Drug Class Review
on
Pegylated Interferons for
Chronic Hepatitis C Infection

Final Report

May 2007

The Agency for Healthcare Research and Quality has not yet seen or approved this report

A literature scan of this topic is done periodically

The purpose of this report is to make available information regarding the comparative effectiveness and safety profiles of different drugs within pharmaceutical classes. Reports are not usage guidelines, nor should they be read as an endorsement of, or recommendation for, any particular drug, use or approach. Oregon Health & Science University does not recommend or endorse any guideline or recommendation developed by users of these reports.

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Note: A scan of the medical literature relating to the topic is done periodically (see http://www.ohsu.edu/ohsuedu/research/policycenter/DERP/about/methods.cfm for scanning process description). Upon review of the last scan, the Drug Effectiveness Review Project governance group elected not to proceed with another full update of this report. Some portions of the report may not be up to date.

TABLE OF CONTENTS

FIGURES

TABLES

APPENDICES

EVIDENCE TABLES: SEE SEPARATE DOCUMENT

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INTRODUCTION

Hepatitis C virus (HCV) is the most common chronic blood borne pathogen in the United States. It is acquired primarily by large or repeated percutaneous exposures to blood, with a history of injection drug use the strongest risk factor. Approximately 1.6% of U.S. adults over the age of 20 (about 4.1 million persons) have antibodies to HCV, indicating prior acute HCV infection.[1] Up to 84% of patients with acute HCV infection develop chronic HCV infection (about 3.2 million U.S. adults).

Chronic HCV infection has a variable course but can cause cirrhosis, liver failure, and hepatocellular cancer after a number of years. Up to 20% of persons with chronic HCV infection develop cirrhosis after 20 years.[2] In the United States, HCV infection is associated with approximately 40% of cases of chronic liver disease.[3] The number of liver-related deaths associated with chronic HCV infection was estimated at 13,000 deaths per year in 2000, but is thought to be on the rise.[4] Around 40% of patients who undergo liver transplantation have chronic HCV infection.[5]

The specific HCV genotype is an important predictor of clinical outcomes and response to antiviral treatment.[6] In the United States, genotype 1 infection is found in up to three-quarters of HCV-infected patients.[7] It is associated with the poorest response to antiviral treatment. Genotypes 2 and 3 are present in about 20% of HVC-infected patients.

Recombinant type I interferons are administered to patients with HCV infection for their antiviral effects. Interferon-based therapy is also associated with flu-like symptoms, fatigue, and neuropsychiatric and hematologic adverse effects.[8] Interferon monotherapy for chronic HCV infection began in the mid-1980s and was only modestly successful at suppressing HCV (Table 1).[9-12] Subsequent trials found dual therapy with interferon and the synthetic nucleoside analogue ribavirin more effective than monotherapy, though the proportion of patients with sustained virologic response (SVR) rates remained under 50%.[9, 10, 12]

Table 1. 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	Reference
Placebo	<2	Not applicable	Poynard et al., 1996[11]
Interferon monotherapy	6-16	7-25	Chander, 2002[9] Kjaegard, 2000[10] Poynard et al., 1996[11] Shepherd et al., 2000[12]
Interferon plus ribavirin	33-41	2.6-3.2	Chander, 2002[9] Kjaergard et al., 2001[10] Shepherd et al., 2000[12]
Pegylated interferon monotherapy	23-39	2.7-4.8	Chander, 2002[9] Zaman et al., 2003[13]
Pegylated interferon plus ribavirin	54-61	1.7-1.9	Shepherd et al., 2005[14] Siebert et al., 2005[15] Zaman et al., 2003[13]

The first "pegylated" interferon was approved by the FDA in 2001. Pegylation refers to the cross-linking of polyethylene glycol (PEG) molecules to the interferon molecule, which delays renal clearance.[16] An advantage of pegylation is that it permits less frequent dosing (once weekly versus three times a week with non-pegylated interferon). Dual therapy with pegylated interferon and ribavirin is associated with higher SVR rates than non-pegylated interferon plus ribavirin or pegylated interferon monotherapy (Table 1). Currently, two pegylated interferons are available. Both are Type I alfa interferons, but differ in size and structure of the interferon and polyethylene glycol molecules, as well as in pharmacokinetic properties (Table 2).[16] One pegylated interferon consists of 31-kilodalton (kDa) interferon alfa-2b conjugated to 12-kilodalton (kDa) polyethylene glycol (trade 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 (Copegus® for pegylated interferon alfa-2a and Rebetol® for alfa-2b). Although each pegylated interferon is approved for combination therapy with a specific brand of ribavirin manufactured by the respective manufacturer, the ribavirin is pharmacologically identical.

Table 2. Pharmacokinetics, indications and dosing of included drugs[17, 18]

Drug Trade Name	How supplied	Pharmacokinetics[19]	FDA labeled indications	Dosing	Dose adjustments for special populations
Peginterferon alfa-2a Pegasys®	Injectable solution 180 µg/1.0 mL vial 180 µg/0.5 mL prefilled syringe	Volume of distribution: 8-12 L/kg Clearance: 60-100 mL/h/kg Absorption half-life: 50 hours Elimination half-life: 65 hours T_{max}: 80 hours Peak-to-trough ratio: 1.5-2.0	Adults with chronic HCV with compensated liver disease who have not been previously treated with interferon alpha.	180 µg once weekly up to 48 weeks (monotherapy or in combination with ribavirin)	*End stage renal disease requiring dialysis*: reduce to 135 µg *ALT>5 times ULN*: monitor and consider reducing to 135 µg *Moderate depression*: reduce to 135 µg, reduction to 90 µg may be necessary *Severe depression*: discontinue *ANC<750 mm^3*: reduce to 135 µg *Platelet <50,000 mm^3*: reduce to 90 µg
Peginterferon alfa-2b PEG-Intron®	74, 118.4, 177.6, and 222 µg vials 67.5, 108, 162, and 202.5 µg Redipen	Volume of distribution: 0.99 L/kg Clearance: 22.0 mL/h/kg Absorption half-life: 4.6 hours Elimination half-life: approximately 40 hours T_{max}: 15-44 hours Peak-to-trough ratio: >10	Adults with chronic HCV with compensated liver disease who have not been previously treated with interferon alpha and are at least 18 years of age.	1.0 µg/kg once weekly for one year (monotherapy); 1.5 µg/kg when administered in combination with ribavirin	*Moderate renal dysfunction* (creatinine clearance 30-50 ml/min): reduce dose by 25% *Severe renal dysfunction, including those requiring dialysis*: reduce by 50%, discontinue if renal function decreases. *Moderate depression*: reduce dose by 50%; *Severe depression*: discontinue;

Drug Trade Name	How supplied	Pharmacokinetics[19]	FDA labeled indications	Dosing	Dose adjustments for special populations
					Hgb <8.5 g/dl: discontinue; *WBC <1.5 x 10^9/L*: reduce dose by 50%; <1.0 x 10^9/L: discontinue; *Neutrophil* <0.75 x 10^9/L: reduce by 50%; <0.05 x 10^9/L: discontinue; *Platelets* <80 x 10^9/L: reduce by 50%; <50 x 10^9/L: discontinue

Dual therapy with pegylated interferon and ribavirin is now recommended as the antiviral regimen of choice for chronic HCV infection in patients who meet criteria for treatment.[6, 20] However, current guidelines make no recommendation for one pegylated interferon over the other, and it is unclear if there are clinically significant differences between dual therapy with pegylated interferon-alfa 2a versus pegylated interferon-alfa 2b. There is also uncertainty about comparative effectiveness and safety of dual therapy with pegylated interferons in subgroups of patients with HCV (such as those co-infected with HIV infection, those with higher fibrosis stage or higher viral load, those infected with genotype 1, or those who have already failed interferon-based therapy) and in how differences in duration of therapy or dose affect estimates of benefits and harms.

Scope and Key Questions

The purpose of this review is to compare the benefits and harms of different pharmacologic treatments for chronic hepatitis C infection. The Oregon Evidence-based Practice Center wrote preliminary key questions, identifying the populations, interventions, and outcomes of interest, and based on these, the eligibility criteria for studies. These were reviewed and revised by representatives of organizations participating in the Drug Effectiveness Review Project (DERP). The participating organizations of DERP are responsible for ensuring that the scope of the review reflects the populations, drugs, and outcome measures of interest to both clinicians and patients. The participating organizations approved the following key questions to guide this review:

1. What is the comparative effectiveness of regimens of peginterferon alfa-2a plus ribavirin versus peginterferon alfa-2b plus ribavirin for treatment of chronic hepatitis C virus infection?
    a. How does duration of treatment or dosing protocols (including weight-based or maintenance dosing or dosing of ribavirin) affect estimates of comparative effectiveness?

2. What is the comparative tolerability and safety of peginterferon alfa-2a plus ribavirin versus peginterferon alfa-2b plus ribavirin for treatment of chronic hepatitis C virus infection?
3. Does the comparative effectiveness or tolerability and safety of peginterferon alfa-2a plus ribavirin versus peginterferon alfa-2b plus ribavirin vary in patient subgroups defined by demographics (age, racial groups, gender, genotype, markers of disease severity), use of other medications, or presence of co-morbidities (such as HIV infection)?

METHODS

Literature Search

To identify articles relevant to each key question, we searched Medline (1966 to July Week 4 2006), the Cochrane Central Register of Controlled Trials (3rd Quarter 2006), the Cochrane Database of Systematic Reviews (2nd Quarter 2006), and the Database of Abstracts of Reviews of Effects (3rd Quarter 2006) (See Appendix A for search strategies). We also searched reference lists of included review articles for additional citations. Pharmaceutical manufacturers were invited to submit dossiers, including citations. All citations were imported into an electronic database (Endnote 9.0).

Study Selection

All citations were reviewed for inclusion using the criteria shown in Table 3. Full-text articles of potentially relevant citations were retrieved and inclusion criteria were re-applied. Title and abstract review was conducted by two independent reviewers (Carson and Care); review of full-text articles was conducted by one reviewer (Carson) and checked by a second (Chou). Disagreements were resolved by consensus.

Table 3. Study inclusion criteria

Populations
• Non-pregnant adult outpatients with chronic Hepatitis C infection
Subgroups include:
• HIV-infected persons
• Non-responders or relapsers (including re-treatment)
• Based on gender, race, or age
• Based on genotype
• Based on viral load
• Based on liver function test abnormalities
• Based on degree of fibrosis, inflammation, or cirrhosis on liver biopsy
• Based on other co-morbid conditions, including obesity, addiction, psychiatric illness
Treatments
• Pegylated interferon alfa-2a plus ribavirin
• Pegylated interferon alfa-2b plus ribavirin
Effectiveness outcomes
• Sustained virologic response (SVR)
• Normalization of liver enzyme abnormalities (sustained biochemical response, or SBR)
• Improvement in inflammation or fibrosis on liver biopsy
• Cirrhosis
• Hepatocellular carcinoma
• Need for liver transplant
• Quality of life

• Mortality
• Early virologic response (only for head-to-head trials)
Safety outcomes
• Overall adverse effects
• Withdrawals due to adverse effects
• Serious adverse events (including depression, suicidality)
• Specific adverse events (including myalgias, flu-like symptoms, fevers, chills, neutropenia, dose reduction)
Study designs
• For assessment of effectiveness in general, controlled clinical trials and good-quality systematic reviews were included.
• For assessment of effectiveness for cirrhosis, hepatocellular cancer, need for transplant, and mortality, controlled clinical trials and *long-term* observational studies were included.
• For assessment of safety, controlled clinical trials and observational studies were included.

We defined a sustained virologic response (SVR) as the absence of detectable HCV RNA in the serum six months after the end of a course of therapy.[21] SVR is the best short-term predictor of long-term virologic remission rates and is associated with improvements in fibrosis and inflammation.[22] End-of-treatment response (ETR) was defined as no detectable virus at the end of a course of therapy. We did not consider ETR a primary outcome since it is not as reliable as SVR for predicting long-term remission. Some trials also measure early virologic response (EVR), which is usually defined as absence of detectable HCV RNA in serum or >2.0 log copy/ml reduction in serum HCV after 12 weeks of therapy. Although assessing EVR is helpful for determining whether to complete a full course of therapy (patients without an EVR are unlikely to achieve an SVR), it is less accurate than ETR for predicting long-term remission. We included head-to-head trials reporting EVR because no head-to-head trials reporting longer-term outcomes are currently available.

We defined a sustained biochemical response (SBR) as normalization of liver transaminases six months after the end of a course of therapy. Some trials also report end-of-treatment biochemical response. Definitions for histological response are less standardized than definitions for reporting virologic outcomes, however traditionally a histologic 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.[21]

Because dual therapy with pegylated interferon has only been available since 2001 and assessment of effects on rates of cirrhosis, hepatocellular cancer, need for liver transplant, and mortality would require studies with extended (a decade or more) follow-up, we believed studies evaluating these outcomes would probably not be available. However, we did search for studies reporting these important clinical outcomes.

We included non-randomized studies as well as randomized trials reporting adverse events (withdrawal due to adverse events, serious adverse events, overall adverse events, hematologic adverse events, flu-like symptoms, and depression) associated with dual therapy with pegylated interferon.

Data Abstraction

The following data were abstracted from included trials: study design, setting, population characteristics (including sex, age, ethnicity, and HCV genotype), eligibility and exclusion criteria, and interventions (dose and duration); numbers screened, eligible, enrolled, and lost to follow-up; method of outcome ascertainment; and results for each outcome (including SVR, ETR, SBR, histological response rates, quality of life, other clinical outcomes, and adverse events). We recorded intention-to-treat results when available. Results were entered into a relational database (Microsoft Access 2003).

Quality Assessment

We assessed internal validity (quality) of controlled clinical trials using predefined criteria adapted from those developed by the US Preventive Services Task Force[23] and the National Health Service Centre for Reviews and Dissemination (Appendix B).[24] For each included study, we assessed methods used for randomization; allocation concealment; blinding of participants, investigators, and assessors of outcomes; similarity of comparison groups at baseline; adequate reporting of attrition, crossover, adherence, and contamination; post-allocation exclusions; and use of intention-to-treat analysis.

These criteria were then used to categorize trials into "good", "fair", and "poor" quality. Studies that had a serious flaw or combination of flaws in design or implementation that seriously compromised the validity of results were categorized as "poor" quality. For example, an open-label study that used improper randomization techniques and failed to use intention-to-treat analysis would be rated poor-quality. Results of poor-quality studies are at least as likely to be due to design flaws or biases as to be due to true effects. Studies which met all quality criteria were rated "good"; the rest were rated "fair". As the "fair" quality category is broad, studies with this rating vary in their strengths and weaknesses.

We did not formally rate quality of non-randomized studies reporting adverse events. Optimal methods for rating quality of such studies is uncertain.[25] In addition, all of the non-randomized studies included in this report were uncontrolled series of patients exposed to dual therapy with pegylated interferon. Such studies are generally considered much less reliable than well-designed randomized controlled trials.

Data Synthesis

We constructed evidence tables showing the study characteristics, quality ratings, and results for all included studies. Trials that evaluated dual therapy with one pegylated interferon against another provided direct evidence of comparative effectiveness and safety. Where possible, these data are the primary focus. We also performed indirect comparisons when direct head-to-head evidence was sparse or unavailable. In theory, trials that compare dual therapy with pegylated interferon to dual therapy with non-pegylated interferon or another common comparator can provide indirect evidence about effectiveness and safety if treatment effects are

consistent across all of the trials.[26, 27] Indirect comparisons usually agree with direct comparisons, though large discrepancies have been reported in some cases.[28, 29] In addition, indirect comparisons also result in less precise estimates of treatment effects compared to the same number of similarly sized head-to-head trials because methods for indirect analyses incorporate additional uncertainty from combining different sets of trials.[26, 27]

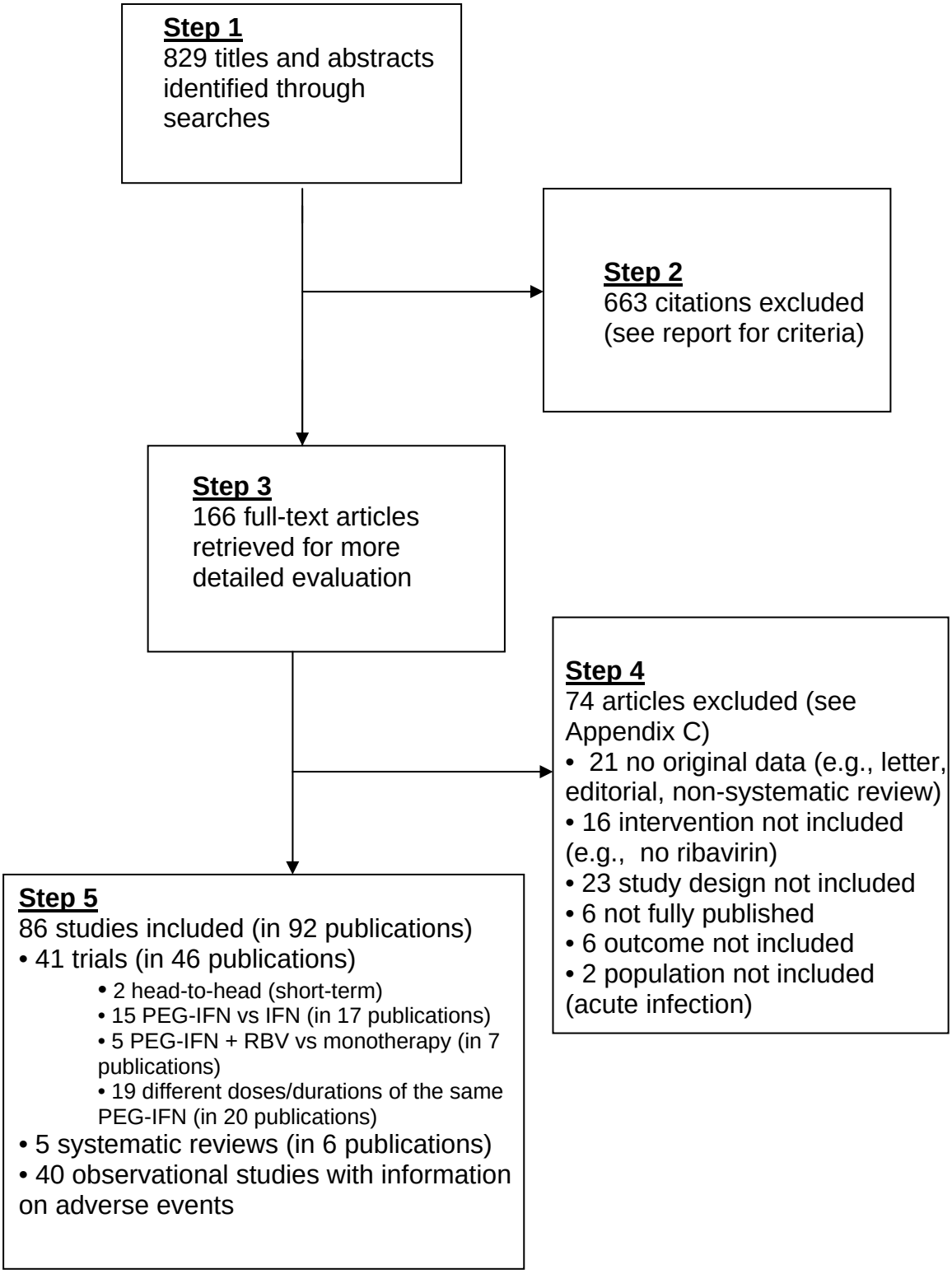
We performed meta-analysis to estimate pooled relative risks and 95% confidence intervals using the DerSimonian-Laird method in a random effects model.[30] We chose the random effects model because trials evaluating the same interventions and outcomes differed in patient populations, dosing of drugs, and other factors. Heterogeneity was assessed by calculating the Q-statistic and the percent of the total variance due to between study variability (I^2 statistic).[31] Subgroup analysis was performed to assess differences in estimates of effect in HIV co-infected versus non-HIV infected populations and for different HCV genotypes. We also performed sensitivity analysis on poor-quality studies, outlier trials, specific populations (such as patients with thalassemia), and unpublished trials to evaluate stability of estimates and conclusions. Funnel plots were produced to assess the likelihood of publication bias if there were an adequate number of studies (at least seven) to plot. Relative risks and confidence intervals were calculated and funnel plots were produced using the meta package in R.[32] Forest plots were generated using RevMan 4.2.8 (Review Manager 4.2 for Windows, The Nordic Cochrane Centre, Copenhagen, Denmark). We used the method described by Bucher et al to perform indirect analyses.[27]

RESULTS

Overview

Figure 1 shows the flow of studies. Literature searches identified 829 citations, and 166 of these were potentially relevant. After review of the full text of these 166, we included 86 studies: 41 reports of randomized controlled trials (in 46 publications),[33-78] five systematic reviews (in 6 publications),[9, 13-15, 79, 80] and 40 uncontrolled studies that provided information on adverse events.[81-120] Excluded studies are listed in Appendix C.

Figure 1. Results of literature search



Among the 41 included randomized controlled trials, two were short-term head-to-head trials of dual therapy with pegylated interferon alfa-2a versus dual therapy with pegylated interferon alfa-2b,[71, 72] 15 trials compared pegylated interferon plus ribavirin to non-pegylated interferon plus ribavirin,[34, 35, 40, 43-46, 58, 59, 61, 63, 68, 70, 73, 74] and five compared dual therapy with pegylated interferon plus ribavirin to pegylated interferon monotherapy (Evidence Table 1).[42, 48, 53, 56, 57] Nineteen trials compared different doses or treatment durations of the same peginterferon (Evidence Table 2).[33, 37, 39, 41, 47, 49, 50, 54, 55, 60, 62-64, 67, 69, 75-78] Two trials directly compared different doses of ribavirin as part of dual therapy with pegylated interferon.[50, 52] Two trials were included in more than one category.[50, 63]

One head-to-head trial available as an abstract was excluded because it only reported interim (8-week) results of a short-term (12 weeks) trial.[121] We identified six other unpublished trials from pharmaceutical company dossiers that otherwise met inclusion criteria (Appendix D). These trials were not included in our primary analyses, but results were considered in sensitivity analyses in order to determine how they affected conclusions. A large (N=4913) trial compared weight-based to fixed, lower-dose ribavirin in patients on dual therapy with pegylated interferon alfa-2b.[122] The other five trials evaluated effects of different doses or duration of therapy[123-126] or compared effects of therapy in different racial groups.[127]

Overview of methodological quality of included trials

Details of our quality assessment of included randomized controlled trials are shown in Evidence Table 3. Two of 41 included trials were rated good quality, 9 were rated poor, and the rest were fair (Table 4). Fourteen of 41 trials (34.1%) described adequate randomization methods, 39% described adequate allocation concealment, 12.2% masked patients and providers, 12.2% masked outcome assessors, and 85.4% reported ITT results.

Table 4. Summary of quality assessment of included published trials

Trial type	Number of trials	Good	Fair	Poor
Head-to-head	2	0	1	1
Peg-IFN vs Non-peg IFN	15	1	11	3
Peg-IFN dual therapy vs. Peg-IFN monotherapy	5	0	4	1
Peg-IFN dose/duration ranging	19	1	14	4
Ribavirin dose ranging	2	1	1	0
Totals	43	3*	31*	9

*One trial included in more than one category

Key Question 1. What is the comparative effectiveness of regimens of peginterferon alfa-2a plus ribavirin versus peginterferon alfa-2b plus ribavirin for treatment of chronic hepatitis C virus infection?

Summary of evidence

We found insufficient evidence to determine if dual therapy with pegylated interferon alfa-2a is superior to dual therapy with pegylated interferon alfa-2b for achieving SVR or SBR. Head-to-head trials data were sparse (two trials), short-term (8 to 12 weeks), clinically diverse, and had methodological flaws. Indirect analysis of trials comparing dual therapy with pegylated interferon alfa-2a or alfa-2b to a common comparator (dual therapy with non-pegylated interferon) indicate no significant differences in rates of SVR, though interpretation of findings is limited by clinical diversity across trials and imprecise estimates of effects. There are also no clear differences in SBR. Data on histologic outcomes and quality of life are sparse and there are no comparative data on other outcomes such as cirrhosis, hepatocellular cancer, liver transplant, or functional status.

Effectiveness versus efficacy

We considered all of the trials included in this report efficacy studies, as they generally applied numerous inclusion criteria, were conducted in specialty settings, used rigid dosing regimens, and evaluated relatively short-term, intermediate outcomes (SVR and SBR rates).[128]

Systematic reviews

We identified five systematic reviews (reported in six publications) on efficacy of dual therapy with pegylated interferon.[9, 13-15, 79, 80] All of the systematic reviews included the same two published trials (one evaluating dual therapy with pegylated interferon alfa-2a[48] and the other pegylated interferon alfa-2b[63]). In both trials, dual therapy with pegylated interferon was compared to dual therapy with non-pegylated interferon or monotherapy with pegylated interferon. We excluded four of the systematic reviews because they did not assess comparative efficacy of dual pegylated interferon regimens and are missing new, relevant trials.[9, 13-15, 79] The fifth systematic review focused on efficacy of dual therapy with pegylated interferon in patients with HCV genotype 4 infection and is reviewed for key question 3.[79]

Head-to-head trials

Two head-to-head trials compared dual therapy with pegylated interferon alfa-2a versus pegylated interferon alfa-2b.[71, 72] Both were short-term (eight to twelve weeks) efficacy trials that only assessed end-of-treatment virologic responses. Results of the two trials cannot be directly compared or combined because of differences in study quality, patient populations, and interventions (Table 5). One trial (rated fair-quality), sponsored by the manufacturer of pegylated interferon alfa-2b, only included treatment-naïve patients infected with HCV genotype 1 and initially placed patients on four weeks of pegylated interferon monotherapy before ribavirin was added for the last four weeks.[71] The other trial, sponsored by the manufacturer of pegylated interferon alfa-2a, was rated poor quality (flaws include allocating consecutive patients to alternating therapy), did not restrict to genotype 1, initiated patients on dual therapy, and included treatment-experienced patients (30% of enrolled population).[72] In both trials, end-of-treatment virologic response was defined as >=2.0 $\log_{10}$ decrease in HCV load.

In the fair-quality trial, there was no significant difference (p=0.09) in 8-week virologic response rates between dual therapy with pegylated interferon alfa-2a (44% or 8/18) and dual therapy with pegylated interferon alfa-2b (72% or 13/18) (Table 5).[71] In the poor-quality trial, there was also no difference in 12-week virologic response rates, though the trend was in the opposite direction (83% or 48/58 for pegylated interferon alfa-2a versus 67% or 39/58 for pegylated interferon alfa-2b, p=0.08).[72] In a subgroup analysis of treatment-naïve patients in this trial, the same trend was observed (90% vs. 75%, p=0.61). Biochemical, histological, and clinical outcomes were not reported in either trial.

Table 5. Head-to-head trials of dual therapy with pegylated interferon alfa-2a vs. dual therapy with pegylated interferon alfa-2b

Trial (quality)	Treatment comparison	Duration	Population characteristics	Early virologic response rates (arm A vs. arm B)
Silva, 2006[71] (fair)	A: Pegylated interferon alfa-2a 180 µg once weekly for 8 weeks + ribavirin 13 mg/kg daily for last four weeks B: Pegylated interferon alfa-2b 1.5 µg /kg once weekly for 8 weeks + ribavirin 13 mg/kg daily for last four weeks	8 weeks	Treatment-naïve Genotype 1 only	44% (8/18) vs. 72% (13/18), p=0.09
Sporea, 2006[72] (poor)	A: Pegylated interferon alfa-2a 180 µg /kg once weekly for 12 weeks + ribavirin 800-1200 mg daily B: Pegylated interferon alfa-2b 1.5 µg /kg once weekly for 12 weeks + ribavirin 800-1200 mg daily	12 weeks	70% treatment-naïve Genotype not reported	83% (48/58) vs. 67% (39/58), p=0.08

A third short-term (12 weeks) head-to-head trial was excluded because only interim results have been reported in a conference abstract.[121] It found no significant difference in rates of virologic response through eight weeks of dual therapy with pegylated interferon alfa-2a versus pegylated interferon alfa-2b (66% or 29/44 versus 50% or 22/44). Results of a large (expected enrollment 2,880), head-to-head trial of 48-week dual pegylated interferon regimens in patients with HCV genotype 1 infection (the IDEAL study) are not yet available, but expected later in 2007.[129] This trial is sponsored by the manufacturer of pegylated interferon alfa-2b.

Active-controlled trials

Dual therapy with pegylated interferon versus dual therapy with non-pegylated interferon

Active-controlled trials of dual therapy with pegylated interferon alfa-2a and pegylated interferon alfa-2b against a common comparator could provide indirect evidence on comparative effectiveness. We identified five trials comparing dual therapy with pegylated interferon alfa-2a plus ribavirin versus dual therapy with non-pegylated interferon alfa-2a plus ribavirin[35, 44, 61, 73] or dual therapy with non-pegylated interferon alfa-2b plus ribavirin[48] and 11 trials comparing dual therapy with pegylated interferon alfa-2b plus ribavirin versus dual therapy with non-pegylated interferon alfa-2b plus ribavirin.[34, 40, 43, 45, 46, 58, 59, 63, 68, 70, 74] One trial was rated good-quality,[73] three trials poor-quality,[35, 46, 68] and the remainder fair-quality. Sample sizes ranged from 21[35] to

1530[63] enrollees. Common methodological shortcomings observed in the trials were inadequate description of randomization and allocation concealment methods and open-label design. All trials of pegylated interferon alfa-2a evaluated a dose of 180 µg /kg once weekly. Seven trials of pegylated interferon alfa-2b evaluated a dose of 1.5 µg/kg once weekly,[43, 45, 46, 59, 63, 70, 74] and the other four[34, 40, 58, 68] evaluated a range of different doses (Table 6). Ribavirin doses varied in both sets of trials, ranging from 600 to 1600 mg daily. In one trial, patients randomized to dual therapy with pegylated interferon and non-pegylated interferon also received amantadine.[61]

Three of the pegylated interferon alfa-2a[35, 44, 73] and four of the pegylated interferon alfa-2b trials[43, 45, 58, 68] evaluated HIV co-infected patients. Two trials did not specify whether patients had previously been exposed to interferon therapy.[35, 68] The other trials evaluated only treatment-naïve patients. Three trials focused exclusively[46, 47] or primarily[34] on patients with HCV genotype 4 infection and three trials[40, 70, 74] evaluated only patients with HCV genotype 1 infection. The proportion of patients with HCV genotype 1 ranged from 44% to 78% in the other trials. All trials required patients to have liver biopsy findings consistent with HCV infection and at least mild inflammation or fibrosis for enrollment. Only one trial specifically included patients with normal transaminases.[77] Three trials (all evaluating HIV co-infected patients)[43, 44, 68] did not use transaminase elevations as an eligibility criterion. In all other trials, transaminase elevation was required for enrollment. No trial included patients with decompensated cirrhosis. Rates of SVR ranged from 27% to 65% on dual therapy with pegylated interferon alfa-2a, and from 27% to 67% on dual therapy with pegylated interferon alfa-2b, with the exception of one poor-quality, non-randomized trial[68] of HIV co-infected patients that reported an SVR of 5% (1/20).

Table 6. Characteristics of trials comparing dual therapy with pegylated interferon to dual therapy with non-pegylated interferon

Trial (quality)	Interferon regimen	Ribavirin daily dose	Population characteristics
Peginterferon alfa-2a vs. interferon alfa-2a			
Arizcoretta 2004[35] (POOR)	A: peginterferon alfa-2a 180 µg / week B: interferon alfa-2a 3 million units 3x/week	800 mg	HIV co-infected Treatment experience not reported 52.8% genotype 1
Chung, 2004[44] (FAIR)	A: peginterferon alfa-2a 180 µg / week B: interferon alfa-2a 3-6 million units 3x/week	600-1000 mg	HIV co-infected Treatment naïve 78.0% genotype 1
Mangia, 2005[61] (FAIR)	A: peginterferon alfa-2a 180 µg/week plus amantadine B: interferon alfa-2a 3 million units 3x/week plus amantadine C: interferon alfa-2a 3 million units 3x/week	1000-1200 mg	Treatment naïve 58.9% genotype 1
Torriani, 2004[73] (GOOD)	A: peginterferon alfa-2a 180 µg/week B: peginterferon alfa-2a 180 µg/week (with no ribavirin)	800 mg	HIV co-infected 60.7% genotype 1 Treatment naive

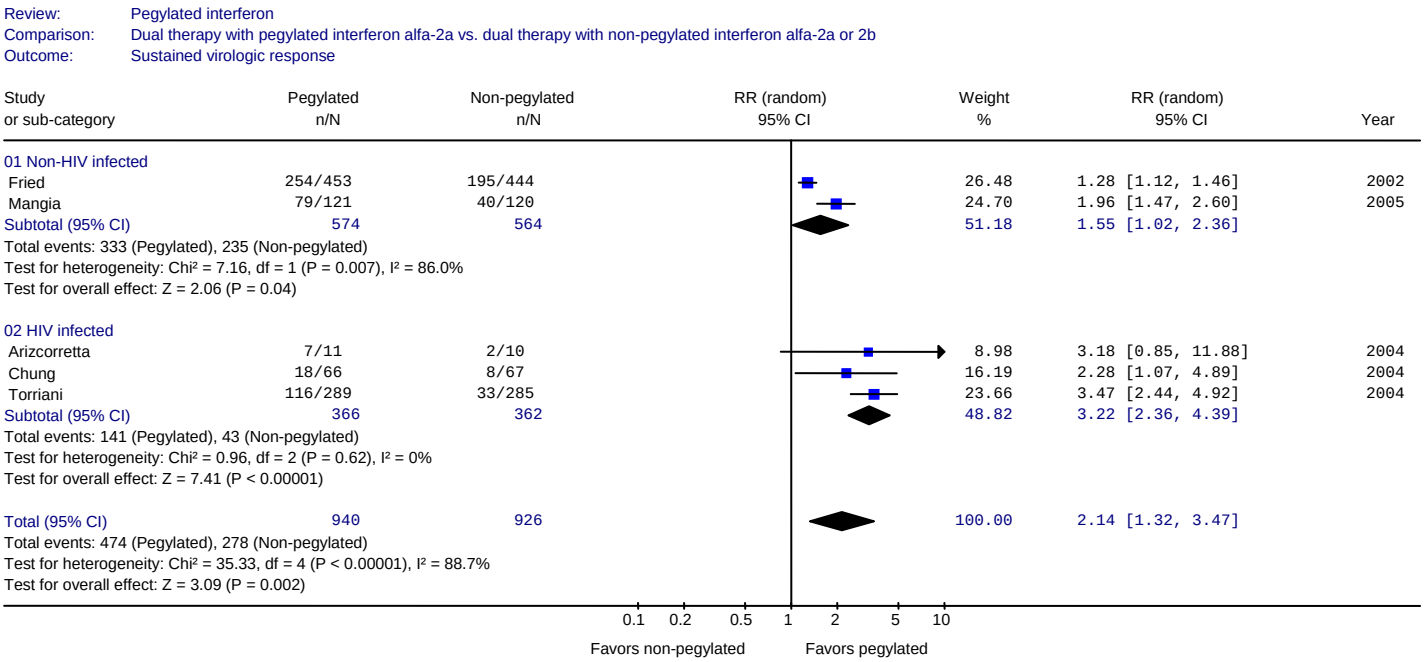
Trial (quality)	Interferon regimen	Ribavirin daily dose	Population characteristics
	B: interferon alfa-2a 3 million units 3x/week		
Peginterferon alfa-2a vs. interferon alfa-2b			
Fried, 2002[48] (FAIR)	A: peginterferon alfa-2a 180 µg / week B: interferon alfa-2b 3-million units 3x/week	1000-1200 mg	63.4% genotype 1 Treatment naïve
Peginterferon alfa-2b vs. interferon alfa-2b			
Alfaleh, 2004[34] (FAIR)	A: peginterferon alfa-2b 100 µg/week B: interferon alfa-2b 3 million units 3x/week	800 mg	Treatment naïve 18.8% genotype 1
Bruno, 2004[40] (FAIR)	A: peginterferon alfa-2b 50-100 µg / week (weight-based) B: interferon alfa-2b 6 million units every other day	1000-1200 mg	Genotype not reported Treatment naïve
Carrat, 2004[43] (FAIR)	A: peginterferon alfa-2b 1.5 µg /kg/week B: interferon alfa-2b 3 million units 3x/week	800 mg	48.1% genotype 1 HIV co-infected Treatment naïve
Crespo, 2007[45] (FAIR)	A: peginterferon alfa-2b 1.5 µg /kg/week B: interferon alfa-2b 3 million units 3x/week	800 mg	48.0% genotype 1 HIV co-infected Treatment naïve
Derbala, 2005[46] (POOR)	A: peginterferon alfa-2b 100 µg/week B: interferon alfa-2b 3 million units 3x/week	800-1200 mg	Treatment experience not reported No genotype 1 (genotype 4 only)
El-Zayadi, 2005[47] (POOR)	A: peginterferon alfa-2b 100 µg/week for 48 weeks A: peginterferon alfa-2b 100 µg/week for 24 weeks C: interferon alfa-2b 3 million units daily	1000-1200 mg	Treatment naïve No genotype 1 (genotype 4 only)
Laguno 2004[58] (FAIR)	A: peginterferon alfa-2b 100-150 µg/week (weight based) B: interferon alfa-2b 3 million units 3x/week	800-1200 mg	HIV co-infected 49.0% genotype 1 Treatment naïve
Lee, 2005[59] (FAIR)	A: peginterferon alfa-2b 1.5 µg/kg/week B: interferon alfa-2b 3 million units 3x/week	1000-1200 mg	Treatment naïve 50.4% genotype 1
Manns, 2001[63] (FAIR)	A: peginterferon alfa-2b 1.5µg/kg/week for 4 weeks and then 0.5 µg/kg/week for 48 weeks B: peginterferon alfa-2b 1.5	A: 1000-1200 mg B: 800 mg C. 1000-1200 mg	68.0% genotype 1 Treatment naive

Trial (quality)	Interferon regimen	Ribavirin daily dose	Population characteristics
	µg/kg/week C: interferon alfa-2b 3MU 3x/week		
Poizot-Martin, 2003[68] (POOR)	A: peginterferon alfa-2b 180 µg/week B: interferon alfa-2b 3 million units 3x/week	"800 mg, two tablets per day" (not clear if 800 or 1600 mg)	Treatment experience not reported HIV co-infected 54.8% genotype
Scotto, 2005[70] (FAIR)	A: peginterferon alfa-2b 1.5 µg/kg/week B: interferon alfa-2b 6 million units 3x/week C: interferon alfa-2b 3 million units daily	800-1200 mg	Treatment naïve 100% genotype 1b
Tsubota, 2005[74] (FAIR)	A: peginterferon alfa-2b 1.5 µg/kg/week B: interferon alfa-2b 6 million units 3x/week	600-1000 mg	100% genotype 1b Treatment naïve

No trial was designed to evaluate rates of cirrhosis, decompensated cirrhosis, hepatocellular carcinoma, or liver transplant. Only one trial[48] reported effects on quality of life.[51]

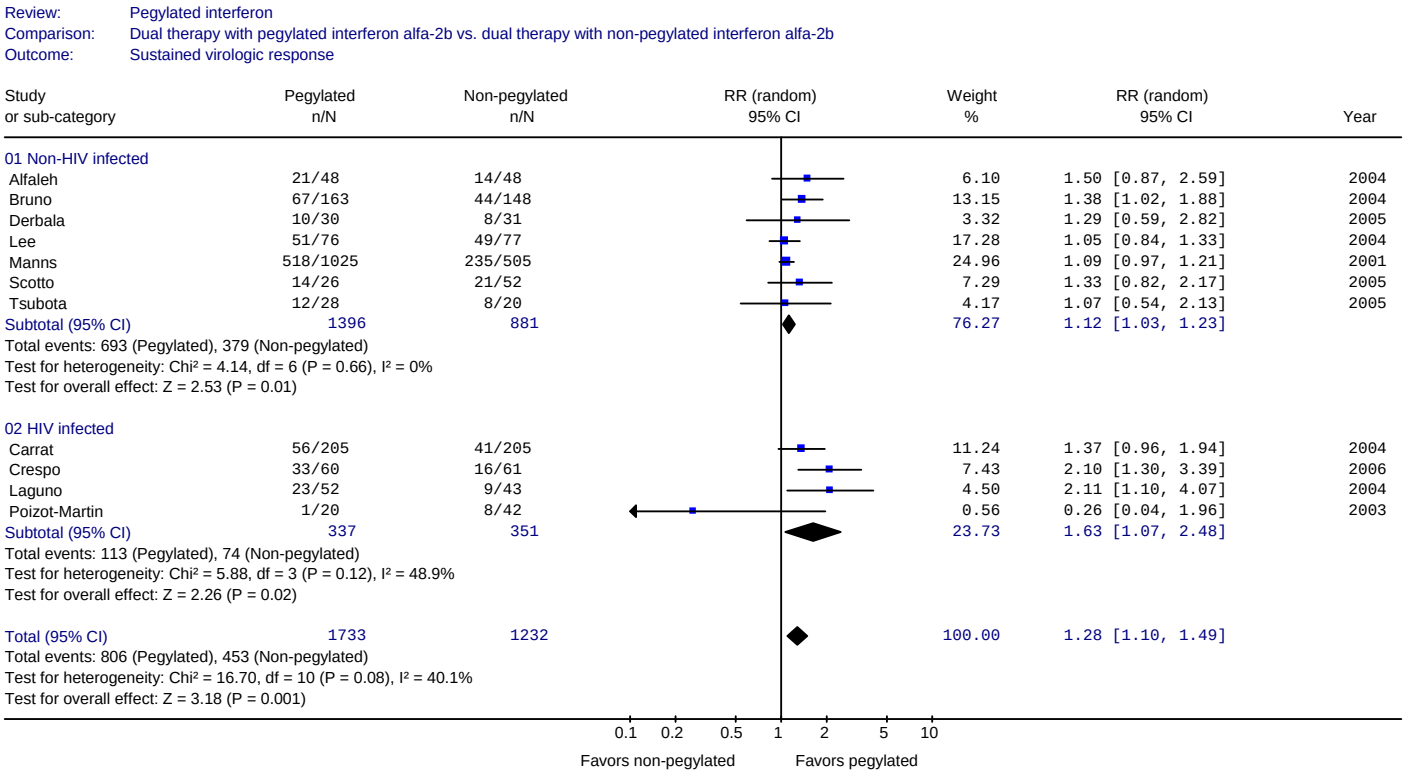
All trials reported rates of SVR. In pooled analysis, dual therapy with pegylated interferon alfa-2a plus ribavirin was superior to non-pegylated interferon alfa-2a or alfa-2b plus ribavirin (five trials, RR 2.14, 95% CI 1.32 to 3.47) (Figure 2). There was a significant difference between estimates based on the subgroup of four trials (N=969)[35, 44, 61, 73] comparing dual therapy with pegylated interferon alfa-2a to dual therapy with non-pegylated interferon alfa-2a (RR 2.55, 95% CI 1.75 to 3.74) and the single, large (N=897) trial[48] comparing dual therapy with pegylated interferon alfa-2a to dual therapy with non-pegylated interferon alfa-2b (RR 1.28, 95% CI 1.12 to 1.46; p=0.038 for difference).

Figure 2. Forest plot on sustained virologic response, dual therapy with pegylated interferon alfa-2a versus dual therapy with non-pegylated interferon alfa-2a or alfa-2b



Pegylated interferon alfa-2b plus ribavirin was also superior to non-pegylated interferon alfa-2b plus ribavirin for achieving an SVR (11 trials, RR 1.28, 95% CI 1.10 to 1.49) (Figure 3).

Figure 3. Forest plot on sustained virologic response, dual therapy with pegylated interferon alfa-2b versus dual therapy with non-pegylated interferon



Excluding trials of HIV-infected patients attenuated the difference in pooled estimates between dual therapy with pegylated interferon alfa-2a (2 trials, RR 1.55, 95% CI 1.02 to 2.36, see Figure 2) and dual therapy with pegylated interferon alfa-2b (7 trials, RR 1.12, 95% CI 1.03 to 1.23, see Figure 3), and decreased heterogeneity in the pegylated interferon alfa-2a trials. Some of the remaining heterogeneity in the two trials of pegylated interferon alfa-2a in patients without HIV co-infection may be related to the addition of amantadine to both treatment arms in one of the trials.[61] Estimates were stable after excluding poor-quality trials or trials evaluating only patients with genotype 1 or genotype 4 infection. Estimates were also stable after excluding results of patients randomized to lower-dose pegylated interferon alfa-2b from a trial that evaluated lower (0.5 µg /kg/wk) and higher (1.5 µg/kg/wk) dose dual therapy.[63]

We performed an adjusted indirect analysis to evaluate relative efficacy of dual therapy with pegylated interferon alfa-2a versus dual therapy with pegylated interferon alfa-2b on rates of SVR, based on trials in which each was compared to dual therapy with non-pegylated interferon. However, results of the indirect analysis should be interpreted with caution. Although indirect meta-analyses usually agree with direct meta-analyses of head-to-head trials, results can be discordant or contradictory if the critical assumption that treatment effects are consistent across all the trials is violated.[25, 27, 28] This can occur when there are methodological flaws in the studies or differences in patient populations, interventions, or other factors. In this set of trials, substantial clinical diversity was observed in patient populations, dosing of interventions (both for pegylated interferon and for ribavirin), and comparator treatments

(interferon alfa-2a versus interferon alfa-2b). In addition, confidence intervals for our estimates are wide, due to a relatively small data set and decreased precision of indirect compared to direct analyses.

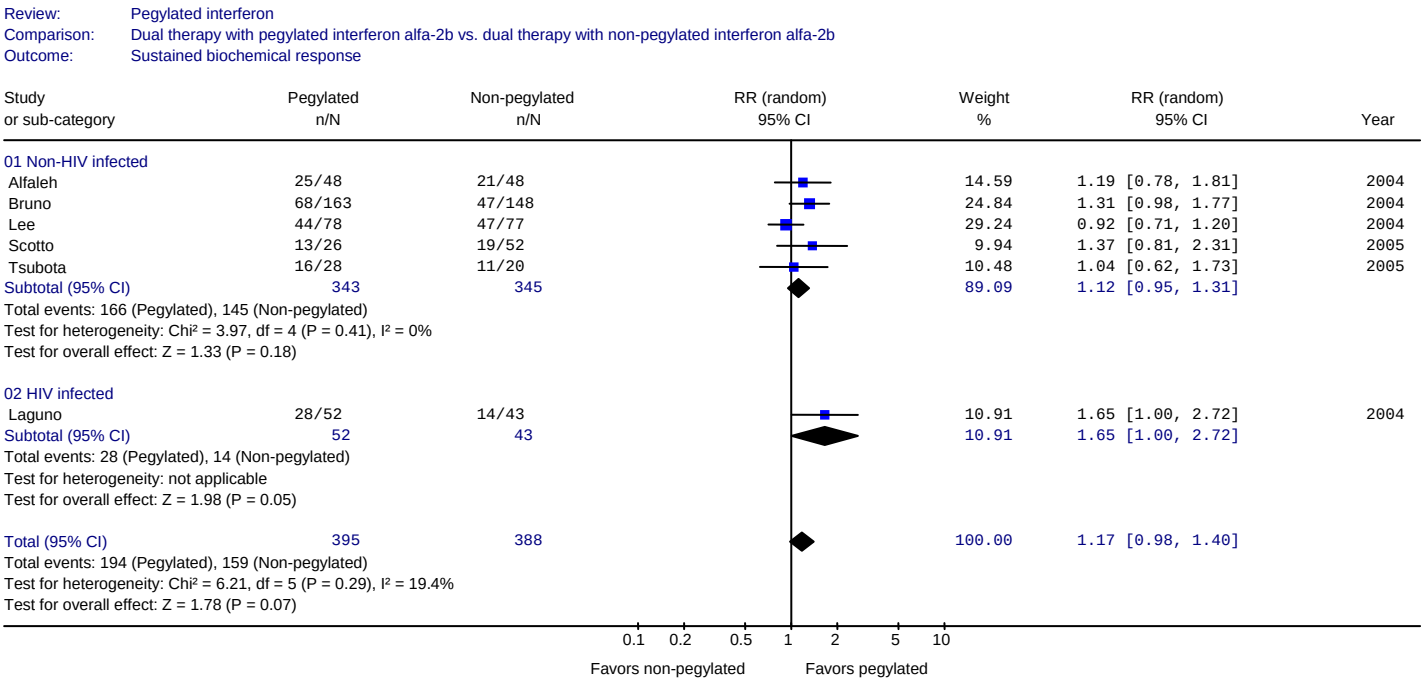
Including all trials, adjusted indirect analysis (Table 7) found no significant differences (and wide confidence intervals) in efficacy for SVR between dual therapy with pegylated interferon alfa-2a versus dual therapy with pegylated interferon alfa-2b, using dual therapy with non-pegylated interferon alfa-2a or alfa-2b as the common comparator (RR 1.67, 95% CI 0.56 to 5.04). Because comparing dual therapy with pegylated interferon to dual therapy with different non-pegylated interferons (alfa-2a or alfa-2b) could violate assumptions about relative treatment effects across both sets of trials, we also performed the indirect analysis using only trials that compared dual therapy with pegylated interferon to dual therapy with non-pegylated interferon alfa-2b. This analysis found no difference in the point estimate of relative efficacy (RR 1.00, 95% CI 0.47 to 2.11). We did not perform an adjusted indirect analysis for the subgroup of trials in non-HIV infected persons, as confidence intervals for estimates of relative risk for SVR from the direct analyses overlapped substantially and the number of available trials was small.

Table 7. Adjusted indirect analysis for sustained virologic response rates

Comparison	Outcome	Common comparator	Adjusted indirect RR (95% CI)
Pegylated interferon alfa-2a + ribavirin versus pegylated interferon alfa-2b + ribavirin	Sustained virologic response	Non-pegylated interferon alfa-2a or non-pegylated alfa-2b + ribavirin	1.67 (0.56 to 5.04)
Pegylated interferon alfa-2a + ribavirin versus pegylated interferon alfa-2b + ribavirin	Sustained virologic response	Non-pegylated interferon alfa-2b + ribavirin	1.00 (0.47 to 2.11)

Seven trials reported rates of SBR. One trial found dual therapy with pegylated interferon alfa-2a superior to dual therapy with non-pegylated interferon alfa-2a, each in combination with amantadine (RR 1.98, 95% CI 1.49 to 2.63).[61] The six other trials evaluated dual therapy with pegylated interferon alfa-2b versus dual therapy with non-pegylated alfa-2b.[34, 40, 58, 59, 70, 74] There was no difference in pooled risk of SBR (RR 1.17, 95% CI 0.98 to 1.40) (Figure 4). There were too few trials reporting SBR to perform indirect meta-analysis.

Figure 4. Forest plot on sustained biochemical response, dual therapy with pegylated interferon alfa-2b versus dual therapy with non-pegylated interferon alfa-2b



The three trials that evaluated histologic outcomes found no differences between dual therapy with pegylated interferon alfa-2b and dual therapy with non-pegylated interferon alfa-2b in liver biopsy scores for fibrosis or inflammation.[43, 59, 63] The one trial reporting health-related quality of life and fatigue severity scores in patients randomized to different treatments (as opposed to responders versus non-responders) found dual therapy with pegylated interferon alfa-2a to be associated with improved scores in a variety of domains during therapy compared to dual therapy with non-pegylated interferon alfa-2b. Yet differences were small (generally less than 5 points on 100 point scales) and scores had returned to baseline values or better in both groups 24 weeks after the end of treatment.[48, 51] In addition, patients in this trial were aware of their virologic response to therapy, which could have affected assessments of health-related quality of life.

The funnel plot for the eleven trials of dual therapy with pegylated interferon alfa-2b versus dual therapy with non-pegylated interferon alfa-2b for SVR is difficult to interpret because of a small outlier trial.[68] However, after excluding this trial, no funnel plot asymmetry was apparent.

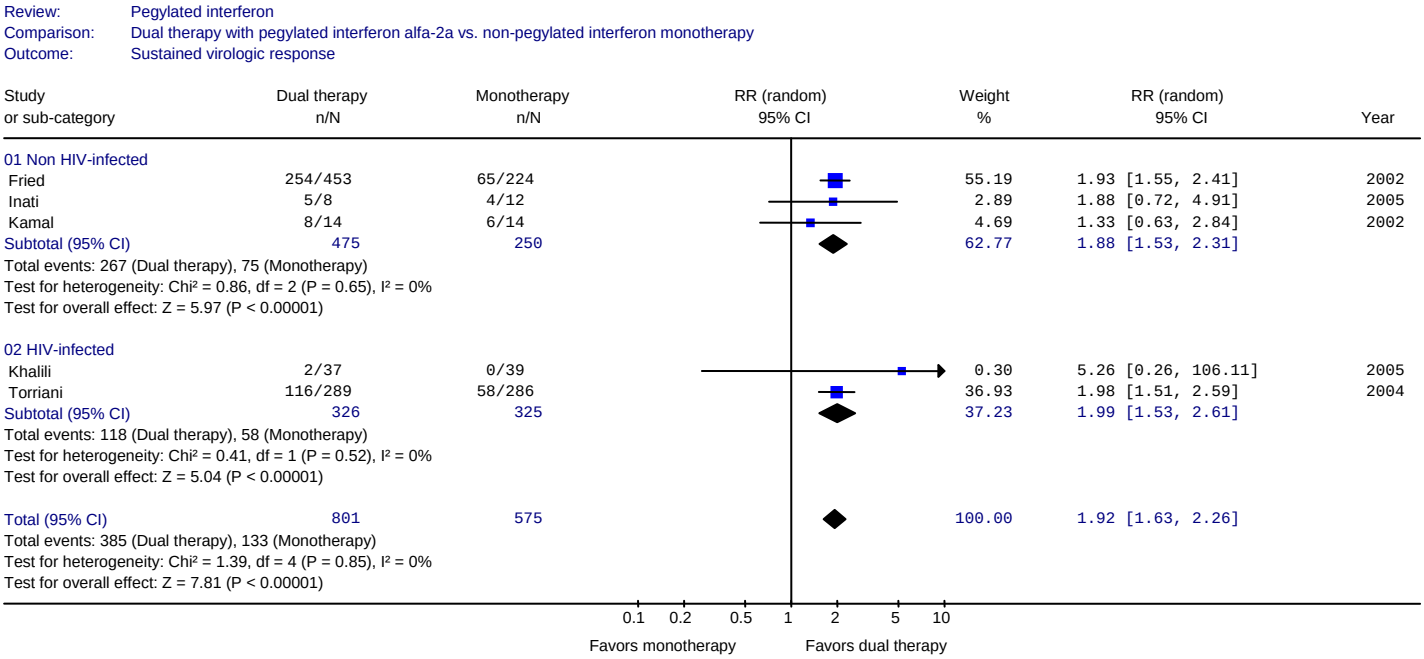
Dual therapy with pegylated interferon versus pegylated interferon monotherapy

We identified six trials of dual therapy with pegylated interferon (5 trials evaluating pegylated interferon alfa-2a[48, 53, 56, 57, 73] and one trial evaluating pegylated interferon alfa-2b[42]) versus pegylated interferon monotherapy. One trial was rated good-quality,[73] one poor-quality,[56] and the remainder fair-quality. The number of patients randomized to pegylated interferon monotherapy or dual therapy ranged from 20[53] to 897[48] enrollees. Two trials[42, 57] evaluated HIV

co-infected patients and one[53] evaluated thalassemic patients. The proportion of patients with HCV genotype 1 infection ranged from 44% to 86%. All trials only evaluated treatment-naïve patients. Rates of SVR for dual therapy ranged from 33% to 57% with pegylated interferon alfa-2a, with the exception of one trial[57] that reported an SVR of 5%. This trial only randomized HIV co-infected patients who failed to respond to 14 weeks of initial pegylated interferon monotherapy. The single trial of dual therapy with pegylated interferon alfa-2b evaluated HIV co-infected patients and reported an SVR of 22%.[42]

The pooled relative risk for an SVR in patients randomized to dual therapy with pegylated interferon alfa-2a versus pegylated interferon alfa-2a monotherapy was 1.92 (5 trials, 95% CI 1.63 to 2.26) (Figure 5). Excluding either the small (N=20) trial[53] of thalassemic patients or the trial of HIV-infected non-responders[57] yielded similar estimates (RR 1.92, 95% CI 1.63 to 2.27 and RR 1.91, 95% CI 1.62 to 2.28, respectively). The small (N=56) trial of dual therapy with pegylated interferon alfa-2b versus pegylated interferon alfa-2b monotherapy reported an RR for SVR of 2.39 (95% CI 0.99 to 5.79).[42] We did not attempt an indirect analysis because estimates of SVR for dual versus monotherapy overlapped and there was only one trial of dual therapy with pegylated interferon alfa-2b. One trial found that patients randomized to dual therapy with pegylated interferon alfa-2a plus ribavirin experienced greater declines in health-related quality of life and fatigue severity scores during treatment compared to those randomized to pegylated interferon alfa-2a monotherapy.[48, 51] No trial reported SBR, histologic outcomes, or other clinical outcomes.

Figure 5. Forest plot on sustained virologic response, dual therapy with pegylated interferon alfa-2a versus pegylated interferon alfa-2a monotherapy



Observational studies of long-term clinical outcomes

We identified no observational studies evaluating long-term clinical outcomes such as cirrhosis, hepatocellular cancer, need for liver transplant, or mortality.

Key Question 1a. How does duration of treatment or dosing protocols (including weight-based or maintenance dosing or dosing of ribovirin) affect estimates of comparative effectiveness?

Summary

Published trials directly comparing different doses of pegylated interferon as part of dual therapy are only available for pegylated interferon alfa-2b. No dose has been shown to be more effective than 1.5 µg/kg/week for achieving an SVR. The optimal dose of pegylated interferon alfa-2b as part of dual therapy in non-responders or relapsers is unclear.

Trials directly comparing different durations of therapy are characterized by substantial clinical diversity. In general, in patients with HCV genotype 1 infection, 48 weeks of dual therapy with pegylated interferon appears to be more effective than shorter courses. On the other hand, in patients with HCV genotype 2 or 3 infection, shorter courses appear equally effective compared to a 48 week course, particularly in early responders to therapy, in whom a 12 week-course of therapy appears as effective as 24 weeks.

Studies evaluating effects of dose and duration are of limited value for evaluating comparative effectiveness of dual therapy with pegylated interferon alfa-2a versus pegylated interferon alfa-2b because none directly compared effects of duration or dose between the two regimens. Pooling trials or performing meta-regression was not possible because of substantial clinical diversity across trials in patient populations, dosing of drugs, and/or duration of therapy.

Overview of trials on dose or duration

Understanding effects of dose and duration on efficacy of dual therapy with pegylated interferon would be very helpful for selecting optimal treatment regimens and interpreting results of clinical trials. We included 19 trials on efficacy of dual therapy with pegylated interferon at different doses, varying duration, or with standardized versus tailored (to early response) treatment.[33, 37, 39, 41, 47, 49, 50, 52, 54, 55, 60, 62, 64, 67, 69, 75-78] None of the 19 trials directly compared dual therapy regimens of pegylated interferon alfa-2a versus pegylated interferon alfa-2b. Two trials directly compared different doses of ribavirin as part of dual therapy with pegylated interferon.[50, 52] We did not pool trial results or perform meta-regression because of differences in study populations, doses of pegylated interferon, doses of ribavirin, and/or duration of therapy. Because of this clinical diversity, the indirect evidence from this set of trials is of limited value for evaluating comparative effectiveness of dual therapy with pegylated interferon alfa-2a versus pegylated interferon alfa-2b.

Dose of pegylated interferon

All eight dose-ranging trials evaluated pegylated interferon alfa-2b (Table 8).[33, 41, 49, 54, 60, 63, 64, 67] No trial evaluated standardized versus weight-based dosing.

In treatment-naïve patients, one large (N=1,025), fair-quality trial found a dose of 0.5 µg/kg/week inferior to 1.5 µg/kg/week for achieving an SVR (47% vs. 54%, p=0.01).[63] Benefits of the higher dose were only observed in the subgroup of patients with genotype 1 infection

(42% vs. 34%). Three smaller, fair-quality trials found no differences in SVR between 0.5 µg/kg/week verses 1.0 µg/kg/week,[41] 1.0 µg/kg/week versus 1.5 µg/kg/week,[67] or 0.75 µg/kg/week versus 1.5 µg/kg/week of pegylated interferon alfa-2b,[33] each in combination with ribavirin 800 mg/day. The latter trial[33] evaluated patients with severe fibrosis (METAVIR fibrosis stage F3 or F4) and the other two trials evaluated patients with less severe biopsy findings. A poor quality trial found both 0.7 µg/kg/week and 1.4 µg/kg/week doses superior to 0.35 µg/kg/week, at varying ribavirin doses.[49] Three trials of relapsers or non-responders to prior interferon-based therapy (two fair-quality, one poor-quality) found no significant differences in SVR rates between higher and lower-dose regimens of peginterferon alfa-2b, though trends favored the higher-dose regimen in each trial.[54, 60, 64] However, each trial evaluated a different dose comparison.

Table 8. Trials evaluating efficacy of different doses in regimens of dual therapy with pegylated interferon alfa-2b

Trial (Quality rating)	Interventions	Ribavirin dose	N analyzed/ Population/ Notes	Main efficacy result	Withdrawals due to adverse events
Abergel, 2006[33] (FAIR)	Arm 1: 1.5 µg/kg Arm 2: 0.75 µg/kg	800 mg	203 Severe fibrosis.	No difference in SVR: 44.6% vs. 37.3% (NS)	7.9% vs. 3.9%
Buti, 2002[41] (FAIR)	Arm 1: 0.5 µg/kg Arm 2: 1.0 µg/kg	800 mg	55 Higher induction dose in arm 2 (3.0 for 1 week, 1.5 for 1 week, then 1.0)	SVR not reported No difference between groups in biochemical response: 71% vs. 61.5% (NS)	14.3% vs. 7.4%
Glue, 2000[49] (POOR)	Arm 1: 0.35 µg/kg Arm 2: 0.7 µg/kg Arm 3: 1.4 µg/kg	600 or 800 mg (arm 1) 600, 800, or 1000 to 1200 mg (arm 2) 600, 800, or 1000 to 1200 mg (arm 3)	42 Also compared each arm with and without ribavirin 24 weeks treatment with 24-week follow up	Lowest dose less effective SVR: 17% vs. 53% vs. 60% (p-value not reported)	Not reported
Meyer-Wyss, 2006[67] (POOR)	Arm 1: 1.0 µg/kg Arm 2: 1.5 µg/kg	800 mg	219 Up to moderate fibrosis. Patients with genotypes 2 or 3 treated for 24 weeks, those with genotype 1 or other treated for 48 weeks.	No difference in SVR: 53% vs. 50% (NS)	12.2% vs. 25.0%

Trial (Quality rating)	Interventions	Ribavirin dose	N analyzed/ Population/ Notes	Main efficacy result	Withdrawals due to adverse events
Non-responders/relapsers					
Jacobson, 2005[54] (FAIR)	Arm 1: 1.0 µg/kg Arm 2: 1.5 µg/kg	1000 to 1200 mg (arm 1) 800 mg (arm 2)	321 Failed prior treatment	No difference in SVR: 13.0% vs. 18.1% (NS)	13.1% vs. 11.2%
Lodato, 2005[60] (FAIR)	Arm 1: 1.5 µg/kg once/weekArm 2: 1.5 µg/kg twice/week	10.6 mg/kg/day	65 60% non-responder/relapser to interferon monotherapy Subgroup analysis by genotype	No difference in SVR:36.4% vs. 60.5% (p=NS) In subgroup analysis, twice/week therapy superior to once/week in patients with genotype 1 or 4 infection (46% vs. 13%, p=0.039), no significant difference for genotypes 2 or 3 (82% vs. 86%, p=NS)	Not reported
Mathew, 2006[64] (POOR)	Arm 1: 0.5 µg/kg Arm 2: 1.5 µg/kg	1000 to 1200 mg	155 Failed prior treatment	No difference in SVR: 12.5% vs. 20.8% (p=NS)	Not reported

Two unpublished trials compared efficacy of different doses of pegylated interferon alfa-2a as part of combination therapy. One small (N=40) trial found no clear difference in rates of SVR between patients randomized to a dose of 180 µg/week versus those randomized to 270 µg/week (70% vs. 79%, p not reported).[123] The second trial compared dual therapy using higher induction doses of pegylated interferon alfa-2a compared to standard dosing in patients without an early virologic response.[124] In addition, this trial evaluated effects of different durations of therapy, however final results are not yet available.

Duration

We identified nine trials evaluating effects of duration of dual therapy with pegylated interferon plus ribavirin on SVR rates (Table 9).[37, 39, 47, 50, 55, 69, 75-77] The only good-quality trial found 48 weeks of dual therapy with pegylated interferon alfa-2a plus ribavirin more effective than 24 weeks of therapy for achieving SVR (OR 1.53, 95% CI 1.17 to 2.01).[50] In subgroup analyses, 48 weeks of therapy was superior to 24 weeks only in patients with genotype 1 infection (OR 2.19, 95% CI 1.52 to 3.16, compared to OR 0.89, 95% CI 0.56 to 1.42 with genotypes 2 or 3). A fair-quality trial also found 48 weeks superior to 24 weeks in patients with normal transaminases, with benefits limited to the subgroup of genotype 1-infected patients.[77]

Table 9. Trials evaluating efficacy of different durations of dual therapy with pegylated interferon

Trial (Quality rating)	Interventions	Ribavirin dose	N analyzed Population/ Notes	Main efficacy result	Withdrawals due to adverse events
Berg, 2006[37] (FAIR)	alfa-2a Arm 1: 48 weeks Arm 2: 72 weeks	800 mg	455 Genotype 1 only	No difference in SVR between 72 and 48 weeks: 54% vs. 53% (p=0.80)	9.1% vs. 11.6%
Brandao, 2006[39] (FAIR)	alfa-2a Arm 1: 24 weeks Arm 2: 48 weeks	800 mg	63 Genotype 1 only	48 weeks more effective than 24 weeks SVR: 48.4% vs. 28.1% (p=0.0175)	6.3% vs. 0%
El-Zayadi, 2005[47] (POOR)	Alfa-2b Arm 1: 24 weeks Arm 2: 48 weeks:	1000-1200 mg	162 Genotype 4 only	No difference in SVR between 24 and 48 weeks: 48.6% vs. 55% (p=0.517)	2.9% vs. 5.0%
Hadziyannis, 2004[50] (GOOD)	alfa-2a Arm 1: 24 weeks Arm 2: 48 weeks	800 mg vs. 1000 to 1200 mg	1284 Also randomized to lower or higher doses of ribavirin	48 weeks more effective than 24 weeks: odds ratio for SVR, 1.53 (95% CI 1.17 to 2.01, p=0.002) Subgroup analyses: 48 weeks superior to 24 weeks (OR 2.19, 95% CI 1.52 to 3.16) and 1000 to 1200 mg ribavirin superior to 800 mg (OR 1.55, 95% CI 1.14 to 2.10) in patients with genotype 1 infection; no differences in patients with genotypes 2 or 3.	24 vs. 48 weeks: Lower ribavirin dose: 4.8% vs. 16.3% Higher ribavirin dose: 4.6% vs. 15.1%
Kamal, 2005[55] (FAIR)	alfa-2b Arm 1: 24 weeks Arm 2: 36 weeks Arm 3: 48 weeks	1000 to 1200 mg	287 Genotype 4 only	36 and 48 weeks more effective than 24 weeks SVR: 65.6% vs. 68.8% vs. 29.5% (p=0.001) No difference between 36 and 48 weeks (p=0.50)	1.1% vs. 2.1% vs. 4.2%
Sanchez-Tapias, 2006[69] (FAIR)	alfa-2a Arm 1: 48 weeks Arm 2: 72 weeks	800 mg	510 Early non-responders to treatment	72 weeks more effective than 48 weeks SVR: 45.3% vs. 32.1% (p=0.01)	8.5% vs. 11.8%
Von Wagner, 2005[75] (FAIR)	alfa-2a Arm 1: 16 weeks Arm 2: 24 weeks	800 to 1200 mg	142 Genotypes 2 or 3 only Only early responders	No difference in SVR between 24 and 16 weeks: 80.3% vs. 81.7% (p=NS)	0% vs. 1.4%

Trial (Quality rating)	Interventions	Ribavirin dose	N analyzed Population/ Notes	Main efficacy result	Withdrawals due to adverse events
			randomized		
Yu, 2006[76] (FAIR)	alfa-2b Arm 1: 24 weeks Arm 2: 48 weeks	1000 to 1200 mg	60 Genotype 1b only	48 weeks more effective than 24 weeks SVR: 80.0% vs. 48.9% ($p<0.05$)	2.2% vs. 13.3%
Zeuzem, 2004[77] (FAIR)	alfa-2a Arm 1: 24 weeks Arm 2: 48 weeks	800 mg	440 Normal ALT levels	Overall, 48 weeks more effective than 24 weeks: SVR 51.9% vs. 29.7% In subgroup analysis, 48 weeks more effective for genotype 1 (40% vs. 13%, $p<0.0001$), but no difference in genotype 2 or 3 (78% vs. 72%, $p=0.452$)	7.1% vs. 18.1%
Standardized vs. tailored treatment					
Mangia, 2005[62] (FAIR)	alfa-2b Randomized to standardized 24 weeks versus tailored therapy (12 or 24 weeks) based on HCV results after 4 weeks	1000 to 1200 mg	283 Genotypes 2 and 3 only	No difference in SVR: 66% vs. 60% ($p>0.05$)	5.7% vs. 2.3%
Zeuzem, 2005[78] (FAIR)	alfa-2a180 µg/week for 48 weeks. Dose, duration, co-interventions tailored according to 6 week response	1000 to 1200 mg	270	No difference in SVR: 60.3% vs. 65.7% (p=NS)	Not reported

Five other trials (all rated fair-quality) also evaluated effect of treatment duration, but limited enrollment to patients with specific HCV genotypes.[37, 47, 55, 75, 76] In patients with HCV genotype 1 infection, two trials found 48 weeks of dual therapy with pegylated interferon alfa-2a[39] or alfa-2b[76] superior to 24 weeks for achieving an SVR (80% vs. 49%, $p<0.05$[76] and 48% vs. 28%, $p=0.0175$[39]). A third trial found no difference between 72 and 48 weeks of dual therapy with pegylated interferon alfa-2a.[37] In this trial, however, the subgroup of patients who were

"slow responders" (defined as HCV-positive at week 12 but negative at week 24) had a better sustained viral response with 72 weeks versus 48 weeks of treatment (29% vs. 17%, *P*=0.04). In patients with HCV genotypes 2 or 3, one trial found 16 weeks of dual therapy with pegylated interferon alfa-2a as effective for achieving an SVR as 24 weeks in patients with an early (six week) response to treatment.[75] In patients with HCV genotype 4, results from two trials were inconsistent, with one trial finding 36 or 48 weeks of dual therapy with pegylated interferon superior to 24 weeks,[55] but no differences between 24 and 48 weeks in the second trial.[47]

Longer courses of dual therapy with pegylated interferon therapy could be more effective in patients who do not respond to treatment within the first four to six weeks. One fair-quality trial found 72 weeks of dual therapy with pegylated interferon alfa-2a superior to 48 weeks for achieving SVR in early non-responders.[69] An alternative to using a fixed interferon regimen is to individualize the dose or duration of therapy based on an individual's early virologic response to treatment. One trial found that in patients with HCV genotype 2 or 3 infection, shortening the duration of therapy from 24 to 12 weeks in patients who cleared their virus by week 4 was as effective as treating all patients for 24 weeks.[62] A second trial found no differences between a standardized 48 week regimen and individualized therapy based on a more complicated protocol for classifying early response and modifying treatment.[78]

Two trials currently available only as abstracts evaluated effects of duration on efficacy of dual therapy with pegylated interferon alfa-2a. One trial found 16 weeks inferior to 24 weeks for achieving SVR in patients with HCV genotype 2 or 3 infection (66% vs. 74%, p<0.005).[126] Unlike other trials evaluating less than 24 weeks of therapy, it was not limited or tailored to patients with an early virologic response. Another trial (N=377) found no difference between 24 and 48 weeks of dual therapy with pegylated interferon plus ribavirin 800 mg (28% vs. 26%) in patients with genotype 1 infection and compensated cirrhosis, though the longer course appeared superior in patients randomized to ribavirin 1000 to 1200 mg (37% vs. 26%, p not reported).[125] There was no difference in patients with non-genotype 1 infection.

Dose of ribavirin

Different ribavirin dosing schemes could influence efficacy of dual therapy regimens, but have only been directly evaluated in two trials.[50,52] One trial found dual therapy with pegylated interferon alfa-2a in combination with higher dose ribavirin (1000 to 1200 mg, depending on weight) more effective than dual therapy with lower dose ribavirin (800 mg) for achieving SVR in the subgroup of patients with genotype 1 infection (OR 1.55, 95% CI 1.14 to 2.10), but not in those with genotype 2 or 3 infection (OR 1.00, 95% CI 0.63 to 1.61).[50] A second trial also found dual therapy with pegylated interferon alfa-2a in combination with higher dose ribavirin more effective than lower dose ribavirin in patients with advanced fibrosis or cirrhosis.[52] However, in contrast to the other trial, higher dose ribavirin (1000 to 1200 mg) was superior to lower dose ribavirin (600 to 800 mg) for SVR (72% vs. 45%, p=0.03) in patients with genotype 2 or 3 infection, but not in patients with genotype 1 or 4 infection (SVR 32% vs. 32%). In two other published trials, patients were randomized to different doses of ribavirin, but pegylated interferon doses also varied, making it difficult to determine dose effects of the individual drugs.[49, 54]

A large (N=4,913, 62% HCV genotype 1) trial available only as an abstract found pegylated interferon alfa-2b modestly more effective combined with higher, weight-based dosing of ribavirin (800 to 1400 mg) than when combined with fixed-dose, 800 mg ribavirin (SVR 44% vs. 41%, p=0.02).[130] A second trial published only as an abstract found 48 weeks of pegylated interferon alfa-2a more effective in combination with weight-based dosing of ribavirin (1000 to

1200 mg) than with fixed-dosing (800 mg) in patients with genotype 1 infection and compensated cirrhosis.[125] In this same trial, the ribavirin dosing regimen was associated with no differences in rates of SVR in patients with non-genotype 1 infection or in those randomized to 24 weeks of therapy.

Effects of duration or dose on adverse events

We found no consistent pattern showing an association between longer duration or higher doses of dual therapy with pegylated interferon and increased rates of withdrawal due to adverse events (Tables 8 and 9). Other adverse events were reported inconsistently.

Key Question 2. What is the comparative tolerability and safety of peginterferon alfa-2a plus ribavirin versus peginterferon alfa-2b plus ribavirin for treatment of chronic hepatitis C virus infection?

Summary

We found insufficient evidence to determine if dual therapy with one pegylated interferon is safer than dual therapy with the other pegylated interferon. Data from head-to-head trials are extremely sparse (one short-term trial) and inadequate for judging comparative safety. Indirect analysis of trials comparing dual therapy with pegylated interferon alfa-2a or alfa-2b to dual therapy with non-pegylated interferon show no significant differences in rates of withdrawal due to adverse events or other adverse events, but interpretation of findings is limited by clinical diversity across trials, imprecise estimates of effects, and inconsistent reporting of adverse events. Observational studies were almost all uncontrolled and provided no additional useful information on comparative safety, as rates of withdrawal due to adverse events on dual therapy ranged widely across trials for the same pegylated interferon and overlapped for therapy based on each of the two pegylated interferons.

Systematic reviews

One systematic review included two large, pivotal trials that reported similar rates of withdrawal due to adverse events in patients randomized to dual therapy with pegylated interferon plus ribavirin versus dual therapy with non-pegylated interferon plus ribavirin (10% vs. 11% in one trial of dual therapy with pegylated interferon alfa-2a[48] and 14% vs. 13% in one trial of pegylated interferon alfa-2b[63]).[13] It did not evaluate other adverse events.

Head-to-head trials

One small, short-term, fair-quality randomized trial found no differences between dual therapy with pegylated interferon alfa-2a and pegylated interferon alfa-2b in withdrawals due to adverse events (11% or 2/18 vs. 22% or 4/18), flu-like symptoms (17% or 3/18 vs. 28% or 5/18), or the proportion of patients with anemia or leukopenia.[71] The only other head-to-head trial did not report adverse events or withdrawals due to adverse events.[72]

Active-controlled trials

Dual therapy with pegylated interferon versus dual therapy with non-pegylated interferon

Adverse events reported in randomized controlled trials are shown in Evidence Table 4 (randomized controlled trials of efficacy) and Evidence Table 5 (dose- or duration-ranging

trials). Eleven trials reported rates of withdrawal due to adverse events in patients randomized to dual therapy with pegylated interferon versus dual therapy with non-pegylated interferon.[34, 35, 40, 43-46, 48, 58, 63, 73] Six deaths were reported during therapy in patients randomized to dual therapy with pegylated interferon,[43, 59] five of which occurred in HIV co-infected patients.[43] Rates of withdrawal due to adverse events on dual therapy with pegylated interferon ranged from 6% to 16%.

In pooled analyses, there was no significant difference in rates of withdrawal due to adverse events for dual therapy with pegylated interferon alfa-2a versus dual therapy with non-pegylated interferon (4 trials, RR 0.80, 95% CI 0.60 to 1.07, Figure 6) or dual therapy with pegylated interferon alfa-2b versus dual therapy with non-pegylated interferon (7 trials, RR 0.94, 95% CI 0.68 to 1.31, Figure 7). Other adverse events were less consistently reported. Compared to dual therapy with non-pegylated interferon, dual therapy with pegylated interferon alfa-2a (one trial, RR 2.33, 95% CI 1.64 to 3.33) and dual therapy with pegylated interferon alfa-2b (four trials, RR 2.58, 955 CI 1.52 to 4.37) were associated with similarly increased risks for neutropenia. A similar trend was observed for risk of anemia. There were no significant differences between dual therapy with pegylated interferon alfa-2a or alfa-2b and dual therapy with non-pegylated interferon in rates of depression or flu-like symptoms.

Figure 6. Forest plot on withdrawal due to adverse events, dual therapy with pegylated interferon alfa-2a versus dual therapy with non-pegylated interferon alfa-2a or -2b

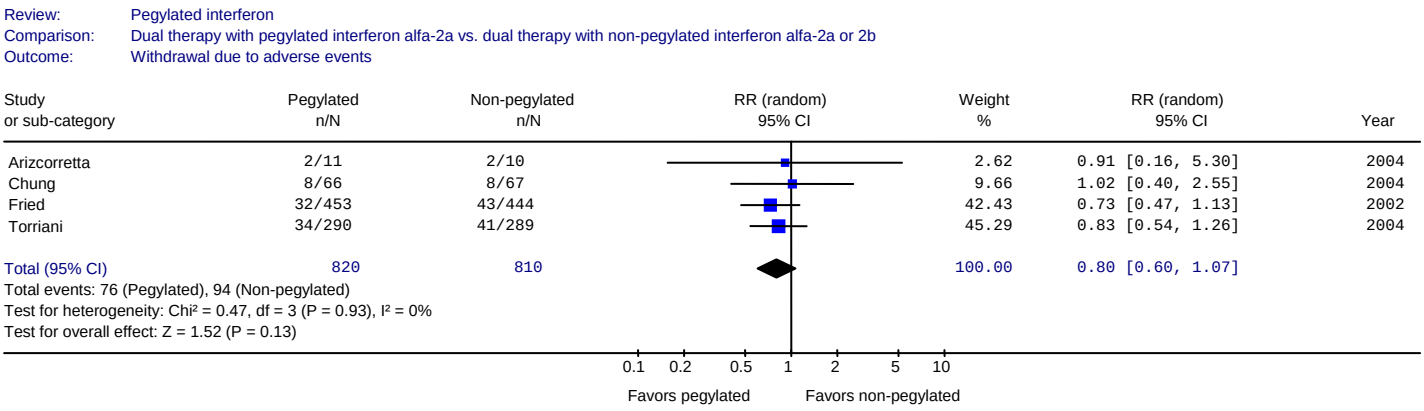
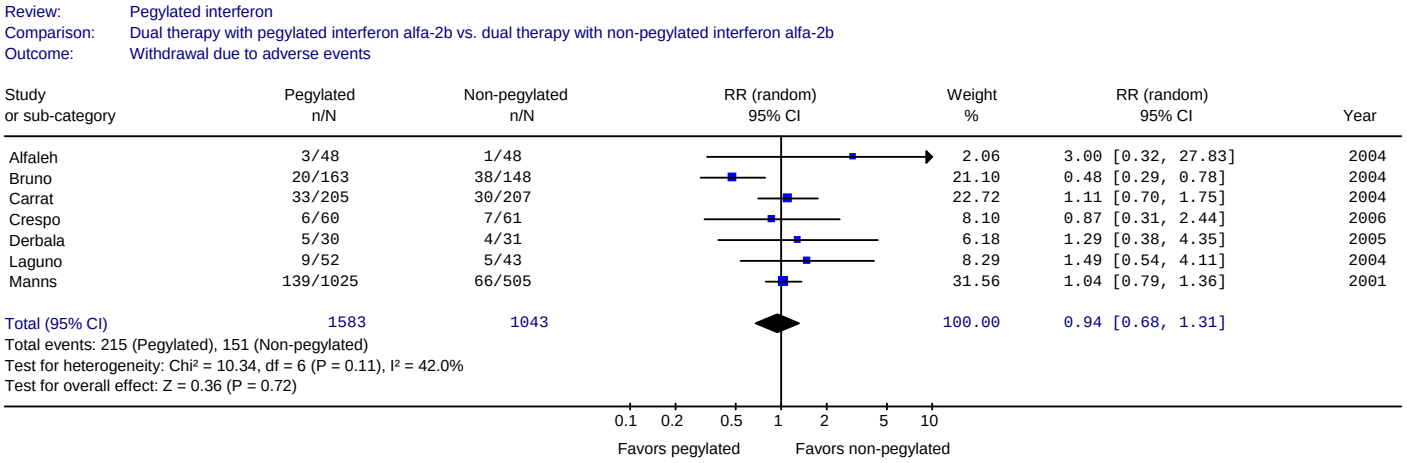


Figure 7. Forest plot on withdrawal due to adverse events, dual therapy with pegylated interferon alfa-2b versus dual therapy with non-pegylated interferon alfa-2b



Dual therapy with pegylated interferon versus pegylated interferon monotherapy

Three of six trials reported rates of withdrawal due to adverse events in patients randomized to dual therapy with pegylated interferon versus patients randomized to pegylated interferon monotherapy. Two trials evaluated pegylated interferon alfa-2a[48, 73] and the third evaluated pegylated interferon alfa-2b.[42] No deaths were reported in patients randomized to dual therapy. Rates of withdrawal due to adverse events on dual therapy ranged from 6% to 12% and were very similar between dual therapy and monotherapy in all three trials (RR 1.07, 95% CI 0.74 to 1.53). There were also no clear differences in rates of depression or in hematologic side effects (each reported by three trials).

In the pegylated interferon alfa-2b trial, rates of flu-like symptoms were higher in patients randomized to dual therapy versus those randomized to pegylated interferon monotherapy (22% vs. 3%).[42] However, the 3% rate of flu-like symptoms associated with pegylated interferon monotherapy appears unusually low.

Adverse events reported in uncontrolled studies

Forty uncontrolled or observational studies provided information about adverse events associated with dual therapy with pegylated interferon (Evidence Table 6).[81-120]

In one study that enrolled patients taking either pegylated interferon alfa-2a or alfa-2b, the type of pegylated interferon was not associated with discontinuation (rates not reported).[88] Nine other studies included patients receiving dual therapy with pegylated interferon alfa-2a[90, 91, 95, 96, 98, 99, 113, 114, 116] and 31 included patients receiving dual therapy with pegylated interferon alfa-2b.[81-89, 92-94, 97, 100-112, 115, 117-120] Six studies were designed to measure specific adverse events, including depression,[87, 109] psychiatric side effects,[97] infections,[96] weight loss,[112] and ocular changes.[89]

Eleven studies, all of dual therapy with pegylated interferon alfa-2b, included patients with HIV co-infection[81, 82, 88, 89, 92, 93, 103, 104, 107, 110, 117] and seven studies included patients who were non-responders or relapsers following standard interferon therapy.[81, 84, 91, 107, 113, 115, 118]

Table 10 shows the ranges for rates of withdrawals due to adverse events reported in these studies. Rates of withdrawal due to adverse events (and other adverse events) overlapped and ranged widely in trials of dual therapy with pegylated interferon alfa-2b.

Table 10. Rates of withdrawals due to adverse events reported in uncontrolled studies

Drug	Number of studies reporting	Withdrawals due to AEs
Pegylated interferon alfa-2a	6[90, 91, 98, 99, 113, 114]	0%-10% (median 5.7%)
Pegylated interferon alfa-2b	20[81-84, 86, 92-94, 100-107, 110, 111, 117, 119]	0%-47% (median 6%)

This body of evidence does not provide additional evidence about comparative safety or tolerability of dual therapy with pegylated interferon beyond data reported in clinical trials. The type and incidence of adverse events observed were similar to those reported in trials. Most studies followed patients for 24 weeks post-treatment. The longest period of follow-up was 84 weeks. Almost all of the studies were non-comparative, and ranges for rates of adverse events overlapped for dual therapy with the two pegylated interferons.

Key Question 3. Does the comparative effectiveness or tolerability and safety of peginterferon alfa-2a plus ribavirin versus peginterferon alfa-2b plus ribavirin vary in patient subgroups defined by demographics (age, racial groups, gender, genotype, markers of disease severity), use of other medications, or presence of co-morbidities (such as HIV infection)?

Summary

There is insufficient evidence to determine if comparative efficacy or safety of dual therapy with pegylated interferon alfa-2a versus dual therapy with pegylated interferon alfa-2b varies in specific patient subgroups. Data from head-to-head trials are limited to one short-term head-to-head trial in patients with genotype 1 infection. Estimates from indirect analysis of SVR for specific HCV genotypes and in HIV co-infected patients are too imprecise to make reliable judgments about comparative efficacy. There are almost no data to determine whether comparative efficacy or safety varies according to race, gender, age, presence of obesity, severity of baseline disease, or other co-morbid conditions.

Race, gender, or age

Some studies have found older age[40, 44, 48, 62] and black race[95, 106, 127] to be associated with poorer response to dual therapy with pegylated interferon. However, we found no studies evaluating whether *comparative* effectiveness and safety of dual therapy with pegylated interferon alfa-2a versus dual therapy with pegylated interferon alfa-2b varies according to race, gender, or age. In all trials except for one,[72] the majority of enrollees were male. Average age in the trials ranged from 34 years[35] to 54 years,[74] with the exception of a trial of thalassemic patients with a mean age of 20 years.[53]

Race was not reported in the two short-term, head-to-head trials.[71, 72] Race was reported in four of 19 other trials comparing dual therapy with pegylated interferon to either dual therapy with non-pegylated interferon or to pegylated interferon monotherapy.[44, 48, 57, 73] The proportion of black enrollees ranged from 5% to 33% in these trials. One small subgroup analysis (N=32)

of Mexican patients enrolled in a large, international multicenter trial[48] reported SVR rates of 50% (7/14) for dual therapy with pegylated interferon alfa-2a versus 33% (4/12) for dual therapy with non-pegylated interferon alfa-2b.[38] Other trials have been conducted in Saudi Arabia or Egypt and in Asia.[34, 46, 47, 59] Two non-randomized studies reported adverse events rates in black patients compared to white patients.[95, 106] However, no study directly compared efficacy or safety of dual therapy with pegylated interferon alfa-2a versus dual therapy with pegylated interferon alfa-2b by ethnic or racial subgroups.

HCV genotype

Several trials of dual therapy with pegylated interferon have found HCV genotype 1 independently associated with a lower likelihood of SVR.[43, 48, 58, 59, 61, 73] One small (N=36), short-term, head-to-head trial directly compared dual therapy with pegylated interferon alfa-2a to dual therapy with pegylated interferon alfa-2b in patients with HCV genotype 1 infection.[71] Because of it's small size, short duration of follow-up, and non-standard dosing (4 weeks of monotherapy followed by 4 weeks of dual therapy), it is of very limited value for judging comparative efficacy (see Key Questions 1 and 2). The large (N=2,880) IDEAL study is a head-to-head trial in patients with HCV genotype 1 infection, but results are not yet available.[129]

Twelve trials provide indirect evidence on efficacy of dual therapy with pegylated interferon alfa-2a versus dual therapy with pegylated interferon alfa-2b. Eight trials of dual therapy with pegylated interferon versus dual therapy with non-pegylated interferon restricted enrollment to genotype 1 patients[70, 74] or reported subgroup results for patients with genotype 1 infection.[44, 45, 48, 59, 63, 73] Four trials reported results for the subgroup of patients with either genotype 1 or 4 infection.[43, 45, 58, 61] Six trials reported results for patients infected with HCV genotype 2 or 3.[45, 48, 58, 61, 63, 73] Three trials reported SVR in patients with genotype 1 or genotypes 1 or 4 randomized to dual therapy with pegylated interferon versus pegylated interferon monotherapy.[42, 48, 56]

There is insufficient evidence from pooled analyses to conclude that dual therapy with one pegylated interferon is superior to the other for HCV genotypes 1, 2, or 3 infection. Estimates of relative risk for SVR on dual therapy with pegylated interferon alfa-2a versus dual therapy with non-pegylated interferon and for dual therapy with pegylated interferon alfa-2b versus non-pegylated interferon were imprecise (particularly for trials of dual therapy with pegylated interferon alfa-2a), with overlapping confidence intervals (Table 11).

Table 11. Pooled analyses on sustained virologic response rates for genotypes 1, 2, and 3

Genotype	Number of trials	Relative risk for SVR (95% CI)	Number of trials	Relative risk for SVR
	Trials of dual therapy with pegylated interferon alfa-2a vs. dual therapy with non-pegylated interferon		Trials of dual therapy with pegylated interferon alfa-2b vs. dual therapy with non-pegylated interferon	
1	3	2.24 (0.90 to 5.56)	5	1.32 (1.03 to 1.69)
1 or 4	1	2.42 (1.53 to 3.83)	3	2.90 (1.75 to 4.81)
2 or 3	3	1.70 (1.08 to 2.65)	3	1.12 (0.87 to 1.45)

We included one systematic review that found dual therapy with pegylated interferon alfa-2a superior to dual therapy with pegylated interferon alfa-2b for achieving SVR in patients with HCV genotype 4.[79] HCV genotype 4 is far more common in Egypt, Saudi Arabia, and other North African Countries (up to two-thirds of infected patients) than in North America and Europe (less than 4% of patients in the two largest trials[48, 63]). The systematic review included subgroup data from the two largest published trials[48, 63] and data from four other trials of patients with HCV genotype 4 infection published as conference abstracts (one trial since published as a journal article).[34] All of the trials compared dual therapy with pegylated interferon to dual therapy with non-pegylated interferon (three trials of pegylated interferon alfa-2a and three pegylated interferon alfa-2b). Compared to dual therapy with non-pegylated interferon, the systematic review found dual therapy with pegylated interferon alfa-2a significantly superior for achieving an SVR (RR 2.41, 95% CI 1.35 to 4.13), but no significant difference for dual therapy with pegylated interferon alfa-2b (RR 1.17, 95% CI 0.80 to 1.70). However, all of the trials of dual therapy with pegylated interferon alfa-2b used lower, non-weight based doses of ribavirin and two of the three trials did not use FDA-approved body-weight based doses of pegylated interferon. In addition, conclusions about relative efficacy from this data are likely to be misleading, as confidence intervals overlap for the two dual pegylated interferon regimens, and no formal indirect analysis was performed. We re-analyzed the data from the systematic review with additional data from two new trials[45, 46] of patients with HCV genotype 4 infection. Our indirect analysis shows no significant differences between pegylated interferon regimens on indirect analysis, with very wide confidence intervals (Table 12).

Table 12. Direct and indirect analyses on sustained virologic response rates for dual therapy with pegylated interferon

Comparison	Number of trials	Relative risk for SVR (95% CI)
Direct analysis		
Dual therapy with pegylated interferon alfa-2a versus dual therapy with non-pegylated interferon	3	2.33 (95% CI 1.38 to 3.95)
Dual therapy with pegylated interferon alfa-2b versus dual therapy with non-pegylated interferon	5	1.23 (95% CI 0.89 to 1.71)
Indirect analysis		
Dual therapy with pegylated interferon alfa-2a versus dual therapy with pegylated interferon alfa-2b	8	1.89 (95% CI 0.52 to 6.87)

Baseline viral load and histologic findings

Several trials of dual therapy with pegylated interferon have found lower viral loads associated with a greater likelihood of achieving an SVR, particularly in patients with genotype 1 infection.[44, 48, 50, 63, 73] Analyses of the association between less severe baseline histologic findings and greater response to dual therapy with pegylated interferon are less consistent, with some trials showing no association after controlling for other factors.[40, 43, 44, 46]

We identified no trials evaluating comparative effectiveness or safety of dual therapy with pegylated interferon alfa-2a versus dual therapy with pegylated interferon alfa-2b in patients with higher viral loads, more severe fibrosis or inflammation, or other markers of more severe baseline HCV disease.

Obese patients

Subgroup analyses of three trials found dual therapy with pegylated interferon alfa-2a[48] and alfa-2b[42, 63] less effective at achieving an SVR in patients over 75 to 80 kg, compared to those below 75 to 80 kg. A potential advantage of pegylated interferon alfa-2b is that it is normally dosed according to weight (compared to uniform dosing for pegylated interferon alfa-2a), which could theoretically help insure adequate drug levels in more obese patients. However, no trials have evaluated whether dual therapy with pegylated interferon alfa-2b is superior to dual therapy with pegylated interferon alfa-2a in obese patients, or whether weight-based versus standardized dosing is more effective in such patients.

HIV co-infection

HCV infection is present in approximately 30% of HIV-infected persons. We identified no head-to-head trial comparing dual therapy with pegylated interferon alfa-2a to dual therapy with pegylated interferon alfa-2b in HIV co-infected patients. We also found insufficient indirect evidence to determine if dual therapy with interferon alfa-2a differs from dual therapy with interferon alfa-2b for efficacy or safety. Three trials[35, 44, 73] compared pegylated interferon alfa-2a versus dual therapy with non-pegylated interferon alfa-2a or alfa-2b, and four trials[43, 45, 58, 68] compared pegylated interferon alfa-2b versus dual therapy with non-pegylated interferon alfa-2b in HIV co-infected patients. Pooled rates of sustained virologic response were 3.22 (95% CI, 2.36 to 4.39) and 1.63 (95% CI 1.07 to 2.48), respectively (see Figures 2 and 3). However, the latter analysis included the only trial to report lower rates of SVR on dual therapy with pegylated interferon compared to dual therapy with non-pegylated interferon.[68] This was the only non-randomized trial and was rated poor-quality. Excluding this trial, the relative risk for SVR was 1.70 (95% CI 1.25 to 2.32). Rates of SBR were only reported in one trial of HIV co-infected patients.[58] Risk of withdrawal due to adverse events were similar in three trials of dual therapy with pegylated interferon alfa-2a versus dual therapy with non-pegylated interferon alfa-2a (RR 0.86, 95% CI 0.59 to 1.25) and three trials of dual therapy with pegylated interferon alfa-2b versus dual therapy with non-pegylated interferon alfa-2b (RR 1.12, 95% CI 0.76 to 1.65). We did not perform indirect analysis because of overlapping confidence intervals and small numbers of trials.

Other co-morbid conditions

There is no evidence to evaluate comparative efficacy or safety of dual therapy with pegylated interferon alfa-2a versus dual therapy with pegylated interferon alfa-2b in patients with severe psychiatric illness or decompensated cirrhosis. Such patients were excluded from the trials and no observational studies were designed to evaluate these patient populations.

Some randomized trials and observational studies included patient populations not represented well in clinical trials, such as patients with thalassemia,[53] patients on hemodialysis,[131] patients with mixed cryoglobulinemia,[83, 102] and patients on methadone maintenance.[101] However, there was no evidence of clear difference in estimates of efficacy or safety from these studies compared to efficacy or safety of dual therapy with pegylated interferon in general.

SUMMARY AND DISCUSSION

Results of this evidence review are summarized in Table 13.

Table 13. Summary of the evidence by key question

Key Question	Quality of the Evidence	Conclusion
1. What is the comparative effectiveness of regimens of peginterferon alfa-2a plus ribavirin versus peginterferon alfa-2b plus ribavirin for treatment of chronic hepatitis C virus infection?	Fair to poor	All trials are efficacy studies. Evidence is insufficient to judge comparative efficacy. Head-to-head trial data are sparse (two trials), short-term (8 to 12 weeks), clinically diverse, and had methodological flaws. Indirect analysis indicates no significant differences in rates of sustained virologic response, though interpretation of findings is limited by clinical diversity across trials and imprecise estimates of effects. There are also no clear differences in sustained biochemical response. Data on histologic outcomes and quality of life are sparse and there are no data on other outcomes such as cirrhosis, hepatocellular cancer, liver transplant, or functional status.
1a. How does duration of treatment or dosing protocols (including weight-based or maintenance dosing or dosing of ribavirin) affect estimates of comparative effectiveness?	Fair to poor	Studies evaluating effects of dose and duration are of limited value for evaluating comparative effectiveness of dual therapy with pegylated interferon alfa-2a versus pegylated interferon alfa-2b because none directly compared effects of duration or dose between the two regimens. Trials comparing different doses of pegylated interferon as part of dual therapy are only available for pegylated interferon alfa-2b. Trials directly comparing different durations of therapy are available for dual therapy with pegylated interferon alfa-2a and for dual therapy with pegylated interferon alfa-2b, but are characterized by substantial clinical diversity across trials in patient populations, dosing of drugs, and/or duration of therapy.
2. What is the comparative tolerability and safety of peginterferon alfa-2a plus ribavirin versus peginterferon alfa-2b plus ribavirin for treatment of chronic hepatitis C virus infection?	Fair to poor	Evidence is insufficient to judge comparative safety. Head-to-head trial data are extremely sparse (one short-term trial) and inadequate for judging comparative safety. Indirect analysis shows no significant differences in rates of withdrawal due to adverse events or other adverse events, but interpretation of findings is limited by clinical diversity across trials, imprecise estimates of effects, and inconsistent reporting of adverse events. Observational studies were almost all non-comparative and provided no additional useful information on comparative safety.

Key Question	Quality of the Evidence	Conclusion
3. Does the comparative effectiveness or tolerability and safety of peginterferon alfa-2a plus ribavirin versus peginterferon alfa-2b plus ribavirin vary in patient subgroups?		
Race, gender, age	Poor	No evidence on comparative effectiveness or safety based on demographics.
Genotype	Fair to poor	There is no direct evidence. Evidence from indirect analysis is insufficient to conclude that dual therapy with one pegylated interferon is superior to the other for infection with specific HCV genotypes.
Severity of baseline disease	Poor	No trials evaluated comparative effectiveness or safety in patients with higher viral loads, more severe fibrosis or inflammation, or other markers of more severe baseline HCV disease.
Obese patients	Poor	Subgroup analyses of three trials found dual therapy with pegylated interferon alfa-2a and alfa-2b less effective at achieving an SVR in patients over 75 to 80 kg, compared to those below 75 to 80 kg. No trials have evaluated comparative effectiveness or safety of weight-based versus standardized dosing of pegylated interferon as part of dual therapy in obese patients.
HIV co-infection	Fair	There is no direct evidence. Indirect analysis indicates no significant differences in rates of sustained virologic response in HIV co-infected patients, though interpretation of findings is limited by clinical diversity across trials and imprecise estimates of effects.
Non-responders or relapsers	Poor	No comparative evidence.

We found insufficient evidence to determine whether dual therapy with pegylated interferon alfa-2a differs from dual therapy with pegylated interferon alfa-2b in efficacy or safety. Evaluating comparative effectiveness and safety is very challenging at this time because the only data from head-to-head trials consist of short-term virologic outcomes. In addition, estimates from indirect analyses are imprecise and may not be reliable because of differences across trials in patient populations, dosing regimens for both pegylated interferon and ribavirin, comparator therapies (dual therapy with non-pegylated interferon alfa-2a or dual therapy with non-pegylated interferon alfa-2b), and other factors. Interestingly, when indirect analyses are limited to trials comparing dual therapy with pegylated interferon alfa-2a and dual therapy with pegylated interferon alfa-2b to the same common comparator (dual therapy with non-pegylated interferon alfa-2b), the point estimate for the likelihood of achieving an SVR is identical (RR 1.00, 95% CI 0.47 to 2.11), though there is only one (albeit large) trial comparing dual therapy with pegylated interferon alfa-2a to dual therapy with non-pegylated interferon alfa-2b.[48]

The trials included in this review are also characterized by frequent methodological shortcomings. For example, nearly all of the trials used an open-label design and did not make

provisions for blinded outcomes assessment. Trials also frequently did not describe randomization or allocation concealment methods in adequate detail. In trials of antiretroviral therapy for HIV infection, which also focus on virologic outcomes, such methodological shortcoming have been shown to exaggerate estimates of treatment effects.[132] Another challenge in assessing the available evidence is that generalizability to real-world practice may be limited, as all of the trials appeared to be efficacy studies. In addition, nearly all of the trials focused on intermediate outcomes such as SVR, ETR, SBR, and histologic changes on biopsy. Although dual therapy with pegylated interferon has not been available long enough to assess outcomes such as rates of cirrhosis, hepatocellular carcinoma, mortality, or need for transplant, other outcomes such as quality of life and functional status were rarely reported. Adverse events were also inconsistently reported, making it difficult to accurately assess overall benefits and harms.[133]

Results of the large (planned enrollment 2,880) IDEAL study, which are expected later in 2007, should provide more insight into comparative efficacy.[129] This trial will directly compare dual therapy with pegylated interferon alfa-2a versus pegylated interferon alfa-2b. However, even though this will be by far the largest trial directly comparing pegylated interferon regimens, enrollment is limited to patients with genotype 1 infection. In addition, nonequivalent dosing and dose adjustments of ribavirin could make it difficult to determine whether findings are due to the use of pegylated interferon alfa-2a versus pegylated interferon alfa-2b, or to differences in the ribavirin dosing scheme.[50] Publication of results from the large (N>4,900) WIN-R study should help interpret potential effects of differences in ribavirin dosing on effectiveness of dual therapy with pegylated interferon.[130]

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Appendix A. Literature Search Strategies

Database: Ovid MEDLINE(R) <1966 to July Week 4 2006>
Search Strategy:

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1 exp Hepatitis C/ or hepatitis C.mp. or hcv.mp. (36716)
2 Pegasys.mp. (50)
3 Peg-intron.mp. (25)
4 peginterferon alfa 2a.mp. (679)
5 peginterferon alfa 2b.mp. (521)
6 Interferon Alfa 2a.mp. or exp Interferon Alfa-2a/ (3015)
7 Interferon Alfa-2b.mp. or exp Interferon Alfa-2b/ (4167)
8 6 or 7 (6677)
9 exp Interferons/ (83358)
10 2a.mp. (21935)
11 2b.mp. (17454)
12 9 and (10 or 11) (7636)
13 exp Polyethylene Glycols/ (26140)
14 pegylat$.mp. (2121)
15 peginterferon$.mp. (967)
16 13 or 14 or 15 (27324)
17 (8 or 12) and 16 (988)
18 2 or 3 or 4 or 5 or 17 (1027)
19 ribavirin.mp. or exp Ribavirin/ (5099)
20 1 and 18 and 19 (697)
21 from 20 keep 1-697 (697)

Database: EBM Reviews - Cochrane Central Register of Controlled Trials <3rd Quarter 2006>
Search Strategy:

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1 exp Hepatitis C/ or hepatitis C.mp. or hcv.mp. (2297)
2 Pegasys.mp. (87)
3 Peg-intron.mp. (17)
4 peginterferon alfa 2a.mp. (93)
5 peginterferon alfa 2b.mp. (28)
6 Interferon Alfa 2a.mp. or exp Interferon Alfa-2a/ (467)
7 Interferon Alfa-2b.mp. or exp Interferon Alfa-2b/ (781)
8 6 or 7 (1189)
9 exp Interferons/ (2779)
10 2a.mp. (1001)
11 2b.mp. (1383)
12 9 and (10 or 11) (1094)
13 exp Polyethylene Glycols/ (781)
14 pegylat$.mp. (250)
15 peginterferon$.mp. (173)
16 13 or 14 or 15 (1074)

17 (8 or 12) and 16 (165)
18 2 or 3 or 4 or 5 or 17 (265)
19 ribavirin.mp. or exp Ribavirin/ (927)
20 1 and 18 and 19 (167)
21 from 20 keep 1-167 (167)

Database: EBM Reviews - Cochrane Database of Systematic Reviews <2nd Quarter 2006>
Search Strategy:
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1 exp Hepatitis C/ or hepatitis C.mp. or hcv.mp. (92)
2 Pegasys.mp. (3)
3 Peg-intron.mp. (1)
4 peginterferon alfa 2a.mp. (0)
5 peginterferon alfa 2b.mp. (1)
6 Interferon Alfa 2a.mp. or exp Interferon Alfa-2a/ (9)
7 Interferon Alfa-2b.mp. or exp Interferon Alfa-2b/ (11)
8 6 or 7 (14)
9 [exp Interferons/] (0)
10 2a.mp. (93)
11 2b.mp. (91)
12 9 and (10 or 11) (0)
13 [exp Polyethylene Glycols/] (0)
14 pegylat$.mp. (20)
15 peginterferon$.mp. (5)
16 13 or 14 or 15 (21)
17 (8 or 12) and 16 (8)
18 2 or 3 or 4 or 5 or 17 (11)
19 ribavirin.mp. or exp Ribavirin/ (23)
20 1 and 18 and 19 (9)
21 from 20 keep 1-9 (9)

Database: EBM Reviews - Database of Abstracts of Reviews of Effects <3rd Quarter 2006>
Search Strategy:
---
1 exp Hepatitis C/ or hepatitis C.mp. or hcv.mp. (42)
2 Pegasys.mp. (0)
3 Peg-intron.mp. (0)
4 peginterferon alfa 2a.mp. (0)
5 peginterferon alfa 2b.mp. (0)
6 Interferon Alfa 2a.mp. or exp Interferon Alfa-2a/ (6)
7 Interferon Alfa-2b.mp. or exp Interferon Alfa-2b/ (9)
8 6 or 7 (9)
9 [exp Interferons/] (0)
10 2a.mp. (18)
11 2b.mp. (26)
12 9 and (10 or 11) (0)

13 [exp Polyethylene Glycols/] (0)
14 pegylat$.mp. (4)
15 peginterferon$.mp. (2)
16 13 or 14 or 15 (5)
17 (8 or 12) and 16 (3)
18 2 or 3 or 4 or 5 or 17 (3)
19 ribavirin.mp. or exp Ribavirin/ (16)
20 1 and 18 and 19 (3)
21 from 20 keep 1-3 (3)

Appendix B. Quality assessment methods for drug class reviews for the Drug Effectiveness Review Project

The purpose of this document is to outline the methods used by the Oregon Evidence-based Practice Center (EPC), based at Oregon Health & Science University, and any subcontracting EPCs, in producing drug class reviews for the Drug Effectiveness Review Project.

The methods outlined in this document ensure that the products created in this process are methodologically sound, scientifically defensible, reproducible, and well documented. This document has been adapted from the Procedure Manual developed by the Methods Work Group of the United States Preventive Services Task Force (version 1.9, September 2001), with additional material from the NHS Centre for Reviews and Dissemination (CRD) report on *Undertaking Systematic Reviews of Research on Effectiveness: CRD's Guidance for Carrying Out or Commissioning Reviews* (2nd edition, 2001) and "The Database of Abstracts of Reviews of Effects (DARE)" in *Effectiveness Matters*, vol. 6, issue 2, December 2002, published by the CRD.

All studies or systematic reviews that are included are assessed for quality, and assigned a rating of "good", "fair" or "poor". Studies that have a fatal flaw in one or more criteria are rated poor quality; studies which meet all criteria, are rated good quality; the remainder are rated fair quality. As the "fair quality" category is broad, 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. A "poor quality" trial is not valid—the results are at least as likely to reflect flaws in the study design as the true difference between the compared drugs.

For Controlled Trials:

Assessment of Internal Validity

1. Was the assignment to the treatment groups really random?
    - Adequate approaches to sequence generation:
        - Computer-generated random numbers
        - Random numbers tables
    - Inferior approaches to sequence generation:
        - Use of alternation, case record numbers, birth dates or week days
    - Not reported

2. Was the treatment allocation concealed?
    - Adequate approaches to concealment of randomization:
        - Centralized or pharmacy-controlled randomization
        - Serially-numbered identical containers
        - On-site computer based system with a randomization sequence that is not readable until allocation
        - Other approaches sequence to clinicians and patients

Inferior approaches to concealment of randomization:
- Use of alternation, case record numbers, birth dates or week days
- Open random numbers lists
- Serially numbered envelopes (even sealed opaque envelopes can be subject to manipulation)

Not reported

3. Were the groups similar at baseline in terms of prognostic factors?

4. Were the eligibility criteria specified?

5. Were outcome assessors blinded to the treatment allocation?

6. Was the care provider blinded?

7. Was the patient kept unaware of the treatment received?

8. Did the article include an intention-to-treat analysis, or provide the data needed to calculate it (i.e., number assigned to each group, number of subjects who finished in each group, and their results)?

9. Did the study maintain comparable groups?

10. Did the article report attrition, crossovers, adherence, and contamination?

11. Is there important differential loss to followup or overall high loss to followup? (give numbers in each group)

Assessment of External Validity (Generalizability)

1. How similar is the population to the population to whom the intervention would be applied?

2. How many patients were recruited?

3. What were the exclusion criteria for recruitment? (Give numbers excluded at each step)

4. What was the funding source and role of funder in the study?

5. Did the control group receive the standard of care?

6. What was the length of followup? (Give numbers at each stage of attrition.)

For Studies Reporting Complications/Adverse Effects

Assessment of Internal Validity

1. Was the selection of patients for inclusion non-biased (Was any group of patients systematically excluded)?

2. Is there important differential loss to followup or overall high loss to followup? (Give numbers in each group.)

3. Were the events investigated specified and defined?

4. Was there a clear description of the techniques used to identify the events?

5. Was there non-biased and accurate ascertainment of events (independent ascertainers; validation of ascertainment technique)?

6. Were potential confounding variables and risk factors identified and examined using acceptable statistical techniques?

7. Did the duration of followup correlate to reasonable timing for investigated events? (Does it meet the stated threshold?)

Assessment of External Validity

1. Was the description of the population adequate?

2. How similar is the population to the population to whom the intervention would be applied?

3. How many patients were recruited?

4. What were the exclusion criteria for recruitment? (Give numbers excluded at each step)

5. What was the funding source and role of funder in the study?

Systematic Reviews:

1. Is there a clear review question and inclusion/exclusion criteria reported relating to the primary studies?

A good quality review should focus on a well-defined question or set of questions, which ideally will refer to the inclusion/exclusion criteria by which decisions are made on whether to include or exclude primary studies. The criteria should relate to the four components of study design, indications (patient populations), interventions (drugs), and outcomes of interest. In addition, details should be reported relating to the process of decision-making,

i.e., how many reviewers were involved, whether the studies were examined independently, and how disagreements between reviewers were resolved.

2. Is there evidence of a substantial effort to search for all relevant research?

This is usually the case if details of electronic database searches and other identification strategies are given. Ideally, details of the search terms used, date and language restrictions should be presented. In addition, descriptions of hand-searching, attempts to identify unpublished material, and any contact with authors, industry, and research institutes should be provided. The appropriateness of the database(s) searched by the authors should also be considered, e.g. if MEDLINE is searched for a review looking at health education, then it is unlikely that all relevant studies will have been located.

3. Is the validity of included studies adequately assessed?

A systematic assessment of the quality of primary studies should include an explanation of the criteria used (e.g., method of randomization, whether outcome assessment was blinded, whether analysis was on an intention-to-treat basis). Authors may use either a published checklist or scale, or one that they have designed specifically for their review. Again, the process relating to the assessment should be explained (i.e. how many reviewers involved, whether the assessment was independent, and how discrepancies between reviewers were resolved).

4. Is sufficient detail of the individual studies presented?

The review should demonstrate that the studies included are suitable to answer the question posed and that a judgement on the appropriateness of the authors' conclusions can be made. If a paper includes a table giving information on the design and results of the individual studies, or includes a narrative description of the studies within the text, this criterion is usually fulfilled. If relevant, the tables or text should include information on study design, sample size in each study group, patient characteristics, description of interventions, settings, outcome measures, follow-up, drop-out rate (withdrawals), effectiveness results and adverse events.

5. Are the primary studies summarized appropriately?

   The authors should attempt to synthesize the results from individual studies. In all cases, there should be a narrative summary of results, which may or may not be accompanied by a quantitative summary (meta-analysis).
   For reviews that use a meta-analysis, heterogeneity between studies should be assessed using statistical techniques. If heterogeneity is present, the possible reasons (including chance) should be investigated. In addition, the individual evaluations should be weighted in some way (e.g., according to sample size, or inverse of the variance) so that studies that are considered to provide the most reliable data have greater impact on the summary statistic.

Appendix C. Table of Excluded Studies

Study	Reason for exclusion
Abbate I, Cappiello G, Lo Iacono O, et al. Heterogeneity of HVR-1 quasispecies is predictive of early but not sustained virological response in genotype 1b-infected patients undergoing combined treatment with PEG- or STD-IFN plus RBV. *J Biol Regul Homeost Agents.* Apr-Jun 2003;17(2):162-165.	Study design not included
Alric L, Plaisier E, Thebault S, et al. Influence of antiviral therapy in hepatitis C virus-associated cryoglobulinemic MPGN. *Am J Kidney Dis.* Apr 2004;43(4):617-623.	Study design not included
Anonymous. Hepatitis drug gets approval for coinfection treatment. *AIDS Patient Care STDS.* May 2005;19(5):351.	No original data (e.g., letter, editorial, non-systematic review)
August-Jorg BS, Borovicka J, Dufour JF, et al. Twenty-four vs. forty-eight weeks of re-therapy with interferon alpha 2b and ribavirin in interferon alpha monotherapy relapsers with chronic hepatitis C. *Swiss Med Wkly.* 2003;133(33-34):455-460.	Intervention not included (e.g., not pegylated interferon, monotherapy only)
Balan V, Schwartz D, Wu GY, et al. Erythropoietic response to anemia in chronic hepatitis C patients receiving combination pegylated interferon/ribavirin. *Am J Gastroenterol.* Feb 2005;100(2):299-307.	Study design not included
Borg BB, Hoofnagle JH. Peginterferon Alfa-2b and ribavirin for 12 versus 24 weeks in HCV infection.[comment]. *N Engl J Med.* Sep 15 2005;353(11):1182-1183; author reply 1182-1183.	No original data (e.g., letter, editorial, non-systematic review)
Brok J, Gluud L, Gluud C. Ribavirin plus interferon versus interferon for chronic hepatitis C. *Cochrane Database of Systematic Reviews.* 2006(3).	Intervention not included (e.g., not pegylated interferon, monotherapy only)
Bruchfeld A, Lindahl K, Reichard O, Carlsson T, Schvarcz R. Pegylated interferon and ribavirin treatment for hepatitis C in haemodialysis patients. *Journal of Viral Hepatitis.* May 2006;13(5):316-321.	Study design not included
Chambers TJ, Fan X, Droll DA, et al. Quasispecies heterogeneity within the E1/E2 region as a pretreatment variable during pegylated interferon therapy of chronic hepatitis C virus infection. *J Virol.* Mar 2005;79(5):3071-3083.	Study design not included
Chisholm JA, Williams G, Spence E, et al. Retinal toxicity during pegylated alpha-interferon therapy for chronic hepatitis C: a multifocal electroretinogram investigation. *Alimentary Pharmacology & Therapeutics.* Mar 15 2005;21(6):723-732.	Outcome not included
Cooksley WG, Piratvisuth T, Lee SD, et al. Peginterferon alpha-2a (40 kDa): an advance in the treatment of hepatitis B e antigen-positive chronic hepatitis B. *Journal of Viral Hepatitis.* 2003;10(4):298-305.	Intervention not included (e.g., not pegylated interferon, monotherapy only)
De Kaita K, Wong S, Renner E, Minuk GY.	Study design not included

Study	Reason for exclusion
Treatment outcomes in a centralized specialty clinic for hepatitis C virus are comparable with those from clinical trials. *Can J Gastroenterol.* Feb 2006;20(2):87-90.	
Desmond CP, Roberts SK, Dudley F, et al. Sustained virological response rates and durability of the response to interferon-based therapies in hepatitis C patients treated in the clinical setting. *Journal of Viral Hepatitis.* May 2006;13(5):311-315.	Study design not included
Di Bisceglie AM, Fan X, Chambers T, Strinko J. Pharmacokinetics, pharmacodynamics, and hepatitis C viral kinetics during antiviral therapy: the null responder. *Journal of Medical Virology.* Apr 2006;78(4):446-451.	Study design not included
Di Bisceglie AM, Rustgi VK, Thuluvath P, et al. Pharmacokinetics and pharmacodynamics of pegylated interferon alfa-2A or alfa-2B with ribavirin in treatment naive patients with genotype 1 chronic hepatitis C. *Hepatology.* 2004(Suppl 1):734.	Study design not included
Dominguez S, Ghosn J, Valantin M-A, et al. Efficacy of early treatment of acute hepatitis C infection with pegylated interferon and ribavirin in HIV-infected patients. *Aids.* May 12 2006;20(8):1157-1161.	Population not included (acute hepatitis C infection)
Ferenci P, Bergholz U, Laferl H, al. e. 24 week treatment regimen with peginterferon alfa-2a (40KD) (PEGASYS) plus ribavirin (CPEGUS) in HCV genotype 1 or 4 'super responders'. Paper presented at: 41st Annual Meeting of the European Association for the Study of the Liver; April 26-30, 2006; Vienna, Austria.	Intervention not included (e.g., not pegylated interferon, monotherapy only)
Formann E, Steindl-Munda P, Hofer H, et al. Long-term follow-up of chronic hepatitis C patients with sustained virological response to various forms of interferon-based anti-viral therapy. *Alimentary Pharmacology & Therapeutics.* Feb 15 2006;23(4):507-511.	Study design not included
Glesby MJ, Bassett R, Alston-Smith B, et al. Pilot study of low-dose interleukin-2, pegylated interferon-alpha 2b, and ribavirin for the treatment of hepatitis C virus infection in patients with HIV infection. *J Infect Dis.* Mar 1 2005;191(5):686-693.	Study design not included
Heathcote E, Shiffman M, Cooksley W, Dusheiko G, Lee S, Balart L. Peginterferon alfa-2a in patients with chronic hepatitis C and cirrhosis. *N Engl J Med.* 2000;343(23):1673-1680.	Intervention not included (e.g., not pegylated interferon, monotherapy only)
Henry MJ. Peginterferon Alfa-2b and ribavirin for 12 versus 24 weeks in HCV infection.[comment]. *N Engl J Med.* Sep 15 2005;353(11):1182-1183; author reply 1182-1183.	No original data (e.g., letter, editorial, non-systematic review)
Herrine SK, Brown RS, Jr., Bernstein DE, Ondovik MS, Lentz E, Te H. Peginterferon alpha-2a combination therapies in chronic hepatitis C patients who relapsed after or had a viral breakthrough on therapy with standard interferon alpha-2b plus ribavirin: a pilot study of efficacy and safety. *Dig Dis Sci.* Apr 2005;50(4):719-726.	Study design not included

Study	Reason for exclusion
Jacobson IM, Ahmed F, Russo MW, et al. Interferon alfa-2b and ribavirin for patients with chronic hepatitis C and normal ALT. *Am J Gastroenterol.* 2004;99(9):1700-1705.	Intervention not included (e.g., not pegylated interferon, monotherapy only)
Jensen DM, Marcellin P. Rationale and design of the REPEAT study: a phase III, randomized, clinical trial of peginterferon alfa-2a (40 kDa) plus ribavirin in non-responders to peginterferon alfa-2b (12 kDa) plus ribavirin. *European Journal of Gastroenterology & Hepatology.* Sep 2005;17(9):899-904.	No original data (e.g., letter, editorial, non-systematic review)
Kraus MR, Schafer A, Wissmann S, Reimer P, Scheurlen M. Neurocognitive changes in patients with hepatitis C receiving interferon alfa-2b and ribavirin. *Clinical Pharmacology & Therapeutics.* Jan 2005;77(1):90-100.	Outcome not included
Krawitt EL, Ashikaga T, Gordon SR, et al. Peginterferon alfa-2b and ribavirin for treatment-refractory chronic hepatitis C. *Journal of Hepatology.* Aug 2005;43(2):243-249.	Study design not included
Lee JS, Hu S, Carlos Lopez-Talavera J. Ribavirin (RBV) dose reduction in patients with HCV genotype 1 infection receiving combination treatment with peginterferon alfa-2A (40KD) (PEGASYS) plus RBV (COPEGUS). *Hepatology (Baltimore, Md.).* 2004;40(4 Suppl 1):335A.	No original data (e.g., letter, editorial, non-systematic review)
Lee SS, Bain V, Peltekian K, et al. Peginterferon alfa-2a (40 kDa) plus ribavirin in cirrhotic patients with chronic hepatitis C: results of a Canadian multicenter open-label expanded access program. *Journal of Hepatology.* 2005;42(Suppl 2):210.	No original data (e.g., letter, editorial, non-systematic review)
Lee WM, Dienstag JL, Lindsay KL, et al. Evolution of the HALT-C Trial: pegylated interferon as maintenance therapy for chronic hepatitis C in previous interferon nonresponders. *Controlled Clinical Trials.* 2004;25(5):472-492.	No original data (e.g., letter, editorial, non-systematic review)
Legrand-Abravanel F, Nicot F, Boulestin A, et al. Pegylated interferon and ribavirin therapy for chronic hepatitis C virus genotype 4 infection. *Journal of Medical Virology.* Sep 2005;77(1):66-69.	Study design not included
Lindsay K, Trepo C, Heintges T, Shiffman M, Gordon S, Hoefs J. A randomized, double-blind trial comparing pegylated interferon alfa-2b to interferon alfa-2b as initial treatment for chronic hepatitis C. *Hepatology.* 2001;34(2):395-403.	Intervention not included (e.g., not pegylated interferon, monotherapy only)
Luo S, Cassidy W, Jeffers L, Reddy KR, Bruno C, Howell CD. Interferon-stimulated gene expression in black and white hepatitis C patients during peginterferon alfa-2a combination therapy. *Clin Gastroenterol Hepatol.* May 2005;3(5):499-506.	Outcome not included
Mangia A, Cimino L, Persico M, et al. Enhanced response to peginterferon-a-2a-based triple therapy in previously non-responsive chronic hepatitis C: final results of PRETTY study. *Journal of Hepatology.* 2005;42(Suppl 2):200.	No original data (e.g., letter, editorial, non-systematic review)

Study	Reason for exclusion
Marino N, Blanc PL, Ble C, Pierotti P, Mazzotta F. Discrepancy in virological and biochemistry response of patients with chronic hepatitis HCV positive on treatment with PEG-IFN plus ribavirin. *J Biol Regul Homeost Agents.* Apr-Jun 2003;17(2):205-206.	No original data (e.g., letter, editorial, non-systematic review)
Matthews SJ, McCoy C. Peginterferon alfa-2a: a review of approved and investigational uses. *Clin Ther.* Jul 2004;26(7):991-1025.	No original data (e.g., letter, editorial, non-systematic review)
Maynard M, Pradat P, Bailly F, et al. Amantadine triple therapy for non-responder hepatitis C patients. Clues for controversies (ANRS HC 03 BITRI). *Journal of Hepatology.* Mar 2006;44(3):484-490.	Study design not included
Mohsen A, Norris S. Chronic hepatitis C. *Clin Evid.* Dec 2005(14):920-930.	No original data (e.g., letter, editorial, non-systematic review)
Myers R, Abdo A, Poynard T. Pegylated interferon alfa for chronic hepatitis C [1]. *Cochrane Database of Systematic Reviews.* 2006;2:2.	No original data (e.g., letter, editorial, non-systematic review)
Myers R, Poynard T. Interferon for interferon nonresponding and relapsing patients with chronic hepatitis C. *Cochrane Database of Systematic Reviews.* 2006;2:2.	Intervention not included (e.g., not pegylated interferon, monotherapy only)
Myers R, Regimbeau C, Thevenot T, et al. Interferon for acute hepatitis C [Systematic Review]. *Cochrane Database of Systematic Reviews.* 2006;2:2.	Population not included (acute hepatitis C infection)
Myers R, Regimbeau C, Thevenot T, et al. Interferon for interferon naive patients with chronic hepatitis C. *Cochrane Database of Systematic Reviews.* 2006;2:2.	Intervention not included (e.g., not pegylated interferon, monotherapy only)
Napoli N, Giannelli G, Parisi CV, Antonaci A, Maddalena G, Antonaci S. Predictive value of early virological response to treatment with different interferon-based regimens plus ribavirin in patients with chronic hepatitis C. *New Microbiol.* Jan 2005;28(1):13-21.	Study design not included
Nevens F, Van Vlierberghe H, D'Heygere F, et al. Peginterferon alfa-2a (40 kDa) plus ribavirin is as effective in patients relapsing after conventional interferon based therapy as in naive patients: results from the BERNAR-1 trial. *Journal of Hepatology.* 2005;42(Suppl 2):214.	No original data (e.g., letter, editorial, non-systematic review)
Nunez M, Camino N, Ramos B, et al. Impact of ribavirin exposure on early virological response to hepatitis C therapy in HIV-infected patients with chronic hepatitis C. *Antiviral Therapy.* 2005;10(5):657-662.	Outcome not included
Perez R, Jimenez M, Crespo J, et al. Comparative study of the efficacy of an induction dose of interferon-alpha2b with ribavirin compared with standard combined treatment in naive patients with chronic hepatitis C. *Journal of Viral Hepatitis.* 2003;10(6):437-445.	Intervention not included (e.g., not pegylated interferon, monotherapy only)
Perrillo R, Rothstein KD, Rubin R, et al. Comparison of quality of life, work productivity and	Intervention not included (e.g., not pegylated interferon, monotherapy only)

Study	Reason for exclusion
medical resource utilization of peginterferon alpha 2a vs the combination of interferon alpha 2b plus ribavirin as initial treatment in patients with chronic hepatitis C. *Journal of Viral Hepatitis.* Mar 2004;11(2):157-165.	
Plosker GL, Keating GM. Peginterferon-alpha-2a (40kD) plus ribavirin: a review of its use in hepatitis C Virus And HIV co-infection. *Drugs.* 2004;64(24):2823-2843.	No original data (e.g., letter, editorial, non-systematic review)
Pockros PJ, Carithers R, Desmond P, et al. Efficacy and safety of two-dose regimens of peginterferon alpha-2a compared with interferon alpha-2a in chronic hepatitis C: a multicenter, randomized controlled trial. *Am J Gastroenterol.* 2004;99(7):1298-1305.	Intervention not included (e.g., not pegylated interferon, monotherapy only)
Poynard T, al. e. EPIC-3 (Evaluation of PEG-Intron in control of hepatitis C cirrhosis). *Data on file.*	Study design not included
Puoti M, Babudieri S, Rezza G, et al. Use of pegylated interferons is associated with an increased incidence of infections during combination treatment of chronic hepatitis C: a side effect of pegylation?[see comment]. *Antiviral Therapy.* Aug 2004;9(4):627-630.	Study design not included
Rasenack J, S. Z, SV. F, et al. Peginterferon alpha-2a (40kD) improves HR-QOL outcomes compared with unmodified interferon alpha-2a: in patients with chronic hepatitis C. *Pharmacoeconomics.* 2003;21(5):341-349.	Intervention not included (e.g., not pegylated interferon, monotherapy only)
Reddy K, Wright T, Pockros P, Shiffman M, Everson G, Reindollar R. Efficacy and safety of pegylated (40-kd) interferon < alpha >-2a compared with interferon < alpha >-2a in noncirrhotic patients with chronic hepatitis C. *Hepatology.* 2001;33(2):433-438.	Intervention not included (e.g., not pegylated interferon, monotherapy only)
Reichenberg A, Gorman JM, Dieterich DT. Interferon-induced depression and cognitive impairment in hepatitis C virus patients: a 72 week prospective study. *Aids.* Oct 2005;19 Suppl 3:S174-178.	Study design not included
Sanchez-Tapias JM, Crespo J, Diago M, Perez R, Romero-Gomez M, Munoz-Sanchez M. Rationale and design of TeraViC-4 study: a phase III, randomized clinical trial to evaluate the effects of treatment duration with peginterferon alfa-2a (40-kDa) and ribavirin in naive patients with chronic hepatitis C virus infection without early virological response at week 4. *Methods Find Exp Clin Pharmacol.* Nov 2002;24(9):579-584.	No original data (e.g., letter, editorial, non-systematic review)
Shiffman ML. Chronic hepatitis C: treatment of pegylated interferon/ribavirin nonresponders. *Current Gastroenterology Reports.* Feb 2006;8(1):46-52.	No original data (e.g., letter, editorial, non-systematic review)
Simin M, Brok J, Stimac D, Gluud C, Gluud L. Pegylated interferon plus ribavirin versus non-pegylated interferon plus ribavirin for chronic hepatitis C [1]. *Cochrane Database of Systematic Reviews.* 2006;2:2.	No original data (e.g., letter, editorial, non-systematic review)
Soriano V, Maida I, Nunez M, et al. Long-term follow-up of HIV-infected patients with chronic hepatitis C virus infection treated with interferon-based	Study design not included

Study	Reason for exclusion
therapies. *Antiviral Therapy.* Dec 2004;9(6):987-992.	
Srivastava S, Bertagnolli M, Lewis JH. Sustained virological response rate to pegylated interferon plus ribavirin for chronic hepatitis C in African Americans: results in treatment-naive patients in a university liver clinic. *J Natl Med Assoc.* Dec 2005;97(12):1703-1707.	Study design not included
Strinko JM, Di Bisceglie AM, Hoffmann JA. A descriptive study of the relationship between mood disorders and hepatitis C treatment compliance: does nursing play a role? *Issues in mental health nursing.* 2004;25(7):715-722.	Study design not included
Suzuki H, Takagi H, Sohara N, et al. Triple therapy of interferon and ribavirin with zinc supplementation for patients with chronic hepatitis C: a randomized controlled clinical trial. *World J Gastroenterol.* 2006;12(8):1265-1269.	Study design not included
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-401A.	No original data (e.g., letter, editorial, non-systematic review)
Torriani FJ, Ribeiro RM, Gilbert TL, et al. Hepatitis C virus (HCV) and human immunodeficiency virus (HIV) dynamics during HCV treatment in HCV/HIV coinfection. *J Infect Dis.* Nov 15 2003;188(10):1498-1507.	Outcome not included
Trapero M, Garcia-Buey L, Munoz C, et al. Maintenance of T1 response as induced during PEG-IFNalpha plus ribavirin therapy controls viral replication in genotype-1 patients with chronic hepatitis C. *Rev Esp Enferm Dig.* Jul 2005;97(7):481-490.	Study design not included
Wietzke-Braun P, Meier V, Neubauer-Saile K, Mihm S, Ramadori G. Treatment of genotype 2 and 3 chronic hepatitis C virus-infected patients. *World J Gastroenterol.* Oct 21 2005;11(39):6188-6192.	Intervention not included (e.g., not pegylated interferon, monotherapy only)
Wilhelmi M, Gubler C, Renner EL, Mullhaupt B. Lymph node enlargement during combination therapy for chronic hepatitis C with pegylated interferon alpha and ribavirin: harmless reaction or harmful disease? *Swiss Med Wkly.* Jan 21 2006;136(3-4):65-67.	Outcome not included
Wright TL. Treatment of patients with hepatitis C and cirrhosis. *Hepatology.* Nov 2002;36(5 Suppl 1):S185-194.	No original data (e.g., letter, editorial, non-systematic review)
Zeuzem S, Feinman S, Rasenack J, Heathcote E, Lai M, Gane E. Peginterferon alfa-2a in patients with chronic hepatitis C. *N Engl J Med.* 2000;343(23):1666-1672.	Intervention not included (e.g., not pegylated interferon, monotherapy only)
Zhang F. Pegylated interferons in the treatment of chronic hepatitis C. *Chin Med J.* Apr 2003;116(4):495-498.	No original data (e.g., letter, editorial, non-systematic review)

Appendix D. Unpublished trials of pegylated interferons for chronic hepatitis C infection

Study, year	N	Comparison	Interventions	Population characteristics/ Notes	SVR	Withdrawals due to AEs
Studies of peginterferon alfa-2b						
Crespo, 2006	121	Peginterferon vs interferon	A: Peginterferon alfa-2b 1.5 µg/kg/week plus ribavirin 800 mg B: Interferon alfa-2b 3 million units 3x/week plus ribavirin 800 mg (24 weeks for genotype 2 or 3, 48 weeks for genotype 1 or 4)	HIV co-infection, Treatment naïve 33.9% genotype 1	A vs B: All patients: 33/60 (55%) vs 16/61 (26%); p=0.002 Genotype 1 or 4: 18/39 (46%) vs 7/40 (18%); p=0.013 Genotype 2 or 3: 15/21 (71%) vs 9/21 (43%); p=0.12	A vs B: 10/60 (16.7%) vs 14/61 (23.0%)
Jacobson	4913	Fixed vs weight-based ribavirin dosing	A: Peginterferon alfa-2b 1.5 µg/kg/week plus ribavirin 800 mg B: Peginterferon alfa-2b 1.5 µg/kg/week plus ribavirin 800-1400 mg (weight-based) (48 weeks for genotype 1, 24 or 48 weeks for genotype 2 and 3)	Treatment naive 62% genotype 1	A vs B: All patients: 853/2102 (41%) vs 939/2121 (44%); p=0.02 Genotype 1: 377/1305 (29%) vs 448/1313 (34%); p=0.004 Genotype 2 or 3: 308/513 (60%) vs 306/494 (62%) (NS)	357/2444 (14.6%) vs 370/2469 (15.0%)
Studies of peginterferon alfa-2a						
Bressler, 2005	40	Dose	A: Peginterferon alfa-2a 180 µg/week plus ribavirin 1000-1200 mg x 48 weeks B: Peginterferon alfa-2a 270 µg/week plus ribavirin 1000-1200 mg x 48 weeks	Treatment naive BMI >30 Primary outcome was pharmacokinetic characteristics	A vs B: 14/20 (70%) vs 16/20 (79%)	Not reported
Conjeevaram, 2005	401	African American vs Caucasian patients	Peginterferon alfa-2a 180 µg/week plus ribavirin 1000-1200 mg x 48 weeks	Genotype 1	African Americans vs Caucasians: 55/196 (28%) vs 107/205 52%; p=0.0001	Not reported

Appendix D. Unpublished trials of pegylated interferons for chronic hepatitis C infection

Study, year	N	Comparison	Interventions	Population characteristics/ Notes	SVR	Withdrawals due to AEs
Marcellin, 2003	377	Treatment duration and ribavirin dose	A: Peginterferon alfa-2a 180 µg/week plus ribavirin 800 mg x 24 weeks B: Peginterferon alfa-2a 180 µg/week plus ribavirin 1000-1200 mg x 24 weeks C: Peginterferon alfa-2a 180 µg/week plus ribavirin 800 mg x 48 weeks D: Peginterferon alfa-2a 180 µg/week plus ribavirin 1000-1200 mg x 48 weeks	Treatment naïve Compensated cirrhosis	A vs B vs C vs D: (Overall results not reported) Genotype 1: 26% vs 26% vs 28% vs 37% Genotype non-1: 71% vs 75% vs 67% vs 73%	Not reported
Jensen, 2006	950	Dose and duration	A: Peginterferon alfa-2a 360 µg/week x 12 weeks followed by 180 µg/week x 36 weeks plus ribavirin 1000-1200 mg B: Peginterferon alfa-2a 360 µg/week x 12 weeks followed by 180 µg/week x 60 weeks plus ribavirin 1000-1200 mg C: Peginterferon alfa-2a 180 µg/week plus ribavirin 1000-1200 mg x 48 weeks D: Peginterferon alfa-2a 180 µg/week plus ribavirin 1000-1200 mg x 72 weeks	Patients who lacked virologic resonse after >12 weeks treatment with peginterferon alfa-2b plus ribavirin	Results for SVR (72 weeks) not yet available. Reports week 12 VR only: 62% for groups A and B vs 45% for groups B and C; p<0.0001	Not reported
Shiffman, 2006	1469	Treatment duration: 16 vs 24 weeks	A: Peginterferon alfa-2a 180 µg/week plus ribavirin 800 mg x 16 weeks B: Peginterferon alfa-2a 180 µg/week plus ribavirin 800 mg x 24 weeks	Genotype 2 or 3 Treatment naïve	A vs B: All patients: 483/732 (66%) vs 541/731 (74%); p<0.005 Genotype 2: 70% vs 86%; p<0.005 Genotype 3: 70% vs 76% (NS)	Not reported