Oregon Health Resources Commission

Pegylated Interferons for Chronic Hepatitis C Infection

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Health Resources Commission

The State of Oregon's Health Resources Commission is a volunteer commission appointed by the Governor. The Health Resources Commission provides a public forum for discussion and development of consensus regarding significant emerging issues related to medical technology. Created by statute in 1991, it consists of four physicians experienced in health research and the evaluation of medical technologies and clinical outcomes; one representative of hospitals; one insurance industry representative; one business representative; one representative of labor organizations; one consumer representative; two pharmacists. All Health Resources Commissioners are selected with conflict of interest guidelines in mind. Any minor conflict of interest is disclosed.

The Commission is charged with conducting medical assessment of selected technologies, including prescription drugs. The commission may use advisory committees or subcommittees, the members to be appointed by the chairperson of the commission subject to approval by a majority of the commission. The appointees have the appropriate expertise to develop a medical technology assessment. Subcommittee meetings and deliberations are public, where public testimony is encouraged. Subcommittee recommendations are presented to the Health Resources Commission in a public forum. The Commission gives strong consideration to the recommendations of the advisory subcommittee meetings and public testimony in developing its final reports.

Overview

The 2001 session of the Oregon Legislature passed Senate Bill 819, authorizing the creation of a Practitioner-managed Prescription Drug Plan (PMPDP). The statute specifically directs the Health Resources Commission (HRC) to advise the Oregon Medical Assistance (OMAP) Department of Human Services (DHS) on this Plan.

In the summer of 2007 the Oregon Health Resources Commission (HRC) appointed a subcommittee to perform an evidence-based review of the use of Pegylated Interferons for the treatment of Hepatitis C. Members of the subcommittee consisted of physicians, a pharmacist, and the director of a Hepatitis C advocacy program. The subcommittee had

XXX meetings. All meetings were held in public with appropriate notice provided. The HRC director worked with the Center for Evidence-based Policy (Center) and the Oregon Health and Science University's (OHSU) Evidence-based Practice Center (EPC) to develop and finalize key questions for this drug class review, specifying patient populations, medications to be studied and outcome measures for analysis, considering both effectiveness and safety. Evidence was specifically sought for subgroups of patients based on race, ethnicity and age, demographics, other medications and co-morbidities. Using standardized methods, the EPC reviewed systematic databases, the medical literature and dossiers submitted by pharmaceutical manufacturers. Inclusion and exclusion criteria were applied to titles and abstracts, and each study was assessed for quality according to predetermined criteria.
The EPC's report, "Drug Class Review on Pegylated Interferons for Chronic Hepatitis C Infection" was completed in May 2007, circulated to subcommittee members and posted on the web. The subcommittee met to review the document and this report is the consensus result of those meetings. Time was allotted for public comment, questions and testimony.
This report does not recite or characterize all the evidence that was discussed by the OHSU EPC, the Subcommittee or the HRC. This report is not a substitute for any of the information provided during the subcommittee process, and readers are encouraged to review the source materials. This report is prepared to facilitate the HRC in providing recommendations to the Department of Human Services. The HRC, working together with the EPC, the Center for Evidence Based Policy, DMAP, and the Oregon State University College of Pharmacy, will monitor medical evidence for new developments in this drug class. Approximately once per year new pharmaceuticals will be reviewed and if appropriate, a recommendation for inclusion in the PMPDP will be made. For pharmaceuticals on the plan, significant new evidence will be assessed and Food and Drug Administration changes in indications and safety recommendations will be evaluated. The Pegylated Interferon report will be updated if indicated. Substantive changes will be brought to the attention of the Health Resources Commission, who may choose to approve the report, or reconvene a subcommittee.

The full OHSU Evidence-based Practice Center's draft report, *Drug Class Review on Pegylated Interferons for Chronic Hepatitis C Infection* is available via the Office for Oregon Health Policy & Research, Practitioner-Managed Prescription Drug Plan website: www.oregon.gov/DAS/OHPPR/ORRX/HRC/evidence_based_reports.shtml
Information regarding the Oregon Health Resources Commission and its subcommittee policy and process can be found on the Office for Oregon Health Policy & Research website: http://www.oregon.gov/DAS/OHPPR/HRC/index.shtml
You may request more information including copies of the draft report, and minutes of subcommittee meetings, from:
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Information dossiers submitted by pharmaceutical manufacturers are available upon request from the OHSU Center for Evidence-based Policy by contacting:
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There will be a charge for copying and handling in providing documents from both the Office of Oregon Health Policy & Research and the Center for Evidence Based Policy.

Critical Policy

Senate Bill 819

– "The Department of Human Services shall adopt a Practitioner-managed Prescription Drug Plan for the Oregon Health Plan. The purpose of the plan is to ensure that enrollees of the Oregon Health Plan receive the most effective prescription drug available at the best possible price."

Health Resources Commission

– "Clinical outcomes are the most important indicators of comparative effectiveness"
– "If evidence is insufficient to answer a question, neither a positive nor a negative association can be assumed."

Clinical Overview

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.

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

Therapeutic interventions for Hepatitis C with recombinant type I interferon as monotherapy began in the 1980's, it was found that the addition of ribavirin (a synthetic nucleoside analogue) to that regimen was more effective (Table 1), however the rate of sustained virologic response (SVR) was still below 50%.[4,5,6]

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[7]
Interferon monotherapy	6-16	7-25	Chander, 2002[4] Kjaegard, 2000[5] Poynard et al., 1996[7] Shepherd et al., 2000[6]
Interferon plus ribavirin	33-41	2.6-3.2	Chander, 2002[4] Kjaegard, 2000[5] Poynard et al., 1996[7] Shepherd et al., 2000[6]
Pegylated interferon monotherapy	23-39	2.7-4.8	Chander, 2002[4] Zaman et al., 2003[8]
Pegylated interferon plus ribavirin	54-61	1.7-1.9	Shepherd et al., 2005[9] Siebert et al., 2005[10] Zaman et al., 2003[8]

Definition of Pegylated Interferons

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. 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). 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[11, 12]

Generic Name, Trade Name	How supplied	Pharmacokinetics	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 mm3*: reduce to 135 µg *Platelet <50,000 mm3*: 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; *Hgb <8.5 g/dl*: discontinue; *WBC <1.5 x 10⁹/L*: reduce dose by 50%; <1.0 x 10⁹/L: discontinue; *Neutrophil* <0.75 x 10⁹/L: reduce by 50%; <0.05 x 10⁹/L: discontinue; *Platelets* <80 x 10⁹/L: reduce by 50%; <50 x 10⁹/L: discontinue

Quality of the Evidence

For quality of evidence the EPC and subcommittee took into account the number of studies, the total number of patients in each study, the length of the study period and the endpoints of the studies. Statistical significance was an important consideration. The subcommittee utilized the EPC's ratings of "good, fair or poor" for grading the body of evidence. Overall quality ratings for an individual study were based on the internal and external validity of the trial.

Internal validity of each trial was based on:

1) Methods used for randomization
2) Allocation concealment and blinding
3) Similarity of compared groups at baseline and maintenance of comparable groups
4) Adequate reporting of dropouts, attrition, and crossover
5) Loss to follow-up
6) Use of intention-to-treat analysis

External validity of trials was assessed based on:
1) Adequate description of the study population
2) Similarity of patients to other populations to whom the intervention would be applied
3) Control group receiving comparable treatment
4) Funding source that might affect publication bias.

Weighing the Evidence

A particular randomized trial might receive two different ratings: one for efficacy and another for adverse events. The overall strength of evidence for a particular key question reflects the quality, consistency, and power of the body of evidence relevant to that question.
The subcommittee's task was to evaluate the pegylated interferons with respect to benefits and harms for treatment of Hepatitis C infection.

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. 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.[2,13] 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.
The following key questions (approved by the organizations governing DERP) were used to guide this review:

Key Questions

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)?

Inclusion Criteria

Populations

• Non-pregnant adult outpatients with chronic Hepatitis C infection

Subgroups include:

- HIV-infected persons
- Nonresponders or relapsers (including retreatment)
- 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

• Peginterferon alfa-2a plus ribavirin
• Peginterferon alfa-2b plus ribavirin

Effectiveness outcomes

• Sustained virologic response (SVR)
• Normalization of liver enzyme abnormalities
• Inflammation or fibrosis on liver biopsy
• Cirrhosis
• Hepatocellular carcinoma
• Need for liver transplant
• Quality of life
• Mortality

Safety outcomes

• Overall adverse effect reports
• Withdrawals due to adverse effects
• Serious adverse events (including depression, suicidality)
• Specific adverse events (including myalgias, flu-like symptoms, fevers, chills, neutropenia)

Study designs

• For effectiveness in general, controlled clinical trials and good-quality systematic reviews
• For effectiveness for cirrhosis, hepatocellular cancer, need for transplant, and mortality, in addition to controlled clinical trials also *long-term* observational studies
• For safety, in addition to controlled clinical trials, observational studies

For the purposes of this evaluation we define 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. SVR is the best short-term predictor of long-term virologic remission rates and is associated with improvements in fibrosis and inflammation.[14] 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 histological response has been defined as a 2-point or greater decrease in the inflammatory score or fibrosis score, or a 1-point decrease in the fibrosis score. 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, hematological adverse events, flu-like symptoms, and depression) associated with dual therapy with pegylated interferon.

Summary of Results

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?

Head-to-head trials

Two head-to-head trials compared dual therapy with pegylated interferon alfa-2a versus pegylated interferon alfa-2b.[15, 16] 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 (Table3). 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.[15] 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).[16] In both trials, end-of-treatment virologic response was defined as >=2.0 $\log_{10}$ decrease in HCV load.

Table 3. 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 [15] (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 [16] (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

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. This trial is sponsored by the manufacturer of pegylated interferon alfa-2b.

Indirect Evidence

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. A total of 16 trials (Table 4) compared dual therapy of pegylated interferons with ribavirin to dual therapy with non-pegylated interferon with ribavirin. Five trials compared dual therapy with pegylated interferon alfa-2a plus ribavirin versus dual therapy with non-pegylated interferon alfa-2a plus ribavirin, 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. Three of these trials were rated poor quality, one was rated good quality, and the remaining studies were rated fair quality. Sample sizes ranged from 21 to 1530 patients. No trial was designed to evaluate rates of

cirrhosis, decompensated cirrhosis, hepatocellular carcinoma, or liver transplant. Only one trial reported effects on quality of life.

Table 4. 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[17] (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[18] (FAIR)	A: peginterferon alfa-2a 180µg / 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[19] (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[20] (GOOD)	A: peginterferon alfa-2a 180 µg/week B: peginterferon alfa-2a 180 µg/week (with no ribavirin) C: interferon alfa-2a 3 million units 3x/week	800 mg	HIV co-infected 60.7% genotype 1 Treatment naive
Peginterferon alfa-2a vs. interferon alfa-2b			
Fried, 2002[21] (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[22] (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[23] (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[24] (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[25] (FAIR)	A: peginterferon alfa-2b 1.5 µg /kg/week B: interferon alfa-2b 3	800 mg	48.0% genotype 1 HIV co-infected Treatment naïve

	million units 3x/week		
Derbala, 2005[26] (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[27] (POOR)	A: peginterferon alfa-2b 100 µg/week for 48 weeks A: peginterferon alfa-2b 100 mµg/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[28] (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[29] (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[30] (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 µg/kg/week C: interferon alfa-2b 3MU 3x/week	A: 1000-1200 mg B: 800 mg C. 1000-1200 mg	68.0% genotype 1 Treatment naive
Poizot-Martin, 2003[31] (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[32] (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[33][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

An adjusted indirect analysis performed (by the EPC) 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 including all trials showed no significant difference (RR 1.67, 95% CI 0.56 to 5.04) The results of the indirect analysis should be interpreted with caution as 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). The wide confidence intervals are attributed

to the small data set and the decreased precision in indirect vs. direct analysis. 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, an indirect analysis using only trials that compared dual therapy with pegylated interferon to dual therapy with non-pegylated interferon alfa-2b was also done (EPC). This analysis found no difference in the point estimate of relative efficacy (RR 1.00, 95% CI 0.47 to 2.11).
Seven trials reported rates of SBR, however, there were too few trials reporting SBR to perform indirect meta-analysis.

Observational studies of long-term clinical outcomes
No observational studies evaluating long-term clinical outcomes such as cirrhosis, hepatocellular cancer, need for liver transplant, or mortality were identified.

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

Dosing Studies

Dose of Pegylated Interferon
There were eight dose ranging studies, all evaluating pegylated interferon alfa-2b. 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).[30] 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[34], 1.0 µg/kg/week versus 1.5 µg/kg/week[35], or 0.75 µg/kg/week versus 1.5 µg/kg/week of pegylated interferon alfa-2b[36], each in combination with ribavirin 800 mg/day. The latter trial evaluated patients with severe fibrosis (METAVIR fibrosis stage F3 or F4) and the other two trials evaluated patients with less severe biopsy findings. 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- b, though trends favored the higher-dose regimen in each trial. Each of these three trials evaluated a different dose comparison.
Two unpublished trials comparing efficacy of different doses of pegylated interferon alfa-2a as part of combination therapy were evaluated by the EPC. 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).[37] 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.[38] In addition, this trial evaluated effects of different durations of therapy, however final results are not yet available.

Duration of Treatment

Nine trials evaluating effects of duration of dual therapy with pegylated interferon plus ribavirin on SVR rates were found. 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).[39] 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.[40]

Five other trials (all rated fair-quality) also evaluated effect of treatment duration, but limited enrollment to patients with specific HCV genotypes.

In patients with HCV genotype 1 infection, two trials[41, 42] found 48 weeks of dual therapy with pegylated interferon alfa- 2a or alfa-2b superior to 24 weeks for achieving an SVR (80% vs. 49%, p<0.05 [alfa-2b] and 48% vs. 28%, p=0.0175[alfa-2a]). In a third trial[43] there was no difference between 48 and 72 weeks of therapy, however those who were labeled as "slow responders", which was defined as HCV positive at 12 weeks but negative at 24 weeks, had a better SVR with 72 weeks of treatment vs. 48 weeks (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.[44]

Two trials in patients with HCV genotype 4 reached conflicting results.

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.[45] 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.[46] 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.[47] 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).[48] 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).[49] 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.[39, 50] 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 (800mg) 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).[39] 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.[50] 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%).

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).[51] 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.[49] The same study found no differences in SVR rates in patients with non genotype 1 HCV.

There appeared to be no effect of duration of therapy or dose on withdrawal due to adverse events.

Key Question 1 Consensus:

KQ 1:

KQ 1a:

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?**

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[21] and 14% vs. 13% in one trial of pegylated interferon alfa-2b[30]).[8]

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.[15]

Indirect Evidence

Active controlled trials were again evaluated. 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) 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). Other adverse events were less consistently reported.

Uncontrolled Studies

Forty uncontrolled or observational studies provided information about adverse events associated with dual therapy with pegylated interferon. Rates of withdrawals due to adverse events reported in uncontrolled studies were 0%-10% (median 5.7%) for Pegylated interferon alfa-2a and 0%-47% (median 6%) for Pegylated interferon alfa-2b. 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 2 consensus:

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)?**

Race Gender or Age

There were no studies found evaluating whether comparative effectiveness and safety of dual therapy with pegylated interferon alfa-2a vs. dual therapy with pegylated interferon alfa-2b varies according to race gender or age.

HCV Genotype

There was one small (N=36) head-to-head trial in patients with HCV genotype 1 comparing dual therapy pegylated interferon alfa-2a vs. dual therapy with pegylated interferon alfa-2b.[15] Due to it's small size and short follow-up and non standard dosing (4 weeks of monotherapy followed by 4 weeks of dual therapy) is of very limited value. The IDEAL study (N=2,880) does directly compare the two pegylated interferons in genotype 1 infection however results are not yet available.[52]

Pooled data also provide insufficient evidence to distinguish differences between the two pegylated interferons in Genotype 1, 2 or 3 infections. One systematic review concluded, using indirect evidence that pegylated interferon alfa-2a was superior to pegylated interferon alfa-2b for genotype 4 infection[53], however the Pegylated alfa-2b trials all utilized lower non-weight based ribavirin dosing. When the data was re-analyzed by the

EPC using data from two additional trials, there was no significant difference and there were wide confidence intervals.

Baseline Viral Load and Histologic Findings

No trials were found evaluating comparative effectiveness or safety of dual therapy with pegylated interferon alfa-2a vs. 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.

Obesity
Subgroup analysis found dual therapy with pegylated interferon alfa-2a and dual therapy with pegylated interferon alfa-2b less effective in patients weighing over 75 to 80kg vs. those weighing below 75-80kg. Theoretically in obese patients there would be a potential advantage in obese patients as it is normally dosed by weight (compared to uniform dosing for pegylated interferon alfa-2a), 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 vs. standardized dosing is more effective in such patients.

HIV co-infection
HCV infection is present in approximately 30% of HIV-infected persons. The EPC 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 (EPC) 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.

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, patients on hemodialysis, patients with mixed cryoglobulinemia, and patients on methadone maintenance. 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.

Key Question 3 Consensus:

Conclusions

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