. C Non cirrhosis: 223/331 (67%) vs. 222/337 (66%) vs. 126/339 (37%); (p<0.001 for A or B vs. C)	NR	A vs. B vs. C Overall withdrawals: 152/367 (41%) vs. 139/368 (38%) vs. 205/364 (56%) (p<0.001 for A or B vs. C) Withdrawals due to adverse events: 60/366 (16%) vs. 45/368 (12%) vs. 57/363 (16%) (p>0.05) Deaths: 1/366 (<1%) vs. 1/368 (<1%) vs. 4/363 (1%) (p>0.05) Serious adverse event: 45/366 (12%) vs. 42/368 (11%) vs. 31/363 (9%) (p>0.05) Fatigue: 209/366 (57%) vs. 196/368 (53%) vs. 217/363 (60%) (p>0.05) Headache: 167/366 (46%) vs. 168/368 (46%) vs. 153/363 (42%) (p>0.05) Nausea: 159/366 (43%) vs. 175/368 (48%) vs. 153/363 (42%) (p>0.05) Pyrexia: 118/366 (32%) vs. 123/368 (33%) vs. 121/363 (33%) (p>0.05) Chills: 121/366 (33%) vs. 134/368 (36%) vs. 102/363 (28%) (p=0.15 for A vs. C, p=0.02 for B vs. C) Dysgeusia: 156/366 (43%) vs. 137/368 (37%) vs. 64/363 (18%) (p<0.001 for A or B vs. C) Neutrophil count <750 per mm^3: 119/366 (32%) vs. 108/368 (29%) vs. 66/363 (18%) (p<0.001 for A or B vs. C) Neutrophil count <500 per mm^3: 29/366 (8%) vs. 21/368 (6%) vs. 16/363 (4%) (p>0.05) Use of granulocyte stimulating agent: 31/366 (8%) vs. 43/368 (12%) vs. 21/363 (6%) (p=0.20 for A vs. C, p=0.006 for B vs. C) Platelet count <50,000 per mm^3: 14/366 (4%) vs. 12/368 (3%) vs. 5/363 (1%) (p=0.99 for A or B vs. C) Hemoglobin <8.0 g/dl: 13/366 (4%) vs. 9/368 (2%) vs. 6/363 (2%) (p>0.05) Red-cell transfusion: 9/366 (2%) vs. 11/368 (3%) vs. 2/363 (1%) (p=0.06 vs. A vs. C and p=0.02 for B vs. C) Erythropoietin use: 159/366 (43%) vs. 159/368 (43%) vs. 87/363 (24%) (p<0.001 for A or B vs. C)	Schering-Plough (now Merck)

Author, Year Country Study Name Quality	Interferon Regimen	Ribavirin Regimen	Protease Inhibitor Regimen	Eligibility	Exclusion	Number Screened/ Eligible/ Enrolled/ Analyzed	Age Sex Race	Genotype Severity of Liver Disease Proportion Treatment-Naïve
Sherman, 2011[21] Europe and US Response-Guided Telaprevir Combination Treatment for Hepatitis C Virus Infection Overall Quality: Fair	A. Pegylated interferon alfa-2a 180 mcg weekly for 24 weeks B. Pegylated interferon alfa-2a 180 mcg weekly for 48 weeks C. Pegylated interferon alfa-2a 180 mcg weekly for 48 weeks (not randomized) Randomization to A and B was done at week 20 in those with an extended rapid virologic response (undetectable HCV RNA in week 4 and week 12). Subjects not achieving ERVR were assigned to group C	A. Ribavirin 1000-1200 mg daily for 24 weeks B. Ribavirin 1000-1200 mg daily for 48 weeks C. Ribavirin 1000-1200 mg daily for 48 weeks (not randomized) Randomization to A and B was done at week 20 in those with an extended rapid virologic response (undetectable HCV RNA in week 4 and week 12). Subjects not achieving ERVR were assigned to group C	A. Telaprevir 750 mg tid for 12 weeks B. Telaprevir 750 mg tid for 12 weeks C. Telaprevir 750 mg for 12 weeks	Treatment-naïve Ages between 18 and 70 years Chronic HCV genotype 1 infection Detectable HCV RNA Diagnosis for at least 6 months before screening Neutrophils $\geq$ 1500/mm^3 Hemoglobin$\geq$12 g/dL for women and $\geq$13 g/dL for men Platelets $\geq$ 90K/mm^3 Liver biopsy in past year	HIV HBV Hepatic decompensation Clinically significant liver disease of other etiology Active cancer in previous 5 years (except basal-cell carcinoma)	NR/544/322/322 Subjects treated for 20 weeks prior to randomization. Only subjects who completed 20 weeks and had an early rapid virologic response were randomized.	A vs. B Age median: 51 vs. 50 Female: 36% vs. 39% Non White: 17% vs. 18%	A vs. B Genotype 1: all Treatment-naïve: 100% Cirrhosis: 11% vs. 8% Minimal or no fibrosis: 27% HCV RNA $\geq$ 800K IU/ml: 77% vs. 79%

Author, Year Country Study Name Quality	Duration of Followup	Outcome	Subgroup Analyses	Subgroup Analyses	Histologic Response	Adverse Events	Funding Source
Sherman, 2011[21] Europe and US Continued	72 weeks	A vs. B vs. C ETR: 159/162 (98%) vs. 154/160 (96%) vs. 97/118 (82%); As B p=NS SVR: 149/162 (92%) vs. 140/160 (88%) vs. 76/118 (64%); A non inferior to B	A vs. B Black: 15/17 (88%) vs. 15/17 (88%) White: 126/135 (93%) vs. 114/131 (87%) Asian/other: 8/10 (80%) vs. 11/12 (92%) BMI>=30: 55/61 (90%) vs. 43/49 (88%) BMI>=25 to <30: 51/56 (91%) vs. 46/51 (90%) BMI <25: 42/44 (95%) vs51/60 (85%)	A vs. B HCV genotype 1a: 103/115 (90%) vs. 10/117 (88%) HCV genotype 1b: 45/46 (98%) vs. 37/43 (86%) Bridging fibrosis or cirrhosis: 31/38 (82%) vs. 29/33 (88%) no Bridging fibrosis or cirrhosis: 118/124 (95%) vs. 111/127 (87%)	NR	A vs. B vs. C Overall withdrawals (after randomization): 1/162 (1%) vs. 41/160 (26%) vs. 39/118 (33%) Withdrawals for adverse events: 1/162 (1%) vs. 20/160 (13%) vs. 12/118 (10%) Serious adverse events: 4/162 (2) vs. 16/160 (10%) vs. 7/118 (6%) Deaths: NR Fatigue: 110/162 (68%) vs. 111/160 (69%) vs. 81/118 (69%) Nausea: 71/162 (44%) vs. 76/160 (48%) vs. 61/118 (52%) Diarrhea: 48/162 (30%) vs. 54/160 (34%) vs. 38/118 (32%) Pruritus: 95/162 (59%) vs. 83/160 (52%) vs. 55/118 (47%) Rash: 60/162 (37%) vs. 62/160 (39%) vs. 47/118 (40%) Headache: 61/162 (38%) vs. 57/160 (36%) vs. 51/118 (43%) Insomnia: 50/162 (31%) vs. 62/160 (39%) vs. 44/118 (37%) Anemia: 68/162 (42%) vs. 66/160 (41%) vs. 38/118 (32%)	Vertex, Tibotec

Evidence Table 4. Quality rating: Trials of protease inhibitors plus pegylated interferon and ribavirin

Author, Year	Randomization adequate?	Allocation concealment adequate?	Groups similar at baseline?	Eligibility criteria specified?	Outcome assessors masked?	Care provider masked?	Patient masked?	Attrition and withdrawals reported?	Loss to followup: differential/ high?	Intention-to-treat analysis	Quality	Funding
Hezode 2009[14]	Unclear	Yes	Yes	Yes	Unclear	Unclear	Unclear	Yes	Unclear	Yes	Fair	Vertex Pharma-ceuticals
Jacobson 2011[15]	Unclear	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Good	Vertex, Tibotec
Kumada 2011[16]	Unclear	Unclear	Yes	Yes	No	No	No	Yes	No	Yes	Fair	NR
Kwo 2010[17]	Yes	Yes	Yes	Yes	No	No	No	Yes	No	Yes	Fair	Merck
Marcellin 2011[18]	Unclear	Unclear	Yes	Yes	No	No	No	Yes	No	No	Fair	Janssen, Vertex Pharma-ceuticals
McHutchison 2009[19]	Unclear	Unclear	Yes	Yes	Unclear	Unclear	Unclear	Yes	Unclear	Yes	Fair	Vertex Pharma-ceuticals
Poordad 2011[20]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Fair	Schering-Plough now Merck)
Sherman 2011[21] ILLUMINATE Study	Unclear	Yes	Yes	Yes	No	No	No	No	No	Yes	Fair	Vertex

Evidence Table 5. Trials of dual therapy with pegylated interferon plus ribavirin: duration effects

Author, Year Country Study Name Quality	Interferon Regimen	Ribavirin Regimen	Protease Inhibitor Regimen	Eligibility	Exclusion	Number Screened/ Eligible/ Enrolled/ Analyzed	Age Sex Race	Genotype Severity of Liver Disease Proportion Treatment-Naïve
Andriulli, 2009[22] Italy Early discontinuation of ribavirin in HCV-2 and HCV-3 patients responding to Peg-interferon alpha-2a and ribavirin Overall Quality: Fair	A: Pegylated interferon alpha-2a 180 mcg / week for 12 weeks B: Pegylated interferon alpha-2a 180 mcg / week for 12 weeks	A: 1000-1200 mg/day depending of body weight for 6 weeks B: 1000-1200 mg/day depending of body weight for 12 weeks Patients with rapid virologic response (undetectable HCV-RNA) at week 4 were randomized to A or B above	None	Treatment-naïve Ages 18-70 years Detectable HCV-RNA levels Infection with genotype 2 or 3 Abnormal ALT	Neutrophils <3000 Platelets <80K Hemoglobin <12 g/dL for females and <13 g/dL for males HIV co-infection Alcohol intake >30 g daily Drug abuse Chronic disease Psychiatric disorders Autoimmune diseases Pregnancy or lactation	NR/NR/149/ 120	A vs. B: Age mean: 53 vs. 53 Female: 41% vs. 51% non white: NR	A vs. B: Genotype 1: none Treatment-naïve: all Fibrosis stage 3 or platelets <140K: 14% vs. 10% HCV-RNA >600K: 64% vs. 52% Cirrhosis: NR

Author, Year Country Study Name Quality	Duration of Followup	Outcome	Subgroup Analyses	Subgroup Analyses	Histologic Response	Adverse Events	Funding Source
Andriulli , 2008[22] Italy Continued	Followup visits at 24 weeks after completion of treatment	A vs. B: SVR: 32 /59 (54%) vs. 50 / 61 (82%); p<0.001	NR (only one arm reported)	A vs. B: Baseline HCV RNA<300K: 12/14 (86%) vs. 17/21 (81%); p=NS Baseline HCV RNA 300K-700K: 7/10 (70%) vs. 10/14 (71%); p=NS Baseline HCV RNA >700K: 13/35 (37%) vs. 23/26 (88%); p<0.001	NR	A vs. B: Overall withdrawals: NR Withdrawals for adverse events: 5/120 (4%) vs. 2/24(8%); p=0.33 Serious adverse events: NR Deaths: NR Interferon-related adverse events: 66% vs. 63% Neutrophils <1000 at 12 weeks: 17% vs. 16%	Investigator funded

Author, Year Country Study Name Quality	Interferon Regimen	Ribavirin Regimen	Protease Inhibitor Regimen	Eligibility	Exclusion	Number Screened/ Eligible/ Enrolled/ Analyzed	Age Sex Race	Genotype Severity of Liver Disease Proportion Treatment-Naïve
Berg, 2006[23] Germany Extended treatment duration for hepatitis C virus type 1: Comparing 48 vs. 72 weeks of pegylated interferon alfa-2a plus ribavirin Overall Quality: Fair	A: Pegylated interferon alfa-2a 180 mcg/week for 48 weeks B: Pegylated interferon alfa-2a 180 mcg/week for 72 weeks	A: 400 mg twice daily for 48 weeks B: 400 mg twice daily for 72 weeks	None	Treatment naïve Ages 18-70 years of age HCV genotype 1 infection HCV RNA >1000 IU/mL Increased ALT at screening Liver biopsy within the preceding 18 months showing chronic hepatitis Neutrophils > 1500 Platelets > 90K Hemoglobin > 12g/dL for women and > 13 g/dL for men Creatinine <1.5 mg/dL	HCV genotype other than type 1 Decompensated liver disease Liver disease of other etiology HBV or HIV co-infection Autoimmune disorder Clinically significant cardiovascular disease Organ grafts Systemic infections Clinically significant bleeding disorders Malignant neoplasm Concomitant immunosuppressive medication use Alcohol or drug abuse in the past year	467/459/455 /455	A vs. B: Age mean: 43 vs. 43 Female: 44% vs. 46% non White: 3% vs. 5%	A vs. B: Genotype 1: all Treatment-naïve: all Fibrosis stage 3-4: 7% vs. 9% HCV RNA (log IU/mL) mean: 5.8 vs. 5.8

Author, Year Country Study Name Quality	Duration of Followup	Outcome	Subgroup Analyses	Subgroup Analyses	Histologic Response	Adverse Events	Funding Source
Berg T, 2006[23] Germany Continued	Followup visits at 24 weeks after completion of treatment	A vs. B: SVR: 121/230 (53%) vs. 121/225 (54%); p=0.8	A vs. B: SVR: White: 115/222 (52%) vs. 115/213 (54%); p=NS non White: 6/8 (75%) vs. 6/12 (50%); p=NS Male: 73/128 (57%) vs. 66/122 (54%); p=NS Female: 48/102 (47%) vs. 55/103 (53%); p=NS	A vs. B: Genotype 1b: 75/155 (48%) vs. 66/132 (50%); p=NS Genotype 1a: 38/60 (63%) vs. 40/67 (60%); p=NS Genotype 1a/1b: 4/6 (67%) vs. 13/18 (72%); p=NS Fibrosis Stage 0-2: 117/214 (55%) vs. 116/205 (57%); p=NS Fibrosis Stage 3-4: 4/16 (25%) vs. 5/20 (25%); p=NS	NR	A vs. B: Overall withdrawals: 55/230 (24%) vs. 92/225 (41%); p<0.001 Withdrawals due to adverse events: 21/230 (9%) vs. 26/225 (12%); p=NS Serious adverse events: 15.6% vs. 11.1%; p=NS Deaths: NR	Roche

Author, Year Country Study Name Quality	Interferon Regimen	Ribavirin Regimen	Protease Inhibitor Regimen	Eligibility	Exclusion	Number Screened/ Eligible/ Enrolled/ Analyzed	Age Sex Race	Genotype Severity of Liver Disease Proportion Treatment-Naïve
Berg T, 2009[24] Germany Continued	A: Pegylated interferon alfa-2b 1.5 mcg/kg for a duration determined by the time required to achieve HCV-RNA negativity at weeks 3,4,5,6,7, or 8 (times a factor of 6) B: Pegylated interferon alfa-2b 1.5 mcg/kg for 48 weeks	A: 800-1400 mg daily for a duration determined by the time required to achieve HCV-RNA negativity at weeks 3,4,5,6,7, or 8 (times a factor of 6) B: 800-1400 mg daily for 48 weeks	None	Treatment-naïve Ages 18-70 years HCV genotype 1 infection Positive test for anti-HCV antibodies HCV-RNA >1000 IU/mL Increased ALT Liver biopsy within 24 months of enrollment confirming chronic hepatitis Neutrophils > 1500 Platelets >80K Hemoglobin >12 g/dL for females and >13 g/dL for males Creatinine <1.5 mg/dL	HCV genotype other than type 1 Decompensated liver disease HBV or HIV co-infection Liver disease of other causes Autoimmune disorder Concomitant immunosuppressive medication use Clinically significant bleeding disorders Clinically significant cardiac abnormalities Organ grafts Systemic infection Preexisting severe psychiatric condition Neoplastic disease Excessive alcohol intake Drug abuse in the past year Unwillingness to use contraception	438/433/433 /433	A vs. B: Age mean: 43 vs. 43 Female: 46% vs. 43% Non White: NR	A vs. B: Genotype 1: all Treatment-naïve: all Fibrosis stage 3-4: 15% vs. 13% HCV-RNA mean: 5.7 vs. 5.7

Author, Year Country Study Name Quality	Duration of Followup	Outcome	Subgroup Analyses	Subgroup Analyses	Histologic Response	Adverse Events	Funding Source
Berg, 2009[24] Germany Individualized treatment strategy according to early viral kinetics in hepatitis C virus type 1-infected patients Quality: Poor	Followup visits at 24 weeks after completion of treatment	A vs. B: SVR: 72/208 (35%) vs. 108/225 (48%); p=0.005	NR	NR	NR	A vs. B: Overall withdrawals: 63/208 (30.3%) vs. 71/225 (31.6%); p=NS Withdrawals for adverse events: 4 / 208 (1.9%) vs. 7/226 (3.1%); p=NS Serious adverse events: 5/208 (2.6%) vs. 14/225 (6.2%); p=NS Deaths: NR Other adverse events not reported	Schering-Plough

Author, Year Country Study Name Quality	Interferon Regimen	Ribavirin Regimen	Protease Inhibitor Regimen	Eligibility	Exclusion	Number Screened/ Eligible/ Enrolled/ Analyzed	Age Sex Race	Genotype Severity of Liver Disease Proportion Treatment-Naïve
Brandao, 2006[25] Brazil Continued	A: Pegylated interferon alfa-2a 180 mcg/week for 24 weeks B: Pegylated interferon alfa-2a 180 mcg/week for 48 weeks	A: 400 mg twice daily for 24 weeks B: 400 mg twice daily for 48 weeks	None	Treatment naïve Aged >18 years HCV RNA >1000 IU/mL ALT above upper limit of normal on two occasions within the last 6 months Liver biopsy in the last 18 month consistent with chronic hepatitis C	Treatment with systemic antivirals, antineoplastics, immunomodulators, or any other investigational drugs with perceived effect against HCV	NR/NR/63/63	A vs. B: Age mean: 41 vs. 41 Female: 41% vs. 39% Non white: 19% vs. 16%	A vs. B: Genotype 1: all HCV RNA >800,000 IU/mL: 72% v 61% Bridging fibrosis: 16% vs. 6%

Author, Year Country Study Name Quality	Duration of Followup	Outcome	Subgroup Analyses	Subgroup Analyses	Histologic Response	Adverse Events	Funding Source
Brandao, 2006[25] Brazil Continued	Followup visits at 24 weeks after completion of treatment	A vs. B: SVR: 6/32 (19%) vs. 15/31 (48%)	NR	A vs. B: Baseline HCV RNA <800K IU/mL: 3/9 (33%) vs. 7/12 (58%); p=NS Baseline HCV RNA >800K IU/mL: 3/23 (13%) vs. 8/19 (43%); p=NS Bridging fibrosis: 0/5 (0%) vs. 1/2 (50%); p=0.04 non bridging fibrosis: 6/27 (22%) vs. 14/29 (48%); p=0.04	NR	A vs. B: Overall withdrawals: 2/32 (6%) vs. 0/31 (0%); p=NS Withdrawals for adverse events: 2/32 (6.3 %) vs. 0/31 (0%); p=NS Serious adverse events: 3/32 (9.4%) vs. 1/31 (3.2%); p=NS Deaths: NR Headache: 14/32 (44%) vs. 16/31 (52%); p=NS Pyrexia: 13/32 (41%) vs. 16/31 (52%); p=NS Influenza-like illness 8/32 (25%) vs. 10/31 (32%); p=NS Neutropenia: 8/32 (25%) vs. 14/31 (45%); p=NS Myalgia: 7/32 (22%) vs. 14/31 (45%); p=0.05 Fatigue: 10/32 (31%) vs. 11/31 (36%); p=NS Asthenia: 7/32 (22%) vs. 13/31 (42%); p=NS Pruritus: 9/32 (28%) vs. 6/31 (19%); p=NS Irritability: 8/32 (25%) vs. 7/31 (23%); p=NS Thrombocytopenia: 3/32 (9%) vs. 7/31 (23%); p=NS Leukopenia: 4/32 (13%) vs. 6/31 (19%); p=NS Nausea: 6/32 (19%) vs. 9/31 (29%); p=NS Alopecia: 7/32 (22%) vs. 9/31 (29%); p=NS Diarrhea: 9/32 (28%) vs. 8/31 (26%); p=NS Arthralgia: 7/32 (22%) vs. 5/31 (16%); p=NS Depression: 5/32 (16%) vs. 5/31 (16%); p=NS Rigors: 3/32 (9%) vs. 6/31 (19%); p=NS Cough: 4/32 (13%) vs. 7/31 (23%); p=NS	Roche

Author, Year Country Study Name Quality	Interferon Regimen	Ribavirin Regimen	Protease Inhibitor Regimen	Eligibility	Exclusion	Number Screened/ Eligible/ Enrolled/ Analyzed	Age Sex Race	Genotype Severity of Liver Disease Proportion Treatment-Naïve
Buti, 2010[26] International Randomized trial of pegylated interferon alfa-2b and ribavirin for 48 or 72 weeks in patients with hepatitis C virus genotype 1 and slow virologic response Overall Quality: Fair	All patients were treated for 12 weeks. Patients with a 2 log drop in HCV RNA and undetectable HCV RNA at week 12 were continued until week 48 (group C). Subjects with a 2 log drop in HCV RNA at week 12 and detectable HCV RNA at 12 weeks were continued for another 12 weeks. Subjects with undetectable HCV RNA at week 24 (slow responders) were randomized to groups A or B A: Pegylated interferon alfa-2b 1.5 mcg/kg/week for 48 weeks B: Pegylated interferon alfa-2b 1.5 mcg/kg/week for 72 weeks Nonrandomized C: Pegylated interferon alfa-2b 1.5 mcg/kg/week for 48 weeks	All patients were treated for 12 weeks. Patients with a 2 log drop in HCV RNA and undetectable HCV RNA at week 12 were continued until week 48 (group C). Subjects with a 2 log drop in HCV RNA at week 12 and detectable HCV RNA at 12 weeks were continued for another 12 weeks. Subjects with undetectable HCV RNA at week 24 (slow responders) were randomized to groups A or B A: 800-1400 mg/day based on body weight for 48 weeks B: 800-1400 mg/day based on body weight for 72 weeks Nonrandomized C: 800-1400 mg/day based on body weight for 48 weeks	None	Treatment naïve Aged 18-70 years Compensated HCV with confirmed diagnosis of hepatitis by ALT and liver biopsy	Weight >125 kg HIV HBV Liver disease of other etiologies	NR/1427/159/159	A vs. B: Age mean: 45 vs. 47 Female: 40% vs. 37% Non white: 0% vs. 4.1%	A vs. B: Genotype 1: all HCV RNA>800,000: 87 vs. 93%

Author, Year Country Study Name Quality	Duration of Followup	Outcome	Subgroup Analyses	Subgroup Analyses	Histologic Response	Adverse Events	Funding Source

Author, Year Country Study Name Quality	Duration of Followup	Outcome	Subgroup Analyses	Subgroup Analyses	Histologic Response	Adverse Events	Funding Source
Buti, 2010[26] International Continued	Followup visits at 24 weeks after completion of treatment	A vs. B: SVR: 37/86 (43%) vs. 35/73 (47.9%); p=NS	NR	NR	NR	(A vs. B vs. C [only A and B randomized]): Overall withdrawals: 8/86 (9.3%) vs. 17/73 (23.3%) vs. 100/816 (12.3%); A vs. B p=NS Withdrawals for adverse events: 3/86 (3.5%) vs. 6/73 (8.2%) vs. 39/816 (5.0%); A vs. B p=NS Serious adverse events: 6/86 (7.0%) vs. 6/73 (8.2%) vs. 57/816 (7.0%); A vs. B p=NS Influenza-like illness: 36/86 (41.9%) vs. 34/73 (46.6%) vs. 347/816 (42.5%); A vs. B p=NS Fatigue: 24/86 (27.9%) vs. 18/73 (24.7%) vs. 202/816 (24.8%); A vs. B p=NS Myalgia: 22/86 (25.6%) vs. 12/73 (16.4%) vs. 162/816 (19.9%); A vs. B p=NS Pyrexia: 21/86 (24.4%) vs. 18/73 (24.7)% vs. 245/816 (30%); A vs. B p=NS Pruritus: 20/86 (23.3%) vs. 12/73 (16.4%) vs. 176/816 (21.6%); A vs. B p=NS Neutropenia: 18/86 (20.9%) vs. 16/73 (21.9%) vs. 175/816 (21.4%); A vs. B p=NS Nausea: 18/86 (20.9%) vs. 15/73 (20.5%) vs. 159/816 (19.5%); A vs. B p=NS	Schering-Plough (now Merck)

Author, Year Country Study Name Quality	Interferon Regimen	Ribavirin Regimen	Protease Inhibitor Regimen	Eligibility	Exclusion	Number Screened/ Eligible/ Enrolled/ Analyzed	Age Sex Race	Genotype Severity of Liver Disease Proportion Treatment-Naïve
Dalgard, 2008[27] Denmark, Sweden, Norway Pegylated interferon alpha and ribavirin for 12 vs. 24 weeks in patients with hepatitis C virus genotype 2 or 3 and rapid virological response Overall Quality: Fair	All patients were treated for 4 weeks. Subjects with rapid virologic response after 4 weeks were randomized to A. or B. Subjects without rapid virologic response were allocated to group C. A: Pegylated interferon alfa-2b 1.5 mcg/kg/week for 14 weeks B: Pegylated interferon alfa-2b 1.5 mcg/kg/week for 24 weeks C: Pegylated interferon alfa-2b 1.5 mcg/kg/week for 24 weeks	All patients were treated for 4 weeks. Subjects with rapid virologic response after 4 weeks were randomized to A or B. Subjects without rapid virologic response were allocated to group C. A: 800-1400 mg/day based on body weight for 14 weeks B: 800-1400 mg/day based on body weight for 24 weeks C: 800-1400 mg/day based on body weight for 24 weeks	None	Treatment naïve HCV RNA positive HCV genotype 2 or 3 Elevated ALT at least once during the prior 6 months	Injection drug use or alcohol abuse in the prior 6 months Poorly controlled psychiatric illnesses Decompensated cirrhosis HBV positive HIV positive Liver disease of other etiologies	NR/428/298/ 298	(A vs. B vs. C) Age median: 38 vs. 38 vs. 43 Female: 36% vs. 35% vs. 41% Non white: NR	(A vs. B vs. C) Genotype 2/3: all Proportion treatment-naïve: all Fibrosis: NR HCV RNA >400,000: 64% vs. 58% vs. 75% Cirrhosis: NR

Author, Year Country Study Name Quality	Duration of Followup	Outcome	Subgroup Analyses	Subgroup Analyses	Histologic Response	Adverse Events	Funding Source
Dalgard, 2008[27] Denmark, Sweden, Norway Continued	Up to 24 weeks after treatment completion (week 48)	(A vs. B vs. C): ETR: 136/148 (91.9%) vs. 144/150 (96.0%) vs. NR; A vs. B p=NS SVR: 120/148 (81.1%) vs. 136/150 (90.7%) vs. 69/126 (58.5%); A vs. B p=NS	A vs. B: SVR: Female: 47/52 (90%) vs. 49/53 (93%); p=NS Male: 73/87 (84%) vs. 87/93 (93%); p=NS Age < 40: 79/89 (89%) vs. 88/90 (98%); p=NS Age >40: 41/50 (82%) vs. 48/56 (86%); p=NS	A vs. B: HCV RNA >400K IU/ml: 77/88 (87%) vs. 75/85 (88%); p=NS HCV RNA <400K IU/ml: 35/42 (83%) vs. 55/55 (100%); p=NS Genotype 3: 93/110 (84%) vs. 106/115 (92%); p=NS Genotype 2: 27/29 (93%) vs. 30/31 (97%); p=NS	NR	A vs. B: Treatment discontinuations (<80% of prescribed injections): 9/148 (6%) vs. 32/150 (21%); p=0.02 Hemoglobin <10g/dL: 9/148 (6.1%) vs. 13/150 (8.7%); p=0.39 Neutrophils <700/mm3: 9/148 (6.1%) vs. 15/149 (10.1%); p=0.31 Depression: 29/110 (26.4%) vs. 37/124 (29.8%); p=0.56	Schering-Plough (now Merck)

Author, Year Country Study Name Quality	Interferon Regimen	Ribavirin Regimen	Protease Inhibitor Regimen	Eligibility	Exclusion	Number Screened/ Eligible/ Enrolled/ Analyzed	Age Sex Race	Genotype Severity of Liver Disease Proportion Treatment-Naïve
Ferenci, 2010[28] Austria Pegylated interferon alfa-2a and ribavirin for 24 weeks in hepatitis C type 1 and 4 patients with rapid virologic response Overall Quality: Poor	All patients were treated for 4 weeks. Subjects with rapid virologic response (HCV-RNA <50 IU/mL) were treated with 24 weeks. Subjects without rapid virologic response continued to week 12 and were re-evaluated. Subjects with early virologic response (HCV RNA <600 IU/mL or a 2 log decrease in serum HCV RNA) were randomized to complete either 48 weeks or 72 weeks of treatment. A: Pegylated interferon alfa-2a 180 mcg/week for 48 weeks B: Pegylated interferon alfa-2a 180 mcg/week for 72 weeks	A: 1000-1200 mg/day depending of body weight for 48 weeks B: 1000-1200 mg/day depending of body weight for 72 weeks	None	Treatment-naïve Ages 18-65 years Chronic HCV genotype 1 or 4 infection Positive HCV antibody test Quantifiable HCV RNA Elevated ALT Histologic findings consistent with chronic hepatitis C on liver biopsy within the previous 6 months Neutrophils >3000 Platelets >100K Hemoglobin > 12 g/dL in women and > 13 g/dL in men Serum creatinine <1.5 times the upper limit of normal Thyroid-stimulating hormone within normal limits	Chronic liver disease of other etiology Evidence of decompensation Co-infection with HBV or HIV Systematic immunomodulatory or antineoplastic therapy within previous 6 months Diabetes mellitus treated with insulin Severe psychiatric disorders History of immunologically mediated disease Other severe chronic or uncontrolled disease	NR/551/289/ 289	A vs. B: Age mean: 45 vs. 44 Female 36% vs. 35% non White: NR	A vs. B: Genotype 1: 91% vs. 89% Treatment-naïve: all HCV-RNA level >800K IU: 38% vs. 44% Fibrosis stage 3-4: 20% vs. 19%

Author, Year Country Study Name Quality	Duration of Followup	Outcome	Subgroup Analyses	Subgroup Analyses	Histologic Response	Adverse Events	Funding Source
Ferenci, 2010[28] Austria Continued	Followup visits at 24 weeks after completion of treatment	A vs. B: SVR: 71 / 139 (51.1%) vs. 88 / 150 (58.7%); p=NS	NR	A vs. B: Genotype 1: 65/127 (51.2%) vs. 81/134 (60.4%); p=NS Genotype 4: 6/12 (50.0%) vs. 7/16 (43.8%); p=NS Baseline HCV-RNA >400K IU/mL: 51/105 (48.6%) vs. 64/113 (56.6%); p=NS Baseline HCV-RNA<400K IU/mL: 20/34 (58.8%) vs. 24/37 (64.9%); p=NS Fibrosis F3-4: 18/32 (56.3) vs. 19/34 (55.9%); p=NS Fibrosis F0-2: 53/107 (49.5%) vs. 69/116 (59.5%); p=NS	NR	A vs. B: Overall withdrawals: 26/139 (18.7%) vs. 48 / 150 (32.0%); p<0.01 Withdrawals for adverse events: 7/139 (5.07%) vs. 8/150 (5.3%); p=NS Serious adverse events: 38 / 139 (27.3%) vs. 51 / 150 (34.0%); p=NS Deaths: NR Serious hematologic adverse event: 1 /139 (0.007%) vs. 2 / 150 (1.3%); p=NS Serious gastrointestinal adverse event: 5/139 (3.6%) vs. 2/150 (1.3%); p=NS Serious infectious adverse event: 2/139 (1.4%) vs. 8/150 (5.3%); p=NS Serious pulmonary adverse event; 3/139 (2.2%) vs. 5/150 (3.3%); p=NS Serious neuropsychiatric adverse event: 5/139(3.6%) vs. 4/150 (2.7%); p=NS Serious cardiovascular adverse event: 3/139 (2.2%) vs. 3/ 150 (2.0%); p=NS Serious skin adverse event: 1/139 (0.007%) vs. 1/150 (1.3%); p=NS	Roche

Author, Year Country Study Name Quality	Interferon Regimen	Ribavirin Regimen	Protease Inhibitor Regimen	Eligibility	Exclusion	Number Screened/ Eligible/ Enrolled/ Analyzed	Age Sex Race	Genotype Severity of Liver Disease Proportion Treatment-Naïve
Hadziyannis, 2004[29] Europe, North & South America, Australia, New Zealand, and Taiwan (99 centers world-wide) Peginterferon-α2a and Ribavirin Combination Therapy in Chronic Hepatitis C Overall Quality: Fair	A: Pegylated interferon alpha-2a 180 µg/week for 24 weeks B: Pegylated interferon alpha-2a 180 µg/week for 24 weeks C: Pegylated interferon alpha-2a 180 µg/week for 48 weeks D: Pegylated interferon alpha-2a 180 µg/week for 48 weeks	A: ("Low dose -24" or "24-LD") Ribavirin 800 mg/day for 24 weeks B: ("Standard dose-24" or "24-SD") Ribavirin 1000 mg/day for 24 weeks, (Body weight <75kg) or Ribavirin 1200 mg/day for 24 weeks, (Body weight >75kg) C: ("Low dose-48" or "48-LD") Ribavirin 800 mg/day for 48 weeks D: ("Standard dose-48" or "48-SD") Ribavirin 1000 mg/day for 48 weeks, (Body weight <75kg) or Ribavirin 1200 mg/day for 48 weeks, (Body weight >75kg)	None	Treatment naive adults with serum hepatitis C virus (Genotype) RNA concentration greater than 2000 copies/mL Elevated serum alanine aminotransferase(ALT) level documented on 2 or more occasions 14 days or more apart within the previous 6 months Compensated liver disease and a liver biopsy specimen consistent with chronic hepatitis C obtained in the previous 15 months Patients with compensated cirrhosis or transition to cirrhosis (Child–Pugh class A) Negative pregnancy test result 24 hours before the first dose of study medications	Neutropenia (neutrophil count <1.5 x109 cells/L) Thrombocytopenia (platelet count <90x109 cells/L) Anemia (hemoglobin level <120 g/L in women and <130 g/L in men) - or a medical condition that would be clinically significantly worsened by anemia Serum creatinine level more than 1.5 times the upper limit of normal Co-infection with hepatitis A or B virus or HIV History of bleeding from esophageal varices or other conditions consistent with Decompensated liver disease Organ transplant Severe or poorly controlled psychiatric disease (especially depression) malignant neoplastic disease Severe cardiac or chronic pulmonary disease Immunologically mediated disease (except controlled thyroid disease) Seizure disorder Severe retinopathy Alcohol or drug dependence within 1 year of study entry Clinically significant co morbid medical conditions Pregnancy or unwillingness to practice contraception	1736/1373/1311/1284	(A vs. B vs. C vs. D): Age (mean): 41 vs. 42 vs. 43 vs. 43 years Female: 32% vs. 34% vs. 27% vs. 34% Race: White - 88% vs. 91% vs. 87% vs. 90% Non White - 12% vs. 9% vs. 13% vs. 10%	(A vs. B vs. C vs. D) Genotype, n (%): Genotype 1 - 101/207(49%) vs. 118/280(42%) vs. 250/361(69%) vs. 271/436(62%) Genotype 2 - 39/207(19%) vs. 53/280(19%) vs. 46/361(13%) vs. 66/436(15%) Genotype 3 - 57/207(28%) vs. 91/280(33%) vs. 53/361(15%) vs. 87/436(20%) Other - 106/207(51%) vs. 162/280(58%) vs. 111/361(31%) vs. 165/436(38%) Histologic diagnosis using Ishak scores: Non cirrhotic - 163/207(79%) vs. 209/280(75%) vs. 270/361(75%) vs. 321/436(74%) Cirrhosis - 10/207(5%) vs. 20/280(7%) vs. 25/361(7%) vs. 35/436(8%)

Author, Year Country Study Name Quality	Interferon Regimen	Ribavirin Regimen	Protease Inhibitor Regimen	Eligibility	Exclusion	Number Screened/ Eligible/ Enrolled/ Analyzed	Age Sex Race	Genotype Severity of Liver Disease Proportion Treatment-Naïve
Hadziyannis, 2004[29] Europe, North & South America, Australia, New Zealand, and Taiwan (99 centers world-wide) Continued					Severe psychiatric disease was defined as treatment with an antidepressant medication or major tranquilizer for major depression or psychosis - for 3+ months /or period of disability due to psychiatric disease History of a suicide attempt/hospitalization			Bridging fibrosis - 34/207(16%) vs. 51/280(18%) vs. 66/361(18%) vs. 80/436(18%) 100% Treatment naive

Author, Year Country Study Name Quality	Duration of Followup	Outcome	Subgroup Analyses	Subgroup Analyses	Histologic Response	Adverse Events	Funding Source
Hadziyannis, 2004[29] Europe, North & South America, Australia, New Zealand, and Taiwan (99 centers world-wide) Peginterferon-α2a and Ribavirin Combination Therapy in Chronic Hepatitis C Overall Quality: Fair	Followup visits at 24 weeks post-treatment	(A vs. B vs. C vs. D): SVR: 112/207 (54%) vs. 177/280 (63%) vs. 180/361 (50%) vs. 259/436 (59%) A vs. C p=NS A vs. B p=0.04 B vs. D p<0.0001 C vs. D p=0.007	NR	(A vs. B vs. C vs. D): SVR: Genotype 1 - 29/101(29%) vs. 42/118(36%) vs. 41/250(16%) vs. 52/271(19%) Genotype 2/3 - 79/96(82%) vs. 117/144(81%) vs. 77/99(78%) vs. 113/153(74%) Bridging fibrosis or cirrhosis: 21/43 (49%) vs. 36/66 (55%) vs. 33/87 (38%) vs. 56/111 (50%) No Bridging fibrosis or cirrhosis: 89/154 (58%) vs. 130/196 (66%) vs. 146/262 (56%) vs. 210/313 (67%) HCV RNA>200: 63/117 (54%) vs. 93/148 (63%) vs. 116/260 (45%) vs. 163/294 (55%) HCV RNA<200: 49/90 (54%) vs. 84/132 (64%) vs. 64/101 (63%) vs. 96/142 (68%)	NR	(A vs. B vs. C vs. D): Pre-mature withdrawal: (for any reason): 14/207(7%) vs. 22/280(8%) vs. 117/361(32%) vs. 117/436(27%) (for AE/abnormal labs): 10/207(5%) vs. 13/280(5%) vs. 59/361(16%) vs. 67/436(15%) (insufficient response): 0/207(0%) 0/280(0%) vs. 31/361(9%) vs.24/436(6%) Deaths: vs. 0/207(0%) 0/280(0%) vs. 1/361(<1%) vs. 2/436(<1%) Severe Adverse Events: 46/207(22%) vs. 63/280(23%) vs. 116/361(32%) vs. 114/436(32%) Adverse events: Headache - 102/207(49%) vs. 136/280(49%) vs. 187/361(52%) vs. 239/436(55%) Fatigue - 98/207(47%) vs. 135/280(48%) vs. 182/361(50%) vs. 211/436(48%) Myalgia - 91/207(44%) vs. 120/280(43%) vs. 154/361(43%) vs. 163/436(37%) Pyrexia - 81/207(39%) vs. 114/280(41%) vs. 156/361(43%) vs. 173/436(40%) Insomnia - 69/207(33%) vs. 99/280(35%) vs. 146/361(40%) vs. 146/436(33%) Nausea - 64/207(31%) vs. 91/280(33%) vs. 107/361(30%) vs. 151/436(35%) Rigors - 64/207(31%) vs. 87/280(31%) vs. 87/361(24%) vs. 119/436(27%) Irritability - 59/207(29%) vs. 76/280(27%) vs. 96/361(27%) vs. 112/436(26%) Alopecia - 53/207(26%) vs. 74/280(265) vs. 106/361(29%) vs. 92/436(21%) Arthralgia - 50/207(24%) vs. 70/280(25%) vs. 106/361(29%) vs. 105/436(24%) Pruritus - 56/207(27%) vs. 60/280(21%) vs. 81/361(22%) vs. 111/436(25%) Depression - 43/207(21%) vs. 42/280(15%) vs. 79/361(22%) vs. 104/436(24%) Diarrhea - 44/207(21%) vs. 46/280(16%) vs. 65/361(18%) vs. 96/436(22%) Dermatitis - 34/207(16%) vs. 49/280(185) vs. 69/361(19) vs. 86/436(20%) Decreased appetite - 30/207(14%) vs. 41/280(15%) vs. 66/361(18%) vs. 91/436(21%)	Roche, Basel, Switzerland

Author, Year Country Study Name Quality	Interferon Regimen	Ribavirin Regimen	Protease Inhibitor Regimen	Eligibility	Exclusion	Number Screened/ Eligible/ Enrolled/ Analyzed	Age Sex Race	Genotype Severity of Liver Disease Proportion Treatment-Naïve
Ide, 2009 Japan[30] A Randomized Study of Extended Treatment with Pegylated interferon alpha-2b Plus Ribavirin Based on Time to HCV RNA Negative-status in Patients with Genotype 1b Chronic Hepatitis C Overall Quality: Fair	A: (Standard group - received a 48-week course of treatment) Pegylated interferon α-2b - 1.5 μg/kg/week for 48 weeks B: (Extended group – treatment course performed for 44 weeks after HCV RNA first became negative) Pegylated interferon α-2b - 1.5 μg/kg/week for 48-68 weeks	A: (Standard group - received a 48-week course of treatment) Ribavirin by body weight: < 60 kg - 600 mg/day for 48 weeks 60-80 kg - 800 mg/day for 48 weeks > 80 kg - 1000 mg/day for 48 weeks B: (Extended group – treatment course performed for 44 weeks after HCV RNA first became negative) Ribavirin by body weight: < 60 kg - 600 mg/day for 48-68 weeks 60-80 kg - 800 mg/day for 48-68 weeks > 80 kg - 1000 mg/day for 48-68 weeks	None	Male and female patients aged 20–75 years Compensated chronic HCV genotype 1b infection Positive for HCV RNA by a quantitative reverse-transcription PCR with a concentration >100K IU / ml At least one elevated serum alanine aminotransferase level at the time of screening or entry into the trial	Patients with an HCV genotype other than 1b infection Hepatitis B surface antigen Autoimmune hepatitis Primary biliary cirrhosis Sclerosing cholangitis Decompensated cirrhosis (Child – Pugh class B or C) Evidence of hepatocellular carcinoma Patients with platelet counts of < 8 × 10 4/mm3 , leukocyte counts of 2,500/ml or less, or hemoglobin levels of < 12 g/dl	NR/NR/113/ 113	A vs. B: Age (Mean): 55.3 vs. 54.6 years Female: 53.6% vs. 47.4% Non white: NR	A vs. B: Genotype 1b: 100% Fibrosis Stage (Desmet et al 1994): 1/2 - 67.8% vs. 52.6% 3/4 - 19.6% vs. 19.3% Treatment naïve: NR

Author, Year Country Study Name Quality	Duration of Followup	Outcome	Subgroup Analyses	Subgroup Analyses	Histologic Response	Adverse Events	Funding Source
Ide, 2009[30] Japan Continued	Followup visits at 24 weeks after completion of treatment	A vs. B: SVR: 20/56(36%) vs. 30/57(53%), p=0.07	NR	NR	NR	A vs. B: Overall withdrawals: 11/56 (20%) vs. 9/57 (16%); p=NS Withdrawal due to adverse event: 7/56 (13%) vs. 6/57 (11%); p=NS	Internal Funding

Author, Year Country Study Name Quality	Interferon Regimen	Ribavirin Regimen	Protease Inhibitor Regimen	Eligibility	Exclusion	Number Screened/ Eligible/ Enrolled/ Analyzed	Age Sex Race	Genotype Severity of Liver Disease Proportion Treatment-Naïve
Kamal, 2005[31] Egypt Pegylated interferon alpha-2b and ribavirin therapy in chronic hepatitis C genotype 4: impact of treatment duration and viral kinetics on sustained virological response Overall Quality: Fair	A: Pegylated interferon alfa-2b 1.5 µg/kg for 24 weeks B: Pegylated interferon alfa-2b 1.5 µg/kg for 36 weeks C: Pegylated interferon alfa-2b 1.5 µg/kg for 48 weeks	A: Ribavirin 10.6 mg/kg/day for 24 weeks B: Ribavirin 10.6 mg/kg/day for 36 weeks C: Ribavirin 10.6 mg/kg/day for 48 weeks	None	Documented chronic hepatitis C according to the following criteria: elevated serum alanine aminotransferase (ALT) above the upper limit of normal (40 U/l) on two occasions during the preceding six months Anti-HCV positive antibody status assessed by second generation enzyme linked immunosorbent assay Positive polymerase chain reaction for HCV RNA Genotype 4 Chronic hepatitis C in liver biopsy performed within the preceding year with no signs of cirrhosis or bridging fibrosis on pretreatment liver biopsy	Previous IFN-a therapy Other liver diseases such as hepatitis A, hepatitis B, schistosomiasis, autoimmune hepatitis, alcoholic liver disease, drug induced hepatitis, or decompensated liver disease Co infection with schistosomiasis or human immunodeficiency virus Neutropenia (1,500/mm3) Thrombocytopenia (90,000/mm3) Creatinine concentration >1.5 x the upper limit of normal Serum a fetoprotein concentration >25 ng/ml Organ transplant Neoplastic disease Severe cardiac or pulmonary disease Unstable thyroid dysfunction Psychiatric disorder Current pregnancy or breast feeding Therapy with immunomodulatory agents within the last six months	335/287/279 /271	(A vs. B vs. C): Age (Mean):42 vs. 44 vs. 41 Female:48 % vs. 47% vs. 48% Non white: NR	(A vs. B vs. C): Genotype 4: 100% (Ishak et al 1995) Inflammation grade (mean): 8.2 vs. 7.6 vs. 9.1 Fibrosis stage (mean): 1.8 vs. 2.3 vs. 2.1 HCVRNA mean: 2.8 vs. 2.7 vs. 2.8 Treatment naïve: 100%

Author, Year Country Study Name Quality	Duration of Followup	Outcome	Subgroup Analyses	Subgroup Analyses	Histologic Response	Adverse Events	Funding Source
Kamal, 2005[31] Egypt Continued	Followup visits at 48 weeks after completion of treatment	(A vs. B vs. C): ETR: 45/95(48%) vs. 65/96(68%) vs. 67/96(70%), p=0.04 (A and B); p=0.02 (A and C), p=0.4(B and C) SVR: 28/95 (29%) vs. 63/96 (66%) vs. 66/96 (69%), p=0.001 (A and B); p=0.001(A and C); p=0.5(B and C)	NR	NR	(A vs. B vs. C): All patients underwent liver biopsy before and after treatment. Pair wise comparison of histological grading and staging scores for the initial and followup biopsies showed no deterioration or progression of fibrosis in any patient and improvement (>2 point necro-inflammatory score improvement) was detected in 155 patients (54%):	(A vs. B vs. C): Deaths: NR Life-threatening Adverse Events: NR Severe Adverse Events: NR Overall Treatment Withdrawals: 3/95 (3%) vs. 5/96 (5%) vs. 5/96 (5%) Withdrawals due to Adverse Events: 1(2%) vs. 2(2%) vs. 4(4%) Neutropenia (<500/mm3) 1/95 (1%) vs. 1/96 (1%) vs. 3/96 (3%) Fatigue- 56/95(60%) vs. 59/96(64%) vs. 62/96(66%) Influenza-like illness- 53 (57%) vs. 58/96(63%) vs. 59/96(63%) Headache- 49/95(53%) vs. 52/96(57%) vs. 58/96(62%) Myalgia- 48/95(52%) vs. 52/96(57%) vs. 58/96(62%) Pyrexia- 41/95(44%) vs. 50/96(54%) vs. 53/96(62%) Insomnia- 31/95(33%) vs. 35/96(38%) vs. 46/96(49%) Injection site erythema - 28/95(30%) vs. 34/96(37%) vs. 39/96(42%) Irritability- 26/95(28%) vs. 33/96(36%) vs. 30/96(32%) Back pain- 23/95(25%) vs. 25/96(27%) vs. 29/96(31%) Rigors- 16/95(17%) vs. 17/96(18%) vs. 21/96(22%) Sore throat- 13/95(14%) vs. 16/96(17%) vs. 20/96(21%) Cough- 12/95(13%) vs. 15/96(16%) vs. 20/96(21%) Pruritus- 10/95(11%) vs. 15/96(16%) vs. 18/96(19%) Anorexia- 9/95(10%) vs. 14/96(15%) vs. 18/96(19%)	Fulbright Foundation Grants(NIAID (R2) AI054887) & the Alexander von Humboldt Foundation (Germany)

Author, Year Country Study Name Quality	Duration of Followup	Outcome	Subgroup Analyses	Subgroup Analyses	Histologic Response	Adverse Events	Funding Source
Kamal, 2005[31] Egypt Continued					Histological response was more likely in those who received longer treatment schedules as Histological improvement was detected in: (>2 point necro-inflammatory score improvement): 12/95(12.6%) vs. 67/96(69.8%) vs. 71/96 (73.9%)	Arthralgia- 8/95(9%) vs. 12/96(13%) vs. 17/96(18%) Dyspnea- 8/95(9%) vs. 11/96(12%) vs. 15/96(16%) Rash- 7/95(8%) vs. 10/96(11%) vs. 12/96(13%) Depression- 3/95(3%) vs. 3/96(3%) vs. 9/96(9%) Dry mouth- 5/95(5%) vs. 7/96(8%) vs. 8/96(9%) Alopecia- 4/95(4%) vs. 6/96(7%) vs. 7/96(7%) Nausea- 4/95(4%) vs. 4/96(4%) vs. 7/96(7%) Dizziness- 3/95(3%) vs. 5/96(5%) vs. 6/96(6%) Abdominal pain- 3/95(3%) vs. 5/96(5%) vs. 7/96(7%) Dry skin- 2/95(2%) vs. 6/96(7%) vs. 7/96(7%) Diarrhea- 2/95(2%) vs. 6/96(7%) vs. 8/96(9%) Vomiting- 1/95(2%) vs. 3/96(3%) vs. 5/96(5%)	

Author, Year Country Study Name Quality	Interferon Regimen	Ribavirin Regimen	Protease Inhibitor Regimen	Eligibility	Exclusion	Number Screened/ Eligible/ Enrolled/ Analyzed	Age Sex Race	Genotype Severity of Liver Disease Proportion Treatment-Naïve
Lagging, 2008[32] Denmark & Finland Randomized Comparison of 12 or 24 Weeks of Pegylated interferon alpha-2a and Ribavirin in Chronic Hepatitis C Virus Genotype 2/3 Infection Overall Quality: Fair	A: Pegylated interferon alfa-2a 180 µg/week for 12 weeks B: Pegylated interferon alfa-2a 180 µg/week for 24 weeks	A: Ribavirin 800 mg/day (2 equal doses) for 12 weeks B: Ribavirin 800 mg/day (2 equal doses) for 24 weeks	None	Adults age 18 years and older Compensated liver disease Treatment-naive for hepatitis C Seronegative for hepatitis B surface antigen and for antibodies to human immunodeficiency virus Positive test for anti-HCV antibody Infection with HCV genotypes 2 and/or 3 but not genotypes 1, 4, 5, or 6 HCV-RNA 600 IU/mL within 6months of treatment initiation Liver biopsy consistent with chronic hepatitis C within 24 months of entry	NR	392/382/382/382	A vs. B: Age (Mean): 42 vs. 42 years Female: 37% vs. 44% Non white: NR	A vs. B: Genotype 2: 28% vs. 26% Genotype 3: 71% vs. 74% Bridging fibrosis (Ishak stage 3-4): 39% vs. 40% Cirrhosis (Ishak stage 5-6): 13% vs. 13% Steatosis present (grade 1-3): 64% vs., 69% Moderate or severe steatosis (grade 2-3): 29% vs. 27% Treatment naive: 100%

Author, Year Country Study Name Quality	Duration of Followup	Outcome	Subgroup Analyses	Subgroup Analyses	Histologic Response	Adverse Events	Funding Source
Lagging, 2008[32] Denmark & Finland Continued	Followup visits at 24 weeks after completion of treatment	A vs. B: SVR: 114/194 (59%) vs. 147/188 (78%); p<0.0001	A vs. B: SVR: Age <40: 61/76 (80%) vs. 63/76 (83%);p=NS Age >40: 53/118 (45%0 vs. 84/112 (84%); p<0.0001	A vs. B: No significant fibrosis - 59/85(69%) vs. 69/83(84%); p=0.022 Bridging fibrosis - 36/70(51%) vs. 53/70(76%); p=0.0051 Cirrhosis - 19/23(84%) vs. 13/23(57%); p=NS Genotype 2: 31/55 (56%) vs. 40/49 (82%); p=0.0057 Genotype 3: 79/137 (58%) vs. 108/139 (78%); p=0.0015	NR	A vs. B: Deaths: NR Life-threatening Adverse Events: NR Severe Adverse Events: NR Withdrawals: 12/194 (6%) vs. 46/188 (24%); p<0.001 Withdrawals due to adverse events: 2/194(1%) vs. 20/188 (11%); P=0.0001	Swedish Society of Medicine, Swedish Medical Council, Swedish Society of Microbiology, Avtal om lakarutbildn-ing och forskning (ALF) Funds, and Roche affiliates (Nordic region)

Author, Year Country Study Name Quality	Duration of Followup	Outcome	Subgroup Analyses	Subgroup Analyses	Histologic Response	Adverse Events	Funding Source
Lagging, 2008[32] Denmark & Finland **Continued**	Followup visits at 24 weeks after completion of treatment	A vs. B: SVR: 114/194 (59%) vs. 147/188 (78%); p<0.0001	A vs. B: SVR: Age <40: 61/76 (80%) vs. 63/76 (83%);p=NS Age >40: 53/118 (45%0 vs. 84/112 (84%); p<0.0001	A vs. B: No significant fibrosis - 59/85(69%) vs. 69/83(84%); p=0.022 Bridging fibrosis - 36/70(51%) vs. 53/70(76%); p=0.0051 Cirrhosis - 19/23(84%) vs. 13/23(57%); p=NS Genotype 2: 31/55 (56%) vs. 40/49 (82%); p=0.0057 Genotype 3: 79/137 (58%) vs. 108/139 (78%); p=0.0015	NR	A vs. B: Deaths: NR Life-threatening Adverse Events: NR Severe Adverse Events: NR Withdrawals: 12/194 (6%) vs. 46/188 (24%); p<0.001 Withdrawals due to adverse events: 2/194(1%) vs. 20/188 (11%); P=0.0001	Swedish Society of Medicine, Swedish Medical Council, Swedish Society of Microbiology, Avtal om lakarutbildn-ing och forskning (ALF) Funds, and Roche affiliates (Nordic region)

Author, Year Country Study Name Quality	Interferon Regimen	Ribavirin Regimen	Protease Inhibitor Regimen	Eligibility	Exclusion	Number Screened/ Eligible/ Enrolled/ Analyzed	Age Sex Race	Genotype Severity of Liver Disease Proportion Treatment-Naïve
Liu, 2008[34] Taiwan Pegylated Interferon-alpha-2a plus Ribavirin for Treatment-Naïve Asian Patients with Hepatitis C Virus Genotype 1 Infection: A Multicenter Randomized Controlled Trial Overall Quality: Fair	A: Pegylated interferon alfa-2a 180 µg/week for 24 weeks B: Pegylated interferon alfa-2a 180 µg/week for 48 weeks	A: (24-week group) Ribavirin by body weight: < 75 kg - 1000 mg/day for 24 weeks > 75 kg - 1200 mg/day for 24 weeks B: (48-week group) Ribavirin by body weight: < 75 kg - 1000 mg/day for 48 weeks > 75 kg - 1200 mg/day for 48 weeks	None	Treatment-naive patients with chronic hepatitis C Aged >18 years Presence of anti-HCV antibody Detectable serum HCV RNA level determined by real-time RT-PCR analysis for 16 months HCV-1 infection confirmed by a reverse hybridization assay Serum alanine aminotransferase (ALT) level > upper limit of normal Liver histologic characteristics consistent with chronic viral hepatitis within the previous 3 months	Anemia (hemoglobin level,<13 g/dL for men and <12 g/dL for women) Neutropenia (neutrophil count, <1500 cells/mm3) Thrombocytopenia (platelet count, <70,000 cells/mm3) Mixed infection with HCV-1 and another genotype of HCV Co infection with hepatitis B virus or HIV Chronic alcohol abuse (daily alcohol consumption, 120 g/day) Decompensated cirrhosis (Child-Pugh class B or C) Serum creatinine level 11.5x the upper limit of normal Autoimmune liver disease Neoplastic disease Organ transplantation or immunosuppressive therapy Evidence of drug abuse Pregnancy Poorly controlled autoimmune disease Cardiopulmonary disease Neuropsychiatric disorders Diabetes mellitus with retinopathy Unwillingness to receive contraception during the study period	768/326/308 /308	A vs. B: Age (Mean): 54 vs. 53 years Female: 42.9% vs. 43.5% Non white: NR	A vs. B: Genotype 1a: 2.6% vs. 1.9% Genotype 1b: 92.9% vs. 94.2% Genotype 1a & 1b: 4.5% vs. 3.9% Fibrosis (Ishak 1995)-> 3: 78.6% vs. 76.0% 6: 22.7% vs. 20.1% Steatosis-present: 44.2% vs. 41.6% absent: 55.8% vs. 58.4% Treatment naïve: 100%

Author, Year Country Study Name Quality	Duration of Followup	Outcome	Subgroup Analyses	Subgroup Analyses	Histologic Response	Adverse Events	Funding Source
Liu, 2008[34] Taiwan Continued	Followup visits at 24 weeks after completion of treatment	A vs. B: SVR: 49/87(56%) vs. 89/117(76%), P<.001	NR	NR	Histological Response: 42/71(59%) vs. 76/97(78%), p=0.001 ALT normalization: 38/75(51%) vs. 77/107(72%), p<0.001	A vs. B: Overall withdrawals: 7/154 (5%) vs. 4/154 (3%); p=NS Withdrawal due to adverse events: 6/154(4%) vs. 4/154 (3%) p=NS Dose reduction due to Adverse Events: 69/154(45%) 82/154(53%) p=NS Deaths: 0/154(0%) vs. 1/154(<1%); p=NS Serious Adverse Event: 4/154(2%) vs. 11/154(7%); p=NS Adverse Events: Fever - 35/154(23%) vs. 33/154(21%); p=NS Rigor - 19/154 (12%) vs. 13/154(8%); p=NS Fatigue - 88/154 (57%) vs. 100/154(65%); p=NS Headache - 28/154 (18%) vs. 35/154(23%); p=NS Myalgia - 40/154(26%) vs. 36/154(23%); p=NS Arthralgia - 8/154(5%) vs. 13/154(8%); p=NS Insomnia - 61/154(40%) vs. 69/154(45%); p=NS Irritability - 19/154(12%) vs. 22/154(14%); p=NS Depression - 36/154(23%) vs. 26/154(17%); p=NS Anorexia - 63/154(41%) vs. 80/154(52%); p=NS Constipation - 10/154(6%) vs. 15/154(10%); p=NS Diarrhea - 14/154(9%) vs. 18/154(12%); p=NS Body weight loss - 29/154(19%) vs. 46/154(30%); p=0.02 Hair loss/alopecia - 24/154(16%) vs. 36/154(23%); p=NS	National Taiwan University Hospital, National Science Council, and Department of Health, Executive Yuan, Taiwan

Author, Year Country Study Name Quality	Duration of Followup	Outcome	Subgroup Analyses	Subgroup Analyses	Histologic Response	Adverse Events	Funding Source
Liu, 2008[34] Taiwan Continued						Aphthous ulcer - 22/154(14%) vs. 34/154(22%); p=NS Cough - 28/154(18%) vs. 32/154(21%); p=NS Nasal congestion - 13/154(8%) vs. 17/154(11%); p=NS Tinnitus - 13/154(8%) vs. 20/154(13%); p=NS Dermatitis - 44/154(29%) vs. 48/154(31%); p=NS Injection reaction - 22/154(14%) vs. 29/154(19%); p=NS Anemia - 60/154(39%) vs. 68/154(44%); p=NS Neutropenia - 34/154(22%) vs. 42/154(27%); p=NS Thrombocytopenia - 25/154(16%) vs. 23/154(15%); p=NS	

Author, Year Country Study Name Quality	Interferon Regimen	Ribavirin Regimen	Protease Inhibitor Regimen	Eligibility	Exclusion	Number Screened/ Eligible/ Enrolled/ Analyzed	Age Sex Race	Genotype Severity of Liver Disease Proportion Treatment-Naïve
Mangia, 2005[35] Italy Pegylated interferon alfa-2b and Ribavirin for 12 vs. 24 Weeks in HCV Genotype 2 or 3 Overall Quality: Fair	A: Pegylated interferon alfa-2b 1.0 µg/kg/week for 24 weeks (control standard duration group) B: Pegylated interferon alfa-2b 1.0 µg/kg/week for 12 or 24 weeks depending on if HCV RNA at week 4 (variable duration group)	A: (control standard duration group) Ribavirin by body weight: < 75 kg - 1000 mg/day for 24 weeks > 75 kg - 1200 mg/day for 24 weeks B: (variable duration group) Ribavirin by body weight: < 75 kg - 1000 mg/day for 48 weeks > 75 kg - 1200 mg/day for 48 weeks	None	18 to 70 years of age Presence of antibodies to HCV Infection with genotype 2 or 3 Abnormal alanine aminotransferase levels Treatment naïve	Leukocyte count < 3000/cubic millimeter Platelet count < 80,000/cubic millimeter Hemoglobin level <12 g/deciliter for women and <13 g/deciliter for men Infection with the human Immunodeficiency virus (HIV) Alcohol intake > 20 g daily Presence of drug abuse Presence of Chronic disease Presence of Psychiatric disease Presence of Autoimmune disease Presence of Pregnancy and lactation	NR/NR/283/ 283	A vs. B: Age (Mean): 49.7 vs. 46.6 years Female: 44% vs. 44% Non white: NR	A vs. B: Genotype 2: 76% vs. 75% Genotype 3: 24% vs. 25% HCV-RNA (>800,00 IU/mL): 66% vs. 64% Liver fibrosis (Scheuer 1991): stage > 3 - 23% vs. 16% Steatosis: (moderate/severe) - 36% vs. 31% Treatment naïve: 100%

Author, Year Country Study Name Quality	Duration of Followup	Outcome	Subgroup Analyses	Subgroup Analyses	Histologic Response	Adverse Events	Funding Source
Mangia, 2005[35] Italy Continued	Followup visits at 24 weeks after completion of treatment	A vs. B: SVR: 53/70(76%) vs. 164/213(77%)	NR	A vs. B: SVR: Genotype 2: 40/53 (75%) vs. 131/160 (82%); p=NS Genotype 3: 13/17 (76%) vs. 33/53 (62%); p=NS	NR	A vs. B: Withdrawals: 4/70 (6%) vs. 5/213 (2.3%); p=NS Withdrawals due to adverse events: NR Deaths: NR Serious adverse events: NR	Italian branch of Schering-Plough

Author, Year Country Study Name Quality	Interferon Regimen	Ribavirin Regimen	Protease Inhibitor Regimen	Eligibility	Exclusion	Number Screened/ Eligible/ Enrolled/ Analyzed	Age Sex Race	Genotype Severity of Liver Disease Proportion Treatment-Naïve
Manns 2011[36] International Reduced dose and duration of peginterferon alfa-2b and weight-based ribavirin in patients with genotype 2 and 3 chronic hepatitis C Overall Quality: Fair	A: Pegylated interferon alfa-2b - 1.5 lg/kg/ Wk for 24 weeks B: (reduced-dose treatment) Pegylated interferon alfa-2b - 1.0 lg/kg/wk for 24 weeks C: (reduced-duration treatment) Pegylated interferon alfa-2b - 1.5 lg/kg/wk for 24 weeks	A: Ribavirin (weight-based) - 800–1200 mg/ day for 24 weeks: <65 kg – 800 mg/day 65–85 kg – 1000 mg/day >85 kg – 1200 mg/day B: Ribavirin (weight-based) - 800–1200 mg/ day for 24 weeks: <65 kg – 800 mg/day 65–85 kg – 1000 mg/day >85 kg – 1200 mg/day C: Ribavirin (weight-based) - 800–1200 mg/ day for 16 weeks: <65 kg – 800 mg/day 65–85 kg – 1000 mg/day >85 kg – 1200 mg/day	None	Patients who had CHC G2 or G3 infection and were treatment naive. All patients had detectable hepatitis C virus (HCV) RNA, abnormal alanine aminotransferase, and compensated liver disease, and were eligible for treatment according to current consensus guidelines [10,11]. Patients were required to have hemoglobin levels P11 g/dl (women) or P12 g/dl (men), platelet count P100,000 cells/ mm3, neutrophil count P1500 cells/mm3, and thyroid stimulating hormone levels within normal limits	Patients with human immunodeficiency virus (HIV) or hepatitis B coinfection, creatinine clearance <50 ml/min, cause of liver disease other than CHC, evidence of advanced liver disease, preexisting psychiatric conditions or history of severe psychiatric disorder. Patients with a history of substance abuse were required to have remained abstinent for 6 months prior to study entry and patients receiving buprenorphine were required to have been stable for 6 months	NR/696/696/ 602	A vs. B vs. C: Age (Mean): 38.8 vs. 39.9 vs. 39.7 years Female: 39.6% vs. 34.8% vs. 35.1% Race: NR	A vs. B: Genotype 2: 16.5% vs. 21.9% vs. 21.1% Genotype 3: 83.5% vs. 78.1% vs. 78.9% HCV-RNA (>600,00 IU/mL): 51.7% vs. 53.6% vs. 53.9% (<600,00 IU/mL): 47.4% vs. 46% vs. 45.2% Treatment naïve: 100%

Author, Year Country Study Name Quality	Duration of Followup	Outcome	Subgroup Analyses	Subgroup Analyses	Histologic Response	Adverse Events	Funding Source
Manns 2011[36] International Continued	24 weeks after end of treatment	A vs. B vs. C: SVR (Hep-Net + International cohort): 153/230(66.5%) vs. 144/224(64.3%) vs. 129/228(56.6%), p=0.495	A vs. B vs. C: SVR: HCV RNA: ≥600,000 IU/ml – 77/109(70.6%) vs. 70/103(68%) vs. 59/103(57.3%) <600,000 IU/ml – 75/119(63%) vs. 74/120(61.7%) vs. 69/123(56.1%)	A vs. B vs. C: SVR: Genotype 2 – (Hep-Net cohort, n=84): 21/27(77.8% vs. 19/314(61.3%) vs. 14/26(53.8%) (International cohort n=51): 8/11(72.7%) vs. 12/18(66.7%) vs. 16/22(72.7%) Genotype 3 – (Hep-Net cohort, n=263): 47/89(52.8%) vs 50/84(59.5%) vs. 41/90(45.6%) (International cohort n=284): 77/103(74.8%) vs. 63/91(69.2%) vs. 58/90(64.4%)	NR	A vs. B vs. C: Deaths - <1% vs. <1% vs. 0% AE leading to interruption, reduction, or increase 15.7% vs. 4.9% vs. 12.3% AE leading to discontinuation 1.3% vs. 1.3% vs. 2.2% Pyrexia-37.8% vs. 37.1% vs. 44.3% Fatigue-22.6% vs. 22.3% vs. 15.8% Headache-22.6% vs. 25.4% vs. 25.4% Alopecia-20.9% vs. 16.1% vs. 13.6% Asthenia-19.1% vs. 27.7% vs. 19.7% Myalgia-15.2% vs. 12.1% vs. 14.9% Influenza-like illness- 12.6% vs. 9.4% vs. 10.1% Pruritus-12.6% vs. 19.6% vs. 10.1% Weight-decrease-12.6% vs. 10.7% vs. 13.6% Anorexia-12.2% vs. 4.9% vs. 9.6% Nausea-11.7% vs. 11.6% vs. 14.0% Injection-site erythema-11.3% vs. 13.8% vs. 7.5% Depressed mood-11.3% vs. 7.1% vs. 8.3% Arthralgia-10.9% vs. 7.6% vs. 10.5% Anemia-10.0% vs. 4.9% vs. 11.0% Diarrhea-9.6% vs. 12.1% vs. 7.0% Dry skin-5.7% vs. 11.2% vs. 6.6% Treatment-emergent SAE-6.1% vs. 4.9% vs. 3.1% Treatment-emergent-7.0% vs. 4.5% vs. 5.3%	Schering-Plough (now Merck)

Author, Year Country Study Name Quality	Interferon Regimen	Ribavirin Regimen	Protease Inhibitor Regimen	Eligibility	Exclusion	Number Screened/ Eligible/ Enrolled/ Analyzed	Age Sex Race	Genotype Severity of Liver Disease Proportion Treatment-Naïve
Mecenate, 2010[37] Italy Short vs. standard treatment with pegylated interferon alfa-2A plus ribavirin in patients with hepatitis C virus genotype 2 or 3: the CLEO trial Overall Quality: Fair	Patients with negative HCV RNA at week 4 randomized to either 12 or 24 weeks of treatment A1: Pegylated interferon alpha-2a 180 µg/week for 12 weeks A2: Pegylated interferon alpha-2a 180 µg/week for 24 weeks B: Pegylated interferon alpha-2a 180 µg/week for 24 weeks (nonrandomized arm of patient without rapid virologic response)	Patients with negative HCV RNA at week 4 randomized to either 12 or 24 weeks A1: Ribavirin 800-1200 mg daily for 12 weeks A2: Ribavirin 800-1200 mg daily for 24 weeks B: Ribavirin 800-1200 mg daily for 24 weeks (nonrandomized arm of patient without rapid virologic response)	None	HCV-RNA positive HCV genotype 2 or 3 Elevated alanine aminotransferase (>40 UI/L) at least 8 months prior to study entry Histologically proven chronic HCV hepatitis	History of injected drugs or alcohol abuse (>40 g ethanol/day) within the 6 months prior to study entry Poorly controlled psychiatric illness Decompensated cirrhosis Positive for human immunodeficiency antibody virus (HIV) or positive for hepatitis B surface antigen (HBV) Pregnancy Lactation Impaired renal function Other concurrent medical conditions of the liver different from HCV infection	NR/210/143/ 143	(All groups - not broken down by arm) Age (Mean): 43 years Female: 19% Non white: NR	(All groups - not broken down by arm) Genotype 2: 55% Genotype 3: 45% Cirrhosis (Ishak stage 5-6): 10% Bridging fibrosis (Ishak stage 3-4): 19% Treatment naïve: NR

Author, Year Country Study Name Quality	Duration of Followup	Outcome	Subgroup Analyses	Subgroup Analyses	Histologic Response	Adverse Events	Funding Source
Mecenate, 2010[37] Italy Continued	Followup visits at 24 weeks after completion of treatment	(A1 vs. A2): SVR: 60/72(83%) vs. 53/71(75%) p=NS	NR	(A1 vs. A2): SVR: Genotype 2: 32/60(53%) vs. 31/53(50%); p=NS Genotype 3: 28/60(47%) vs. 22/53(42%); p=NS	NR	(A1 vs. A2): Withdrawals: 0/72 (0%) vs. 5/71 (7%) Discontinuation due to Adverse Events - 0/72(0%) vs. 5/71(7%) Deaths: NR Life-threatening Adverse Events: NR Serious Adverse Events: NR Adverse events: Anemia: 5/72(7%) vs. 6/71(8%); p=NS Neutropenia: 2/72(3%) vs. 1/71(1%); p=NS Depression: 2/72(3%) vs. 2/71(3%); p=NS Cutaneous rash: 0/72(0%) vs. 0/71(0%); p=NS Alopecia: 0/72(0%) vs. 1/71(1%); p=NS Fatigue: 2/72(3%) vs. 4/71(5%); p=NS	NR

Author, Year Country Study Name Quality	Interferon Regimen	Ribavirin Regimen	Protease Inhibitor Regimen	Eligibility	Exclusion	Number Screened/ Eligible/ Enrolled/ Analyzed	Age Sex Race	Genotype Severity of Liver Disease Proportion Treatment-Naïve
Pearlman, 2007[38] Atlanta, GA - USA Treatment Extension of 72 Weeks of Pegylated interferon and Ribavirin in Hepatitis C Genotype 1-Infected Slow Responders Overall Quality: Fair	A: (Standard) Pegylated interferon α-2b - 1.5 µg/kg/week for 48 weeks B: (Extended) Pegylated interferon α-2b - 1.5 µg/kg/week for 72 weeks	A: (Standard) Ribavirin by body weight: < 64 kg - 800 mg/day for 48 weeks 65 - 84 kg - 1000 mg/day for 48 weeks 85 - 104 kg - 1200 mg/day for 48 weeks >105 kg - 1400 mg/day for 48 weeks B: (Extended) Ribavirin by body weight: < 64 kg - 800 mg/day for 72 weeks 65 - 84 kg - 1000 mg/day for 72 weeks 85 - 104 kg - 1200 mg/day for 72 weeks >105 kg - 1400 mg/day for 72 weeks	None	Chronic HCV genotype 1–infected patients Baseline elevated serum alanine aminotransferase levels Detectable serum HCV-RNA via nucleic acid testing Treatment-naive Age >18 years Liver biopsy in the past 2 years consistent with chronic hepatitis	HCV/human immunodeficiency virus co infection HCV genotype other than 1 Decompensated cirrhosis Other causes of liver disease, including co infection with hepatitis B Creatinine clearance <50 mL/minute (modification of diet in renal disease equation) Platelet count <80x109/L Neutrophil count <1.5x109/L Hemoglobin concentration 13 g/dL and 12 g/dL in men and women Co-existing uncontrolled psychiatric or cardiopulmonary disorders Hemoglobinopathy Sarcoidosis Malignant neoplasm Receipt of immunosuppressive or immunomodulatory therapy in the previous 6 months Pregnancy Men whose partners were pregnant or unwilling to use contraception during the study period Patients were also excluded if they imbibed significant amounts of alcohol (30 g/day) Active substance abusers in the past 6 months	NR/112/101/ 101	A vs. B: Age (Mean): 56 vs. 54 years Female: 33% vs. 35% Non white: 47% vs. 48%	A vs. B: Genotype 1: 100% Fibrosis (METAVIR) F3/F4 - 27% vs. 25%, p=0.86 Treatment-naïve: 100%

Author, Year Country Study Name Quality	Duration of Followup	Outcome	Subgroup Analyses	Subgroup Analyses	Histologic Response	Adverse Events	Funding Source
Pearlman, 2007[38] Atlanta, GA - USA Continued	Followup visits at 24 weeks after completion of treatment	A vs. B: SVR: 9/49 (18%) vs. 20/52 (38%), p=0.03	A vs. B: SVR: African Americans: 12% vs. 21%, p=0.02	NR	NR	A vs. B: Overall withdrawals: 7/49(14%) vs. 8/52(15%); p=NS Withdrawals due to adverse events: 6/49(12%) vs. 5/52(10%); p=NS Deaths: NR Life-threatening Adverse Events: NR Serious Adverse Events: NR Dose Reduction due to Adverse Event: (Week 1 -19) - 14/49(29%) vs. 15/52(29%); p=NS (Week 24-48) - 4/49(8%) vs. 2/52(4%); p=NS Discontinuation due to Adverse Event: (Week 24-48) - 7/49(14%) vs. 8/52(15%); p=NS	NR

Author, Year Country Study Name Quality	Interferon Regimen	Ribavirin Regimen	Protease Inhibitor Regimen	Eligibility	Exclusion	Number Screened/ Eligible/ Enrolled/ Analyzed	Age Sex Race	Genotype Severity of Liver Disease Proportion Treatment-Naïve
Sanchez-Tapias, 2006[39] Spain Peginterferon-Alfa2a Plus Ribavirin for 48 Vs. 72 weeks in Patients with Detectable Hepatitis C Virus RNA at Week 4 of Treatment Overall Quality: Fair	Patients with positive HCV RNA at week 4 randomized to 48 or 72 weeks A: (Total treatment duration, 48 weeks) Pegylated interferon-alfa-2a 180 µg/week for 48 weeks B: (Total treatment duration, 72 weeks) Pegylated interferon-alfa-2a 180 µg/week for 72 weeks Arms C and D not randomized (24 or 48 by genotype) C: (Total treatment duration, 24 weeks: RVR at week 4 and HCV-RNA levels <800,000 IU/mL) Pegylated interferon-alfa-2a 180 µg/week for 24 weeks D: (Total treatment duration, 48 weeks: Genotype 1/4 , RVR at week 4 and HCV-RNA levels >800,000 IU/mL) Pegylated interferon-alfa-2a 180 µg/week for 48 weeks	Patients with positive HCV RNA at week 4 randomized to 48 or 72 weeks A: (Total treatment duration, 48 weeks) Ribavirin 800 mg/day for 48 weeks B: (Total treatment duration, 72 weeks) Ribavirin 800 mg/day for 72 weeks Arms C and D not randomized (24 or 48 by genotype) C: (Total treatment duration, 24 weeks: RVR at week 4 and HCV-RNA levels <800,000 IU/mL) Ribavirin 800 mg/day for 24 weeks D: (Total treatment duration, 48 weeks: Genotype 1/4 , RVR at week 4 and HCV-RNA levels >800,000 IU/mL) Ribavirin 800 mg/day for 48 weeks	None	Treatment-naive patients with CHC consecutively referred to 28 specialist hepatology centers in Spain Older than 18 years Persistent increase of serum alanine transaminase levels during the past 6 months Positive anti-HCV antibody test Serum HCV-RNA concentration greater than 600 IU/mL Histologic evidence of chronic hepatitis in a liver biopsy specimen obtained within the preceding 24 months Written informed consent to participate in the study All participants had to use 2 forms of effective contraception during treatment and throughout the 24-week followup phase of the study	Decompensated liver disease Co-existing serious medical or psychiatric illness Liver disease other than that caused by HCV infection Neutrophil count less than 1.5 x109/L Platelet count less than 90x109/L Hemoglobin concentration less than 12 g/dL in women or less than 13 g/dL in men Serum creatinine level greater than 1.5 times the upper limit of the normal range Presence of co-infection with hepatitis A virus Hepatitis B virus or human immunodeficiency virus (HIV) Patients who received any systemic antiviral, antineoplastic, or immunomodulatory therapy within 6 months before the study Pregnant and breast-feeding women and male partners of pregnant women	NR/NR/522/ 522 Randomized population: 326/326	(A vs. B vs. C vs. D): Age (Mean): 42.8 vs. 43.2 vs. 39.3 vs. 42.4 years Female: 21% vs. 27% vs. 30% vs. 44% Non white: NR	(A vs. B vs. C vs. D): Genotype 1: 90.3% vs. 88.2% vs. 30.4% vs. 97% Genotype 2: .6% vs. .6% vs. 12.2% vs. 0% Genotype 3: 4% vs. 5% vs. 50.7% vs. 0% Genotype 4: 5% vs. 5% vs. 6.8% vs. 3% Other (not-typeable): 0% vs. 1.2% vs. 0% vs. 0% HCV-RNA>800,00 IU/mL (Mean): 963 vs. 1110 vs. 648 vs. 1612 Treatment naive: 100%

Author, Year Country Study Name Quality	Duration of Followup	Outcome	Subgroup Analyses	Subgroup Analyses	Histologic Response	Adverse Events	Funding Source
Sanchez-Tapias, 2006[39] Spain Continued	Followup visits at 24 weeks after completion of treatment	A vs. B: SVR: 53/165(32%) vs. 72/161(45%)	NR	NR	NR	A vs. B: Deaths: NR Serious Adverse Events: 4.8% vs. 8%; p=NS Treatment discontinuation - 29/165(18%) vs. 58/161(36%); p<0.001 Discontinuation due to Adverse event - 14/165(8%) vs. 19/161 (12%); p=NS Dose reduction - 74/165(45%) vs. 96/161 (59%); p=NS Adverse Events: Asthenia - 98/165(59%) vs. 95/161 (59%); p=NS Headache - 50/165(30%) vs. 53/161 (33%); p=NS Fever - 45/165(27%) vs. 45/161 (28%); p=NS Neutropenia - 40/165(24%) vs. 41/161 (25%); p=NS Influenza-like symptoms - 39/165(24%) vs. 28/148 (17%); p=NS Pruritus - 34/165(21%) vs. 41/161 (25%); p=NS Insomnia - 29/165(18%) vs. 41/161 (25%); p=NS Anorexia - 34/165(21%) vs. 23/161 (14%); p=NS Irritability - 28/165(17%) vs. 35/161 (22%); p=NS Anemia - 30/165(18%) vs. 34/161 (21%); p=NS Depression - 19/165(12%) vs. 31/161 (19%); p=NS Myalgia - 23/165(14%) vs. 22/161 (14%); p=NS Alopecia - 22/165(13%) vs. 27/161 (17%); p=NS	NR

Author, Year Country Study Name Quality	Duration of Followup	Outcome	Subgroup Analyses	Subgroup Analyses	Histologic Response	Adverse Events	Funding Source
Sanchez-Tapias, 2006[39] Spain Continued						Leukopenia - 18/165(11%) vs. 18/161 (11%); p=NS Injection site reaction - 12/165(7%) vs. 19/161 (12%); p=NS	

Author, Year Country Study Name Quality	Interferon Regimen	Ribavirin Regimen	Protease Inhibitor Regimen	Eligibility	Exclusion	Number Screened/ Eligible/ Enrolled/ Analyzed	Age Sex Race	Genotype Severity of Liver Disease Proportion Treatment-Naïve
Shiffman, 2007[40] 132 centers worldwide Pegylated interferon alfa-2a and Ribavirin for 16 or 24 Weeks in HCV Genotype 2 or 3 Overall Quality: Good	A: Pegylated interferon alfa-2a 180 µg/week for 16 weeks B: Pegylated interferon alfa-2a 180 µg/week for 24 weeks	A: Ribavirin 800 mg/day for 16 weeks B: Ribavirin 800 mg/day for 24 weeks	None	Eligible patients were those who were 18 years of age or older Infected with HCV genotype 2 or 3 Had a quantifiable serum HCV RNA level (>600 IU per milliliter) Elevated serum alanine transaminase level Findings on liver biopsy consistent with chronic HCV infection	Other liver diseases Human immunodeficiency virus (HIV) Hepatocellular carcinoma Severe depression or another severe psychiatric disease Clinically significant cardiovascular or renal disease Uncontrolled seizure disorder Severe retinopathy Previously received interferon or ribavirin (not treatment naive) Patients with cirrhosis had to have a Child–Pugh score of less than 7 to be eligible	1810/1469/1469/1465	A vs. B: Age (Mean): 46 vs. 45.6 years Female: 39% vs. 37% Non white: 13% vs. 13%	A vs. B: Genotype 2: 50.8% vs. 48.7% Genotype 3: 49.2% vs. 51.3% Steatosis (% of hepatocytes): none - 20% vs. 21% >0-5% - 26% vs. 25% 6-33% - 12% vs. 12% 34-66% - 7% vs. 7% >66% - 2% vs. <1% unknown - 33% vs. 34% Treatment naïve: 100%

Author, Year Country Study Name Quality	Duration of Followup	Outcome	Subgroup Analyses	Subgroup Analyses	Histologic Response	Adverse Events	Funding Source
Shiffman et al, 2007 132 centers worldwide Continued	Followup visits at 24 weeks after completion of treatment	A vs. B: ETR: 651/732(89%) vs. 599/731(82%) SVR: 455/732(62%) vs. 515/731(70%); p<0.001	NR	A vs. B: (p-value for interaction) Genotype 2: 232/358(62%) vs. 268/356(75%); p=0.06 Genotype 3: 221/358(62%) vs. 244/369(66%); HCVRNA >800: 280/506 (55%) vs. 344/501 (67%): p=0.26 HCVRNA 400-800: 43/65 (66%) vs. 59/80 (74%) HCVRNA<400: 132/161 (82%) vs. 122/150 (81%) Cirrhosis or bridging fibrosis: 88/185 (48%) vs. 95/165 (58%); p=0.82 No Cirrhosis or bridging fibrosis: 367/547 (67%) vs. 420/566 (74%)	NR	A vs. B: Deaths: NR Life-threatening Adverse Events: NR Serious Adverse Events: 5% vs. 6% Withdrawals: 41/736(5%) vs. 91/731(12%); p<0.0001 Withdrawal due to Adverse Events: 30/736(4%) vs. 25/731(5%); p=ns Neutropenia (Grade 4): 13/733 (2%) vs. 20/732 (3%); p=ns Anemia (<8.5 g/dL): 4/733 (<1%) vs. 4/732 (<1%); p=ns	Roche

Author, Year Country Study Name Quality	Interferon Regimen	Ribavirin Regimen	Protease Inhibitor Regimen	Eligibility	Exclusion	Number Screened/ Eligible/ Enrolled/ Analyzed	Age Sex Race	Genotype Severity of Liver Disease Proportion Treatment-Naïve
Von Wagner, 2005[41] Germany Peginterferon-alpha-2a (40KD) and Ribavirin for 16 or 24 Weeks in Patients with Genotype 2 or 3 Chronic Hepatitis C Overall Quality: Fair	Patients with negative HCV RNA at week 4 randomized to either 16 or 24 weeks of treatment A: Pegylated interferon alfa-2a 180 µg/week for 16 weeks B: Pegylated interferon alfa-2a 180 µg/week for 24 weeks C: Pegylated interferon alfa-2a 180 µg/week for 24 weeks (non randomized patients who did not achieve RVR)	A: Ribavirin by body weight: < 65 kg - 800 mg/day for 16 weeks 65 - 85 kg - 1000 mg/day for 16 weeks > 85 kg - 1200 mg/day for 16 weeks B: Ribavirin by body weight: < 65 kg - 800 mg/day for 24 weeks 65 - 85 kg - 1000 mg/day for 24 weeks > 85 kg - 1200 mg/day for 24 weeks C: (Nonrandomized): Ribavirin by body weight: < 65 kg - 800 mg/day for 24 weeks 65 - 85 kg - 1000 mg/day for 24 weeks > 85 kg - 1200 mg/day for 24 weeks	None	Male and female patients above 18 years of age with compensated chronic HCV infection not previously treated with interferon and/or ribavirin Tested positive for anti-HCV antibody and for HCV RNA (600 IU/mL by quantitative reverse transcription-polymerase chain reaction) Had a liver biopsy specimen taken within 18 months prior to the screening visit showing chronic hepatitis Had at least 1 serum alanine aminotransferase (ALT) level elevated at screening or entry into the trial Entry neutrophil and platelet counts at least 1500/ L and 90,000/ L, respectively Hemoglobin values at entry visit at least 12 g/dL for females and at least 13 g/dL for males	Any other cause of liver disease or other relevant disorders including human immunodeficiency or hepatitis B virus co infection Clinically significant hematologic, hepatic, metabolic, renal, rheumatologic, neurologic, or psychiatric disease Clinically significant cardiac or cardiovascular abnormalities; Organ grafts Systemic infection Clinically significant bleeding disorders Evidence of malignant neoplastic disease Concomitant immunosuppressive medication Excessive daily intake of alcohol or drug abuse within the past year Pregnancy and lactation, and male partners of pregnant women	NR/153/153/ 153	(A vs. B vs. C): Age (Mean): 38 vs. 39 vs. 42 years Female: 26% vs. 42% vs. 64% Non white: MR	(A vs. B vs. C): Genotype 2: 27% vs. 27% vs. 9% Genotype 3: 72% vs. 73% vs. 91% Fibrosis (Mean Ishak score): A (interface hepatitis) - 1 vs. 1.1 vs. 1.4 B (confluent necrosis) - 0.3 vs. 0.4 vs. 0.4 C (focal inflammation) - 1.4 vs. 1.4 vs. 1.4 D (portal inflammation) - 1.6 vs. 1.7 vs. 1.8 A-D(total inflammation) - 4.3 vs. 4.6 vs. 5.0 F (fibrosis) - 1.6 vs. 1.6 vs. 2.4 Cirrhosis: NR Treatment naive: 100%

Author, Year Country Study Name Quality	Duration of Followup	Outcome	Subgroup Analyses	Subgroup Analyses	Histologic Response	Adverse Events	Funding Source
Von Wagner, 2005[41] Germany Continued	Followup visits at 4, 12 and 24 weeks after completion of treatment	A vs. B: SVR: 58/71(82%) vs. 57/71(80%); p=NS	NR	A vs. B: SVR: Genotype 2:18/19 (95%) vs. 18/19 (95%); p=NS Genotype 3: 39/51 (76%) vs. 39/52 (75%); p=NS HCVRNA <800: 33/35 (94%) vs. 27/31 (87%); p=NS HCVRNA>800: 24/35 (69%) vs. 30/40 (75%); p=NS	NR	A vs. B: Withdrawals: 1/71 (1.4%) vs. 6/71 (8.5%) Withdrawal due to Adverse Events: NR Deaths: NR Life-threatening Adverse Events: NR Severe Adverse Events: NR Withdrawals: NR Adverse events: Flu-like symptoms: 37/71(52.1%) vs. 33/71 (46.5%); p=NS Fatigue: 26/71(36.6%) vs. 30/71 (42.3%); p=NS Pruritus: 19/71(26.8%) vs. 24/71 (33.8%); p=NS Headache: 18/71(25.4%) vs. 22/71 (31.0%); p=NS Anorexia: 16/71(22.5%) vs. 19/71 (26.8%); p=NS Alopecia: 15/71(21.1%) vs. 18/71 (25.4%); p=NS Asthenia: 12/71(16.9%) vs. 18/71(25.4%); p=NS Pain: 9/71(12.7%) vs. 16/71(22.5%); p=NS Dyspnea: 10/71(14.1%) vs. 16/71(22.5%); p=NS Sleeping disturbance: 9/71(12.7%) vs. 16 (22.5%); p=NS Pyrexia: 10/71(14.1%) vs. 13/71(18.3%); p=NS Dry skin: 13/71(18.3%) vs. 9/71(12.7%); p=NS Aggressivity: 8/71(11.3%) vs. 12/71(16.9%); p=NS Depression: 8/71(11.3%) vs. 10/71 (14.1%); p=NS Chills: 10/71(14.1%) vs. 8/71(11.3%); p=NS Nausea: 5/71(7.0%) vs. 11/71(15.5%); p=NS Dry Mouth: 4/71(5.6%) vs. 8/71(11.3%); p=NS	Hoffman-La Roche (Grenzach, Germany) & the German Hepatitis Network of Competence (Hep-Net)

Author, Year Country Study Name Quality	Interferon Regimen	Ribavirin Regimen	Protease Inhibitor Regimen	Eligibility	Exclusion	Number Screened/ Eligible/ Enrolled/ Analyzed	Age Sex Race	Genotype Severity of Liver Disease Proportion Treatment-Naïve
Yu, 2006[42] Taiwan A randomized trial of 24- vs. 48-week courses of PEG interferon alpha-2b plus ribavirin for genotype-1b-infected chronic hepatitis C patients: a pilot study in Taiwan Overall Quality: Fair	A: Pegylated interferon alpha-2b by body weight: < 60 kg - 80 µg/week for 24 weeks > 60 kg - 100 µg/week for 24 weeks B: Pegylated interferon alpha-2b by body weight: < 60 kg - 80 µg/week for 48 weeks > 60 kg - 100 µg/week for 48 weeks	A: Ribavirin by body weight: < 75 kg - 1000 mg/day for 24 weeks > 75 kg - 1200 mg/day for 24 weeks B: Ribavirin by body weight: < 75 kg - 1000 mg/day for 48 weeks > 75 kg - 1200 mg/day for 48 weeks	None	Eligible subjects were previously untreated Taiwanese chronic hepatitis C patients 18 to 65 years old, who: (1) Were seropositive for HCV antibodies and HCV RNA by polymerase chain reaction (PCR); (2) Had undergone a liver biopsy within 1 year before entry that was consistent with chronic hepatitis; (3) Had displayed elevated serum alanine transaminase (ALT), defined as >1.5 times the upper limit of the normal range for at least two measurements within 6 months preceding the trial entry; (4) Possessed an HCV genotype 1b infection Neutrophil count greater than 1500/mm^3	Patients with HCV genotype other than 1b infection Hepatitis B surface antigen Human immunodeficiency virus infection Autoimmune hepatitis Primary biliary cirrhosis Sclerosing cholangitis Wilson's disease a1-antitrypsin deficiency Decompensated cirrhosis (Child–Pugh class B or C) Overt hepatic failure History of alcohol abuse Psychiatric condition Previous liver transplantation or with evidence of hepatocellular carcinoma	NR/NR/60/60	A vs. B: Age (Mean): 45.4 vs. 45.1 years Female: 38% vs. 27% Non white: NR	A vs. B: Genotype 1b: 100% Fibrosis Score (Knodell , 1981): Score 0–2 - 71.1% vs. 73.3% Score 3–4 - 28.9% vs. 26.7% Treatment naïve: 100%

Author, Year Country Study Name Quality	Interferon Regimen	Ribavirin Regimen	Protease Inhibitor Regimen	Eligibility	Exclusion	Number Screened/ Eligible/ Enrolled/ Analyzed	Age Sex Race	Genotype Severity of Liver Disease Proportion Treatment-Naïve
Yu, 2006[42] Taiwan Continued				Platelet count greater than 1x105/mm3 Hemoglobin level greater than 13 g/dl for males and 12 g/dl for females Serum creatinine level less than 1.5 mg/dl No pregnancy or lactation and the use of a reliable method of contraception				

Author, Year Country Study Name Quality	Duration of Followup	Outcome	Subgroup Analyses	Subgroup Analyses	Histologic Response	Adverse Events	Funding Source
Yu, 2006[42] Taiwan Continued	Followup visits at 24 weeks after completion of treatment	A vs. B: SVR: 22/45(48.9%) vs. 12/15(80%)	A vs. B: SVR: Male: 14/28 (50%) vs. 8/11 (72%); p=NS Female: 8/17 (47%) vs. 4/4 (100%); p=NS	A vs. B: SVR: Fibrosis score 0-2: 18/32(56.3%) vs. 8/11(72.7%), p=NS Fibrosis score 3-4: 4/13(30.8%) vs. 4/4(100%), p=0.029 Baseline HCV-RNA <400,000 IU/mL: 14/22(63.6%) vs. 4/5(80%), p=NS Baseline HCV-RNA >400,000 IU/mL: 8/23(34.8%) vs. 8/10(80%), p=0.026	NR	A vs. B: Deaths: NR Life-threatening Adverse Events: NR Severe Adverse Events: NR Withdrawals: 1/45 (2%) vs. 3/15 (20%); p=0.02 Withdrawal due to Adverse Events:1/45 (2%) vs. 2/15 (13%); p=NS Dose reduction due to Adverse Events: 19/45 (42.2%) vs. 7/15 (46.7%); p=NS Adverse Events: Fever - 31/45 (68.9%) vs. 10/15 (66.7%); p=NS Chills - 10/45 (22.2%) vs. 4/15 (26.7%); p=NS Myalgia - 26/45 (57.7%) vs. 6/15 (40.0%); p=NS Headache - 32/45 (71.1%) vs. 9/15 (60.0%); p=NS Asthenia - 29/45 (64.4%) vs. 8/15 (53.3%); p=NS Anorexia - 14/45 (31.1%) vs. 3/15 (20.0%); p=NS Nausea - 16/45 (35.6%) vs. 6/15 (40.0%); p=NS Diarrhea - 3/45 (6.7%) vs. 3/15 (20.0%); p=NS Anxiety/depression - 19/45 (42.2%) vs. 8/15 (53.3%); p=NS Insomnia - 26/45 (57.7%) vs. 10/15 (66.6%); p=NS Hair loss - 24/45 (53.3%) vs. 10/15 (66.6%); p=NS Skin rash - 30/45 (66.7%) vs. 9/15 (60.0%); p=NS Injection site erythema - 16/45 (35.5%) vs. 6/15 (40.0%); p=NS	Taiwan Liver Research Foundation

Author, Year Country Study Name Quality	Duration of Followup	Outcome	Subgroup Analyses	Subgroup Analyses	Histologic Response	Adverse Events	Funding Source
Yu, 2006[42] Taiwan Continued						Body weight loss - 8/45 (17.7%) vs. 2/15 (13.3%); p=NS Anemia (hemoglobin o10 g/dl) - 20/45 (44.4%) vs. 8/15 (53.3%); p=NS Leukopenia White cell count <3000/mm3 - 34/45 (75.5%) vs. 11/15 (73.3%); p=NS White cell count <1500/mm3 - 1/45 (2.2%) vs. 2/15 (13.3%); p=NS Thrombocytopenia (<100 K/mm3) - 20/45 (44.4%) vs. 4/15 (26.6%); p=NS Abnormal thyroid function tests - 4/45 (8.8%) vs. 1/15 (6.6%); p=NS	

Author, Year Country Study Name Quality	Interferon Regimen	Ribavirin Regimen	Protease Inhibitor Regimen	Eligibility	Exclusion	Number Screened/ Eligible/ Enrolled/ Analyzed	Age Sex Race	Genotype Severity of Liver Disease Proportion Treatment-Naïve
Yu, 2007[43] Taiwan A randomized study of pegylated interferon and ribavirin for 16 vs. 24 weeks in patients with genotype 2 chronic hepatitis C Overall Quality: Fair	A: Pegylated interferon alfa-2a 180 µg/week for 24 weeks B: Pegylated interferon alfa-2a 180 µg/week for 16 weeks	A: Ribavirin by body weight: < 75 kg - 1000 mg/day for 24 weeks > 75 kg - 1200 mg/day for 24 weeks B: Ribavirin by body weight: < 75 kg - 1000 mg/day for 16 weeks > 75 kg - 1200 mg/day for 16 weeks	None	Eligible patients were previously untreated Taiwanese patients with CHC, aged 18–65 years, who: (1) Were seropositive for HCV antibodies (2) Had undergone a liver biopsy within 1 year before entry, the result of which was consistent with chronic hepatitis (3) Displayed an increased serum alanine transaminase level, defined as >1.5 times the upper limit of the normal range for at least two measurements within 6 months preceding the trial entry (4) Had HCV2 infection	Patients with an HCV genotype infection other than type 2 infection Hepatitis B surface antigen HIV infection Autoimmune hepatitis Primary biliary cirrhosis Sclerosing cholangitis Wilson's disease a1-antitrypsin deficiency Decompensated cirrhosis (Child–Pugh class B or C) Overt hepatic failure Current alcohol misuse or history of alcohol misuse (>20 g/day) Psychiatric condition Previous liver transplantation Evidence of hepatocellular carcinoma were excluded from the study	326/152/150 /150	A vs. B: Age (Mean): 49.4 vs. 50.2 years Female: 40% vs. 34% Non white: NR	A vs. B: Genotype 2 - 100% Fibrosis (Knodell) F 0–2 - 80% vs. 78% F 3–4 - 20% vs. 22% Steatosis None (0) - 67% vs. 68% Mild (1) - 28% vs. 26% Moderate to severe (2–3) - 5% vs. 6% Treatment naïve: NR

Author, Year Country Study Name Quality	Interferon Regimen	Ribavirin Regimen	Protease Inhibitor Regimen	Eligibility	Exclusion	Number Screened/ Eligible/ Enrolled/ Analyzed	Age Sex Race	Genotype Severity of Liver Disease Proportion Treatment-Naïve
Yu, 2007[43] Taiwan Continued				Neutrophil count >1500/mm3 Platelet count >9x104/mm3 Hemoglobin concentration >12 g/dl for men, and 11 g/dl for women Serum creatinine concentration < 1.5 mg/dl No pregnancy or lactation Use of a reliable method of contraception for women				

Author, Year Country Study Name Quality	Duration of Followup	Outcome	Subgroup Analyses	Subgroup Analyses	Histologic Response	Adverse Events	Funding Source
Yu, 2007[43] Taiwan Continued	Followup visits at 24 weeks after completion of treatment	A vs. B: 95/100 (95%) vs. 47/50 (94%); p=NS	A vs. B: Age: <50 years - 46/46(100%) vs. 19/19(100%);p=NS >50 years - 49/54(91%) vs. 28/31(90%); p=NS Female: 38/42(91%) vs. 16/18(89%); p=NS Male: 57/58 (98%) vs. 31/32 (97%): p=NS BMI <25: 49/53 (93%) vs. 25/27 (93%); p=NS BMI>25: 46/47 (98%) vs. 22/23 (96%); p=NS	A vs. B: Fibrosis F0-2: 76/80 (95%) vs. 34/39 (95%); p=NS Fibrosis F3-4: 19/20 (95%) vs. 10/11 (91%); p=NS HCVRNA <800K: 81/85 (95%) vs. 39/41 (95%); p=NS HCVRNA>800K: 14/15 (93%) vs. 8/9 (89%); p=NS	NR	A vs. B: Deaths: NR Life-threatening Adverse Events: NR Severe Adverse Events: NR Withdrawals: 1/100(1%) vs. 0/50(0%); p=1 Withdrawal due to Adverse Events: 1/100(1%) vs. 0/50(0%); p=1 Dose reduction due to Adverse Events - 54/100(54%) vs. 26/50 (52%), p=0.817 Adverse Events: Fever: 55/100 (55%) vs. 29/50 (58%), p=0.727 Chills: 28/100 (28%) vs. 12/50 (24%), p=0.602 Headache: 39/100 (39%) vs. 21 /50 (42%), p=0.724 Anorexia: 46/100 (46%) vs. 20/50 (40%), p=0.601 Nausea: 15/100 (15%) vs. 3/50 (6%), p=0.181 Diarrhea: 9/100 (9%) vs. 5/50 (10%), p=1 Anxiety: 7/100 (7%) vs. 4/50 (8%), p=1 Depression: 10/100 (10%) vs. 3/50 (6%), p=0.545 Insomnia: 57/100 (57%) vs. 23/50 (46%), p=0.227 Hair loss: 49/100 (49%) vs. 10/50 (20%), p=0.001* Skin rash: 54/100 (54%) vs. 22/50 (44%), p= 0.248 Leukopenia(white cell count,1500/mm3): 2/100 (2%) vs. 1/50 (2%), p=1 Anemia (hemoglobin level<10g/dl): 53/100(53%) vs. 27/50 (54%), p=0.908 Thrombocytopenia(<50,000/mm3: 1/100 (1%) vs. 0/50 (0%), p=1 Abnormal thyroid function tests: 13/100 (13%) vs. 4/50 (8%), p=0.362	Taiwan Liver Research Foundation

Author, Year Country Study Name Quality	Interferon Regimen	Ribavirin Regimen	Protease Inhibitor Regimen	Eligibility	Exclusion	Number Screened/ Eligible/ Enrolled/ Analyzed	Age Sex Race	Genotype Severity of Liver Disease Proportion Treatment-Naïve
Yu, 2008[44] Taiwan Rapid Virological Response and Treatment Duration for Chronic Hepatitis C Genotype 1 Patients: A Randomized Trial Overall Quality: Fair	A: Pegylated interferon alfa-2a 180 µg/week for 24 weeks B: Pegylated interferon alfa-2a 180 µg/week for 48 weeks	A: Ribavirin by body weight: < 75 kg - 1000 mg/day for 24 weeks > 75 kg - 1200 mg/day for 24 weeks B: Ribavirin by body weight: < 75 kg - 1000 mg/day for 48 weeks > 75 kg - 1200 mg/day for 48 weeks	None	Eligible patients were previously untreated Taiwanese patients with CHC, aged 18–65 years, who: (1) Were seropositive for HCV antibodies (2) Had undergone a liver biopsy within 1 year before entry, the result of which was consistent with chronic hepatitis (3) Displayed an increased serum alanine transaminase level, defined as >1.5 times the upper limit of the normal range for at least two measurements within 6 months preceding the trial entry (4) Had HCV2 infection Neutrophil count >1500/mm3 Platelet count >9x104/mm3 Hemoglobin concentration >12 g/dl for men, and 11 g/dl for women Serum creatinine concentration < 1.5 mg/dl	Patients with an HCV genotype infection other than type 1 infection Hepatitis B surface antigen HIV infection Autoimmune hepatitis Primary biliary cirrhosis Sclerosing cholangitis Wilson's disease a1-antitrypsin deficiency Decompensated cirrhosis (Child–Pugh class B or C) Overt hepatic failure Current alcohol misuse or history of alcohol misuse (>20 g/day) Psychiatric condition Previous liver transplantation Evidence of hepatocellular carcinoma were excluded from the study	NR/NR/200/ 200	A vs. B: Age (Mean): 49.7 vs. 49.1 years Female: 43% vs. 42% Non white: NR	A vs. B: Genotype 1 - 100% Fibrosis (Knodell) F 0–2 - 75% vs. 81% F 3–4 - 25% vs. 19% Treatment naïve: NR

Author, Year Country Study Name Quality	Duration of Followup	Outcome	Subgroup Analyses	Subgroup Analyses	Histologic Response	Adverse Events	Funding Source
Yu, 2008[44] Taiwan Continued	Followup visits at 24 weeks after completion of treatment	A vs. B: SVR: 59/100(59%) vs. 79/100(79%)	A vs. B: SVR: Male: 34/57 (60%) vs. 46/58 (79%); p=NS Female: NR	A vs. B: SVR: Fibrosis score F0-2: 48/75 (64%) vs. 62/84 (77%); p=NS Fibrosis score F3-4: 11/25 (44%) vs. 17/19 (89%); p=0.002 HCV RNA <400K: 34/45 (76%) vs. 36/44 (82%); p=NS HCV RNA>400K: 25/55 (45%) vs. 43/56 (77%); p<0.001	NR	A vs. B: Withdrawals: 3/100(3%) vs. 10/100(10%), p=0.045 Withdrawal due to Adverse Events: 3/100 (3%) vs. 9/100 (9%); p=NS Deaths: NR Life-threatening Adverse Events: NR Serious Adverse Events: 1/100 (1%) vs. 1/100 (1%); p=NS Dose reduction due to adverse events: 54/100(54.0%) vs. 65/100(65.0%), p=0.113 Influenza-like symptoms (fever, chills, headache): 76/100(76%) vs. 74/100(74%), p=0.744 Anorexia and/or nausea - 50 (50%) vs. 53 (53%), p=0.671 Diarrhea - 18 (18%) vs. 26 (26%), p=0.172 Anxiety - 31 (32%) vs. 36/100(36%), p=0.454 Depression - 24 (24%) vs. 34/100(34%), p=0.119 Insomnia - 59 (59%) vs. 65/100(65%), p=0.382 Hair loss – 66/100(66%) vs. 72/100(72%), p=0.359 Skin rash – 54/100(54%) vs. 66/100(66%), p=0.083 Leukopenia (white cell count < 1500 mm−3) – 5/100(5%) vs. 8/100(8%), p=0.39 Anemia (hemoglobin < 10 g/dl) – 39/100(39%) vs. 48/100(48%), p=0.199 Thrombocytopenia (< 50,000 mm−3) – 2/100(2%) vs. 6/100(6%), p=0.279 Abnormal thyroid function tests – 13/100(13%) vs. 15/100(15%), p=0.684	Taiwan Liver Research Foundation

Author, Year Country Study Name Quality	Interferon Regimen	Ribavirin Regimen	Protease Inhibitor Regimen	Eligibility	Exclusion	Number Screened/ Eligible/ Enrolled/ Analyzed	Age Sex Race	Genotype Severity of Liver Disease Proportion Treatment-Naïve
Zeuzem, 2004[45] Australia, Europe, New Zealand, North & South America Pegylated interferon alfa-2a (40 Kilodaltons) and Ribavirin in Patients with Chronic Hepatitis C and Normal Aminotransferase Levels Overall Quality: Fair	A: Pegylated interferon alfa-2a 180 µg/week for 24 weeks B: Pegylated interferon alfa-2a 180 µg/week for 48 weeks C: No treatment	A: Ribavirin 800 mg/day (2 equal doses) for 24 weeks B: Ribavirin 800 mg/day (2 equal doses) for 48 weeks C: No treatment	None	Treatment-naive patients aged 18 years or older with a positive antibody to hepatitis C virus (HCV) antibody test Detectable HCV RNA in serum Biopsy findings consistent with a diagnosis of chronic hepatitis C Persistently normal ALT levels (equal to or below the upper limit) of normal (ULN) documented on at least 3 occasions, a minimum of 4 weeks apart, with at least one value obtained during the 42-day screening period and at least one value obtained 6-18 months before screening.	No histologic evidence of liver disease One or more elevated ALT values (i.e., greater than the ULN) within the previous 18 months Patients with transition to cirrhosis or cirrhosis on liver biopsy History of bleeding from esophageal varices Other conditions consistent with decompensated liver disease were excluded to avoid the possibility of including individuals whose ALT levels had returned to the normal range as a consequence of advanced liver disease Neutropenia (absolute neutrophil count 1500 cells/mm3) Thrombocytopenia(90,000 platelets/mm3) Anemia (hemoglobin concentration 12 g/dL in women and 13 g/dL in men) or a medical condition that would be significantly worsened by anemia Serologic evidence of infection with human immunodeficiency virus or hepatitis A or B virus, and serum creatinine level 1.5 times the ULN Organ transplant recipients Individuals with severe cardiac disease History of severe psychiatric disease (especially depression) Evidence of drug abuse (including excessive alcohol consumption) within the preceding year	NR/NR/514/ 491	A vs. B vs. C: Age (Mean): 44 vs. 44 vs. 41 years Female: 58% vs. 61% vs. 62% Non white race: 14% vs.14% vs. 17%	(A vs. B vs. C): Genotype 1: 68% vs. 67% vs. 68% Genotype 1a: 36% vs. 42% vs. 38% Genotype 1b: 31% vs. 25% vs. 30% Genotype (other type 1): 1% vs. 0% vs. 0% Genotype 2: 18% vs. 20% vs. 19% Genotype 3: 9% vs. 9% vs. 9% Genotype 4: 4% vs. 4% vs. 3% Genotype 5: 1% vs. 0% vs. 0% Genotype 6: 1% vs. 1% vs. 1% Cirrhosis: 0% vs. 1% vs. 0% Fibrosis (Ishak): 0-1: 66% vs. 69% vs. 77% 2: 21% vs. 20% vs. 14% 3-4: 12% vs. 9% vs. 7% >4: 0% vs. 1% vs. 0% Treatment naive: 100%

Author, Year Country Study Name Quality	Interferon Regimen	Ribavirin Regimen	Protease Inhibitor Regimen	Eligibility	Exclusion	Number Screened/ Eligible/ Enrolled/ Analyzed	Age Sex Race	Genotype Severity of Liver Disease Proportion Treatment-Naïve
Zeuzem, 2004[45] Australia, Europe, New Zealand, North & South America Continued					Other serious systemic disease Pregnant or lactating women and male partners of pregnant women. All fertile men and women who participated in the trial were required to use two forms of effective contraception during treatment and for 6 months after the end of treatment			

Author, Year Country Study Name Quality	Interferon Regimen	Ribavirin Regimen	Protease Inhibitor Regimen	Eligibility	Exclusion	Number Screened/ Eligible/ Enrolled/ Analyzed	Age Sex Race	Genotype Severity of Liver Disease Proportion Treatment-Naïve
Zeuzem, 2004[45] Australia, Europe, New Zealand, North & South America Continued					Other serious systemic disease Pregnant or lactating women and male partners of pregnant women. All fertile men and women who participated in the trial were required to use two forms of effective contraception during treatment and for 6 months after the end of treatment			

Author, Year Country Study Name Quality	Duration of Followup	Outcome	Subgroup Analyses	Subgroup Analyses	Histologic Response	Adverse Events	Funding Source
Zeuzem, 2004[45] Australia, Europe, New Zealand, North & South America Continued	Followup visits at 24 weeks after completion of treatment	A vs. B: ETR: NR SVR: 63/212(30%) vs. 109/210(52%); p<0.001	NR	A vs. B: ETR: NR SVR: Genotype 1 - 19/144(13%) vs. 57/141(40%); p<0.001 Genotypes 2/3 - 42/58(72%) vs. 46/59(78%); p=NS Genotypes 4 - 1/8(13%) vs. 5/9(56%); p=NS HCV RNA <800 IU/mL: 39/123 (32%) vs. 72/127 (57%); p<0.001 HCV RNA >800 IU/mL: 24/87(28%) vs. 36/82(44%); p=0.03	NR	A vs. B: Withdrawals: 20/212 (9%) vs. 58/210 (28%); p<0.001 Withdrawals due to adverse events: 15/212 (7%) vs. 38/210 (18%); p<0.001 Severe adverse events 56/212 (26%) vs. 70/210 (33%); p=NS Life-threatening adverse events - 3/212 (1%) vs. 8/210 (4%) Serious adverse events - 18/212 (8%) vs. 34/210 (16%); p=0.02 Deaths - 0/212(0%) vs. 0/210(0%); p=NS Dose reduction due to adverse events - 65/212(32%) vs. 102/210(49%); p<0.001 Adverse Events: Headache - 93/212 (44%) vs. 117/210 (56%); p=0.02 Fatigue - 109/212 (51%) vs. 107/210 (51%); p=NS Myalgia - 81/212 (38%) vs. 93/210 (44%); p=NS Pyrexia – 64/212 (30%) vs. 90/210 (43%); p<0.01 Insomnia - 74/212 (35%) vs. 76/210 (36%); p=NS Nausea - 68/212 (32%) vs. 84/210 (40%); p=NS Arthralgia - 68/212 (32%) vs. 62/210 (30%); p=NS Depression - 55/212 (26%) vs. 57/210 (27%); p=NS Irritability - 58/212 (27%) vs. 55/210 (26%); p=NS Rigors - 50/212 (24%) vs. 53/210 (25%); p=NS Alopecia - 43/212 (20%) vs. 59/210 (28%); p=NS Asthenia - 47/212 (22%) vs. 48/210 (23%); p=NS	Roche (Basel, Switzerland)

Author, Year Country Study Name Quality	Duration of Followup	Outcome	Subgroup Analyses	Subgroup Analyses	Histologic Response	Adverse Events	Funding Source
Zeuzem, 2004[45] Australia, Europe, New Zealand, North & South America Continued						Diarrhea - 40/212 (19%) vs. 55/210 (26%); p=NS Pruritus - 34/212 (16%) vs. 42/210 (20%); p=0.03 Hemoglobin <10.0 to >8.5 g/dL - 10/212 (5%) vs. 24/210 (11%); p=0.01 Hemoglobin <8.5 g/dL - 3/212 (1%) vs. 1/210 (1%); p=NS Neutrophils <0.5 x109/L - 10/212 (5%) vs. 10/210 (5%); p=NS Platelets <50 x109/L - 3/212 (1%) vs. 4/210 (2%); p=NS Hypothyroidism - 0/212 (0%) vs. 5/210 (2%); p=NS Hyperthyroidism - 1/212 (1%) vs. 3/210 (1%); p=NS	

Evidence Table 6. Quality rating: Trials of dual therapy with pegylated interferon plus ribavirin: duration effects

Author, Year	Randomization adequate?	Allocation concealment adequate?	Groups similar at baseline?	Eligibility criteria specified?	Outcome assessors masked?	Care provider masked?	Patient masked?	Attrition and withdrawals reported?	Loss to followup: differential/high?	Intention-to-treat analysis	Quality	Funding
Andriulli, 2009[22]	Unclear	Yes	Unclear	Yes	No, open label	No, open label	No, open label	Yes	No	Yes	Fair	Investigator funded
Berg, 2006[23]	Unclear	Unclear	Yes	Yes	No, open label	No, open label	No, open label	yes	No	Yes	Fair	Roche
Berg, 2009[24]	Unclear	Unclear	Unclear	Yes	No, open label	No, open label	No, open label	Yes	Yes	Yes	Poor	Schering-Plough
Brandao, 2006[25]	Yes	Unclear	Yes	Yes	No, open label	No, open label	No, open label	Yes	No	Yes	Fair	Roche
Bronowicki, 2006[46]	Yes	Unclear	Unclear	Yes	No, open label	No, open label	No, open label	Yes	No	Yes	Fair	Roche
Buti, 2010[26]	Yes	Unclear	Yes	Yes	No, open label	No, open label	No, open label	Yes	No	Yes	Fair	Schering-Plough (now Merck)
Dalgard, 2008[27]	Unclear	Unclear	Yes	Yes	No, open label	No, open label	No, open label	Yes	No	Yes	Fair	Schering-Plough (now Merck)
Ferenci, 2010[28]	Unclear	unclear	Unclear	Yes	Unclear	Unclear	Unclear	Yes	Yes	Yes	Poor	Roche
Ide, 2009[30]	Unclear	Yes	Unclear	Yes	Unclear	Unclear	Unclear	Yes	Yes	Yes	Fair	Internal Funding
Kamal, 2005[31]	Unclear	Unclear	Yes	Yes	Unclear	Unclear	Unclear	Yes	No	Yes	Fair	Fulbright Foundation Grants(NIAID (R2) AI054887) & the Alexander von Humboldt Foundation (Germany)

Author, Year	Randomization adequate?	Allocation concealment adequate?	Groups similar at baseline?	Eligibility criteria specified?	Outcome assessors masked?	Care provider masked?	Patient masked?	Attrition and withdrawals reported?	Loss to followup: differential/high?	Intention-to-treat analysis	Quality	Funding
Lagging, 2008[32]	Unclear	Unclear	Yes	Yes	No, open label	No, open label	No, open label	Yes	No	Yes	Fair	Swedish Society of Medicine, Swedish Medical Council, Swedish Society of Microbiology, Avtal om lakarutbildning och forskning (ALF) Funds, and Roche affiliates (Nordic region)
Lam, 2010[33]	Unclear	Yes	Yes	Yes	No, open label	No, open label	No, open label	No	No	Yes	Fair	investigator initiated research grant from Roche Laboratories, LLC to Pacific Health Foundation
Liu, 2008[34]	Unclear	Unclear	Yes	Yes	No, open label	No, open label	No, open label	Yes	No	Yes	Fair	National Taiwan University Hospital, National Science Council, and Department of Health, Executive Yuan, Taiwan
Mangia, 2005[35]	Unclear	Unclear	Yes	Yes	No, open label	No, open label	No, open label	No	No	Yes	Fair	Italian branch of Schering-Plough
Manns 2011[36]	No	Yes	Unclear	Yes	No, open label	No, open label	No, open label	Yes	Yes	Yes	Poor	Schering-Plough (now Merck)

Author, Year	Randomization adequate?	Allocation concealment adequate?	Groups similar at baseline?	Eligibility criteria specified?	Outcome assessors masked?	Care provider masked?	Patient masked?	Attrition and withdrawals reported?	Loss to followup: differential/high?	Intention-to-treat analysis	Quality	Funding
Mecenate, 2010[37]	Unclear	Unclear	Unclear	Yes	No, open label	No, open label	No, open label	Yes	No	Yes	Fair	NR
Pearlman, 2007[38]	Unclear	Unclear	Yes	Yes	No, not described	No, not described	No, not described	Yes	No	Yes	Fair	NR
Sanchez-Tapias, 2006[39]	Yes	Yes	Unclear	Yes	No, open label	No, open label	No, open label	Yes	No	Yes	Fair	NR
Shiffman, 2007[40]	Unclear	Yes	Yes	Yes	No	Yes	Yes	Yes	No	Yes	Good	Roche
Von Wagner, 2005[41]	Unclear	Unclear	Unclear	Yes	Unclear	Unclear	Unclear	Yes	No	Yes	Fair	Hoffman-La Roche (Grenzach, Germany) & the German Hepatitis Network of Competence (Hep-Net)
Yu, 2006[42]	Yes	Unclear	Unclear	Yes	No, open label	No, open label	No, open label	Yes	No	Yes	Fair	Taiwan Liver Research Foundation
Yu, 2007[43]	Yes	Unclear	Unclear	Yes	No, open label	No, open label	No, open label	Yes	No	Yes	Fair	Taiwan Liver Research Foundation
Yu, 2008[44]	Yes	Yes	Unclear	Yes	No - open label	No - open label	No - open label	Yes	No	Yes	Fair	Taiwan Liver Research Foundation
Zeuzem, 2004[45]	Unclear	Unclear	Yes	Yes	No, open label	No, open label	No, open label	Yes	Yes	Yes	Fair	Roche (Basel, Switzerland)

Evidence Table 7. Trials of dual therapy with pegylated interferon plus ribavirin: dose effects

Author, Year Country Study Name Quality	Interferon Regimen	Ribavirin Regimen	Protease Inhibitor Regimen	Eligibility	Exclusion	Number Screened/ Eligible/ Enrolled/ Analyzed	Age Sex Race	Genotype Severity of Liver Disease Proportion Treatment-Naïve
Abergel, 2006[47] France Pegylated interferon alpha-2b plus ribavirin for treatment of chronic hepatitis C with severe fibrosis: a multicenter randomized controlled trial comparing two doses of Pegylated interferon alpha-2b Overall Quality: Fair	A: (standard-dose) Pegylated interferon alpha-2b 1.5 µg/kg 1x/week/48 weeks B: (low-dose) Pegylated interferon alpha-2b 0.75 µg/kg 1x/week/48 weeks	A: Ribavirin 800 mg/day/48weeks B: Ribavirin 800 mg/day/48 weeks	None	Age between 18 and 75 years No previous treatment with IFN and/or ribavirin Alanine aminotransferase (ALT) > upper limit of normal (ULN) at least once during the last 12 months Positive serum HCV-RNA using qualitative polymerase chain reaction (PCR) and severe fibrosis on liver biopsy defined by a METAVIR fibrosis stage of F3 or F4 at histological examination of the liver	Recent history of alcohol abuse or IV drug addiction Hemoglobin <12 g/dL in women and <13 g/dL in men Platelets <75 000/lL Neutrophils <1500/lL Decompensated cirrhosis (ascites, variceal hemorrhage encephalopathy) Albumin <30 g/L Prothrombin <60% Bilirubin >34 lmol/L HCC Chronic hepatitis B infection HIV infection	NR/210/ 210/203	A vs. B Age(Mean): 49.3 vs. 51.1 years Female: 36% vs. 32% Race: NR	A vs. B Genotype 1 - 50/101(49.5%) vs. 54/102(529%) Genotype 2 - 11/101(10.9%) vs. 9/102(8.8%) Genotype 3 - 30/101(29.7%) vs. 28/102(27.5%) Genotype 4 - 5/101(5%) vs. 4/102(3.9%) Genotype 5 - 5/101(5%) vs. 7/102(6.9%) Fibrosis stage: F3 - 55/101(54.4%) vs. 44/102(43.1%) F4 - 46/101(45.6%) vs. 58/102(56.9%) Cirrhosis: 46% vs. 57% 100% Treatment naïve

Author, Year Country Study Name Quality	Duration of Followup	Outcome	Subgroup Analyses	Subgroup Analyses	Histologic Response	Adverse Events	Funding Source
Abergel, 2006[47] France Continued	Followup visits at 24 weeks after completion of treatment	A vs. B ETR: 59/101(62.8%) vs. 57/102(59.4%) SVR: 50/101(49.5%) vs. 38/102(37.2%)	A vs. B ETR: NR SVR: BMI <27 kg/m2 - 35/70 (50.0%) vs. 26/70 (37.1%); p=NS BMI ≥27 kg/m2 - 10/31 (32.3%) vs. 12/32 (37.5%); p=NS gamma glutamyl transpeptidase (GGT) used as a marker for steatosis: GGT <1.6 ULN - 29/48 (60.4%) vs. 23/48 (47.9%); p=NS GGT ≥1.6 ULN - 13/50 (26.0%) vs. 13/51 (25.5%); p=NS	A vs. B ETR: NR SVR: Genotypes 1, 4, 5, - 15/60(25.0%) vs. 11/65 (16.9%); p=NS Genotype 1 - 12/50 (24.0%) vs. 09/54 (16.7%); p=NS Genotypes 2, 3 - 30/41 (73.2%) vs. 27/37 (73.0%); p=NS Viremia <800.000 IU/mL - 25/55 (45.5%) vs. 20/47 (42.5%); p=NS Viremia ≥800 000 IU/mL - 20/44 (45.5%) vs. 17/53 (32.1%); p=NS Cirrhosis (F4) - 18/46 (39.1%) vs. 20/58 (34.5%); p=NS Severe fibrosis(F3) - 27/55 (49.1%) vs. 18/44 (40.1%); p=NS	None	A vs. B Discontinuation - 30/101(31 %) vs. 28/102(27 %) Discontinuation or treatment reduction – 53/101(54%) vs. 37/102(36 %), p <0.03 Treatment reduction - 36/101(37%) vs. 13/102(12%), p <0.0002 Overall withdrawals - NR Deaths - NR Severe Adverse Events: Adverse event - 8/101(9%) vs. 4/102(3%) Cytopenia -7/101(7%) vs. 1/102(1%) Others - 7/101(8%) vs. 3/102(2 %) Adverse events Adverse event - 15/101(16%) vs. 4/102(3%), p <0.01 Cytopenia - 20/101(21 %) vs. 9/102(8%), <0.03 Anemia - 9/101(10%) vs. 5/102(4 %) Neutropenia - 10/101(11 %) vs. 4/102(3%) Thrombopenia - 3/101(3 %) vs. 0/102(0%) Others - 2/101(1%) vs. 0/102(1%) Hemoglobin < 10g/dL - 27/101(27 %) vs. 16/102(15%), p=0.054 Neutrophils < 750/ µL - 21/101(21%) vs. 8/102(7%), p <0.01 Platelets < 50 000/ µL - 7/101(7%) vs. 7/102(6 %) Depression - 13/101(12%) vs. 15/102(14%) Suicide - 2/101(1%) vs. 0/102(0%) Hypothyroidism (treated) - 9/101(10%) vs. 1/102(.5%)	Schering-Plough, France and Delegation Regionale a la Recherche Clinique, Clermont-Ferrand, France

Author, Year Country Study Name Quality	Interferon Regimen	Ribavirin Regimen	Protease Inhibitor Regimen	Eligibility	Exclusion	Number Screened/ Eligible/ Enrolled/ Analyzed	Age Sex Race	Genotype Severity of Liver Disease Proportion Treatment-Naïve
Brady, 2010[48] United States Induction pegylated interferon alfa-2b combination with ribavirin in patients with genotype 1 and 4 chronic hepatitis C: a prospective, randomized, multicenter, open-label study Overall Quality: Fair	A. Pegylated interferon alfa-2b 3.0 mcg/kg/week for 12 weeks followed by 1.5 mcg/kg/week for 36 weeks B. Pegylated interferon alfa-2b 1.5 mcg/kg/week for 48 weeks	A. 800-1400 mg/day for 48 weeks B. 800-1400 mg/day for 48 weeks	NA	Treatment-naïve patients Genotype 1 or 4 Positive HCV antibodies and detectable HCV RNA Liver biopsy consistent with viral hepatitis within the past 48 months Cirrhosis no worse than Child-Pugh Class A Hemoglobin ≥12 g/dL in females and 13 g/dL in males White blood cells ≥3000 Neutrophil ≥1500 Platelet ≥ 65K Direct bilirubin within 20% of upper limits of normal Creatinine within 20% of upper limits of normal Albumin within normal limits	Non genotype 1 or 4 HCV infection Decompensated liver disease Evidence of coexisting liver disease Coinfection with HIV or HBV Hemochromatosis Alpha-1 antitrypsin deficiency Wilson disease Autoimmune hepatitis Alcoholic liver disease Hepatocellular carcinoma Pregnancy Psychiatric conditions Significant cardiovascular dysfunction within the past 1 year Poorly controlled diabetes mellitus Chronic pulmonary disease Clinically significant retinal abnormalities Immunologically mediated diseases Any medical condition requiring systemic steroids Active clinical gout Substance abuse in the past 6 months	NR/NR/ 623/610	A vs. B Age mean: 45 vs. 45 Female: 50% vs. 50% non White: 32% vs. 28%	A vs. B genotype 1: 99% vs. 99% Treatment-naïve: all Fibrosis stage 3 or 4: 26% vs. 23% HCV- RNA ≥800K: 71% vs. 62%

Author, Year Country Study Name Quality	Duration of Followup	Outcome	Subgroup Analyses	Subgroup Analyses	Histologic Response	Adverse Events	Funding Source
Brady, 2010[48] United States Continued	24 weeks following treatment completion	A vs. B ETR: 126/299 (42.1%) vs. 121/311 (38.9%); p= SVR: 96/299 (32.1%) vs. 92/311 (29.6%); p=0.434	A vs. B Black: 13/36 (36.1%) vs. 12/37 (32.4%); p=0.9 Hispanic: 29.9% vs. 22.5%; p=0.292 (absolute numbers NR) Weight <85 kg: 26% vs. 31% (p=NS); (absolute numbers NR) Weight ≥85 kg: 38% vs. 28% (p=0.08); (absolute numbers NR)	NR	NR	A vs. B Overall withdrawals: 146/299 (48.8%) vs. 133/311 (42.7%); p=0.2 Withdrawals for adverse events: NR Serious adverse events: NR Deaths: NR Neutropenia <500: 10/299 (3.4%) vs. 5/311 (1.6%); p=0.261 Anemia hemoglobin <10: 50/299 (16.7%) vs. 50/311 (16.1%); p=0.916 Thrombocytopenia platelets <50: 3/299 (1.0%) vs. 4/311 (1.3%); p=1.0 Pyrexia: 68/299 (22.7%) vs. 80/311 (25.7); p=0.445 Myalgia: 114/299 (38.1%) vs. 108/311 (34.7%); p=0.430 Rash: 34/299 (11.4%) vs. 58/311 (18.6%); p=0.016 Fatigue: 131/299 (43.8%) vs. 156/311 (50.2%); p=0.136 Headache: 30/299 (10.0%) vs. 47/311 (15.1%); p=0.077 Insomnia: 47/299 (15.7%) vs. 51/311 (16.4%); p=0.906 Depression: 55/299 (18.4%) vs. 70/311 (22.5%); p=0.247 Nausea: 37/299 (12.4%) vs. 40/311 (12.9%); p=0.953	Schering Plough

Author, Year Country Study Name Quality	Interferon Regimen	Ribavirin Regimen	Protease Inhibitor Regimen	Eligibility	Exclusion	Number Screened/ Eligible/ Enrolled/ Analyzed	Age Sex Race	Genotype Severity of Liver Disease Proportion Treatment-Naïve
Bronowicki, 2006[46] France Effect of ribavirin in genotype 1 patients with hepatitis C responding to pegylated interferon alfa-2a plus ribavirin Overall Quality: Fair	A. Pegylated interferon alfa-2a 180 mcg/week for 48 weeks B. Pegylated interferon alfa-2a 180 mcg/week for 48 weeks	All patients treated for 24 weeks of ribavirin 400 mg twice daily. At week 24 patients with indictable HCV RNA were randomized at week 26 to 22 more weeks (48 weeks total) of: A. 400 mg twice daily B. Placebo	NA	Treatment naïve Aged ≥18 years HCV genotype 1 infection HCV RNA >600 IU/mL Increased ALT levels documented 2 times in last 6 months Liver biopsy consistent with chronic hepatitis C obtained within 18 months before therapy	chronic liver disease of other etiology Evidence of decompensation Coinfection with HBV or HIV Neutrophils <1500/mm3 platelets <90,000/mm3 Hemoglobin level less than 12 g/dL (women) or less than 13 g/dL (men) Risk factor for anemia Serum creatinine >1.5 times upper limit of number Severe psychiatric disease Significant comorbid medical conditions	NR/516/ 349/349	A vs. B Age mean: 44.2 vs. 45.4 Female: 43% vs. 43% Non White: NR	A vs. B Genotype 1: all HCV RNA>800,000: 62% vs. 71% Fibrosis score F3 or F4: 27% vs. 28%

Author, Year Country Study Name Quality	Duration of Followup	Outcome	Subgroup Analyses	Subgroup Analyses	Histologic Response	Adverse Events	Funding Source
Bronowicki, 2006[46] France Continued	24 weeks following treatment completion	A vs. B SVR: 93/176 (52.8%) vs. 118/173 (68.2%); p=0.004 Hepatitis Quality of Life Questionnaire: Scores for all domains not significantly different between two treatment regimens at any point in time	NR	NR	NR	A vs. B Overall withdrawals: NR Withdrawals for adverse events: 3/173 (1.7%) vs. 4/176 (2.3%); p=NS Serious adverse events: 13/173 (7.5%) vs. 12/176 (6.8%); p=NS Deaths: 1/173 (0.5%) vs. 0/176 (0%); p=NS Asthenia: 19/173 (10.6%) vs. 13/176 (7.3%); p=NS Headache: 7/173 (3.9%) vs. 6/176 (3.4%); p=NS Depression: 13/173 (7.5%) vs. 16/176 (9.1%); p=NS Myalgia: 6/173 (3.4%) vs. 6/176 (3.4%); p=NS Leukopenia: 5/173 (2.8%) vs. 5/176 (2.8%); p=NS	Roche

Author, Year Country Study Name Quality	Interferon Regimen	Ribavirin Regimen	Protease Inhibitor Regimen	Eligibility	Exclusion	Number Screened/ Eligible/ Enrolled/ Analyzed	Age Sex Race	Genotype Severity of Liver Disease Proportion Treatment-Naïve
Ferenci, 2008[49] Austria A Randomized, Prospective Trial of Ribavirin 400 mg/Day Vs. 800 mg/Day in Combination with Pegylated interferon Alfa-2a in Hepatitis C Virus Genotypes 2 and 3 Overall Quality: Fair	A: Pegylated interferon alpha-2a 180 µg/week/24 weeks B: Pegylated interferon alpha-2a 180 µg/week/24 weeks	A: Ribavirin 800 mg/day/24 weeks B: Ribavirin 400 mg/day/24 weeks	None	Treatment-naive adult Aged 18 to 65 years Chronic hepatitis C HCV genotype 2 or 3 infection Quantifiable HCV RNA in serum and elevated serum ALT activity (1.5 times the upper limit of normal [ULN] in the previous 6 months and during screening) Hemoglobin value 12 g/dL (women) or 13 g/dL (men) Leukocyte count 3000/ L Platelet count 100,000/ L Serum creatinine level 1.5 times the ULN. Women of childbearing potential were required to have a negative pregnancy test within 24 hours of the first dose All fertile male and female participants were required to use two forms of effective contraception during treatment and for 6 months after the end of treatment	Pregnant or breast-feeding women and male partners of pregnant women Received prior treatment with interferon or ribavirin at any time Co infected with hepatitis B virus or human immunodeficiency virus Decompensated liver disease or chronic liver disease attributable to another cause Coronary heart disease Diabetes mellitus requiring insulin therapy Autoimmune disorders Any other unstable chronic medical condition Severe psychiatric disease, especially depression History of active alcohol or drug addiction within the previous 6 months *Patients on opiate substitution therapy were eligible if they were treated by the drug treatment centre in the Department of Psychiatry, Medical University of Vienna	291/282/ 250/250	A vs. B Age (Mean): 37 vs. 36 years Female: 40% vs. 38% Race: NR	A vs. B Genotype 2 – 18/141(13%) vs. 19/141(14%) Genotype 3 - 123/141(87%) vs. 122/141(86%) Severity of liver disease- HCV RNA < 800,000 IU/mL - 5.9 vs. 5.7 Cirrhosis: NR Minimal or no fibrosis: NR 100% Treatment naïve

Author, Year Country Study Name Quality	Duration of Followup	Outcome	Subgroup Analyses	Subgroup Analyses	Histologic Response	Adverse Events	Funding Source
Ferenci, 2008[49] Austria Continued	Followup visits at 24 weeks after completion of treatment	A vs. B ETR: NR SVR: 97/141(68.8%) vs. 90/141(63.8%)	NR	A vs. B SVR: Genotype 2 - 14/18(77.8%) vs. 12/16(63.2%); p=NS Genotype 3 - 83/12(67.5%) vs. 78/122(63.9%); p=NS	NR	A vs. B Overall withdrawals: 13/141 (9%) vs. 22/141 (16%) p=NS Withdrawals due to adverse events: NR Deaths: NR Severe Adverse Events: NR Adverse events: Pruritus: 48/141 (34%) vs. 50/141 (35%); p=NS Psychiatric events (mostly depression): 49/141 (35%) vs. 56/141 (40%); p=NS Hemoglobin <8.5 g/dL: 2/141 (1.4%) vs. 1/141 (0.7%); p=NS Neutrophils <1000/mm3: 73/141 (52%) vs. 71/141 (50%); p=NS Platelets <50K/mm3: 6/141(4%) vs. 6/141 (4%); p=NS	Roche, Austria

Author, Year Country Study Name Quality	Interferon Regimen	Ribavirin Regimen	Protease Inhibitor Regimen	Eligibility	Exclusion	Number Screened/ Eligible/ Enrolled/ Analyzed	Age Sex Race	Genotype Severity of Liver Disease Proportion Treatment-Naïve
Fried., 2008[50] USA Improved Outcomes in Patients with Hepatitis C with Difficult-to-Treat Characteristics: Randomized Study of Higher Doses of Pegylated interferon ά-2a and Ribavirin Overall Quality: Fair	A: Pegylated interferon alfa-2a 180 µg/week/48 weeks B: Pegylated interferon alfa-2a 180 µg/week/48 weeks C: Pegylated interferon alfa-2a 270 µg/week/48 weeks D: Pegylated interferon alfa-2a 270 µg/week/48 weeks	A: Ribavirin 1200 mg/day/48 weeks B: Ribavirin 1600 mg/day/48 weeks C: Ribavirin 1200 mg/day/48 weeks D: Ribavirin 1600 mg/day/48 weeks	None	Treatment-naïve Age 18 years or older Weighing 85 kg Chronic hepatitis C infection with genotype 1 Baseline HCV RNA level 800,000 IU/mL determined by quantitative polymerase chain reaction (PCR) assay Positive anti-HCV antibody test Elevated serum alanine aminotransferase level within the previous 6 months Compensated liver disease Liver biopsy specimen consistent with chronic hepatitis C obtained within the previous 24 months	Infection with an HCV genotype other than 1 Previous treatment with interferon-based therapy, ribavirin, or any investigational drug for chronic hepatitis C History or other evidence of liver disease not associated with chronic hepatitis C Neutrophil count 1.5 x 10^9 cells/L Platelet count 90 109 cells/L Hemoglobin level 12 g/dL in women and 13 g/dL in men Increased risk of anemia or for whom anemia would be medically problematic Serum creatinine level more than 1.5 times the upper limit of normal Co infection with hepatitis B virus or human immunodeficiency virus Other serious chronic disease History of severe psychiatric disease (a history of a suicide attempt, hospitalization or period of disability due to psychiatric disease, and/or a Beck Depression Inventory score 20) Evidence of alcohol or drug abuse within 1 year of study entry	301/193/ 188/187	A vs. B vs. C vs. D Age (Mean): 47.1 vs. 49.6 vs. 47.1 vs. 48.5 years Female: 20% vs. 13% vs. 26% vs. 21% Race: White - 70% vs. 62% vs. 74% vs. 68% Non White-30% vs. 38% vs. 26% vs. 32%	A vs. B vs. C vs. D Genotype 1 – 100% Histologic diagnosis: Non cirrhotic -83% vs. 81% vs. 83% vs. 81% Cirrhosis - 17% vs. 19% vs. 17% vs. 19% HCV RNA (IU/mLx106): 4.9 vs. 6.2 vs. 5.5 vs. 5.2 100% Treatment naïve

Author, Year Country Study Name Quality	Duration of Followup	Outcome	Subgroup Analyses	Subgroup Analyses	Histologic Response	Adverse Events	Funding Source
Fried, 2008[50] USA Continued	Followup visits at 24 weeks after completion of treatment	A vs. B vs. C vs. D ETR: 21/46(45.7%) vs. 27/47(57.4%) vs. 26/47(55.3%) vs. 26/47(55.3%) SVR: 13/46(28.3%) vs. 15/47(31.9%) vs. 17/47(36.2%) vs. 22/47(46.8%)	NR	NR	NR	A vs. B vs. C vs. D Overall withdrawals: 13/46(28%) vs. 9/47(19%) vs. 15/47(32%) vs. 17/47(36%) Withdrawals for adverse events: 5/46(11%) vs. 1/47(2%) vs. 7/47(15%) vs. 9/47(19%) Deaths: NR Serious Adverse Events: 4/46(9%) vs. 6/47(13%) vs. 6/47(13%) vs. 5/47(11%) Adverse events: (significant p-values noted for A vs. B, A vs. C, or C vs. D) Fatigue - 36/46(78%) vs. 32/47(68%) vs. 35/47(74%) vs. 34/47(72%) Headache - 24/46(52%) vs. 18/47(38%) vs. 22/47(47%) vs. 21/47(45%) Insomnia - 18/46(39%) vs. 20/47(43%) vs. 22/47(47%) vs. 24/47(51%) Nausea - 18/46(39%) vs. 20/47(43%) vs. 18/47(38%) vs. 18/47(38%) Chills - 15/46(33%) vs. 14/47(30%) vs. 19/47(40%) vs. 17/47(36%) Myalgia - 14/46(30%) vs. 16/47(34%) vs. 19/47(40%) vs. 16/47(34%) Depression - 14/46 (30%) vs. 20/47(43%) vs. 12/47(26%) vs. 16/47(34%) Arthralgia - 13/46(28%) vs. 16/47(34%) vs. 16/47(34%) vs. 15/47(32%) Irritability - 14/46(30%) vs. 14/47(30%) vs. 12/47(26%) vs. 16/47(34%) Pyrexia - 12/46(26%) vs. 14/47(30%) vs. 16/47(34%) vs. 14/47(30%) Rash - 12/46(26%) vs. 11/47(23%) vs. 15/47(32%) vs. 12/47(26%) Diarrhea - 12/46(26%) vs. 9/47(19%) vs. 11/47(23%) vs. 10/47(21%) Cough - 9/46(20%) vs. 12/47(26%) vs. 12/47(26%) vs. 8/47(17%) Dyspnea - 9/46(20%) vs. 12/47(26%) vs. 8/47(17%) vs. 12/47(26%) Dizziness - 12/46(26%) vs. 9/47(19%) vs. 7/47(15%) vs. 9/47(19%) Back pain - 1/46(2%) vs. 11/47(23%) vs. 4/47(9%) vs. 3/47(6%); (B vs. D p=0.02) Injection site erythema - 10/46(22%) vs. 9/47(19%) vs. 6/47(13%) vs. 5/47(11%)	Hoffman La Roche

Author, Year Country Study Name Quality	Interferon Regimen	Ribavirin Regimen	Protease Inhibitor Regimen	Eligibility	Exclusion	Number Screened/ Eligible/ Enrolled/ Analyzed	Age Sex Race	Genotype Severity of Liver Disease Proportion Treatment-Naïve
Helbling, 2006[51] Switzerland HCV-related advanced fibrosis/cirrhosis: randomized controlled trial of pegylated interferon α-2a and ribavirin Overall Quality: Fair	A: Pegylated interferon alpha-2a 180 µg/week/48 weeks B: Pegylated interferon alpha-2a 180 µg/week/48 weeks	A: (standard dose)Ribavirin <75 kg - 1000 mg/day/48 weeks >75 kg - 1200 mg/day in 2 divided doses/48 weeks B: (low dose) Ribavirin <75 kg - 600 mg/day/48 weeks >75 kg - 800 mg/day in 2 divided doses/48 weeks	None	Age 18–70 years Biopsy proved (within ≤12 months) chronic hepatitis C with advanced fibrosis/cirrhosis (Ishak stage F4–F6 <7 Child–Pugh points No previous antiviral treatment Elevated alanine aminotransferase (ALT; on ≥2 occasions within >6 months) Serum HCV RNA positive Hemoglobin ≥11 g/dL Neutrophil count >1500/lL Platelet count ≥75 000/lL Serum creatinine ≤1.5 times upper limit of normal Normal fasting glucose (or ≤8 µmol/L provided HbA1c ≤8.5%) Hbs-antigen negative antinuclear antibodies ≤1:160 Normal thyroid stimulating hormone Normal alpha-fetoprotein Focal lesions ruled out by ultrasound (within 1 month of study entry)	Concomitant liver disease Ongoing substance abuse including alcohol (≥80 g/day) Hepatocellular carcinoma Clinically relevant disorders of other organs/systems Pregnancy or lactation Refusal to practice effective contraception during treatment/followup Immunomodulatory treatment within 6 months or treatment with any investigational drug within 30 days of study entry	NR/126/ 126/124	A vs. B Age - Median: 47 vs. 47 years Female: 30% vs. 40% Race: NR	A vs. B Genotype 1 – 30/64(47%) vs. 25/60(42%) Genotype 2 – 11/64(17%) vs. 7/60(12%) Genotype 3 - 18/64(28%) vs. 24/60(40%) Genotype 4 - 4/64(6%) vs. 3/60(4%) Histologic stage (Ishak): 3 - 3/64(5%) vs. 4/60(7%) 4 - 26/64(41%) vs. 18/60(30%) 5 - 19/64(30%) vs. 21/60(35%) 6 - 14/64(22%) vs. 13/60(22%) Cirrhosis: 57% vs. 52% Minimal or no fibrosis: 6% vs. 2% 100% Treatment naïve

Author, Year Country Study Name Quality	Duration of Followup	Outcome	Subgroup Analyses	Subgroup Analyses	Histologic Response	Adverse Events	Funding Source
Helbling, 2006[51] Switzerland Continued	Followup visits at 24 weeks post-treatment	A vs. B ETR: NR SVR: 33/64(52%) vs. 23/60(38%), p=0.153	NR	A vs. B ETR: NR SVR: Fibrosis (Ishak): F4 - 15/26(58%) vs. 6/18(33%) F5-6 - 14/33(42%) vs. 14/34(41%) Genotype 1/4 - 11/34(32%) vs. 9/28(32%) Genotype 2/3 – 21/29(72%) vs. 14/31(45%)	NR	A vs. B Discontinuation: 15/64 (23%) vs. 16/60 (27%); p=NS Discontinuation (due to AE): 6/64(9%) vs. 9/60(15%); p=NS Overall withdrawals: 18/64(28%) vs. 23/60(38%); p=NS Deaths: 0/64(0%) vs. 2/60(3%); p=NS Severe Adverse Events: 9/64(14%) vs. 11/60(18%); p=NS Adverse events: Psychiatric - 1/64(2%) vs. 4/60(7%); p=NS Neurologic - 3/64 (5%) vs. 1/60(2%); p=NS Infectious - 1/64(2%) vs. 2/60(3%); p=NS Neoplastic - 2/64 (3%) vs. 1/60(2%); p=NS Skin - 0/64(0%) vs. 1/60(2%); p=NS Endocrine and Metabolism - 0/64(0%) vs. 1/60(2%); p=NS Eye - 1/64(2%) vs. 0/60(0%); p=NS Gastrointestinal - 0/64(0%) vs. 1/60(2%); p=NS Cardiovascular - 1/64(2%) vs. 0/60(0%); p=NS	NR

Author, Year Country Study Name Quality	Interferon Regimen	Ribavirin Regimen	Protease Inhibitor Regimen	Eligibility	Exclusion	Number Screened/ Eligible/ Enrolled/ Analyzed	Age Sex Race	Genotype Severity of Liver Disease Proportion Treatment-Naïve
Jacobson, 2007[52] USA (236 practice sites nation-wide) Pegylated interferon alfa-2b and Weight-Based or Flat-Dose Ribavirin in Chronic Hepatitis C Patients: A Randomized Trial Jacobson, 2007[53] (African-American sub-group) USA (236 practice sites nation-wide) Impact of Weight-based Ribavirin with Pegylated interferon alfa-2b in African-Americans with Hepatitis C Virus Genotype 1 Overall Quality: Fair	A: Pegylated interferon alfa-2b 1.5 µg/kg 1x/week/24 - 48 weeks depending on genotype B: Pegylated interferon alfa-2b 1.5 µg/kg 1x/week/24 - 48 weeks depending on genotype	A: Ribavirin 800 mg/day 24- 48 weeks depending on genotype B: Ribavirin 800-1400 mg/day for 24-48 weeks depending on genotype <65kg - Ribavirin 800 mg/week/48 weeks 65-85 kg - Ribavirin 1000 mg/week/48 weeks >85-105 kg - Ribavirin 1200 mg/week/48 weeks >105 kg but <125 kg - Ribavirin 1400 mg/week/48 weeks	None	Treatment-naive chronic hepatitis C patients 18 to 70 years old Body weight less than 125 kg Treatment-naive adult patients with HCV RNA levels detectable by (PCR)/branched DNA assay Compensated liver disease Liver biopsy showing HCV infection within 36 months prior to screening Elevated ALT at least once during the 6 months prior to screening Alpha-fetoprotein level of ≤100 ng/mL in the year preceding entry	Positive test result for hepatitis B surface antigen or human immunodeficiency virus (HIV)	Paper 1: NR/ NR/ 5519/ 4913 Paper 2: 4913/ 387/ 387/ 387 (sub population from Jacobson , 2007a)	A vs. B Age - Mean: - 45.8 vs. 45.8 years Female - 37.7% vs. 36.2% Race: White - 80.7% vs. 78.8% Non White - 19.3% vs. 21.2% Paper 2: Race: 100% Non White (African-American)	A vs. B Genotype 1 - 1512/2469 (61.2%) vs. 1506/2444 (61.6%) Genotype 2 - 499/2469 (20.2%) vs. 525/2444 (21.5%) Genotype 3 - 421/2469 (17.1%) vs. 386/2444 (15.8%) Genotype 4/5/6 - 33/2469 (1.3%) vs. 23/2444 (0.9%) Genotype viral load >600,000 IU/mL - 1232/2469 (49.9%) vs. 1125/2444 (46.0%) METAVIR stage: F0–F2 - 1729/2469 (70.0%) vs. 1709/2444 (69.9%) F3 - 486/2469 (19.7%) vs. 489/2444 (20.0%) F4 - 254/2469 (10.3%) vs. 246/2444 (10.1%) ALT abnormal: 2119/2469 (85.8%) vs. 2105/2444 (86.1%) HCV viral load (> 600,000 IU/mL): 1232/2469(49.9%) vs. 1125/2444(46%) 100% Treatment naive Paper 2: (African-Americans) Genotype 1: 100% HCV viral load > 600,000 IU/mL - 119/202(59%) vs. 116/185(63%) METAVIR stage F3-F4 (%) - 60/202(30%) vs. 58/185(31%) Cirrhosis: 10% vs. 10% Minimal or no fibrosis: NR 100% Treatment naïve

Author, Year Country Study Name Quality	Duration of Followup	Outcome	Subgroup Analyses	Subgroup Analyses	Histologic Response	Adverse Events	Funding Source

Author, Year Country Study Name Quality	Duration of Followup	Outcome	Subgroup Analyses	Subgroup Analyses	Histologic Response	Adverse Events	Funding Source
Jacobson, 2007[52] USA (236 practice sites nation-wide) Jacobson, 2007[53] (African-American subgroup) USA (236 practice sites nation-wide) Continued	Followup visits at 24 weeks after completion of treatment	A vs. B ETR: 1193/2102(56.8%) vs. 1255/2121(59.2%), p= 0.082 SVR: 852/2102(40.5%) vs. 938/2121(44.2%), p=0.010	A vs. B 65-85 kg: 43.8% vs. 45.2% 85-105 kg: 38.8% vs. 42% >105 kg: 33.5% vs. 47.3% African-Americans Genotype 1: 19/188(10.1%) vs. 36/174(20.7%), p=0.006	A vs. B Genotype1: 337/1305 (29%) vs. 447/1313 (34%); p=0.005 Genotype 2/3: 462/777 (60%) vs. 479/775 (62%); p=0.252 Genotype 1 High Viral Load - 199/744(26.7%) vs. 246/789(31.2%), p=0.056 Genotype 1 Low Viral Load - 149/427(34.9%) vs. 151/381(39.6%); p=0.164	NR	A vs. B Discontinuation: 354/2444(14.5%) vs. 369/2469(14.9%); p=NS Overall withdrawals: 913/2444(37.3%) vs. 895/2469(36.2%); p=NS Death: 5/2444(<1%) vs. 9/2469(<1%); p=NS Serious Adverse Event: 279/2444(11.4%) vs. 287/2469(11.6%); p=NS Adverse events: Cardiovascular – 136/2444(5.6%) vs.162/2469(6.6%); p=NS Psychiatric - 1685/2444(68.9%) vs. 1667/2469(67.5%); p=NS Anemia - 473/2444(19.4%) vs. 721/2469(29.2%); p<0.001 Paper 2 (African Americans): Discontinuation: 85/202(42%) vs. 68/165(41%); p=NS Overall withdrawals: 35/202(17%) vs. 30/165(18%); p=NS Deaths: NR Severe Adverse Events: NR Adverse events: Nadir hemoglobin- <10 g/dL - 30/202(15%) vs. 37/185(20%); p=NS <8.5 g/dL - 2/202(1%) vs. 8/185(4%); p=0.04 RBV dose-reduction - 53/202(26%) vs. 69/185(37%);p=0.02 Nadir Absolute Neutrophil Count- <750 cells/mm3 - 56/202(28%) vs. 44/185(24%); p=NS <500 cells/mm3 - 10/202(5%) vs. 15/185(8%); p=NS Nadir platelets: <100 x 103 cells/mm3 - 30/202(15%) vs. 21/185(11%); p=NS <50 x 103 cells/mm3 - 2/202(1%) vs. 2/185(1%); p=NS	Schering-Plough Corp., Kenilworth, NJ

Author, Year Country Study Name Quality	Interferon Regimen	Ribavirin Regimen	Protease Inhibitor Regimen	Eligibility	Exclusion	Number Screened/ Eligible/ Enrolled/ Analyzed	Age Sex Race	Genotype Severity of Liver Disease Proportion Treatment-Naïve
Kawaoka, 2009[54] Japan Dose comparison study of pegylated interferon-α-2b plus ribavirin in naïve Japanese patients with hepatitis C virus genotype 2: A randomized clinical trial Overall Quality: Fair	A: Pegylated interferon alpha-2a 1.0 µg/kg/week/24 weeks B: Pegylated interferon alpha-2a 1.5 µg/kg/week/24 weeks	A: Ribavirin 60 kg - 600 mg/week/24 weeks >60 kg-≤80 kg - 800 mg/week/24 weeks >80 kg - 1000 mg/week/24 weeks B: Ribavirin 60 kg - 600 mg/week/24 weeks >60 kg-<80 kg - 800 mg/week/24 weeks >80 kg - 1000 mg/week/24 weeks	None	Patients with chronic hepatitis C Age >20 years Treatment naïve Genotype 2	Patients treated with Shosaiko-to, a Japanese herbal medicine considered to improve liver function Patients with autoimmune hepatitis Patients with a history of hypersensitivity to Pegylated Interferon-alpha-2a or other interferons History of hypersensitivity to biological products, such as vaccines Decompensated liver cirrhosis (LC) Hepatocellular carcinoma (HCC) or malignant tumors in other tissues History of severe psychosis, such as being severely depressed and/or suicidal Women who were pregnant or lactating or who were suspected of being pregnant Patients judged by the investigator not to be appropriate for inclusion	NR/ 55/ 53/ 53	A vs. B Age - Median: 57 vs. 55 years Female: 65% vs. 44% Race: NR (study conducted in Japan)	A vs. B Genotype 2a: 13/26(50%) vs. 13/27(48%) Genotype 2b: 13/26(50%) vs. 14/27(52%) Histological stage (Desmet): F0 - 1/26(4%) vs. 0/27(0%) F1 - 14/26(51%) vs. 13/27(48%) F2 - 8/26(31%) vs. 9/27(33%) F3 - 3/26(12 %%) vs. 5/27(19%) Cirrhosis: None Minimal or no fibrosis: 55% vs. 48% 100% Treatment naive

Author, Year Country Study Name Quality	Duration of Followup	Outcome	Subgroup Analyses	Subgroup Analyses	Histologic Response	Adverse Events	Funding Source
Kawaoka, 2009[54] Japan Continued	24 weeks following treatment completion	A vs. B ETR: 23/26(88.5%) vs. 25/27(92.6%), p=0.13 SVR: 10/26(38.5%) vs. 20/27(74.1%), p=0.013	NR	NR	NR	A vs. B Overall withdrawals/drop-out: 2/26(7.2%) vs. 2/27(7.6%); p=NS Discontinuation (pre-mature withdrawal of treatment due to AE): 3/26(11.5%) vs. 2/27(7.4%); p=NS Depression - 1/26(3.8%) vs. 0/27(0%); p=NS Fatigue - 1/26(3.8%) vs. 1/27(4%); p=NS Excitability - 0/26(0%) vs. 1/27(4%); p=NS Deaths: NR Severe Adverse Events: NR Adverse events (leading to dose-reduction): Thrombocytopenia - 1/26(4%) vs. 0/27(0%); p=NS Fatigue - 1/26(4%) vs. 3/27(11%); p=NS Neutropenia - 0/26(0%) vs. 1/27(4%); p=NS Anemia - 15/26 (57.7%) vs. 10/27 (37%); p=NS Reduced Ribavirin - 21/26 (80.7%) vs. 22/27(81.5%); p=NS	NR

Author, Year **Country** **Study Name** **Quality**	**Interferon Regimen**	**Ribavirin Regimen**	**Protease Inhibitor Regimen**	**Eligibility**	**Exclusion**	**Number Screened/ Eligible/ Enrolled/ Analyzed**	**Age** **Sex** **Race**	**Genotype** **Severity of Liver Disease** **Proportion Treatment-Naïve**
Krawitt, 2006[55] USA (New York/New England) A Study of Low Dose Pegylated interferon Alpha-2b with Ribavirin for the Initial Treatment of Chronic Hepatitis C Overall Quality: Fair	A: (low dose) Pegylated interferon alpha-2b 50 µg/week/24 weeks (treatment continued for additional 24 weeks if HCV RNA undetectable by PCR at week 24) B: (standard dose) pegylated interferon alpha-2b <75 kg - 100 µg/week/24 weeks ≥75kg - 150 µg/week/24 weeks (treatment continued for additional 24 weeks if HCV RNA undetectable by PCR at week 24)	A: Ribavirin 1000 mg/day/24 weeks (treatment continued for additional 24 weeks if HCV RNA undetectable by PCR at week 24) B: Ribavirin 1000 mg/day/24 weeks (treatment continued for additional 24 weeks if HCV RNA undetectable by PCR at week 24)	None	Age ≥ 18 years older Detectable serum hepatitis C virus (HCV) RNA Treatment naive Liver biopsy consistent with the diagnosis of chronic hepatitis C, performed not longer than 5 yr prior to entry, with histological interpretation performed by pathologists at the study site locations Chronic hepatitis alone (F0) Chronic hepatitis with fibrosis, including bridging fibrosis (F1–F3) Chronic hepatitis with cirrhosis (F4)	Positive serum hepatitis B surface antigen Any chronic liver disease other than chronic hepatitis C Hemoglobinopathies Evidence of hepatic decompensation(ascites, encephalopathy, gastrointestinal bleeding secondary to portal hypertension) Other conditions that could interfere with participation in the protocol - (i.e. coronary artery disease, uncontrolled hypertension, clinically significant retinal abnormalities, pregnancy, nursing, severe preexisting psychiatric disorders Active substance dependency within 6 months of screening for entry into the study Methadone maintenance (unless a program of continual testing was in use) History of organ transplantation Participation in any other clinical trial or use of another investigational drug within 30 days of entry	NR/NR/ 314/301	A vs. B Age: > 50 years - 18% vs. 19% Female - 38% vs. 36% Race: Non White - 4.6% vs. 3.1%	A vs. B Genotype 1 - 109/152(71.7%) vs. 119/162(73.5%) Genotype 2/3 - 43/152(28.3%) vs. 43/162(26.5%) Histology Fibrosis - 80/152(52.6%) vs. 92/162(56.8%) Cirrhosis - 26/152(17.1%) vs. 17/162(10.5%) Baseline HCV RNA: ≤ 2 x 10^6 copies/ml - 67/152(44.1%) vs. 86/162(40.7%) > 2 x 10^6 copies/ml - 85/152(55.9%) vs. 96/162(59.3%) 100% Treatment naive

Author, Year Country Study Name Quality	Duration of Followup	Outcome	Subgroup Analyses	Subgroup Analyses	Histologic Response	Adverse Events	Funding Source
Krawitt, 2006[55] USA (New York/New England) Continued	Followup visits at 24 weeks Post-treatment	A vs. B ETR: NR SVR: 50/152(33%) vs. 73/162(45%), p=0.02	A vs. B ETR: NR SVR: Age: ≤ 40 years - 13/33(39%) vs. 18/38(47%), p= 0.63 > 40 - ≥ 50 years - 28/91(31%) vs. 40/93(43%), p= 0.09 > 50 years - 9/28 (32%) vs. 15/31 (48%), p= 0.29 Male: 29/94 (31%) vs. 44/110 (40%); p=0.14 Female - 21/58(36%) vs. 29/52(56%), p=0.06 Race: Caucasian - 50/145 (34%) vs. 70/157 (45%), p= 0.08 African-American - 0/6 (0%) vs. 3/4 (75%), p= 0.03 Hispanic/Other - 0/1 (0%) vs. 0/1 (0%), p= 1.00 Weight: < 75 kg - 20/50 (40%) vs. 24/42 (57%), p= 0.14 ≥ 75 kg - 30/102 (29%) vs. 49/120 (41%), p= 0.09	A vs. B ETR: NR SVR: HCV Genotype: Genotype 1 - 26/109 (24%) vs. 45/119 (38%), p= 0.03 Genotype 2/3 - 24/43 (56%) vs. 28/43 (65%), p= 0.51 Baseline HCV RNA: ≤ 2×106 copies/ml - 19/67 (28%) vs. 37/66 (56%), p= 0.002 > 2×106 copies/ml - 31/85 (36%) vs. 36/96 (38%), p= 1.00 Histology: No fibrosis or cirrhosis: 17/46 (37%) vs. 29/53 (55%); p=0.11 Fibrosis - 27/80 (34%) vs. 39/92 (42%), p= 0.27 Cirrhosis - 6/26 (23%) vs. 5/17 (29%), p= 0.73	NR	A vs. B Total Discontinuation: 9/147(6%) vs. 28/154(18%); p=0.0015 Discontinuation due to AE: 5/147(3%) vs. 14/154(9%); p=0.04 Overall withdrawals: NR Deaths: NR Severe Adverse Events: NR	Integrated Therapeutics Group (Schering-Plough)

Author, Year **Country** **Study Name** **Quality**	**Interferon Regimen**	**Ribavirin Regimen**	**Protease Inhibitor Regimen**	**Eligibility**	**Exclusion**	**Number Screened/ Eligible/ Enrolled/ Analyzed**	**Age** **Sex** **Race**	**Genotype** **Severity of Liver Disease** **Proportion Treatment-Naïve**
Manns, 2001[56] US & UK Peginterferon alfa-2b plus ribavirin compared with interferon alfa-2b plus ribavirin for initial treatment of chronic hepatitis C: a randomized trial Overall Quality: Fair	A: Pegylated interferon alfa-2b 1·5 g/kg/4 weeks followed by Pegylated interferon 0·5 g/kg/week/44 weeks B: interferon alfa-2b 3 million units/3x week/48 weeks	A: (weight-based) Ribavirin 1000–1200 mg/day/48 weeks 75 kg > 1000 mg 75 kg < 1200 mg B: (weight-based) Ribavirin 1000–1200 mg/day/48 weeks 75 kg > 1000 mg 75 kg < 1200 mg	NA	Eligible patients were previously untreated adults who had HCV RNA detectable in serum by PCR, who had undergone a liver biopsy within 1 year before entry that was consistent with chronic hepatitis, and who had high serum values of alanine aminotransferase (above the upper limit of normal >43 IU/L for men, >34 IU/L for women) with minimum hematological and biochemical values of: hemoglobin 120 g/L for women and 130 g/L for men; white-blood-cell count 3 109/L; neutrophil count 1·5 109/L; platelet count 100 109/L; and bilirubin, albumin, and creatinine within normal limits.	Patients were excluded if they had decompensated cirrhosis, serum-fetoprotein concentration of more than 50 g/L, HIV infection, previous organ transplantation, other causes of liver disease, pre-existing psychiatric disease, seizure disorders, cardiovascular disease, hemoglobinopathies, hemophilia, poorly controlled diabetes, or autoimmune type disease, or if they were unable to use contraception.	NR/2316/1530/1530	**A vs. B:** Age (Mean): 44 vs. 43 years Female: 168/514(33 %) vs. 169/505(33 %) Race: NR	**A vs. B** Genotype 1: 68% vs. 68% Genotype 2/3: 30% vs. 29% Genotype 4, 5, or 6: 2% vs.3% Histology Mean (SD) baseline Knodell inflammatory score: 7·9 (2·3) vs. 7·8 (2·5) Bridging fibrosis/cirrhosis: 146/491(30%) vs. 132/468(28%) Treatment naive: 100%

Author, Year Country Study Name Quality	Duration of Followup	Outcome	Subgroup Analyses	Subgroup Analyses	Histologic Response	Adverse Events	Funding Source
Manns, 2001[56] US & UK Continued	24 weeks following treatment completion	SVR: 333/511(65%) vs. 289/514(56%) vs. 271/505(54%), p<0·001 (A vs. B), p=0·41 (A vs. C)	NR	**A vs. B vs. C:** SVR: Genotype 1: 42% (145/348) vs. 34% (118/349) vs. 33% (114/343), p=0·02 (A vs. B), p=0·94(A vs C) Genotype 2/3: 82% (121/147) vs. 80% (122/153) vs. 79% (115/146), p=0·46(A vs. B), p=0·89 (A vs. C) Genotype 4/5/6: 50% (8/16) vs. 33% (4/12) vs. 38% (6/16), p=0·72 (A vs B), p>0·99 (A vs. C) SVR by baseline HCV: >2 10^6/mL: 42% (149/351) vs. 42% (144/345) vs. 42% (145/344) 2 10^6/mL: 78% (125/160) vs. 59% (100/169) vs. 56% (90/161) SVR by degree of fibrosis: No/minimal fibrosis - 57% (189/333) vs. 51% (175/345) vs. 49% (164/336) Bridging fibrosis/cirrhosis - 44% (60/136) vs. 43% (63/146) vs. 41% (54/132)	NR	A vs B vs. C: Overall withdrawals: NR Withdrawals for adverse events: 42/511 vs. 36/514 vs. 34/505 Serious adverse events: NR Deaths: NR Adverse Events: Anemia: 9/511 vs. 12/514 vs. 13/505 Neutropenia: 18/511 vs. 10/514 vs. 8/505 Asthenia 18/511 vs. 16/514 vs. 18/505 Fatigue 64/511 vs. 62/514 vs. 60/505 Fever 46/511 vs. 44/514 vs. 33/505 Headache 62/511 vs. 58/514 vs. 58/505 Rigors 48/511 vs. 45/514 vs. 41/505 Weight decrease 29/511 vs. 17/514 vs. 20/505 Dizziness 21/511 vs. 21/514 vs. 17/505 Arthralgia 34/511 vs. 34/514 vs. 28/505 Musculoskeletal pain 21/511 vs. 17/514 vs. 19/505 Myalgia 56/511 vs. 48/514 vs. 50/505 Anorexia 32/511 vs. 29/514 vs. 27/505 Diarrhea 22/511 vs. 16/514 vs. 17/505 Nausea 43/511 vs. 36/514 vs. 33/505 Vomiting 14/511 vs. 14/514 vs. 12/505 Concentration impairment 17/511 vs. 16/514 vs. 21/505 Depression 31/511 vs. 29/514 vs. 34/505 Insomnia 40/511 vs. 40/514 vs. 41/505 Irritability 35/511 vs. 34/514 vs. 34/505 Coughing 17/511 vs. 15/514 vs. 13/505 Dyspnea 26/511 vs. 23/514 vs. 24/505 Alopecia 36/511 vs. 29/514 vs. 32/505 Pruritus 29/511 vs. 26/514 vs. 28/505 Rash 24/511 vs. 22/514 vs. 23/505 Dry skin 24/511 vs. 18/514 vs. 23/505 Injection-site inflammation 25/511 vs. 27/514 vs. 18/505 Injection-site reaction 58/511 vs. 59/514 vs. 36/505	Schering Plough Research Institute, Kenilworth, NJ, and clinical research centre grants from Massachusetts General Hospital (MO1-RR01066), Scripps Clinic (MO1-RR00833), and University of Florida (5MO1-RR00082).

Author, Year Country Study Name Quality	Interferon Regimen	Ribavirin Regimen	Protease Inhibitor Regimen	Eligibility	Exclusion	Number Screened/ Eligible/ Enrolled/ Analyzed	Age Sex Race	Genotype Severity of Liver Disease Proportion Treatment-Naïve
Meyer-Wyss, 2006[57] Switzerland Comparison of two PEG-interferon alpha-2b doses (1.0 or 1.5µg/kg) combined with ribavirin in interferon-naïve patients with chronic hepatitis C and up to moderate fibrosis Overall Quality: Poor	A: Pegylated-interferon alpha-2b 1.0 µg/kg/week/24-48 depending on genotype B: Pegylated-interferon alpha-2b 1.5 µg/kg/week/24-48 depending on genotype	A: Ribavirin 800mg/day/24-48 depending on genotype B: Ribavirin 800mg/day/24-48 depending on genotype	None	Treatment-naive patients Aged 18–65 years Biopsy-proven chronic hepatitis C within ≤12 months Up to moderate fibrosis (METAVIR score ≤F2) with elevated alanine aminotransferase levels (ALT; on at least two occasions, at least 6 months apart) HCV-RNA positive serum	Subjects participating in any study within 30 days prior to entry into the trial Pregnant or nursing women Positive human immunodeficiency virus (HIV)status Liver disease other than chronic hepatitis C Elevated levels of fasting blood glucose Abnormal values of thyroid stimulating hormone Hemophilia or Hemoglobinopathy Any known pre-existing medical condition that could interfere with the patient's participation and completion of the study including: History of severe psychiatric disorders Central nervous system trauma/active seizure disorders Significant cardiovascular Pulmonary, or retinal disorders Clinically manifested gout Substance abuse Chronic systemic administration of steroids/other immunosuppressants Immunologically mediated disease.	NR/NR/ 227/219	A vs. B Age - Median: 39 vs. 42 years Female: 43% vs. 28% Race: NR	A vs. B Genotype 1 - 49/113(43%) vs. 64/106(60%) Genotype 2 - 14/113(12%) vs. 10/106(%) Genotype 3 - 41/113(36%) vs. 26/106(9%) Genotype 4 - 9/113(8%) vs. 6/106(6%) Histological stage (METAVIR score): 0 - 21/113(19%) vs. 13/106(12%) 1 - 44/113(39%) vs. 39/106(37%) 2 - 48/113(42%) vs. 54/106(51%) Cirrhosis: None Minimal of no fibrosis: NR 100% Treatment naive

Author, Year Country Study Name Quality	Duration of Followup	Outcome	Subgroup Analyses	Subgroup Analyses	Histologic Response	Adverse Events	Funding Source
Meyer-Wyss , 2006[57] Switzerland Continued	Followup visits at 4 and 24 weeks post-treatment	A vs. B ETR: NR SVR: 61/113(53%) vs. 56/106(53%), p= ns	NR	A vs. B ETR: 17/39(49%) vs. 23/49(47%) SVR: Genotype 1/4: 22/58 (38%) vs. 27/70 (39%), p= ns Genotypes 2/3: 39/55 (71%) vs. 29 /36 (81%), p = ns >800K IU/mL: 28/48 (58%) vs. 40/69 (43%); p=NS <800 IU/mL: 34/65 (52%) vs. 40/69 (58%): p=NS	NR	A vs. B Discontinuation: 14/115(12%) vs. 28/112(25%); p=0.01 Deaths: 0/115(0%) vs. 1/112(0%); p=NS Life-threatening Adverse Events: 4/115(3%) vs. 9/112(9%); p=NS Severe Adverse Events: 62/115(54%) vs. 59/112(53%); p=NS Withdrawals due to AE: 22/115 (19%) vs. 34/112 (30%); p=0.05 Adverse events (only body systems listed with at least 10% of patients reporting): Thrombocytopenia: 1/115(1%) vs. 1/112(1%); p=NS Leukopenia: 9/115(8%) vs. 5/112(4%); p=NS Neutropenia: 20/115(17%) vs. 18/112(16%); p=NS Hemolytic anemia: 3/115(3%) vs. 3/112(3%); p=NS Blood and lymphatic system disorders - 44/115(38.3%)vs. 41/112 (36.6%); p=NS General disorders and administration site conditions - 112/115(97.4%) vs. 108/112(96.4%); p=NS Gastrointestinal disorders - 81/115(70.4%)vs. 84/112(75.0%); p=NS Metabolism and nutrition disorders -16/115(13.9%) vs. 29/112(25.9%); p=0.02 Musculoskeletal and connective tissue disorders - 27/115(23.5%) vs. 33/112(29.5%); p=NS Nervous system disorders - 70/115(60.9%) vs. 80/112(71.4%); p=NS Psychiatric disorders - 71/115(61.7%) vs. 76/112(67.9%); p=NS Respiratory, thoracic and mediastinal disorders 18/115(15.7%) vs. 24/112(21.4%); p=NS Skin and subcutaneous disorders - 83/115(72.2%) vs. 76/112(67.9%); p=NS	Essex Chemie AG, Lucerne

Author, Year Country Study Name Quality	Interferon Regimen	Ribavirin Regimen	Protease Inhibitor Regimen	Eligibility	Exclusion	Number Screened/ Eligible/ Enrolled/ Analyzed	Age Sex Race	Genotype Severity of Liver Disease Proportion Treatment-Naïve

Mimidis, 2006[58] Greece Hepatitis C virus survival curve analysis in naïve patients treated with Pegylated interferon alpha-2b plus ribavirin. A randomized controlled trial for induction with high doses of Pegylated interferon and predictability of sustained viral response from early virologic data Overall Quality: Poor	A. Pegylated interferon alfa-2b 3.0 mcg/kg weekly for 12 weeks followed by 1.5 mcg/kg weekly for 36 weeks B. Pegylated interferon alfa-2b 1.5 mcg/kg weekly for 48 weeks	A. 800-1200 mg daily (11 mg/kg) B. 800-1200 mg daily (11 mg/kg)	NA	Treatment-naïve HCV RNA detected in serum Liver biopsy consistent with chronic hepatitis within 6 months before enrollment Elevated ALT at entry and at least once in 6 months before screening	HBV HIV coinfection Hemochromatosis Alpha-1 anti-trypsin deficiency Wilson's disease Autoimmune hepatitis Alcohol drug or obesity induced liver disease Substance abuse Any known pre-existing condition that could interfere with patient's participation Creatinine >1.5 mg/dL Neutrophils <1000/mL^3 Platelets <50K/mL^3 Hemoglobin <11 g/dL	NR/NR/ 188/120	A vs. B Age mean: NR Sex: 36% vs. 38% non White: NR	A vs. B genotype 1/4: 46% vs. 52% Treatment-naïve: all Fibrosis: NR Cirrhosis: NR HCV RNA$\geq$ 800k IU/mL: NR

Author, Year Country Study Name Quality	Duration of Followup	Outcome	Subgroup Analyses	Subgroup Analyses	Histologic Response	Adverse Events	Funding Source
Mimidis, 2006[58] Greece Continued	Week 72	A vs. B ETR: NR SVR: 38/89 (42.7%) vs. 47/87 (54%)	NR	A vs. B Genotype 1: 9/35 (25.7%) vs. 18/40 (45%); p=NS Genotype 2/3: 23/48 (47.9%) vs. 25/42 (59.5%); p=NS Genotype 4: 6/6 (100%) vs. 4/5 (80%); p=NS	NA	NR	NR

Author, Year Country Study Name Quality	Interferon Regimen	Ribavirin Regimen	Protease Inhibitor Regimen	Eligibility	Exclusion	Number Screened/ Eligible/ Enrolled/ Analyzed	Age Sex Race	Genotype Severity of Liver Disease Proportion Treatment-Naïve
Reddy, 2010[59] International, 14 countries Induction pegylated interferon alfa-2a and high dose ribavirin do not increase SVR in heavy patients with HCV genotype 1 and high viral loads Overall Quality: Fair	A. Pegylated interferon alpha-2a 360 mcg weekly for 12 weeks then 180 mcg weekly for 36 weeks B. Pegylated interferon alpha-2a 360 mcg/weekly for 12 weeks then 180 mcg weekly for 36 weeks C. Pegylated interferon alpha-2a 180 mcg weekly for 48 weeks D. Pegylated interferon alpha-2a 180 mcg weekly for 48 weeks	A. 1400 - 1600 mg/day for 48 weeks depending on weight B. 1200 mg/day for 48 weeks C. 1400 - 1600 mg/day for 48 weeks depending on weight D. 1200 mg/day for 48 weeks	NA	Treatment-naïve Aged 18 years or older Weight $\geq$ 85 kg HCV genotype 1 infection HCV RNA $\geq$ 400k IU/mL Liver biopsy in past 24 months consistent with chronic hepatitis C	coinfection with HBV, HAV, or HIV Chronic liver disease of other origin Current or past history of chronic systemic disease including severe psychiatric disease Increased baseline risk of anemia Neutrophils <1500/mL^3 Platelets <90K/mL^3 Hemoglobin<12 g/dL in men or <13 g/dL in women Creatinine >1.5 times upper limit of normal Pregnant or breastfeeding women and male partners	NR/NR/ 1175/1145	A vs. B vs. C vs. D Age mean: 46 vs. 46 vs. 45 vs. 46 Female: 19% vs. 24% vs. 22% vs. 19% non White: 14% vs. 13% vs. 19% vs. 13%	A vs. B vs. C vs. D genotype 1: all Treatment-naïve: all Bridging fibrosis/cirrhosis: 12% vs. 8% vs. 10% vs. 12% HCV RNA $\geq$800k IU/mL: 86% vs. 83% vs. 84% vs. 82%

Author, Year Country Study Name Quality	Duration of Followup	Outcome	Subgroup Analyses	Subgroup Analyses	Histologic Response	Adverse Events	Funding Source
Reddy, 2010[59] International, 14 countries Continued	Week 72	A vs. B vs. C vs. D ETR: NR SVR: 156/383 (40.7%) vs. 166/382 (43.5%) vs. 81/189 (42.9%) vs. 72/191 (37.7%); (p=NS for all comparisons)	A vs. B vs. C vs. D (counts not reported) Weight <95 kg: 44% vs. 46% vs. 44% vs. 49% Weight ≥95 kg: 38% vs. 41% vs. 41% vs. 29%	A vs. B vs. C vs. D (counts not reported) Steatosis score <5%: 42% vs. 48% vs. 48% vs. 47% Steatosis score ≥5%: 36% vs. 30% vs. 32% vs. 13%	NA	A vs. B vs. C vs. D Overall withdrawals: 117/383 (31%) vs. 109/382 (29%) vs. 53/189 (28%) vs. 54/191 (28%); A vs. C p=NS; B vs. D p=NS Withdrawals for adverse events: 47/383 (12%) vs. 40/382 (10%) vs. 17/189 (9%) vs. 22/191 (12%); A vs. C p=NS; B vs. D p=NS Serious adverse events: 39/383 (10%) vs. 36/382 (9%) vs. 20/189 (11%) vs. 22/191 (12%); A vs. C p=NS; B vs. D p=NS Deaths: 2/383 (<1%) vs. 2/382 (<1%) vs. 3/189 (1%) vs. 1/191 (<1%); A vs. C p=NS; B vs. D p=NS Pyrexia: 205/383 (54%) vs. 176/382 (46%) vs. 78/189 (41%) vs. 83/191 (43%); A vs. C p=NS; B vs. D p=NS Fatigue: 182/383 (48%) vs. 185/382 (48%) vs. 102/189 (54%) vs. 66/191 (35%); A vs. C p=NS; B vs. D p=NS Headache: 168/383 (44%) vs. 152/382 (40%) vs. 76/189 (76%) vs. 75/191 (39%); A vs. C p=0.006; B vs. D p=0.002 Chills: 132/383 (34%) vs. 122/382 (32%) vs. 55/189 (29%) vs. 42/191 (22%); A vs. C p=NS; B vs. D p=0.001 Myalgia: 113/383 (30%) vs. 98/382 (26%) vs. 45/189 (24%) vs. 46/191 (24%); A vs. C p=NS; B vs. D p=NS Arthralgia: 89/383 (23%) vs. 88/382 (23%) vs. 49/189 (26%) vs. 50/191 (26%); A vs. C p=NS; B vs. D p=NS Depression: 58/383 (15%) vs. 72/382 (19%) vs. 36/189 (19%) vs. 32/191 (17%); A vs. C p=NS; B vs. D p=NS Hemoglobin <8.5 g/dL: 22/383 (6%) vs. 9/382 (2%) vs. 12/189 (6%) vs. 6/191 (3%); A vs. C p=NS; B vs. D p=NS	Roche

Author, Year Country Study Name Quality	Duration of Followup	Outcome	Subgroup Analyses	Subgroup Analyses	Histologic Response	Adverse Events	Funding Source
Reddy, 2010[59] International, 14 countries Continued						Neutrophils <500/mL3: 26/383 (7%) vs. 25/382 (7%) vs. 10/189 (5%) vs. 9/191 (5%); A vs. C p=NS; B vs. D p=NS Platelets <20K/mL3: 3/383 (1%) vs. 0/382 (0%) vs. 0/189 (0%) vs. 3/191 (2%); A vs. C p=NS; B vs. D p=NS	

Author, Year **Country** **Study Name** **Quality**	**Interferon Regimen**	**Ribavirin Regimen**	**Protease Inhibitor Regimen**	**Eligibility**	**Exclusion**	**Number Screened/ Eligible/ Enrolled/ Analyzed**	**Age** **Sex** **Race**	**Genotype** **Severity of Liver Disease** **Proportion Treatment-Naïve**
Roberts, 2009[60] Australia Impact of high-dose Pegylated interferon alfa-2a on virologic response rates in patients with hepatitis C genotype 1: a randomized controlled trial Overall Quality: Fair	A. Pegylated interferon alfa-2a 360 mcg weekly for 12 weeks followed by 180 mcg for 36 weeks (48 weeks total) B. Pegylated interferon alfa-2a 180 mcg weekly for 48 weeks	A. 1000-1200 mg/day for 48 weeks B. 1000-1200 mg/day for 48 weeks	NA	Treatment naïve Ages 18 -75 years HCV genotype 1 infection HCV RNA >600 IU/mL Elevated ALT Compensated liver disease (Child-Pugh score <7) Histologic findings consistent with chronic hepatitis on liver biopsy within last 36 months *Protocol modified during study to remove ALT, pretreatment biopsy, and compensated cirrhosis inclusion/exclusion requirements	HBV HIV coinfection History of decompensated liver disease Evidence of hepatocellular carcinoma Liver disease of other origin Therapy with systemic antiviral, antineoplastic, or immunomodulatory agents within 6 months Pregnancy or breast feeding and male partner of women Neutrophils <1500/mL^3 Hemoglobin <12 g/dL in women and <13 g/dL in men Creatinine >1.5 times the upper limit of normal Active severe psychiatric disease Any severe chronic or uncontrolled disease Current or recent drug or alcohol abuse Cirrhosis	NR/NR/ 896/871	A vs. B Age mean: 44 vs. 43 Female: 31% vs. 35% non White: 18% vs. 17%	A vs. B genotype 1: all Treatment-naïve: all Fibrosis stage 3 or 4: 14% vs. 16% HCV RNA $\geq$ 800K: 70% vs. 67%

Author, Year Country Study Name Quality	Duration of Followup	Outcome	Subgroup Analyses	Subgroup Analyses	Histologic Response	Adverse Events	Funding Source
Roberts, 2009[60] Australia Continued	24 weeks after end of treatment (week 72)	A vs. B ETR: 70% vs. 66%; p=0.18 SVR: (230/433) 53% vs. (219/438) 50%; p=0.29	A vs. B White: 183/355 (52%) vs. 167/365 (46%); p=NS Asian: 40/61 (66%) vs. 40/55 (73%); p=NS Other: 7/17 (41%) vs. 12/18 (67%); p=NS Male: 149/298 (50%) vs. 134/285 (47%); p=NS Female: 81/135 (60%) vs. 85/153 (56%); p=NS <40 years: 104/146 (71%) vs. 97/141 (69%); p=NS >40 years: 126/287 (44%) vs. 122/297 (41%); p=NS Weight <85 kg: 167/294 (57%) vs. 156/297 (53%); p=NS Weight >85 kg: 63/139 (45%) vs. 63/141 (45%); p=NS	A vs. B HCV RNA <800K: 81/125 (65%) vs. 84/138 (61%); p=NS HCV RNA ≥800K: 147/302 (49%) vs. 132/293 (45%); p=NS Fibrosis METAVIR stage 3 or 4: 17/60 (28%) vs. 16/67 (24%); p=NS Fibrosis METAVIR stage 0,1,or 2: 148/256 (58%) vs. 134/242 (55%); p=NS	NR	A vs. B Overall withdrawals: 113/433 (26%) vs. 136/438 (31%); p=NS Withdrawals due to adverse events: 44/433 (10%) vs. 36/438 (8%); p=NS Deaths: NR Serious adverse events: 46/433 (11%) vs. 45/438 (10%); p=NS Headache: 227/433 (52%) vs. 208/438 (47%); p=NS Influenza like illness: 180/443 (42%) vs. 183/438 (42%); p=NS Nausea: 179/433 (41%) vs. 169/438 (39%); p=NS Fatigue: 159/433 (37%) vs. 174/438 (40%); p=NS Myalgia: 114/433 (26%) vs. 97/438 (22%); p=NS Rash: 110/433 (25%) vs. 116/438 (26%); p=NS Depression: 84/433 (19%) vs. 85/438 (19%); p=NS Arthralgia: 82/433 (19%) vs. 76/438 (17%); p=NS Pyrexia: 66/433 (15%) vs. 47/438 (11%); p=NS Chills: 64/433 (15%) vs. 34/438 (8%); p<0.001 Neutropenia: 76/433 (21%) vs. 55/438 (13%); p=0.05 Thrombocytopenia: 17 (4%) vs. 6 (1%); p=0.02 Anemia: 5 (1%) vs. 3 (1%); p=NS	Roche

Author, Year Country Study Name Quality	Interferon Regimen	Ribavirin Regimen	Protease Inhibitor Regimen	Eligibility	Exclusion	Number Screened/ Eligible/ Enrolled/ Analyzed	Age Sex Race	Genotype Severity of Liver Disease Proportion Treatment-Naïve
Sood, 2008[61] India Comparison of low-dose pegylated interferon vs. standard high-dose pegylated interferon in combination with ribavirin in patients with chronic hepatitis C with genotype 3: An Indian Experience Overall Quality: Fair	A: Pegylated-interferon alpha-2b 1.0 µg/kg/week/24 weeks B: Pegylated-interferon alpha-2B 1.5 µg/kg/week/24 weeks	A: Ribavirin 10-12 mg.kg/day/24 weeks B: Ribavirin 10-12 mg.kg/day/24 weeks	None	Aged between 16–70-years-old HCV-RNA positive with genotype 3 Treatment naïve ALT >1.2 x Upper limit of Normal (ULN) at screening and for at least the previous 6 months Liver biopsy–proven chronic HCV within 6 months prior to inclusion	Chronic HCV patients with genotypes other than Genotype 3 Total leukocyte count < 3000 per cubic millimeter Platelet count < 70 000 per cubic millimeter, Hemoglobin level lower than 10 g per deciliter co infection with hepatitis B virus or human immunodeficiency virus, Alcohol intake exceeding 20 g/day Presence of drug abuse, psychiatric illness, or thyroid dysfunction Pregnancy and lactation Decompensated liver disease Evidence of liver disease due to other etiology such as autoimmune or drug-induced hepatitis Serious concurrent medical illnesses (such as malignancy, severe cardiopulmonary disease, or uncontrolled diabetes mellitus) Inability to give an informed written consent	NR/103/ 103/103	A vs. B Age - Mean: 43 vs. 37 years Female: 12% vs. 22% Race: NR	A vs. B Genotype 3: 100% (Knodell) HAI score - Mean (SD): 7.2 (3.15) vs. 4.68(2.12) Fibrosis score - Mean(SD): 2.34(1.27) vs. 1.64(1.29) Cirrhosis: NR 100% Treatment naïve

Author, Year Country Study Name Quality	Duration of Followup	Outcome	Subgroup Analyses	Subgroup Analyses	Histologic Response	Adverse Events	Funding Source
Sood, 2008[61] India Continued	Followup visits at 24 weeks post-treatment	A vs. B ETR: 72/76(94.7%) vs. 24/27(88.9%), p=0.375 SVR: 60/76(78.9%) vs. 25/27(926%), p=0.145	NR	NR	NR	A vs. B Overall withdrawals: 1/76 (1.3%) vs. 2/27 (7.4%); p=NS Withdrawals (due to AE): 0/76 vs. 1/27 (4%); p=NS Deaths: NR Severe Adverse Events: NR Adverse events: Influenza-like symptoms - 20/27(74.0 %%) vs. 44/76(57.9%); p=NS Malaise or fatigue -10/27(37.0%) vs. 22/76(29.0%); p=NS Nausea or vomiting - 5/27(18.5%) vs. 11/76(14.5%) p=NS Headache - . 4/27 (14.8%) vs. 8/76(10.5%); p=NS Abdominal discomfort - 4/27(14.8%) vs. 8/76 (10.5%); p=NS Diarrhea - . 4/27(14.8%) vs. 9 /76(11.8%); p=NS Grade III or IV laboratory abnormalities Neutrophils - 3/27(11.1%) vs. 1/76(1.3%); p=0.02 Platelets - 4/27(14.8%) vs. 2/76(2.6%); p=0.02	NR

Evidence Table 8. Quality rating: Trials of dual therapy with pegylated interferon plus ribavirin: dose effects

Author, Year	Randomization adequate?	Allocation concealment adequate?	Groups similar at baseline?	Eligibility criteria specified?	Outcome assessors masked?	Care provider masked?	Patient masked?	Attrition and withdrawals reported?	Loss to followup: differential/high?	Intention-to-treat analysis	Quality	Funding
Abergel, 2006[47]	Unclear	Unclear	Unclear	Yes	Unclear	Unclear	Unclear	No	Unclear	Yes	Fair	NR
Brady, 2010[48]	Yes	Unclear	Yes	Yes	No, open label	No, open label	No, open label	Yes	Yes	Yes	Fair	Schering Plough
Fried, 2008[50]	Unclear	Unclear	Yes	Yes	Unclear	Yes	Yes	Yes	Yes	Yes	Fair	NR
Hadziyannis, 2004[29]	Yes	Yes	No	Yes	Yes	Unclear	Unclear	Yes	Unclear	Yes	Fair	Roche, Basel, Switzerland
Helbling, 2006[51]	Yes	Yes	Yes	Yes	No, open label	No, open label	No, open label	Yes	No	Yes	Fair	NR
Jacobson, 2007a[52]	Yes	Yes	Yes	Yes	No, open label	No, open label	No, open label	Yes	Yes	Yes	Fair	Schering-Plough Corp. , Kenilworth, NJ
Jacobson, 2007b[53]	Yes	Yes	Yes	Yes	No, open label	No, open label	No, open label	Yes	Yes	Yes	Fair	Schering-Plough Corp. , Kenilworth, NJ
Kawaoka, 2009[54]	Unclear	Unclear	Unclear	Yes	No, open label	No, open label	No, open label	Yes	No	Yes	Fair	NR
Krawitt, 2006[55]	Unclear	Unclear	Yes	Yes	Unclear	Unclear	Unclear	Unclear	Unclear	Yes	Fair	Integrated Therapeutics Group (Schering-Plough)
McHutichson, 2009[62]	Unclear	Unclear	Yes	Yes	Unclear	Unclear	Unclear	Yes	Unclear	Yes	Fair	Schering-Plough
Meyer-Wyss, 2006[57]	Unclear	Yes	No	Yes	No, open label	No, open label	No, open label	Yes	Yes	Yes	Poor	Essex Chemie AG, Lucerne
Mimidis, 2006[58]	Unclear	Unclear	Unclear	Yes	No (not described)	No (not described)	No (not described)	No	No	No	Poor	NR
Reddy, 2010[59]	Yes	Yes	Yes	Yes	Unclear	Yes	Yes	Yes	Yes	Yes	Fair	Roche

Author, Year	Randomization adequate?	Allocation concealment adequate?	Groups similar at baseline?	Eligibility criteria specified?	Outcome assessors masked?	Care provider masked?	Patient masked?	Attrition and withdrawals reported?	Loss to followup: differential/high?	Intention-to-treat analysis	Quality	Funding
Roberts, 2009[60]	Unclear	Unclear	Yes	Yes	No, open label	No, open label	No, open label	Yes	Yes	Yes	Fair	NR
Sood, 2008[61]	Unclear	Unclear	Unclear	Yes	Unclear	Unclear	Unclear	Yes	No	Yes	Fair	NR

Key Question 4

Evidence Table 9. Studies on sustained virologic response and clinical outcomes

Author, Year Country Quality	Study Type Duration of Followup	Comparison Definition of Sustained Virological Response	Inclusion Criteria	Exclusion Criteria	Number analyzed Number meeting inclusion criteria excluded due to missing data or lost to followup	Population Characteristics
Arase, 2007[63] Japan Overall Quality: Fair	Retrospective cohort study Duration of followup: Mean 7.4 years	SVR vs. no SVR SVR=Undetectable HCV RNA 6 months after completion of long-term IFN therapy	>=60 years of age; ALT elevation greater than double upper limits within 6 months (ALT normal range 12-50IU/l); no corticosteroid immunosuppressive agents or antiviral agents used in last 6 months; no hepatitis B surface antigens, antinuclear antibodies, or antimitochondrial antibodies detectable in serum; leukocytes>3000/mm^3, platelet count >80,000/mm^3, and bilirubin <2.0 mg/ml; IFN therapy >4 weeks	History of alcohol abuse or advanced liver cirrhosis, encephalopathy, bleeding esophageal varices, or ascites	Number analyzed: 500 Excluded due to missing data or lost to followup: Unclear	SVR (n=140) vs. no SVR (n=360) Mean age (years): 63 vs. 64 (p=0.07) Female: 41% vs. 53% (p=0.01) Race: Not reported Genotype 1b: 34% vs. 71% (p<0.0001) Viral load (kIU/ml): 172 vs. 661 (p<0.0001) Cirrhosis (Knodell F4): 9% vs. 16% (p=0.009)

Author, Year Country Quality	Treatments	Variables Assessed as Univariate Predictors	Variables Included in Multivariate Models	Results	Funding Source
Arase, 2007[63] Japan Continued	Interferon alpha-2a or - Interferon alpha-2b monotherapy: 94% Interferon plus ribavirin combination therapy: 6%	Age, sex, liver fibrosis, liver activity, viral load, genotype, AST, ALT	Hepatocellular cancer: Sex, liver fibrosis All-cause and liver-related mortality: Sex, liver fibrosis	SVR vs. no SVR Hepatocellular cancer: Adjusted HR 0.19 (0.08-0.45) All-cause mortality: Adjusted HR 0.39 (0.16-0.93) Liver-related mortality: Adjusted HR 0.13 (0.03-0.59)	Okinaka Memorial Institute for Medical Research and Japanese Ministry of Health, Labor and Welfare

Author, Year Country Quality	Study Type Duration of Followup	Comparison Definition of Sustained Virological Response	Inclusion Criteria	Exclusion Criteria	Number analyzed Number meeting inclusion criteria excluded due to missing data or lost to followup	Population Characteristics
Backus, 2011[64] USA Overall Quality: Fair	Retrospective cohort study Duration of followup: Median 3.8 years	SVR vs. no SVR SVR=Undetectable HCV RNA 6 months after completion of antiviral therapy	HCV genotype 1, 2, or 3; started pegylated interferon + ribavirin between January 2001 and June 2007; stopped treatment by June 2008; HCV RNA test after end of treatment	HIV infection, hepatocellular cancer prior to treatment	Number analyzed: 16,864 Excluded due to missing data or lost to followup: 5365	SVR vs. no SVR (genotypes 1 [n=12,166], 2 [n=2904], and 3 [n=1794]) Mean age (years): 51 vs. 52, 53 vs. 53. and 51 vs. 51 Female: 5% vs. 4%, 4% vs. 3%, and 4% vs. 3% Non white: 40% vs. 51%, 33% vs. 31%, and 30% vs. 29% Genotype: Results stratified by genotype Viral load >=500,000 IU/mL: 70% vs. 82%, 78% vs. 83%, and 64% vs. 68% Cirrhosis: 9% vs. 15%, 7% vs. 12%, and 12% vs. 20%

Author, Year Country Quality	Treatments	Variables Assessed as Univariate Predictors	Variables Included in Multivariate Models	Results	Funding Source
Backus, 2011[64] USA Continued	Pegylated interferon (alfa-2aa or 2b) plus ribavirin	Age, sex, albumin, AST, AST/ALT ratio, creatinine clearance, platelets, sodium, cirrhosis, Chronic obstructive pulmonary disease (COPD), diabetes, HTN, tobacco use, treatment duration <60% recommended, bilirubin, body mass index, HBV co-infection, viral load, hemoglobin, CAD, cancer, congestive heart failure, cerebrovascular disease, schizophrenia, recent alcohol abuse, anxiety disorder, depression, hard drug use, post-traumatic stress disorder (PTSD), socioeconomic status instability, multiple treatment course, erythropoiesis stimulating agent use, granulocyte colony stimulating factor use, year of treatment start	Age, sex, albumin, AST, AST/ALT ratio, creatinine clearance, platelets, sodium, cirrhosis, Chronic obstructive pulmonary disease (COPD), diabetes, HTN, tobacco use, treatment duration <60% recommended, bilirubin, body mass index, HBV co-infection, viral load, hemoglobin, coronary artery disease, cancer, congestive heart failure, cerebrovascular disease, schizophrenia, recent alcohol abuse, anxiety disorder, depression, hard drug use, post-traumatic stress disorder (PTSD), socioeconomic status instability, multiple treatment course, erythropoiesis stimulating agent use, granulocyte colony stimulating factor use, year of treatment start	SVR vs. no SVR (genotypes 1, 2, and 3, respectively) All-cause mortality: Adjusted HR 0.71 (0.60-0.86), 0.62 (0.44-0.87), and 0.51 (0.35-0.75)	US Department of Veterans Affairs, Veterans Health Administration, Office of Public Health and Environmental Hazards

Author, Year Country Quality	Study Type Duration of Followup	Comparison Definition of Sustained Virological Response	Inclusion Criteria	Exclusion Criteria	Number analyzed Number meeting inclusion criteria excluded due to missing data or lost to followup	Population Characteristics
Bruno, 2007[65] Italy Overall Quality: Fair	Retrospective cohort study Duration of followup: Mean 8 years	SVR vs. no SVR SVR=Undetectable HCV RNA 6 months after completion of antiviral therapy	Anti-HCV and HCV-RNA positive and diagnosis of complete cirrhosis by histological criteria (Ishak score of 6 or Knodell score of 4); liver biopsy within 18 months of start of IFN treatment	Over 70 years of age; lack of histological diagnosis of cirrhosis, gastroesophageal varices; previous episodes of decompensation or bleeding; Child class B or C, concurrent Hepatocellular carcinoma or extra hepatic tumors; subjects co-infected with hepatitis B or HIV	Number analyzed: 883 Excluded due to missing data or lost to followup: Unclear	SVR (n=124) vs. no SVR (n=759) Mean age (years): 53 vs. 44 (p=0.004) Female: 27% vs. 38% (p<0.001) Non White: 0 (0%) vs. 0 (0%) Race: Not reported Genotypes 1 and 4: 37% vs. 63% (p<0.001) Viral load: Not reported Cirrhosis: All (inclusion criterion)

Author, Year Country Quality	Treatments	Variables Assessed as Univariate Predictors	Variables Included in Multivariate Models	Results	Funding Source
Bruno, 2007[65] Italy Continued	Interferon monotherapy	Age, sex, platelet count, genotype	Hepatocellular carcinoma: Age, sex, platelet count Liver-related mortality: Age, platelet count	SVR vs. no SVR Ascites, encephalopathy, or gastrointestinal bleeding: Not calculated, 0 events/1061 person-years vs. 107 events/5703 person-years (1.88 events/100 person-years) Hepatocellular carcinoma: Adjusted HR 0.39 (0.17-0.88) Liver-related mortality: 0.14 (0.04-0.59)	Associazione per la Ricera sulle Malattie Epatiche (ARME), Bologna, Italy

Author, Year Country Quality	Study Type Duration of Followup	Comparison Definition of Sustained Virological Response	Inclusion Criteria	Exclusion Criteria	Number analyzed Number meeting inclusion criteria excluded due to missing data or lost to followup	Population Characteristics
Cardoso, 2010[66] France Overall Quality: Fair	Retrospective cohort study (of patients originally enrolled in clinical trials) Duration of followup: Median 3.5 years	SVR vs. no SVR SVR=Undetectable HCV RNA 6 months after completion of antiviral therapy	Anti-HCV and HCV RNA positive, documented chronic hepatitis C, biopsy-proven bridging fibrosis or cirrhosis, treated with interferon-based therapy in clinical trials between 1987 and 2007	HBV, hepatitis D virus, or HIV infection co-infection; history of hepatic decompensation	Number analyzed: 307 Excluded due to missing data or lost to followup: Unclear	SVR (n=103) vs. no-SVR (n=204) Mean age (years): 55 vs. 55 (p=0.93) Female: 30% vs. 34% (p=0.51) Race: Not reported Genotype 1: 36% vs. 72% (p<0.001) Viral load (log_{10} l/ml): 5.5 vs. 5.7 (p=0.08) Cirrhosis (METAVIR F4): 53% vs. 61% (p=0.19)

Author, Year Country Quality	Treatments	Variables Assessed as Univariate Predictors	Variables Included in Multivariate Models	Results	Funding Source
Cardoso, 2010[66] France Continued	Pegylated interferon and ribavirin: 252 (82%) Pegylated interferon monotherapy: 22 (7%) Conventional interferon with or without ribavirin: 33 (11%)	Age, sex, BMI, alcohol consumption, diabetes, ALT, bilirubin, albumin, platelets, genotype, viral load, inflammation, fibrosis and steatosis scores	Hepatocellular carcinoma: Age, bilirubin, albumin, platelet count Ascites/variceal bleeding and liver-related mortality: Bilirubin, albumin, platelets	SVR vs. no SVR Hepatocellular carcinoma: Adjusted HR 0.33 (0.23-0.89) Ascites or variceal bleeding: Adjusted HR 0.21 (0.05-0.92) Liver-related mortality: Adjusted HR 0.27 (0.08-0.95)	Schering Plough

Author, Year Country Quality	Study Type Duration of Followup	Comparison Definition of Sustained Virological Response	Inclusion Criteria	Exclusion Criteria	Number analyzed Number meeting inclusion criteria excluded due to missing data or lost to followup	Population Characteristics
Coverdale, 2004[67] Australia Overall Quality: Poor	Prospective cohort study (some patients originally enrolled in randomized trials) Duration of followup: Median 9 years	SVR vs. response relapse vs. nonresponse SVR=Undetectable HCV RNA on at least 2 occasions at least 2 years after completion of therapy	Virologically and histologically proven chronic hepatitis C	Clinical or imaging evidence of liver-related complications	Number analyzed: 343 Excluded due to missing data or lost to followup: Unclear	Demographics for all treated patients (not reported by SVR status) Median age (years): 37 Female: 33% Race: Not reported Genotype 1: 38% Viral load: Not reported Median fibrosis score (Scheuer): 2

Author, Year Country Quality	Treatments	Variables Assessed as Univariate Predictors	Variables Included in Multivariate Models	Results	Funding Source
Coverdale, 2004[67] Australia Continued	Interferon alpha-2a or Interferon alpha-2b	Statistically significant predictors of outcomes in univariate analyses were age, duration, place of birth, mode of transmission, genotype, fibrosis score, albumin, bilirubin, prothrombin time. Other tested variables not reported.	Age, duration, place of birth, mode of transmission, genotype, fibrosis score, albumin, bilirubin, prothrombin time	SVR vs. response-relapse vs. nonresponse Liver-related complications (hepatic decompensation, complications of portal hypertension, hepatocellular carcinoma, liver transplantation, and liver-related mortality) at 10 years: Not statistically significant in multivariate analysis, adjusted HR not reported (p=0.06) Hepatocellular carcinoma at 10 years: Not statistically significant in multivariate analysis, adjusted HR and p value not reported Liver transplant or liver-related death at 10 years: Not statistically significant in multivariate analysis, adjusted HR not reported (p=0.20)	National Institutes of Health

Author, Year Country Quality	Study Type Duration of Followup	Comparison Definition of Sustained Virological Response	Inclusion Criteria	Exclusion Criteria	Number analyzed Number meeting inclusion criteria excluded due to missing data or lost to followup	Population Characteristics
El Braks, 2007[68] France Overall Quality: Poor	Retrospective cohort study Duration of followup: Mean 7.7 years	SVR vs. no SVR SVR=Undetectable HCV RNA 6 months after completion of antiviral therapy	HCV-related cirrhosis defined by association of positive serum HCV antibodies and RNA, with typical liver histology; absence of complication before or at inclusion; daily alcohol consumption <50 g; at least 3 month course of antiviral treatment using standard or pegylated interferon with or without ribavirin, according to therapeutic advance over time and initial guidelines; a regular followup >=30 months after the starting of first treatment; residence in France allowing regular followup	HBV or HIV co-infection; contraindication to antiviral treatment, particularly platelet and polymorphonuclear counts ≤80,000/mm3 and 1500/mm3, respectively; Hepatocellular carcinoma or suspicious findings such as liver nodule or serum level of alpha-fetoprotein above 50 ng/mL	Number analyzed: 113 Excluded due to missing data or lost to followup: Unclear	SVR (n=37) vs. no SVR (n=76) Mean age (years): 51 vs. 56 (p=0.02) Female: 16% vs. 50% (p=0.0005) Race: Not reported HCV genotype 1: 36% vs. 73% (p=0.0001) Viral load: Not reported Cirrhosis: All (inclusion criterion)

Author, Year Country Quality	Treatments	Variables Assessed as Univariate Predictors	Variables Included in Multivariate Models	Results	Funding Source
El Braks, 2007[68] France Continued	Interferon monotherapy: 35/113 (31%) Interferon + ribavirin: 40/113 (35%) Pegylated interferon + ribavirin: 38/113 (34%)	Age, sex, genotype, duration of treatment	Duration of treatment	SVR (n=37) vs. no SVR (n=76) Clinical events (hepatocellular cancer, ascites, hepatic encephalopathy, or death): Adjusted HR 0.14 (0.04-0.45)	Not reported

Author, Year Country Quality	Study Type Duration of Followup	Comparison Definition of Sustained Virological Response	Inclusion Criteria	Exclusion Criteria	Number analyzed Number meeting inclusion criteria excluded due to missing data or lost to followup	Population Characteristics
Fernandez-Rodriguez, 2010[69] Spain Overall Quality: Poor	Retrospective cohort study Duration of followup: Median 35 months	SVR vs. no SVR SVR=Undetectable HCV RNA 6 months after completion of antiviral therapy	HCV-associated cirrhosis	Child-Pugh-Turcotte's score (CPT) >6; HIV or HBV co infection; alcohol intake >40 g per day in males or >20 g per day in females; present or past psychosis or severe depression; neutropenia <1500 per ml and/or thrombocytopenia <100,000 platelets per ml; organ transplantation; severe heart disease; uncontrolled seizures; uncontrolled diabetes; autoimmune disorders; end-stage renal failure; anemia; hemoglobinopathies; severe heart disease; pregnancy; no reliable method of contraception; uncontrolled arterial hypertension; age older than 70 years	Number analyzed: 509 Excluded due to missing data or lost to followup: 59	SVR (n=174) vs. no SVR (n=394) Mean age (years): 51 vs. 52 (p=0.31) Female: 69% vs. 73%, p=0.37 Genotype 1: 24% vs. 55% (p=0.001) Race: Not reported Viral load (10^6 IU/ml): 1.7 vs. 3.1 (p=0.001) Cirrhosis: All (inclusion criterion)

Author, Year Country Quality	Treatments	Variables Assessed as Univariate Predictors	Variables Included in Multivariate Models	Results	Funding Source
Fernandez-Rodriguez, 2010[69] Spain Continued	Pegylated interferon-2a or 2b	Statistically significant predictors of outcomes in univariate analyses were age, albumin, esophageal varices, ultrasonographic signs of portal hypertension, platelet count, bilirubin, prothrombin activity. Other tested variables not reported.	Age, albumin, esophageal varices, ultrasonographic signs of portal hypertension, platelet count, bilirubin, prothrombin activity	SVR vs. no SVR Combined clinical endpoint (hepatic decompensation, upper gastrointestinal bleeding secondary to rupture of esophageal or gastric varices, hepatocellular carcinoma, liver transplantation, and liver-related or liver-unrelated mortality): Adjusted HR 0.38 (0.18-0.76)	Study conducted on behalf of the Group for the Assessment of Prevention of Cirrhosis Complications and Virological Response (APREVIR). No additional funding sources.

Author, Year Country Quality	Study Type Duration of Followup	Comparison Definition of Sustained Virological Response	Inclusion Criteria	Exclusion Criteria	Number analyzed Number meeting inclusion criteria excluded due to missing data or lost to followup	Population Characteristics
Hasegawa, 2007[70] Japan Overall Quality: Fair	Retrospective cohort study Duration of followup: Median 4.6 years	SVR vs. no SVR SVR=Sustained undetectable HCV RNA after completion of antiviral therapy (duration of undetectability not specified)	HCV-associated cirrhosis	HBV co-infection	Number analyzed: 105 Excluded due to missing data or lost to followup: Unclear	SVR (n=48) vs. no SVR (n=58) Age >56 years: 60% vs. 55% (p>0.05) Male: 65% vs. 66% (p>0.05) Race: Not reported Genotype 1b: 19% vs. 21% (p>0.05) Viral load >=100 KIU/ml or >=1 Meq/mL: 25% vs. 62% (p<0.001) Cirrhosis: All (inclusion criterion)

Author, Year Country Quality	Treatments	Variables Assessed as Univariate Predictors	Variables Included in Multivariate Models	Results	Funding Source
Hasegawa, 2007[70] Japan Continued	Natural or recombinant Interferon alpha: 67% Natural Interferon-beta: 31% Both: 1.6%	Age, sex, BMI, albumin, cholinesterase, platelet count, alpha-fetoprotein, indocyanine green retention rate at 15 minutes, fasting blood glucose, AST, ALT, viral load, genotype, use of combination therapy, total dose of interferon, daily dose of interferon, use of induction therapy, type of interferon	Choline esterase, alpha-fetoprotein, viral load, daily dose of interferon, duration of interferon, use of induction therapy	SVR vs. no SVR Hepatocellular carcinoma: Adjusted HR 0.18 (0.04-0.81)	Not reported

Author, Year Country Quality	Study Type Duration of Followup	Comparison Definition of Sustained Virological Response	Inclusion Criteria	Exclusion Criteria	Number analyzed Number meeting inclusion criteria excluded due to missing data or lost to followup	Population Characteristics
Hung, 2006[71] Taiwan Overall Quality: Fair	Cohort study (unclear if retrospective or prospective) Duration of followup: Median 37 months	SVR vs. no SVR SVR=Undetectable HCV RNA 6 months after completion of antiviral therapy	Anti-HCV positive; elevated ALT values for at least 6 months; Child-Pugh score A	HIV or HBV co-infection; alcoholism; autoimmune hepatitis; major contraindications to IFN or ribavirin therapy; severe thrombocytopenia or a history of hepatic encephalopathy, bleeding esophageal varices and ascites	Number analyzed: 132 Excluded due to missing data or lost to followup: Unclear	SVR (n=73) vs. no SVR (n=59) Mean age (years): 55 vs. 58 (p=0.07) Female: 43% vs. 54% (p=0.12) Race: Not reported Genotype 1b: 27% vs. 78% (p<0.001) Viral load >=2 x 10^6 copies/ml: 21% vs. 51% (p<0.001) Cirrhosis: 100% (inclusion criterion)

Author, Year Country Quality	Treatments	Variables Assessed as Univariate Predictors	Variables Included in Multivariate Models	Results	Funding Source
Hung, 2006[71] Taiwan Continued	Interferon-2b plus ribavirin	Age, sex, body weight, viral load, platelet count, ALT, Histological Activity Index score, genotype	Age, sex, body weight, viral load, platelet count, ALT, Histological Activity Index score, genotype	SVR vs. no SVR Hepatocellular carcinoma: Adjusted HR 0.28 (0.09-0.92)	Chang Gung Memorial Hospital and Department of Health of Taiwan

Author, Year Country Quality	Study Type Duration of Followup	Comparison Definition of Sustained Virological Response	Inclusion Criteria	Exclusion Criteria	Number analyzed Number meeting inclusion criteria excluded due to missing data or lost to followup	Population Characteristics
Imazeki, 2003[72] Japan Overall Quality: Fair	Retrospective cohort study Duration of followup: Mean 8.2 years	SVR vs. no SVR SVR=Undetectable HCV RNA 6 months after completion of antiviral therapy	HCV RNA positive who underwent liver biopsy	Hepatocellular carcinoma detected within six months of liver biopsy	Number analyzed: 459 Excluded due to missing data or lost to followup: 9	Demographics for all treated patients (not reported by SVR status) Mean age (years): 49 Female: 36% Race: Not reported Genotype 1: 74% Viral load: Not reported Cirrhosis (Desmet F4): 13%

Author, Year Country Quality	Treatments	Variables Assessed as Univariate Predictors	Variables Included in Multivariate Models	Results	Funding Source
Imazeki, 2003[72] Japan Continued	Interferon-2a: 84% Interferon-2b: 12% Both: 4%	Age, sex, fibrosis stage, AST, ALT, albumin, platelet count, viral load, genotype, alcohol consumption, duration of disease, BMI, co morbidities, diabetes mellitus, hypertension, fatty liver, cardiopulmonary disease	Age, sex, fibrosis stage, AST, ALT, albumin, platelet count, alcohol consumption, duration of disease	SVR vs. untreated and no SVR vs. untreated Liver-related mortality: Adjusted HR 0.06 (0.007-0.43) and 0.55 (0.27-1.1) All-cause mortality: Adjusted HR 0.030 (0.003-0.27) and 0.26 (0.11-0.61) SVR vs. no SVR# Liver-related mortality: Adjusted HR 0.11 (0.01-0.96) All-cause mortality: Adjusted HR 0.12 (0.01-1.3)	Not reported

Author, Year Country Quality	Study Type Duration of Followup	Comparison Definition of Sustained Virological Response	Inclusion Criteria	Exclusion Criteria	Number analyzed Number meeting inclusion criteria excluded due to missing data or lost to followup	Population Characteristics
Innes, 2011[73] UK Overall Quality: Fair	Retrospective cohort study Duration of followup: Mean 5.3 years	SVR vs. no SVR SVR=Undetectable HCV RNA >6 months after completion of antiviral therapy	Initial course of antiviral therapy	Unsustained SVR (presence of viremia subsequent to meeting definition for SVR), HIV-positive, unknown treatment response	Number analyzed: 1215 Number excluded: 48	SVR (560) vs. no SVR (655) Mean age (years): 42 overall Female: 34% vs. 28% Non white: 10% vs. 6% Genotype 1: 19% vs. 50% Viral load: Not reported Cirrhosis: 10% vs. 18%

Author, Year Country Quality	Treatments	Variables Assessed as Univariate Predictors	Variables Included in Multivariate Models	Results	Funding Source
Innes, 2011[73] UK Continued	Pegylated interferon plus ribavirin: 61% Pegylated interferon monotherapy: 1% Interferon plus ribavirin: 21% Interferon monotherapy: 18%	Sex, age, race, injection drug use, genotype, cirrhosis, alcohol-related hospitalization, elevated ALT	Age, race (liver-related hospitalizations only), injection drug use (liver-related hospitalizations only), cirrhosis, alcohol-related hospitalization, elevated ALT	SVR vs. no SVR Liver-related mortality: Adjusted HR 0.22 (0.09-0.58) Liver-related hospital episode: Adjusted HR 0.22 (0.15-0.34)	Scottish government

Author, Year Country Quality	Study Type Duration of Followup	Comparison Definition of Sustained Virological Response	Inclusion Criteria	Exclusion Criteria	Number analyzed Number meeting inclusion criteria excluded due to missing data or lost to followup	Population Characteristics
Izumi, 2005[74] Japan Overall Quality: Fair	Cohort study, appears retrospective Duration of followup: Not reported	SVR vs. no SVR SVR=Undetectable HCV RNA 6 months after completion of antiviral therapy	Chronic HCV infection, underwent antiviral therapy	Not reported	Number analyzed: 495 Excluded due to missing data or lost to followup: Unclear	Demographics for patients treated with interferon monotherapy and interferon plus ribavirin combination therapy, respectively (not reported by SVR status) Mean age (years): 52 and 58 Female: 43% and 44% Race: Not reported Genotype 1b: 71% and 80% Median viral load (kIU/ml): 470 and 680 Cirrhosis: 35% and 2%

Author, Year Country Quality	Treatments	Variables Assessed as Univariate Predictors	Variables Included in Multivariate Models	Results	Funding Source
Izumi, 2005[74] Japan Continued	Interferon monotherapy:69% Interferon-2b plus ribavirin combination therapy: 34%	Not reported	Unclear; age, sex, and fibrosis stage reported as statistically significant predictors of outcomes in multivariate model	SVR vs. no SVR Hepatocellular carcinoma: Adjusted HR 0.36 (0.04-0.83)	Japanese Ministry of Health Labor and Welfare

Author, Year Country Quality	Study Type Duration of Followup	Comparison Definition of Sustained Virological Response	Inclusion Criteria	Exclusion Criteria	Number analyzed Number meeting inclusion criteria excluded due to missing data or lost to followup	Population Characteristics
Kasahara, 2004[75] Japan Overall Quality: Poor	Retrospective cohort Duration of followup: Mean 6 years	SVR vs. no SVR SVR=Undetectable HCV RNA 6 months after completion of antiviral therapy	Histological diagnosis of chronic hepatitis or cirrhosis	History of clinical signs at entry into the study of complications of cirrhosis, i.e. ascites, jaundice, encephalopathy, or variceal bleeding; evidence of Hepatocellular carcinoma at entry as assessed by ultrasonography and/or computed tomography; HBV co-infection; co-existing liver diseases such as autoimmune hepatitis or primary biliary cirrhosis; excessive alcohol consumption (>80 g/day); HIV co-infection	Number analyzed: 2698 Excluded due to missing data or lost to followup: Unclear	SVR (n=738) vs. no-SVR (n=1930) Median age (years): 51 vs. 54 (p=0.12) Female: 31% vs. 37% (p=0.32) Race: Not reported Genotype 1: Not reported Viral load: Not reported Cirrhosis (Desmet F4): 3.0% vs. 5.4% (p=0.34)

Author, Year Country Quality	Treatments	Variables Assessed as Univariate Predictors	Variables Included in Multivariate Models	Results	Funding Source
Kasahara, 2004[75] Japan Continued	Interferon	Univariate analyses not performed	Age, sex, fibrosis score, time at liver biopsy	SVR vs. no SVR Liver-related mortality: Adjusted HR 0.04 (0.005-0.30) All-cause mortality: Adjusted HR 0.14 (0.06-0.35)	Not reported

Author, Year Country Quality	Study Type Duration of Followup	Comparison Definition of Sustained Virological Response	Inclusion Criteria	Exclusion Criteria	Number analyzed Number meeting inclusion criteria excluded due to missing data or lost to followup	Population Characteristics
Maruoka, 2012[76] Japan Overall Quality: Fair	Retrospective cohort study Duration of followup: Mean 9.9 years	SVR vs. no SVR SVR=Undetectable HCV RNA >6 months after completion of antiviral therapy	HCV positive, underwent liver biopsy	Other causes of chronic liver disease, HIV-positive, detection of hepatocellular cancer within 1 year of antiviral therapy, dropout within one year	Number analyzed: 577 (received antiviral therapy) Excluded due to missing data or loss to followup: Unclear for those treated with antiviral therapy, including persons untreated 114/835 lost to followup within 1 year	For all treated patients (not reported by SVR status) Mean age (years): 50 Female: 36% Non white: Not reported Genotype 1: 73% Viral load high (≥100 KIU, 100 kc, 1.0 Meq, 10^4/50 mcL, or 30 core antigens): 69% Cirrhosis: 10%

Author, Year Country Quality	Treatments	Variables Assessed as Univariate Predictors	Variables Included in Multivariate Models	Results	Funding Source
Maruoka, 2012[76] Japan Continued	Interferon-□□ or-□ monotherapy: 83% Interferon-□□ or-□□ sequential therapy: 3.3% Interferon-□□□□ ribavirin combination therapy: 14%	Sex, age, fibrosis stage, inflammatory grade, genotype, high viral load, genotype 1 and high viral load, elevated ALT, low platelets, low albumin	Sex (mortality only), age (hepatocellular cancer only), fibrosis stage, inflammatory grade, genotype 1 and high viral load (hepatocellular cancer only), elevated ALT, low platelets, low albumin	SVR vs. untreated patients and no SVR vs. untreated patients All-cause mortality: Adjusted HR 0.17 (0.08-0.40) and 0.84 (0.50-1.4) Hepatocellular carcinoma: Adjusted HR: 0.14 (0.05-0.42) and 1.2 (0.69-2.0) SVR vs. no SVR# All-cause mortality: Adjusted HR 0.20 (0.08-0.54) Hepatocellular carcinoma: Adjusted HR 0.12 (0.04-0.40)	Not reported

Author, Year Country Quality	Study Type Duration of Followup	Comparison Definition of Sustained Virological Response	Inclusion Criteria	Exclusion Criteria	Number analyzed Number meeting inclusion criteria excluded due to missing data or lost to followup	Population Characteristics
Morgan, 2010[77] USA Overall Quality: Fair	Prospective cohort study of patient enrolled in a randomized trial Duration of followup: Median 79 to 86 months	SVR vs. no SVR SVR=Undetectable HCV RNA 6 months after completion of antiviral therapy	Advanced hepatic fibrosis (Ishak fibrosis score 3) according to liver biopsy performed within 12 months; lack of SVR to previous treatment for at least 24 weeks with standard interferon with or without ribavirin; no history of hepatic decompensation or Hepatocellular carcinoma	Not reported	Number analyzed: 526 Excluded due to missing data or lost to followup: 30 of 180 patients with SVR, not reported for breakthrough/relapse and nonresponder groups	SVR (n=140) vs. breakthrough/relapse (n=77) vs. no SVR (n=309) Mean age (years): 49 vs. 49 vs. 50 (p=0.23) Female: 24% vs. 26% vs. 30% (p=0.30) Non white: 20% vs. 20% vs. 32% (p=0.001) Genotype 1: 72% vs. 86% vs. 94% (p<0.0001) Viral load: Not reported Cirrhosis (Ishak 5 or 6): 21% vs. 31% vs. 43% (p<0.0001)

Author, Year Country Quality	Treatments	Variables Assessed as Univariate Predictors	Variables Included in Multivariate Models	Results	Funding Source
Morgan, 2010[77] USA Continued	Pegylated interferon-2a-180 µg/week + ribavirin 1000-12000 mg/day for 24weeks	Not reported	Age, race, platelet count, AST/ALT ratio, albumin, alkaline phosphatase, alpha-fetoprotein	SVR vs. no SVR All-cause mortality or liver transplantation: Adjusted HR 0.17 (0.06-0.46) Any liver-related outcome (decompensated liver disease [ascites, variceal bleeding, hepatic encephalopathy, spontaneous bacterial peritonitis], hepatocellular carcinoma, liver transplantation, liver-related mortality): Adjusted HR 0.15 (0.06-0.38) Decompensated liver disease: Adjusted HR 0.13 (0.03-0.53) Hepatocellular carcinoma: Adjusted HR 0.19 (0.04-0.80) Liver-related mortality or liver transplantation: Adjusted HR 0.12 (0.03-0.48)	National Institute of Diabetes and Digestive and Kidney Diseases, National Institute of Allergy and Infectious Diseases, the National Cancer Institute, the National Institutes of Health, and Hoffmann-La Roche, Inc

Author, Year Country Quality	Study Type Duration of Followup	Comparison Definition of Sustained Virological Response	Inclusion Criteria	Exclusion Criteria	Number analyzed Number meeting inclusion criteria excluded due to missing data or lost to followup	Population Characteristics
Shiratori, 2005[78] Japan Overall Quality: Poor	Prospective cohort study of patients enrolled in randomized trials Duration of followup: Median 6.8 years	SVR vs. no SVR SVR=Undetectable HCV RNA 6 months after completion of antiviral therapy	HCV positive, elevated ALT levels for more than 6 months, abnormal histologic findings on liver biopsy specimens, indicating fibrotic state F4, platelet county greater than 3 x 10^9 cells/L and Child-Pugh A classification	HBV infection, autoimmune hepatitis, primary biliary cirrhosis, drug-induced liver disease, hepatocellular carcinoma on imaging prior to enrollment	Number analyzed: 271 Excluded due to missing data or lost to followup: 30 at 3 years, 86 at 7 years	For all treated patients (not reported by SVR status) Mean age (years): 57 Female: 62% Race: Not reported Genotype 1: 75% Viral load (log_{10} copies/ml): 5.8 Cirrhosis: 100% (inclusion criterion)

Author, Year Country Quality	Treatments	Variables Assessed as Univariate Predictors	Variables Included in Multivariate Models	Results	Funding Source
Shiratori, 2005[78] Japan Continued	Interferon α-2a: 58% Natural interferon α: 42%	Univariate analyses not performed	Age	SVR vs. untreated patients and no SVR vs. untreated patients Hepatocellular carcinoma: Adjusted HR 0.31 (0.16-0.61) and 0.77 (0.51-1.2) All-cause mortality: Adjusted HR 0.05 (0.006-0.34) and 0.71 (0.43-1.2) SVR vs. no SVR# Hepatocellular carcinoma: Adjusted HR 0.40 (0.18-0.89) All-cause mortality: Adjusted HR 0.07 (0.01-0.56)	None declared

Author, Year Country Quality	Study Type Duration of Followup	Comparison Definition of Sustained Virological Response	Inclusion Criteria	Exclusion Criteria	Number analyzed Number meeting inclusion criteria excluded due to missing data or lost to followup	Population Characteristics
Veldt, 2007[79] Europe and Canada Overall Quality: Poor	Retrospective cohort Duration of followup: Median 2.1 years	SVR vs. no SVR SVR=Undetectable HCV RNA 6 months after completion of antiviral therapy	Biopsy-proven advanced fibrosis or cirrhosis (Ishak score, 4 to 6) treated with interferon-based regimen	HIV or HBV co-infection; decompensated liver disease	Number analyzed: 479 Excluded due to missing data or lost to followup: Unclear	SVR (n=142) vs. no-SVR (n=337) Mean age (years): 48 vs. 49 (p=0.45) Female: 27% vs. 32% (p=0.23) Race: Not reported Genotype 1: 39% vs. 67% (p<0.001) Viral load ($x10^5$ IU/mL): 8.5 vs. 8.0 (p=0.75) Cirrhosis (Ishak 5 or 6): 71% vs. 77% (p=0.45)

Author, Year Country Quality	Treatments	Variables Assessed as Univariate Predictors	Variables Included in Multivariate Models	Results	Funding Source
Veldt, 2007[79] Europe and Canada Continued	Interferon monotherapy: 27% Interferon and ribavirin: 27% Pegylated interferon monotherapy: 2.1% Pegylated interferon and ribavirin: 43%	Univariate analyses not performed	All outcomes: Age, sex, previous non response, bilirubin level, albumin level, platelet count, treatment center, treatment period Hepatocellular carcinoma: Also adjusted for anti-hepatitis B core antigen positivity	SVR vs. no SVR Any event (death, liver failure, and hepatocellular cancer): Adjusted HR 0.20 (0.07-0.58) All-cause mortality: Adjusted HR 0.31 (0.07-1.4) Liver-related mortality: Adjusted HR 0.19 (0.02-1.4) Hepatocellular carcinoma: Adjusted HR 0.46 (0.12-1.70)	Netherlands Organisation for Health Research and Development

Author, Year Country Quality	Study Type Duration of Followup	Comparison Definition of Sustained Virological Response	Inclusion Criteria	Exclusion Criteria	Number analyzed Number meeting inclusion criteria excluded due to missing data or lost to followup	Population Characteristics
Yoshida, 2002[80] Japan Overall Quality: Poor	Retrospective cohort Duration of followup: Mean 5.4 years	SVR vs. no SVR SVR=Undetectable HCV RNA 6 months after completion of antiviral therapy	HCV antibody positive; received liver biopsy	HBV co-infection, alcoholic liver disease, autoimmune hepatitis, or primary biliary cirrhosis.	Number analyzed: 2889 Excluded due to missing data or lost to followup: Unclear	SVR (817) vs. non SVR (1613) Mean age (years): 48 vs. 51 Female: 30% vs. 40% Race: Not reported Genotype: Not reported Viral load: Not reported Cirrhosis (Desmet F4): 6.5% vs. 11%

Author, Year Country Quality	Treatments	Variables Assessed as Univariate Predictors	Variables Included in Multivariate Models	Results	Funding Source
Yoshida, 2002[80] Japan Continued	Interferon-alpha: 84% Interferon-beta: 14% Both: 2%	Univariate analyses not performed	Age, sex	SVR vs. untreated and no SVR vs. untreated Liver-related mortality: Adjusted HR 0.050 (0.01-0.22) and 0.39 (0.22-0.68) All-cause mortality: Adjusted HR 0.15 (0.06-0.34) and 0.47 (0.29-0.76) SVR vs. no SVR# Liver-related mortality: Adjusted HR 0.13 (0.02-0.66) All-cause mortality Adjusted HR 0.32 (0.12-0.86)	Ministry of Health, Labour, and Welfare of Japan and Ministry of Education, Culture, Sports, Science, and Technology of Japan

Author, Year Country Quality	Study Type Duration of Followup	Comparison Definition of Sustained Virological Response	Inclusion Criteria	Exclusion Criteria	Number analyzed Number meeting inclusion criteria excluded due to missing data or lost to followup	Population Characteristics
Yu, 2006[81] Taiwan Overall Quality: Poor	Retrospective cohort Duration of followup: Mean 5.2 years	SVR vs. no SVR SVR=Undetectable HCV RNA 6 months after completion of antiviral therapy	Seropositive for anti-HCV antibody and HCV RNA and biopsy-proven chronic hepatitis with or without cirrhosis	Concurrent HBV infection, HIV infection, autoimmune hepatitis, heavy ETOH use (>80g/day), or evidence of Hepatocellular carcinoma	Number analyzed: 1057 Excluded due to missing data or lost to followup: Unclear	For all treated patients (not reported by SVR status) Mean age (years): 47 Female: 40% Race: Not reported Genotype 1: 46% Viral load: Not reported Cirrhosis (criteria not reported): 16%

Author, Year Country Quality	Treatments	Variables Assessed as Univariate Predictors	Variables Included in Multivariate Models	Results	Funding Source
Yu, 2006[81] Taiwan Continued	Interferon monotherapy: 28% Interferon plus ribavirin combination therapy: 72%	Univariate analyses not reported	Age, sex, ALT, genotype, interferon monotherapy or interferon plus ribavirin combination therapy	SVR vs. untreated and no SVR vs. untreated Hepatocellular carcinoma: Adjusted HR 0.25 (0.13-0.46) and 0.99 (0.64-1.5) All-cause mortality: Adjusted HR 0.37 (0.14-0.99) and 1.3 (0.56-3.1) SVR vs. no SVR# Hepatocellular carcinoma: Adjusted HR 0.25 (0.13-0.50) All-cause mortality: 0.28 (0.08-1.0)	Department of Health, Taiwan and Taiwan Liver Research Foundation

Evidence Table 10. Quality rating: Studies on sustained virologic response and clinical outcomes

Author, Year	(1) Did the study attempt to enroll all (or a random sample of) patients meeting inclusion criteria, or a random sample (inception cohort)?	(2) Were the groups comparable at baseline on key prognostic factors (e.g., by restriction or matching)?	(3) Did the study use accurate methods for ascertaining exposures, potential confounders, and outcomes?	(4) Were outcome assessors and/or data analysts blinded to treatment?	(5) Did the article the number of patients who met inclusion criteria excluded due to missing data or loss to followup?	(6) Did the study perform appropriate statistical analyses on potential confounders (should evaluate at least age, sex, genotype, fibrosis stage, viral load)?	(7) Is there important (overall or differential) exclusion of patients due to missing data or loss to followup?	(8) Were outcomes pre-specified and defined, and ascertained using accurate methods?	Overall Quality (good, fair, poor)
Arase, 2007[63]	Yes	No	Yes	Unclear	No	Yes	Unclear	Yes	Fair
Backus, 2011[64]	Yes	No	Yes	No	Yes	Yes	Yes	Yes	Fair
Bruno, 2007[65]	Yes	No	Yes	Unclear	No	No	Unclear	Yes	Fair
Cardoso, 2010[66]	Yes	No	Yes	Unclear	No	Yes	Unclear	Yes	Fair
Coverdale, 2004[67]	Unclear	No	Unclear	No	No	Unclear	Unclear	Yes	Poor
El Braks, 2007[68]	Yes	No	Yes	Unclear	No	No	Unclear	Yes	Poor
Fernandez-Rodriguez, 2010[69]	Unclear	No	Yes	No	Yes	Unclear	No	Yes	Poor
Hasegawa, 2007[70]	Unclear	Unclear	Yes	Unclear	No	Yes	Unclear	Yes	Fair
Hung, 2006[71]	Yes	No	Yes	Unclear	No	Yes	Unclear	Yes	Fair
Imazeki, 2003[72]	Yes	No	Yes	Unclear	Yes	Yes	No	Yes	Fair
Innes, 2011[73]	Yes	No	Yes	Unclear	Yes	Yes	No	Yes	Fair
Izumi, 2005[74]	Yes	Unclear	Yes	Unclear	No	Unclear	Unclear	Yes	Fair
Kasahara, 2004[75]	No	Yes	Yes	Unclear	No	No	Unclear	Yes	Poor
Maruoka, 2012[76]	Yes	Unclear	Yes	Unclear	Yes	Yes	Yes	Yes	Fair
Morgan, 2010[77]	Yes	No	Yes	Unclear	No	Unclear	Unclear	Yes	Fair
Shiratori, 2005[78]	Unclear	Yes	Yes	Unclear	Yes	No	Yes	Yes	Poor
Veldt, 2007[79]	Yes	No	Yes	No	No	No	Unclear	Yes	Poor
Yoshida, 2002[80]	Yes	No	Yes	No	No	No	Unclear	Yes	Poor
Yu, 2006[81]	Yes	No	Yes	No	No	No	Unclear	Yes	Poor

Evidence Table 11. Sustained virologic response and clinical outcomes summary results

Author, Year Country Quality	Study Type Number Analyzed Duration of Followup Proportion with Cirrhosis: SVR vs. no SVR	Hepatocellular Carcinoma: Adjusted Hazards Ratio (95% CI)	Liver-Related Mortality: Adjusted Hazard Ratio (95% CI)	All-Cause Mortality: Adjusted Hazard Ratio (95% CI)	Other Clinical Outcomes: Adjusted Hazard Ratio (95% CI)	Results Adjusted for at Least Age, Sex, Viral Load, Genotype, and Fibrosis Stage, or no Association Found in Univariate Analyses
Studies of general populations of treated patients with HCV infection						
Arase, 2007[63] Japan Overall Quality: Fair	Retrospective cohort n=500 Mean 7.4 years Cirrhosis: 9% vs. 16%	SVR vs. no SVR: 0.19 (0.08-0.45)	SVR vs. no SVR: 0.13 (0.03-0.59)	SVR vs. no SVR: 0.39 (0.16-0.93)	NR	Yes
Backus, 2011[64]# USA Overall Quality: Fair	Retrospective cohort n=16,864 Median 3.8 years Cirrhosis: 9-12% vs. 12-20%	NR	NR	SVR vs. no SVR (genotypes 1, 2, and 3, respectively): 0.71 (0.60-0.86), 0.62 (0.44-0.87), and 0.51 (0.35-0.75)	NR	Yes
Coverdale, 2004[67]* Australia Overall Quality: Poor	Prospective cohort (some patients originally enrolled in randomized trials) n=343 Median 9 years Cirrhosis: Not reported, median fibrosis score F2 (Scheuer)	SVR vs. response-relapse vs. nonresponse Adjusted HR not reported (p>0.05)	SVR vs. response-relapse vs. nonresponse Liver transplant or liver-related death: Adjusted HR not reported (p=0.20)	NR	SVR vs. response-relapse vs. nonresponse Liver-related complications:** Adjusted HR not reported (p=0.06)	Unclear
Imazeki, 2003[72] Japan Overall Quality: Fair	Retrospective cohort n=459 Mean 8.2 years Cirrhosis: 13% overall	NR	SVR vs. no SVR: 0.11 (0.01-0.96)##	SVR vs. no SVR: 0.12 (0.01-1.3)##	NR	Yes
Innes, 2011[73] UK Overall Quality: Fair	Retrospective cohort n=1215 Mean 5.3 years Cirrhosis: 10% vs. 18%	NR	SVR vs. no SVR: 0.22 (0.09-0.58)	NR	SVR vs. no SVR Liver-related hospital episode: 0.22 (0.15-0.34)	Yes

Author, Year Country Quality	Study Type Number Analyzed Duration of Followup Proportion with Cirrhosis: SVR vs. no SVR	Hepatocellular Carcinoma: Adjusted Hazards Ratio (95% CI)	Liver-Related Mortality: Adjusted Hazard Ratio (95% CI)	All-Cause Mortality: Adjusted Hazard Ratio (95% CI)	Other Clinical Outcomes: Adjusted Hazard Ratio (95% CI)	Results Adjusted for at Least Age, Sex, Viral Load, Genotype, and Fibrosis Stage, or no Association Found in Univariate Analyses
Izumi, 2005[74] Japan Overall Quality: Fair	Cohort study, appears retrospective n=495 Duration of followup: Not reported Cirrhosis: 5.1% overall	SVR vs. no SVR: 0.36 (0.04-0.83)	NR	NR	NR	Unclear
Kasahara, 2004[75] Japan Overall Quality: Poor	Retrospective cohort n=2698 Mean 6 years Cirrhosis: 3.0% vs. 5.4%	NR	SVR vs. no SVR: 0.04 (0.005-0.30)	SVR vs. no SVR: 0.14 (0.06-0.35)	NR	No
Maruoka, 2012[76] Japan Overall Quality: Fair	Retrospective cohort n=577 Mean 9.9 years Cirrhosis: 10% overall	SVR vs. no SVR: 0.12 (0.04-0.40)##	NR	SVR vs. no SVR: 0.20 (0.08-0.54)##	NR	Yes
Yoshida, 2002[80] Japan Overall Quality: Poor	Retrospective cohort n=2889 Mean 5.4 years Cirrhosis: 6.5% vs. 11%	NR	SVR vs. no SVR: 0.13 (0.02-0.66)##	SVR vs. no SVR: 0.32 (0.12-0.86)##	NR	No
Yu, 2006[42] Taiwan Overall Quality: Poor	Retrospective cohort n=1057 Mean 5.2 years Cirrhosis: 16% overall	S SVR vs. no SVR: 0.25 (0.13-0.54)##	NR	SVR vs. no SVR: 0.28 (0.08-1.0)##	NR	No
Studies of populations with advanced fibrosis and cirrhosis						
Bruno, 2007[65] Italy Overall Quality: Fair	Retrospective cohort study n=883 Mean 8 years Cirrhosis: All	SVR vs. no SVR: 0.39 (0.17-0.88)	SVR vs. no SVR: 0.14 (0.04-0.59)	NR	SVR vs. no SVR Ascites, encephalopathy, or gastrointestinal bleeding: Not calculated, 0 events/1061 person-years vs. 107 events/5703 person-years (1.88 events/100 person-years)	No

Author, Year Country Quality	Study Type Number Analyzed Duration of Followup Proportion with Cirrhosis: SVR vs. no SVR	Hepatocellular Carcinoma: Adjusted Hazards Ratio (95% CI)	Liver-Related Mortality: Adjusted Hazard Ratio (95% CI)	All-Cause Mortality: Adjusted Hazard Ratio (95% CI)	Other Clinical Outcomes: Adjusted Hazard Ratio (95% CI)	Results Adjusted for at Least Age, Sex, Viral Load, Genotype, and Fibrosis Stage, or no Association Found in Univariate Analyses
Cardoso, 2010[66] France Overall Quality: Fair	Retrospective cohort study (of patients originally enrolled in clinical trials) n=307 Median 3.5 years Cirrhosis: 53% vs. 61%	SVR vs. no SVR: 0.33 (0.23-0.89)	SVR vs. no SVR: 0.27 (0.08-0.95)	NR	SVR vs. no SVR Ascites or variceal bleeding: 0.21 (0.05-0.92)	Yes
El Braks, 2007[68] France Overall Quality: Poor	Retrospective cohort study n=113 Mean 7.7 years Cirrhosis: All	NR	NR	NR	SVR vs. no SVR Clinical events (hepatocellular cancer, ascites, hepatic encephalopathy, or death): 0.14 (0.04-0.45)	No
Fernandez-Rodriguez, 2010[69]# Spain Overall Quality: Poor	Retrospective cohort study n=509 Median 35 months Cirrhosis: All	NR	NR	NR	SVR vs. no SVR Combined clinical endpoint:*** 0.38 (0.18-0.76)	Unclear
Hasegawa, 2007[70]^ Japan Overall Quality: Fair	Retrospective cohort study n=105 Median 4.6 years Cirrhosis: All	SVR vs. no SVR: 0.18 (0.04-0.81)	NR	NR	NR	Yes
Hung, 2006[71] Taiwan Overall Quality: Fair	Cohort study (unclear if retrospective or prospective) n=132 Median 37 months Cirrhosis: All	SVR vs. no SVR: 0.28 (0.09-0.92)	NR	NR	NR	Yes
Morgan, 2010[77]# USA Overall Quality: Fair	Prospective cohort study of patient enrolled in a randomized trial n=526 Median 79 to 86 months Cirrhosis: 21% vs. 43%	SVR vs. no SVR: 0.19 (0.04-0.80)	SVR vs. no SVR Liver-related mortality or liver transplantation: 0.12 (0.03-0.48)	SVR vs. no SVR All-cause mortality or liver transplantation: 0.17 (0.06-0.46)	SVR vs. no SVR Any liver-related outcome:^^ 0.15 (0.06-0.38) Decompensated liver disease: 0.13 (0.03-0.53)	Unclear

Author, Year Country Quality	Study Type Number Analyzed Duration of Followup Proportion with Cirrhosis: SVR vs. no SVR	Hepatocellular Carcinoma: Adjusted Hazards Ratio (95% CI)	Liver-Related Mortality: Adjusted Hazard Ratio (95% CI)	All-Cause Mortality: Adjusted Hazard Ratio (95% CI)	Other Clinical Outcomes: Adjusted Hazard Ratio (95% CI)	Results Adjusted for at Least Age, Sex, Viral Load, Genotype, and Fibrosis Stage, or no Association Found in Univariate Analyses
Shiratori, 2005[78] Japan Overall Quality: Poor	Prospective cohort study of patients enrolled in randomized trials n=271 Median 6.8 years Cirrhosis: All	SVR vs. no SVR: 0.40 (0.18-0.89)##	NR	SVR vs. no SVR: 0.07 (0.01-0.56)##	NR	No
Veldt, 2007[79] Europe and Canada Overall Quality: Fair	Retrospective cohort n=479 Median 2.1 years Cirrhosis: 71% vs. 77%	SVR vs. no SVR: 0.46 (0.12-1.7)	SVR vs. no SVR: 0.19 (0.02-1.4)	SVR vs. no SVR: 0.31 (0.07-1.4)	SVR vs. no SVR Any event (death, liver failure, and hepatocellular cancer): 0.20 (0.07-0.58)	No

Abbreviations: HCV, hepatitis C virus; NR, not reported; SVR, sustained virologic response.
Note: SVR defined in all studies as undetectable HCV RNA in serum 6 months after the end of antiviral therapy, except as noted.
* SVR defined as undetectable HCV RNA on at least 2 occasions at least 2 years after completion of therapy.
^ Duration of undetectability to meet criteria for SVR not reported.
# Study primarily evaluated patients who received pegylated interferon plus ribavirin.
** Hepatic decompensation, complications of portal hypertension, hepatocellular carcinoma, liver transplantation, and liver-related mortality.
*** Hepatic decompensation, upper gastrointestinal bleeding secondary to rupture of esophageal or gastric varices, hepatocellular carcinoma, liver transplantation, and liver-related or liver-unrelated mortality.
^^ Decompensated liver disease (ascites, variceal bleeding, hepatic encephalopathy, spontaneous bacterial peritonitis), hepatocellular carcinoma, liver transplantation, and liver-related mortality.
Calculated from estimates for SVR vs. untreated and no SVR vs. untreated

Evidence Table 12. Studies on sustained virologic response and quality of life

Author, Year Country Quality	Study Type	Comparison	Duration of Followup	Inclusion Criteria	Exclusion Criteria	Number Screened/ Eligible/ Enrolled/ Analyzed
Arora, 2006[82] Australia, Europe, New Zealand, North America, and South America Overall Quality: Poor	Cohort study (patients enrolled in an randomized trial)	SVR vs. no SVR SVR=No detectable HCV RNA at end of followup (72 weeks)	72 weeks	No prior treatment for chronic hepatitis C infection, positive HCV RNA, normal ALT	Cirrhosis, other chronic liver disease, HIV infection, other serious chronic illness, pregnancy	Number screened: Not reported Number eligible: Not reported Number enrolled: 440 (randomized to an antiviral treatment arm) Number analyzed: Unclear

Author, Year Country Quality	Demographic Characteristics of Study Population (Age, Race, Mean Viral Load) Genotype HCV Viral Load HIV Infection IV Drug Use	Treatments	Confounders Assessed in Analysis	Results (by Clinical Outcome)	Funding Source
Arora, 2006[82] Australia, Europe, New Zealand, North America, and South America Continued	Not reported by SVR status Mean age: 43 years Female: 60% Non white: 14% Not reported by SVR status Advanced fibrosis: 10% Genotype 1: 68% Viral load: 1.1-1.2 x 10^6 copies/ml IVDU: 30% HIV positive: excluded	Pegylated interferon alfa-2a (24 or 48 weeks)	Genotype, country, treatment, fibrosis stage, baseline score	SVR vs. no SVR, mean difference in change from baseline SF-36 physical function: +4.7 (p<0.05) SF-36 role limitations-physical: +13 (p<0.05) SF-36 bodily pain: +11 (p<0.0001) SF-36 general health: +10 (p<0.0001) SF-36 vitality: +9.3 (p<0.0001) SF-36 social function: +5.1 (p>0.05) SF-36 role limitations-emotional: +7.3 (p>0.05) SF-36 mental health: +3.1 (p>0.05) SF-36 physical component summary: +4.9 (p<0.0001) SF-36 mental component summary: +2.0 (p>0.05) Fatigue Severity Scale, total score: -4.4 (p<0.01) Fatigue Severity Scale, VAS: -10 (p<0.01)	Roche Pharmaceuticals

Author, Year Country Quality	Study Type	Comparison	Duration of Followup	Inclusion Criteria	Exclusion Criteria	Number Screened/ Eligible/ Enrolled/ Analyzed
Bernstein, 2002[83] Australia, North America, Europe, Taiwan, New Zealand Overall Quality: Poor	Cohort study (patients originally enrolled in 3 randomized trials)	SVR vs. no SVR SVR=No detectable HCV RNA 24 weeks after completion of antiviral therapy	72 weeks	Not previously treated with interferon-based therapies, positive HCV antibody, elevated serum ALT level, positive HCV RNA	Other chronic liver disease, significant co morbid conditions, pregnancy, evidence of substance abuse within 1 year	Number screened: Not reported Number eligible: Not reported Number enrolled: 1441 Number analyzed: 983 (275 SVR, 708 no SVR)

Author, Year Country Quality	Demographic Characteristics of Study Population (Age, Race, Mean Viral Load) Genotype HCV Viral Load HIV Infection IV Drug Use	Treatments	Confounders Assessed in Analysis	Results (by Clinical Outcome)	Funding Source
Bernstein, 2002[83] Australia, North America, Europe, Taiwan, New Zealand Continued	Not reported by SVR status Mean age <=40 years: 41% Female: 32% Non white: 14% Not reported by SVR status Cirrhosis: 32% Genotype, viral load, HIV infection, IV drug use not reported	Pegylated interferon alfa-2a or interferon alfa-2a	None	SVR vs. no SVR, mean difference in change from baseline SF-36 physical function: +4.6 (p<0.001) SF-36 role limitations-physical: +9.8 (p<0.001) SF-36 bodily pain: +2.9 (p<0.01) SF-36 general health: +9.1 (p<0.001) SF-36 vitality: +9.6 (p<0.001) SF-36 social function: +6.2 (p<0.001) SF-36 role limitations-emotional: +8.4 (p<0.01) SF-36 mental health: +4.6 (p<0.001) SF-36 physical component summary: +2.8 (p<0.001) SF-36 mental component summary: +3.0 (p<0.001) Fatigue Severity Scale, total score: -0.5 (p<0.001) Fatigue Severity Scale, VAS: -11.5 (p<0.001)	F. Hoffman-La Roche

Author, Year Country Quality	Study Type	Comparison	Duration of Followup	Inclusion Criteria	Exclusion Criteria	Number Screened/ Eligible/ Enrolled/ Analyzed
Bini, 2006[84] USA Overall Quality: Poor	Prospective cohort study	SVR vs. no SVR SVR=No detectable HCV RNA 24 weeks after completion of antiviral therapy	48 or 72 weeks (24 weeks after end of treatment)	No prior treatment for chronic hepatitis C infection, positive HCV antibody, positive HCV RNA, liver biopsy consistent with chronic HCV infection Each patient with normal ALT matched with 2 patients with elevated ALT on genotype, HCV viral load, and presence of cirrhosis	HBV infection, HIV infection, neutropenia, anemia, thrombocytopenia, renal insufficiency, AFP >50 ng/ml, decompensated cirrhosis, prior organ transplantation, cancer, severe co morbid condition, poorly controlled diabetes or thyroid disease, autoimmune disease, seizure disorder, concurrent immunosuppressive therapy, more than 10 g alcohol/day or illicit drugs within 6 months	Number screened: Not reported Number eligible: Not reported Number enrolled: 138 (46 normal ALT, 92 elevated ALT) Number analyzed: 138

Author, Year Country Quality	Demographic Characteristics of Study Population (Age, Race, Mean Viral Load) Genotype HCV Viral Load HIV Infection IV Drug Use	Treatments	Confounders Assessed in Analysis	Results (by Clinical Outcome)	Funding Source
Bini, 2006[84] USA Continued	Normal ALT and elevated ALT groups, respectively (not reported by SVR status) Mean age: 50 and 49 years Female: 11% and 8% Non white: 59% and 66% Normal ALT and elevated ALT groups, respectively (not reported by SVR status) Cirrhosis: 11% and 11% Genotype 1: 78% and 78% Viral load >2 x 10^6 copies/ml: 44% and 44% IVDU: 67% and 65% HIV positive: excluded	Interferon alfa-2b + ribavirin	None	SVR vs. no SVR, mean difference in change from baseline (normal ALT and elevated ALT subgroups, respectively; p values not reported) SF-36 physical function: +18 and +15 SF-36 role limitations-physical: +22 and +27 SF-36 bodily pain: +3.4 and +9.3 SF-36 general health: +3.0 and +9.9 SF-36 vitality: +12 and +12 SF-36 social function: +9.5 and +11 SF-36 role limitations-emotional: +20 and +18 SF-36 mental health: +14 and +18 SF-36 physical component summary: +3.8 and +7.1 SF-36 mental component summary: +6.0 and +2.1 Positive well being: +14 and -3.1 Sleep somnolence: +11 and +5.4 Health distress: +9.3 and +11 Hepatitis-specific health distress: +5.4 and +2.6 Hepatitis-specific limitations: +13 and +3.8	No external funding

Author, Year Country Quality	Study Type	Comparison	Duration of Followup	Inclusion Criteria	Exclusion Criteria	Number Screened/ Eligible/ Enrolled/ Analyzed
Bonkovsky, 1999[85] USA and Canada Overall Quality: Poor`	Cohort study (patients enrolled in a randomized trial)	SVR vs. no SVR SVR=No detectable HCV RNA 24 weeks after completion of antiviral therapy	72 weeks	Positive HCV antibody, positive HCV RNA, ALT >1.5 times upper limit of normal, liver biopsy confirming diagnoses of chronic hepatitis	Malignancy, depressive illness, HIV infection, decompensated liver disease, previous use of interferon, previous use of chemotherapeutic of other agents, thyroid abnormality	Number screened: Not reported Number eligible: Not reported Number enrolled: 704 Number analyzed: 437 (41 SVR, 396 no SVR)

Author, Year Country Quality	Demographic Characteristics of Study Population (Age, Race, Mean Viral Load) Genotype HCV Viral Load HIV Infection IV Drug Use	Treatments	Confounders Assessed in Analysis	Results (by Clinical Outcome)	Funding Source
Bonkovsky, 1999[85] USA and Canada Continued	Not reported by SVR status Mean age: 43 years Female: 27% Non white: 23% Not reported by SVR status Cirrhosis: 16% Genotype 1: 68% Viral load: Not reported IVDU: 41% HIV positive: excluded	Consensus interferon or interferon alfa-2b	None	SVR vs. no SVR, mean difference in change from baseline (values estimated from graph) SF-36 physical function: +6.0 ($p<0.05$) SF-36 role limitations-physical: +22 ($p<0.01$) SF-36 bodily pain: -0.5 ($p>0.05$) SF-36 general health: +7.5 ($p<0.01$) SF-36 vitality: +9.5 ($p<0.05$) SF-36 social function: +10 ($p<0.05$) SF-36 role limitations-emotional: +11 ($p>0.05$) SF-36 mental health: +4.0 ($p>0.05$)	Amgen Inc.; United States Public Health Service

Author, Year Country Quality	Study Type	Comparison	Duration of Followup	Inclusion Criteria	Exclusion Criteria	Number Screened/ Eligible/ Enrolled/ Analyzed
Hassanein, 2004[86] Australia, North America, Europe, Taiwan, Brazil, Mexico Overall Quality: Poor	Cohort study (patients enrolled in a randomized trial)	SVR vs. no SVR SVR=No detectable HCV RNA 24 weeks after completion of antiviral therapy	72 weeks	No prior interferon, HCV RNA >=2000 copies/ml, ALT >upper limit of normal, liver biopsy consistent with chronic hepatitis C	Neutrophils <1500 per cubic millimeter, platelets <90.000 per cubic millimeter, hemoglobin <12 g/dl in women or <13 g/dl in men, HIV infection, decompensated liver disease, serum creatinine >1.5 times upper limit of normal, poorly controlled psychiatric disease, alcohol or drug dependence within one year before study entry, substantial coexisting medical conditions	Number screened: 1459 Number eligible: Not reported Number enrolled: 1149 Number analyzed: 649

Author, Year Country Quality	Demographic Characteristics of Study Population (Age, Race, Mean Viral Load) Genotype HCV Viral Load HIV Infection IV Drug Use	Treatments	Confounders Assessed in Analysis	Results (by Clinical Outcome)	Funding Source
Hassanein, 2004[86] Australia, North America, Europe, Taiwan, Brazil, Mexico Continued	Not reported by SVR status Mean age: 43 years Female: 29% Non white: 16% Not reported by SVR status Cirrhosis: 13% Genotype 1: 63% Viral load: 5.9 to 6.0 x 10^6 copies/ml IVDU: Not reported HIV positive: excluded	Pegylated interferon alfa-2a, pegylated interferon alf-2a +ribavirin, or interferon alfa-2b + ribavirin	None	SVR vs. no SVR, mean difference in change from baseline SF-36 physical function: +5.5 (p<0.01) SF-36 role limitations-physical: +5.7 (p<0.05) SF-36 bodily pain: +4.1 (p<0.05) SF-36 general health: +8.6 (p<0.01) SF-36 vitality: +6.3 (p >0.05) SF-36 social function: +5.8 (p<0.01) SF-36 role limitations-emotional: +9.3 (p<0.01) SF-36 mental health: +5.0 (p<0.01) SF-36 physical component summary: +2.2 (p<0.01) SF-36 mental component summary: +2.6 (p<0.01) Total fatigue: +3.3 (p<0.01) Fatigue severity: +7.4 (p<0.01)	Roche Pharmaceuticals

Author, Year Country Quality	Study Type	Comparison	Duration of Followup	Inclusion Criteria	Exclusion Criteria	Number Screened/ Eligible/ Enrolled/ Analyzed
McHutchison, 2001[87] USA Overall Quality: Poor	Cohort study (patients enrolled in a randomized trial)	SVR vs. relapse vs. non responder SVR=No detectable HCV RNA 24 weeks after completion of antiviral therapy Relapse: Not defined	72 weeks	Positive HCV RNA, liver biopsy consistent with chronic hepatitis, elevated serum ALT	Decompensated cirrhosis, AFP >50 ng/ml, anemia (hemoglobin <12 g/dl in women and <13 g/dl in men), HIV infection, psychiatric conditions, seizure disorders, cardiovascular disease, hemophilia, poorly controlled diabetes mellitus, autoimmune diseases, s/p organ transplantation, unable to practice contraception	Number screened: 1337 Number eligible: 933 Number enrolled: 933 Number analyzed: 824 (195 SVR, 150 relapse, 478 non responder)

Author, Year Country Quality	Demographic Characteristics of Study Population (Age, Race, Mean Viral Load) Genotype HCV Viral Load HIV Infection IV Drug Use	Treatments	Confounders Assessed in Analysis	Results (by Clinical Outcome)	Funding Source
McHutchison, 2001[87] USA Continued	Mean age: 43 vs. 44 years Female: 42% vs. 32% Non white: 8% vs. 12% Cirrhosis: Not reported Genotype 1: 43% vs. 81% Viral load >2 million copies/ml: 58% vs. 74% IVDU: Not reported HIV positive: excluded	Interferon alfa-2a for 24 or 48 weeks, with or without ribavirin	None	SVR and relapse, mean difference in change from baseline vs. non responder (p not reported, values estimated from graph) SF-36 physical function: +2.4 and +0.8 SF-36 role limitations-physical: +5.2 and +3.2 SF-36 bodily pain: +1.6 and +1.7 SF-36 general health: +5.2 and +1.5 SF-36 vitality: +4.7 and +2.0 SF-36 social function: +3.1 and +0.4 SF-36 role limitations-emotional: +3.0 and +1.2 SF-36 mental health: +2.0 and 0.0 Sleep somnolence: +3.4 and +2.3 Health distress: +5.4 and +1.2 Hepatitis-related health distress: +5.7 and +1.1 Hepatitis-related limitations: +4.6 and +2.1	Schering-Plough and Scripps Clinic

Author, Year Country Quality	Study Type	Comparison	Duration of Followup	Inclusion Criteria	Exclusion Criteria	Number Screened/ Eligible/ Enrolled/ Analyzed
Neary, 1999[88] USA, Europe, Australia Overall Quality: Poor	Cohort study (patients enrolled in a randomized trial)	SVR vs. no SVR and overall response vs. no overall response SVR=No detectable HCV RNA 24 weeks after completion of antiviral therapy Overall response=SVR plus >=2-point improvement in Knodell HAI score	72 weeks (24 weeks after end of treatment)	Chronic HCV infection, previously treated with one or two courses of interferon alpha with relapse on most recent course, liver biopsy showing chronic hepatitis after relapse	Women not using effective birth control, decompensated cirrhosis, anemia (hemoglobin <12 g/dl in women and <13 g/dl in men), white blood cell count <3000 per cubic mm, neutrophil count <1500 per cubic mm, platelet count less than 100,000 per cubic mm, HIV infection, prior organ transplantation, severe psychiatric conditions, seizure disorder, cardiovascular disease, renal insufficiency, hemoglobinopathy, hemophilia, poorly controlled diabetes mellitus, immunologically mediated diseases	Number screened: 495 Number eligible: Unclear Number enrolled: 349 Number analyzed: Unclear (257 with "complete data"

Author, Year Country Quality	Demographic Characteristics of Study Population (Age, Race, Mean Viral Load) Genotype HCV Viral Load HIV Infection IV Drug Use	Treatments	Confounders Assessed in Analysis	Results (by Clinical Outcome)	Funding Source
Neary, 1999[88] USA, Europe, Australia Continued	Not reported by SVR or overall response status Mean age: 43 years Female: 35% Non white: 6.4% Not reported by SVR or overall response status Bridging fibrosis or cirrhosis: 17% Genotype 1: 56% Viral load >2 million copies/ml: 75% IVDU: 40% HIV positive: excluded	Interferon alfa-2b with or without ribavirin	None	SVR and relapse. mean difference in change from baseline vs. non responder (estimated from graph) (p values not reported) SF-36 physical function: +8.0 and +3.8 SF-36 role limitations-physical: +7.6 and +4.9 SF-36 bodily pain: +2.4 and +2.7 SF-36 general health: +9.4 and +5.6 SF-36 vitality: +7.8 and +5.6 SF-36 social function: +9.4 and +4.1 SF-36 role limitations-emotional: +6.0 and +12 SF-36 mental health: +2.8 and +1.8 Sleep somnolence: +2.1 and +3.8 Health distress: +8.9 and +1.6 Hepatitis-related health distress: +11 and -0.8 Hepatitis-related limitations: +6.7 and +2.6 Mental health-18: +3.4 and +2.3 Overall response vs. no response (estimated from graph) SF-36 physical function: +8.3 (p<0.05) SF-36 role limitations-physical: +10 (p>0.05) SF-36 bodily pain: +3.7 (p>0-.05) SF-36 general health: +6.9 (p<0.05) SF-36 vitality: +5.8 (p<0.05) SF-36 social function: +9.2 (p<0.05) SF-36 role limitations-emotional: +3.6 (p>0.05) SF-36 mental health: +1.3 (p>0.05) Sleep somnolence: +1.5 (p>0.05) Health distress: +6.4 (p<0.05) Hepatitis-related health distress: +12 (p<0.05) Hepatitis-related limitations: +7.8 (p<0.05) Mental health-18: +1.5 (p>0.05)	Schering-Plough

Author, Year Country Quality	Study Type	Comparison	Duration of Followup	Inclusion Criteria	Exclusion Criteria	Number Screened/ Eligible/ Enrolled/ Analyzed

Author, Year Country Quality	Study Type	Comparison	Duration of Followup	Inclusion Criteria	Exclusion Criteria	Number Screened/ Eligible/ Enrolled/ Analyzed
Rasenack, 2003[89] Germany, Canada, New Zealand, Spain Overall Quality: Poor	Cohort study (patients enrolled in a randomized trial)	SVR vs. no SVR SVR=No detectable HCV RNA 24 weeks after completion of antiviral therapy	72 weeks (24 weeks after end of treatment)	Positive HCV antibody, positive HCV RNA, persistently elevated ALT, liver biopsies consistent with chronic hepatitis C	Prior interferon therapy, other disease of the liver or other major diseases, pregnant, substance abuse within the last year	Number screened: Not reported Number eligible: Not reported Number enrolled: 531 Number analyzed: Unclear

Author, Year Country Quality	Demographic Characteristics of Study Population (Age, Race, Mean Viral Load)	Genotype HCV Viral Load HIV Infection IV Drug Use	Treatments	Confounders Assessed in Analysis	Results (by Clinical Outcome)	Funding Source
Rasenack, 2003[89] Germany, Canada, New Zealand, Spain Continued	Not reported by SVR status Mean age: 41 years Female: 33% Non white: 15%	Not reported by SVR status Bridging fibrosis/cirrhosis: 13% Injection drug use: 37% Viral load: 7.4 to 8.2 x 10^6 copies/ml HIV positive: Not reported Genotype: Not reported	Pegylated interferon alfa-2a or interferon alfa-2a	None	SVR vs. no SVR, mean difference in change from baseline SF-36 physical function: +5.0 (p=0.001) SF-36 role limitations-physical: +14 (p<0.001) SF-36 bodily pain: +5.2 (p=0.014) SF-36 general health: 12 (p<0.001) SF-36 vitality: +9.4 (p<0.001) SF-36 social function: +5.8 (p=0.005) SF-36 role limitations-emotional: +8.4 (p=0.02) SF-36 mental health: +5.3 (p=0.001) SF-36 physical component summary: +3.2 (p<0.001) SF-36 mental component summary: +2.9 (p=0.005) Fatigue Severity Scale, total score: -0.5 (p=0.001) Fatigue Severity Scale, VAS: -8.4 (p<0.001)	F. Hoffman-La Roche

Author, Year Country Quality	Study Type	Comparison	Duration of Followup	Inclusion Criteria	Exclusion Criteria	Number Screened/ Eligible/ Enrolled/ Analyzed
Ware, 1999[90] Australia, North America, and Europe Overall Quality: Poor	Cohort study (patients enrolled in a randomized trial)	SVR vs. no SVR SVR=No detectable HCV RNA 24 weeks after completion of antiviral therapy Overall response vs. no overall response Overall response=SVR + Knodell histology activity index inflammation score improved by 2 U or more	72 weeks (24 weeks after end of treatment)	Chronic HCV infection, relapsed after response to interferon treatment,	Decompensated cirrhosis, hemoglobin <12 g/dl in women and <13 g/dl in men, WBC <3000 per cubic millimeter, neutrophil count <1500 per cubic millimeter, platelet count <100,000 per cubic millimeter, HIV infection, prior organ transplantation, severe psychiatric conditions, seizure disorder, cardiovascular disease, renal insufficiency, hemoglobinopathy, hemophilia, poorly controlled diabetes mellitus, immunologically mediated diseases	Number screened: 495 Number eligible: 349 Number enrolled: 349 Number analyzed: 250 (66 SVR and 184 no SVR)

Author, Year Country Quality	Demographic Characteristics of Study Population (Age, Race, Mean Viral Load) Genotype HCV Viral Load HIV Infection IV Drug Use	Treatments	Confounders Assessed in Analysis	Results (by Clinical Outcome)	Funding Source
Ware, 1999[90] Australia, North America, and Europe Continued	Not reported by response status Mean age: 43 years Female: 35% Non white: 6.4% Not reported by response status Bridging fibrosis/cirrhosis: 18% Injection drug use: 40% Viral load: 4.8 to 5.2 x 10^6 copies/ml HIV positive: Excluded Genotype 1: 56%	Interferon alfa-2b or interferon alfa-2b + ribavirin	None	SVR vs. no SVR and overall response vs. no overall response, mean difference in change from baseline (p values not reported) SF-36 physical function: +2.6 and +3.5 SF-36 role limitations-physical: +1.5 and +3.1 SF-36 bodily pain: +0.45 and +1.6 SF-36 general health: +3.3 and +3.5 SF-36 vitality: +2.2 and +2.8 SF-36 social function: +3.4 and +4.3 SF-36 role limitations-emotional: -0.02 and +1.1 SF-36 mental health: +1.3 and +0.62 Sleep: +0.02 and +1.2 Health distress: +7.6 and +6.2 Chronic hepatitis C health distress: +11.5 and +11.3 Chronic hepatitis C limitations: +5.3 and +7.5	Integrated Therapeutics Group, Inc (subsidiary of Schering-Plough)

Evidence Table 13. Quality rating: Studies on sustained virologic response and quality of life

Author, Year	(1) Did the study attempt to enroll all (or a random sample of) patients meeting inclusion criteria, or a random sample (inception cohort)?	(2) Were the groups comparable at baseline on key prognostic factors (e.g., by restriction or matching)?	(3) Did the study use accurate methods for ascertaining exposures, potential confounders, and outcomes?	(4) Were outcome assessors and/or data analysts blinded to treatment?	(5) Did the article report attrition?	(6) Did the study perform appropriate statistical analyses on potential confounders (should adjust for at least age, sex, genotype, fibrosis stage)?	(7) Is there important differential loss to followup or overall high loss to followup?	(8) Were outcomes pre-specified and defined, and ascertained using accurate methods?	Overall Quality
Arora, 2006[82]	Yes	Unclear	Yes	No (patients aware of SVR status)	No	Yes	Unclear	Yes	Poor
Bernstein 2002[83]	Yes	Unclear	Yes	No (patients aware of SVR status)	No	No	Unclear	Yes	Poor
Bini 2006[84]	Unclear	Unclear	Yes	No (patients aware of SVR status)	No	No	Unclear	Yes	Poor
Bonkovsky 1999[85]	Yes	Unclear	Yes	Yes (blinded to virological status, though not histological status)	Yes	No	Yes (high)	Yes	Poor
Hassanein 2004[86]	Yes	Unclear	Yes	No (patients aware of SVR status)	Yes	No	Yes (high)	Yes	Poor
McHutchison 2001[87]	Yes	No	Yes	Unclear	Yes	No	No	Yes	Poor
Neary 1999[88]	Yes	Unclear	Yes	Unclear	Yes	No	Yes (high)	Yes	Poor
Rasenack 2003[89]	Yes	Unclear	Yes	No (patient aware of SVR status)	Yes	No	Yes (high)	Yes	Poor
Ware 1999[90]	Yes	Unclear	Yes	No (patient aware of SVR status)	Yes	No	Yes (high)	Yes	Poor

Evidence Table 14. Sustained virologic response and quality of life summary table scores

Author, Year Country	SF-36 Physical Function	SF-36 Role Limitations-Physical	SF-36 Bodily Pain	SF-36 General Health	SF-36 Vitality	SF-36 Social Function	SF-36 Role Limitations-Emotional	SF-36 Mental Health
Arora, 2006[82] Australia, Europe, New Zealand, North America, and South America	+4.7 (p<0.05)	+13 (p<0.05)	+11 (p<0.0001)	+10 (p<0.0001)	+9.3 (p<0.0001)	+5.1 (p>0.05)	+7.3 (p>0.05)	+3.1 (p>0.05)
Bernstein, 2002[83] Australia, North America, Europe, Taiwan, New Zealand	+4.6 (p<0.001)	+9.8 (p<0.001)	+2.9 (p<0.01)	+9.1 (p<0.001)	+9.1 (p<0.001)	+6.2 (p<0.001)	+8.4 (p<0.01)	+4.6 (p<0.001)
Bini 2006[84]* USA	+18 and +15	+22 and +27	+3.4 and +9.3	+3.0 and +9.9	+12 and +12	+9.5 and +11	+20 and +18	+14 and +18
Bonkovsky 1999[85] USA and Canada	+6.0 (p<0.05)	+22 (p<0.01)	-0.5 (p>0.05)	+7.5 (p<0.01)	+9.5 (p<0.05)	+10 (p<0.05)	+11 (p>0.05)	+4.0 (p>0.05)
Hassanein, 2004[86] Australia, North America, Europe, Taiwan, Brazil, Mexico	+5.5 (p<0.01)	+5.7 (p<0.05)	+4.1 (p<0.5)	+8.6 (p<0.01)	+6.3 (p>0.05)	+5.8 (p<0.01)	+9.3 (p<0.01)	=5.0 (p<0.01)
McHutchison, 2001[87]^ USA	+2.4	+5.2	+1.6	+5.2	+4.7	+3.1	+3.0	+2.0
Neary, 1999[88]^# USA, Europe, Australia	+8.0	+7.6	+2.4	+9.4	+7.8	+9.4	+6.0	+2.8
Rasenack, 2003[89]** Germany, Canada, New Zealand, Spain	+5.0 (p=0.001)	+14 (p<0.001)	+5.2 (p=0.014)	+12 (p<0.001)	+9.4 (p<0.001)	+5.8 (p=0.005)	+8.4 (p=0.02)	+5.3 (p=0.001)
Ware, 1999[90]^ Australia, North America, and Europe	+2.6	+1.5	+0.45	+3.3	+2.2	+3.4	-0.02	+1.3

Author, Year Country Study Name	SF-36 Physical Component Summary	SF-36 Mental Component Summary	Sleep Somnolence	Fatigue Severity Scale, Total Score	Fatigue Severity Scale, Visual Analogue Scale	Health Distress	Hepatitis-Specific Health Distress	Hepatitis-Specific Limitations
Arora, 2006[82] Australia, Europe, New Zealand, North America, and South America	+4.9 (p<0.0001)	+2.0 (p>0.05)	NR	+4.4 (p<0.01)	-10 (p<0.01)	NR	NR	NR
Bernstein, 2002[83] Australia, North America, Europe, Taiwan, New Zealand	+2.8 (p<0.001)	+3.0 (p>0.001)	NR	-0.5 (p<0.001)	-12 (p<0.001)	NR	NR	NR
Bini 2006[84]* USA	+3.8 and +7.1	+6.0 and +2.1	+11 and +5.4	NR	NR	+9.3 and +11	+5.4 and +2.6	+13 and +3.8
Bonkovsky 1999[85] USA and Canada	NR	NR	NR	NR	NR	NR	NR	NR
Hassanein, 2004[86] Australia, North America, Europe, Taiwan, Brazil, Mexico	+5.0 (p<0.01)	+2.6 (p<0.01)	NR	+3.3 (p<0.01)	+7.4 (p<0.01)	NR	NR	NR
McHutchison, 2001[87]^ USA	NR	NR	+3.4	NR	NR	+5.4	+5.7	+4.6
Neary, 1999[88]^# USA, Europe, Australia	NR	NR	+2.1	NR	NR	+8.9	+11	+6.7
Rasenack, 2003[89]** Germany, Canada, New Zealand, Spain	+3.2 (p<0.001)	+2.9 (p=0.005)	NR	-0.5 (p=0.001)	-8.4 (p<0.001)	NR	NR	NR
Ware, 1999[90]^ Australia, North America, and Europe	+0.02	None	NR	NR	NR	+7.6	+12	+5.3

Abbreviations: NR, not reported.
Note: Absence of p values indicates that they were not reported.
* Results reported for normal alanine transaminase and elevated alanine transaminase subgroups, respectively
^ Results for relapsers reported separately and excluded from table.
# Same cohort as Ware, 1999.
** Cohort included in Bernstein, 2002.

Appendix H References

1. Ascione A, De Luca M, Tartaglione MT, et al. Peginterferon alfa-2a plus ribavirin is more effective than peginterferon alfa-2b plus ribavirin for treating chronic hepatitis C virus infection. Gastroenterol. 2010 Jan;138(1):116-22. PMID: 19852964.

2. Bruno R, Sacchi P, Ciappina V, et al. Viral dynamics and pharmacokinetics of peginterferon alpha-2a and peginterferon alpha-2b in naive patients with chronic hepatitis c: a randomized, controlled study. Antiver Ther. 2004;9(4):491-7. PMID: 15456079.

3. Di Bisceglie AM, Ghalib RH, Hamzeh FM, et al. Early virologic response after peginterferon alpha-2a plus ribavirin or peginterferon alpha-2b plus ribavirin treatment in patients with chronic hepatitis C. J Viral Hepat. 2007 Oct;14(10):721-9. PMID: 17875007.

4. Escudero A, Rodriguez F, Serra MA, et al. Pegylated alpha-interferon-2a plus ribavirin compared with pegylated alpha-interferon-2b plus ribavirin for initial treatment of chronic hepatitis C virus: prospective, non-randomized study. J Gastroenterol Hepatol. 2008 Jun;23(6):861-6. PMID: 18422960.

5. Kamal SM, Ahmed A, Mahmoud S, et al. Enhanced efficacy of pegylated interferon alpha-2a over pegylated interferon and ribavirin in chronic hepatitis C genotype 4A randomized trial and quality of life analysis. Liver Int. 2011;31(3):401-11. PMID: 21281434.

6. Khan A, Awan A, Shahbuddin S, et al. Abstract # S1231: Peginterferon alfa 2a / ribavirin versus peginterferon alfa 2b / ribavirin combination therapy in chronic hepatitis C genotype 3. Gastroenterol. 2007;132(4):A200.

7. Mach TH, Ciesla A, Warunek W, et al. Efficacy of pegylated interferon alfa-2a or alfa-2b in combination with ribavirin in the treatment of chronic hepatitis caused by hepatitis C virus genotype 1b. Polskie Archiwum Medycyny Wewnetrznej. 2011;121(12):434-40.

8. Magni C NF, Argenteri B, Giorgi R, Mainini A, Pastecchia C, Ricci E, Schiavini M, Terzi R, Vivirito MC, Resta M. Abstract #883: Antiviral activity and tolerability between pegylated interferon alpha 2a and alpha 2b in naive patients with chronic hepatitis C: Results of a prospective monocentric randomized trial. Hepatology. 2009;50(S4):720A.

9. McHutchison J, Sulkowski M. Scientific rationale and study design of the individualized dosing efficacy vs flat dosing to assess optimal pegylated interferon therapy (IDEAL) trial: determining optimal dosing in patients with genotype 1 chronic hepatitis C. J Viral Hepat. 2008;15(7):475-81. PMID: 18363672.

10. Miyase S, Haraoka K, Ouchida Y, et al. Randomized trial of peginterferon α-2a plus ribavirin versus peginterferon α-2b plus ribavirin for chronic hepatitis C in Japanese patients. J Gastroenterol. 2012:1-8. PMID: 22382633.

11. Rumi MG, Aghemo A, Prati GM, et al. Randomized study of peginterferon-alpha2a plus ribavirin vs peginterferon-alpha2b plus ribavirin in chronic hepatitis C. Gastroenterol. 2010 Jan;138(1):108-15. PMID: 19766645.

12. Silva M, Poo JL, Wagner F, et al. A randomised trial to compare the pharmacokinetic, pharmacodynamic, and antiviral effects of peginterferon alfa-2b and peginterferon alfa-2a in patients with chronic hepatitis C (COMPARE). J Hepatol. 2006;45(2):204-13. PMID: 16780997.

13. Yenice N, Mehtap O, Gumrah M, et al. The efficacy of pegylated interferon alpha 2a or 2b plus ribavirin in chronic hepatitis C patients. Turk J Gastroenterol. 2006 Jun;17(2):94-8. PMID: 16830289.

14. Hezode C, Forestier N, Dusheiko G, et al. Telaprevir and peginterferon with or without ribavirin for chronic HCV infection. N Engl J Med. 2009 Apr 30;360(18):1839-50. PMID: 19403903.

15. Jacobson IM, McHutchison JG, Dusheiko G, et al. Telaprevir for previously untreated chronic hepatitis C virus infection. N Engl J Med. 2011;364(25):2405-16. PMID: 21696307.

16. Kumada H, Toyota J, Okanoue T, et al. Telaprevir with peginterferon and ribavirin for treatment-naive patients chronically infected with HCV of genotype 1 in Japan. J Hepatol. 2012;56(1):78-84. PMID: 21827730.

17. Kwo PY, Lawitz EJ, McCone J, et al. Efficacy of boceprevir, an NS3 protease inhibitor, in combination with peginterferon alfa-2b and ribavirin in treatment-naive patients with genotype 1 hepatitis C infection (SPRINT-1): an open-label, randomised, multicentre phase 2 trial.[Erratum appears in Lancet. 2010 Oct 9;376(9748):1224 Note: SPRINT-1 investigators [added]; multiple investigator names added]. Lancet. 2010 Aug 28;376(9742):705-16. PMID: 20692693.

18. Marcellin P, Forns X, Goeser T, et al. Telaprevir is effective given every 8 or 12 hours with ribavirin and peginterferon alfa-2a or -2b to patients with chronic hepatitis C. Gastroenterol. 2011 Feb;140(2):459-68.e1; quiz e14. PMID: 21034744.

19. McHutchison JG, Everson GT, Gordon SC, et al. Telaprevir with peginterferon and ribavirin for chronic HCV genotype 1 infection. N Engl J Med. 2009;360(18):1827-38. PMID: 19403902.

20. Poordad F, McCone J, Jr., Bacon BR, et al. Boceprevir for untreated chronic HCV genotype 1 infection. N Engl J Med. 2011 Mar 31;364(13):1195-206. PMID: 21449783.

21. Sherman KE, Flamm SL, Afdhal NH, et al. Response-guided telaprevir combination treatment for hepatitis C virus infection. N Engl J Med. 2011;365(11):1014-24. PMID: 21916639.

22. Andriulli A, Cursaro C, Cozzolongo R, et al. Early discontinuation of ribavirin in HCV-2 and HCV-3 patients

responding to Peg-interferon alpha-2a and ribavirin. J Viral Hepat. 2009 Jan;16(1):28-35. PMID: 18761603.

23. Berg T, von Wagner M, Nasser S, et al. Extended treatment duration for hepatitis C virus type 1: comparing 48 versus 72 weeks of peginterferon-alfa-2a plus ribavirin. Gastroenterology. 2006 Apr;130(4):1086-97. PMID: 16618403.

24. Berg T, Weich V, Teuber G, et al. Individualized treatment strategy according to early viral kinetics in hepatitis C virus type 1-infected patients. Hepatology. 2009 Aug;50(2):369-77. PMID: 19575366.

25. Brandao C, Barone A, Carrilho F, et al. The results of a randomized trial looking at 24 weeks vs 48 weeks of treatment with peginterferon alpha-2a (40 kDa) and ribavirin combination therapy in patients with chronic hepatitis C genotype 1. J Viral Hepat. 2006 Aug;13(8):552-9. PMID: 16901286.

26. Buti M, Lurie Y, Zakharova NG, et al. Randomized trial of peginterferon alfa-2b and ribavirin for 48 or 72 weeks in patients with hepatitis C virus genotype 1 and slow virologic response. Hepatology. 2010 Oct;52(4):1201-7. PMID: 20683847.

27. Dalgard O, Bjoro K, Ring-Larsen H, et al. Pegylated interferon alfa and ribavirin for 14 versus 24 weeks in patients with hepatitis C virus genotype 2 or 3 and rapid virological response. Hepatology. 2008 Jan;47(1):35-42. PMID: 17975791.

28. Ferenci P, Laferl H, Scherzer T-M, et al. Peginterferon alfa-2a/ribavirin for 48 or 72 weeks in hepatitis C genotypes 1 and 4 patients with slow virologic response. [Reprint in Korean J Hepatol. 2010 Jun;16(2):201-5; PMID: 20606507]. Gastroenterol. 2010 Feb;138(2):503-12. PMID: 19909752.

29. Hadziyannis SJ, Sette H, Jr., Morgan TR, et al. Peginterferon-alpha2a and ribavirin combination therapy in chronic hepatitis C: a randomized study of treatment duration and ribavirin dose. Ann Intern Med. 2004 Mar 2;140(5):346-55. PMID: 14996676.

30. Ide T, Hino T, Ogata K, et al. A randomized study of extended treatment with peginterferon alpha-2b plus ribavirin based on time to HCV RNA negative-status in patients with genotype 1b chronic hepatitis C. Am J Gastroenterol. 2009 Jan;104(1):70-5. PMID: 19098852.

31. Kamal SM, El Tawil AA, Nakano T, et al. Peginterferon {alpha}-2b and ribavirin therapy in chronic hepatitis C genotype 4: impact of treatment duration and viral kinetics on sustained virological response. Gut. 2005 Jun;54(6):858-66. PMID: 15888797.

32. Lagging M, Langeland N, Pedersen C, et al. Randomized comparison of 12 or 24 weeks of peginterferon alpha-2a and ribavirin in chronic hepatitis C virus genotype 2/3 infection. Hepatology. 2008 Jun;47(6):1837-45. PMID: 18454508.

33. Lam KD, Trinh HN, Do ST, et al. Randomized controlled trial of pegylated interferon-alfa 2a and ribavirin in treatment-naive chronic hepatitis C genotype 6. Hepatology. 2010 Nov;52(5):1573-80. PMID: 21038410.

34. Liu C-H, Liu C-J, Lin C-L, et al. Pegylated interferon-alpha-2a plus ribavirin for treatment-naive Asian patients with hepatitis C virus genotype 1 infection: a multicenter, randomized controlled trial. Clin Infect Dis. 2008 Nov 15;47(10):1260-9. PMID: 18834319.

35. Mangia A, Santoro R, Minerva N, et al. Peginterferon alfa-2b and ribavirin for 12 vs. 24 weeks in HCV genotype 2 or 3. N Engl J Med. 2005 Jun 23;352(25):2609-17. PMID: 15972867.

36. Manns M, Zeuzem S, Sood A, et al. Reduced dose and duration of peginterferon alfa-2b and weight-based ribavirin in patients with genotype 2 and 3 chronic hepatitis C. J Hepatol. 2011b;55(3):554-63. PMID: 21237227.

37. Mecenate F, Pellicelli AM, Barbaro G, et al. Short versus standard treatment with pegylated interferon alfa-2A plus ribavirin in patients with hepatitis C virus genotype 2 or 3: the cleo trial. BMC Gastroenterol. 2010;10:21. PMID: 20170514.

38. Pearlman BL, Ehleben C, Saifee S. Treatment extension to 72 weeks of peginterferon and ribavirin in hepatitis C genotype 1-infected slow responders. Hepatology. 2007 Dec;46(6):1688-94. PMID: 18046717.

39. Sanchez-Tapias JM, Diago M, Escartin P, et al. Peginterferon-alfa2a plus ribavirin for 48 versus 72 weeks in patients with detectable hepatitis C virus RNA at week 4 of treatment.[Erratum appears in Gastroenterology. 2006 Oct;131(4):1363]. Gastroenterol. 2006 Aug;131(2):451-60. PMID: 16890599.

40. Shiffman ML, Suter F, Bacon BR, et al. Peginterferon alfa-2a and ribavirin for 16 or 24 weeks in HCV genotype 2 or 3. N Engl J Med. 2007 Jul 12;357(2):124-34. PMID: 17625124.

41. von Wagner M, Huber M, Berg T, et al. Peginterferon-alpha-2a (40KD) and ribavirin for 16 or 24 weeks in patients with genotype 2 or 3 chronic hepatitis C. Gastroenterol. 2005 Aug;129(2):522-7. PMID: 16083709.

42. Yu M-L, Dai C-Y, Lin Z-Y, et al. A randomized trial of 24- vs. 48-week courses of PEG interferon alpha-2b plus ribavirin for genotype-1b-infected chronic hepatitis C patients: a pilot study in Taiwan. Liver Int. 2006 Feb;26(1):73-81. PMID: 16420512.

43. Yu M-L, Dai C-Y, Huang J-F, et al. A randomised study of peginterferon and ribavirin for 16 versus 24 weeks in patients with genotype 2 chronic hepatitis C. Gut. 2007 Apr;56(4):553-9. PMID: 16956917.

44. Yu M-L, Dai C-Y, Huang J-F, et al. Rapid virological response and treatment duration for chronic hepatitis C genotype 1 patients: a randomized trial. Hepatology. 2008 Jun;47(6):1884-93. PMID: 18508296.

45. Zeuzem S, Diago M, Gane E, et al. Peginterferon alfa-2a (40 kilodaltons) and ribavirin in patients with chronic hepatitis C and normal aminotransferase levels. Gastroenterol. 2004 Dec;127(6):1724-32. PMID: 15578510.

46. Bronowicki J-P, Ouzan D, Asselah T, et al. Effect of ribavirin in genotype 1 patients with hepatitis C responding to pegylated interferon alfa-2a plus ribavirin. Gastroenterol. 2006 Oct;131(4):1040-8. PMID: 17030174.

47. Abergel A, Hezode C, Leroy V, et al. Peginterferon alpha-2b plus ribavirin for treatment of chronic hepatitis C with severe fibrosis: a multicentre randomized controlled trial comparing two doses of peginterferon alpha-2b. J Viral Hepat. 2006 Dec;13(12):811-20. PMID: 17109680.

48. Brady DE, Torres DM, An JW, et al. Induction pegylated interferon alfa-2b in combination with ribavirin in patients with genotypes 1 and 4 chronic hepatitis C: a prospective, randomized, multicenter, open-label study. Clin Gastroenterol Hepatol. 2010 Jan;8(1):66-71.e1. PMID: 19747986.

49. Ferenci P, Brunner H, Laferl H, et al. A randomized, prospective trial of ribavirin 400 mg/day versus 800 mg/day in combination with peginterferon alfa-2a in hepatitis C virus genotypes 2 and 3. Hepatology. 2008 Jun;47(6):1816-23. PMID: 18454510.

50. Fried MW, Jensen DM, Rodriguez-Torres M, et al. Improved outcomes in patients with hepatitis C with difficult-to-treat characteristics: randomized study of higher doses of peginterferon alpha-2a and ribavirin. Hepatology. 2008 Oct;48(4):1033-43. PMID: 18697207.

51. Helbling B, Jochum W, Stamenic I, et al. HCV-related advanced fibrosis/cirrhosis: randomized controlled trial of pegylated interferon alpha-2a and ribavirin. J Viral Hepat. 2006 Nov;13(11):762-9. PMID: 17052276.

52. Jacobson (a) IM, Brown RS, Jr., Freilich B, et al. Peginterferon alfa-2b and weight-based or flat-dose ribavirin in chronic hepatitis C patients: a randomized trial. Hepatology. 2007 Oct;46(4):971-81. PMID: 17894303.

53. Jacobson (b) IM, Brown RS, Jr., McCone J, et al. Impact of weight-based ribavirin with peginterferon alfa-2b in African Americans with hepatitis C virus genotype 1. Hepatology. 2007 Oct;46(4):982-90. PMID: 17894323.

54. Kawaoka T, Kawakami Y, Tsuji K, et al. Dose comparison study of pegylated interferon-alpha-2b plus ribavirin in naive Japanese patients with hepatitis C virus genotype 2: a randomized clinical trial. J Gastroenterol Hepatol. 2009 Mar;24(3):366-71. PMID: 19032459.

55. Krawitt EL, Gordon SR, Grace ND, et al. A study of low dose peginterferon alpha-2b with ribavirin for the initial treatment of chronic hepatitis C. Am J Gastroenterol. 2006 Jun;101(6):1268-73. PMID: 16771948.

56. Manns MP, McHutchison JG, Gordon SC, et al. Peginterferon alfa-2b plus ribavirin compared with interferon alfa-2b plus ribavirin for initial treatment of chronic hepatitis C: a randomised trial. Lancet. 2001;358(9286):958-65. PMID: 11583749.

57. Meyer-Wyss B, Rich P, Egger H, et al. Comparison of two PEG-interferon alpha-2b doses (1.0 or 1.5 microg/kg) combined with ribavirin in interferon-naive patients with chronic hepatitis C and up to moderate fibrosis. J Viral Hepat. 2006 Jul;13(7):457-65. PMID: 16792539.

58. Mimidis K, Papadopoulos VP, Elefsiniotis I, et al. Hepatitis C virus survival curve analysis in naive patients treated with peginterferon alpha-2b plus ribavirin. A randomized controlled trial for induction with high doses of peginterferon and predictability of sustained viral response from early virologic data. J Gastrointestin Liver Dis. 2006 Sep;15(3):213-9. PMID: 17013444.

59. Reddy KR, Shiffman ML, Rodriguez-Torres M, et al. Induction pegylated interferon alfa-2a and high dose ribavirin do not increase SVR in heavy patients with HCV genotype 1 and high viral loads. Gastroenterol. 2010 Dec;139(6):1972-83. PMID: 20816836.

60. Roberts SK, Weltman MD, Crawford DHG, et al. Impact of high-dose peginterferon alfa-2A on virological response rates in patients with hepatitis C genotype 1: a randomized controlled trial. Hepatology. 2009 Oct;50(4):1045-55. PMID: 19676125.

61. Sood A, Midha V, Hissar S, et al. Comparison of low-dose pegylated interferon versus standard high-dose pegylated interferon in combination with ribavirin in patients with chronic hepatitis C with genotype 3: an Indian experience. J Gastroenterol Hepatol. 2008 Feb;23(2):203-7. PMID: 17645472.

62. McHutchison JG, Lawitz EJ, Shiffman ML, et al. Peginterferon alfa-2b or alfa-2a with ribavirin for treatment of hepatitis C infection.[Erratum appears in N Engl J Med. 2009 Sep 3;361(10):1027]. N Engl J Med. 2009 Aug 6;361(6):580-93. PMID: 19625712.

63. Arase Y, Ikeda K, Suzuki F, et al. Long-term outcome after interferon therapy in elderly patients with chronic hepatitis C. Intervirology. 2007;50(1):16-23. PMID: 17164553.

64. Backus LI, Boothroyd DB, Phillips BR, et al. A sustained virologic response reduces risk of all-cause mortality in patients with hepatitis C. Clin Gastroenterol Hepatol. 2011;9:509-16. PMID: 21397729.

65. Bruno S, Stroffolini T, Colombo M, et al. Sustained virological response to interferon-alpha is associated with improved outcome in HCV-related cirrhosis: a retrospective study. Hepatology. 2007 Mar;45(3):579-87. PMID: 17326216.

66. Cardoso A-C, Moucari R, Figueiredo-Mendes C, et al. Impact of peginterferon and ribavirin therapy on hepatocellular carcinoma: incidence and survival in hepatitis C patients with advanced fibrosis. J Hepatol. 2010 May;52(5):652-7. PMID: 20346533.

67. Coverdale SA, Khan MH, Byth K, et al. Effects of interferon treatment response on liver complications of chronic hepatitis C: 9-year follow-up study. Am J Gastroenterol. 2004 Apr;99(4):636-44. PMID: 15089895.

68. El Braks RE, Ganne-Carrie N, Fontaine H, et al. Effect of sustained virological response on long-term clinical outcome in 113 patients with compensated hepatitis C-related cirrhosis treated by interferon alpha and ribavirin. World J Gastroenterol. 2007;13(42):5648-53. PMID: 17948941.

69. Fernández-Rodríguez CM, Alonso S, Martinez SM, et al. Peginterferon plus ribavirin and sustained virological response in HCV-related cirrhosis: Outcomes and factors predicting response. Am J Gastroenterol. 2010PMID: 20927082.

70. Hasegawa E, Kobayashi M, Kawamura Y, et al. Efficacy and anticarcinogenic activity of interferon for hepatitis C virus-related compensated cirrhosis in patients with genotype 1b low viral load or genotype 2. Hepatol Res. 2007;37(10):793-800. PMID: 17593231.

71. Hung CH, Lee CM, Lu SN, et al. Long-term effect of interferon alpha-2b plus ribavirin therapy on incidence of hepatocellular carcinoma in patients with hepatitis C virus-related cirrhosis. J Viral Hepat. 2006;13(6):409-14. PMID: 16842444.

72. Imazeki F, Yokosuka O, Fukai K, et al. Favorable prognosis of chronic hepatitis C after interferon therapy by long-term cohort study. Hepatology. 2003 Aug;38(2):493-502. PMID: 12883494.

73. Innes HA, Hutchinson SJ, Allen S, et al. Excess liver-related morbidity of chronic hepatitis C patients, who achieve a sustained viral response, and are discharged from care. Hepatology. 2011;54(5):1547-58. PMID: 22045672.

74. Izumi N, Yasuhiro A, Kurosaki M, et al. Development of hepatocellular carcinoma after interferon therapy in chronic hepatitis C. Is it possible to reduce the incidence by ribanirin and IFN combination therapy? Intervirology. 2005;48(1):59-63. PMID: 15785091.

75. Kasahara A, Tanaka H, Okanoue T, et al. Interferon treatment improves survival in chronic hepatitis C patients showing biochemical as well as virological responses by preventing liver-related death. J Viral Hepat. 2004 Mar;11(2):148-56. PMID: 14996350.

76. Maruoka D, Imazeki F, Arai M, et al. Long-term cohort study of chronic hepatitis C according to interferon efficacy. J Gastroenterol Hepatol. 2012b;27(2):291-9. PMID: 21793911.

77. Morgan TR, Ghany MG, Kim H-Y, et al. Outcome of sustained virological responders with histologically advanced chronic hepatitis C. Hepatology. 2010 Sep;52(3):833-44. PMID: 20564351.

78. Shiratori Y, Ito Y, Yokosuka O, et al. Antiviral therapy for cirrhotic hepatitis C: association with reduced hepatocellular carcinoma development and improved survival. Ann Intern Med. 2005 Jan 18;142(2):105-14. PMID: 15657158.

79. Veldt BJ, Heathcote EJ, Wedemeyer H, et al. Sustained virologic response and clinical outcomes in patients with chronic hepatitis C and advanced fibrosis. Ann Intern Med. 2007;147(10):677-84. PMID: 18025443.

80. Yoshida H, Arakawa Y, Sata M, et al. Interferon therapy prolonged life expectancy among chronic hepatitis C patients. Gastroenterol. 2002 Aug;123(2):483-91. PMID: 12145802.

81. Yu M-L, Lin S-M, Chuang W-L, et al. A sustained virological response to interferon or interferon/ribavirin reduces hepatocellular carcinoma and improves survival in chronic hepatitis C: a nationwide, multicentre study in Taiwan. Antiver Ther. 2006;11(8):985-94. PMID: 17302368.

82. Arora S, O'Brien C, Zeuzem S, et al. Treatment of chronic hepatitis C patients with persistently normal alanine aminotransferase levels with the combination of peginterferon alpha-2a (40 kDa) plus ribavirin: impact on health-related quality of life. J Gastroenterol Hepatol. 2006 Feb;21(2):406-12. PMID: 16509866.

83. Bernstein D, Kleinman L, Barker CM, et al. Relationship of health-related quality of life to treatment adherence and sustained response in chronic hepatitis C patients. Hepatology. 2002 Mar;35(3):704-8. PMID: 11870387.

84. Bini EJ, Mehandru S. Sustained virological response rates and health-related quality of life after interferon and ribavirin therapy in patients with chronic hepatitis C virus infection and persistently normal alanine aminotransferase levels. Aliment Pharmacol Ther. 2006;23(6):777-85. PMID: 16556180.

85. Bonkovsky HL, Woolley JM. Reduction of health-related quality of life in chronic hepatitis C and improvement with interferon therapy.The Consensus Interferon Study Group. Hepatology. 1999;29(1):264-70. PMID: 9862876.

86. Hassanein T, Cooksley G, Sulkowski M, et al. The impact of peginterferon alfa-2a plus ribavirin combination therapy on health-related quality of life in chronic hepatitis C. J Hepatol. 2004 Apr;40(4):675-81. PMID: 15030985.

87. McHutchison J, Manns M, Harvey J, et al. Adherence to therapy enhanges sustained response in chronic hepatitis C patients receiving PEG-Interferon alfa-2b plus Ribavirin [abstract]. J Hepatol. 2001;34(1):2-3.

88. Neary MP, Cort S, Bayliss MS, et al. Sustained virologic response is associated with improved health-related quality of life in relapsed chronic hepatitis C patients. Semin Liver Dis. 1999;19 Suppl 1:77-85. PMID: 10349695.

89. Rasenack J, Zeuzem S, Feinman SV, et al. Peginterferon alpha-2a (40kD) [Pegasys] improves HR-QOL outcomes compared with unmodified interferon alpha-2a [Roferon-A]: in patients with chronic hepatitis C.[Erratum appears in Pharmacoeconomics. 2003;21(17):1290]. Pharmacoeconomics. 2003;21(5):341-9. PMID: 12627987.

90. Ware JE, Bayliss MS, Mannocchia M, et al. Health-related quality of life in chronic hepatitis C: impact of disease and treatment response. The Interventional Therapy Group. Hepatology. 1999;30(2):550-5. PMID: 10421667