Systematic review: peginterferon vs. standard interferon in the treatment of chronic hepatitis C
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CRD summary
This fairly well-conducted review concluded that peginterferon-based treatments for patients with chronic hepatitis C were superior to standard interferon treatments. The conclusions may not have been definitive because the treatments used in the included studies varied and non-Caucasian patients were not well represented. Some relevant studies may also have been missed.

Authors' objectives
To compare the treatment efficacy of standard interferon (with and without ribavirin) and peginterferon (with and without ribavirin) in patients with chronic hepatitis C.

Searching
MEDLINE (from 1989 to 2003) and PubMed were searched; the search terms were reported. The reference lists of all relevant articles were checked, and experts were contacted for additional studies. Only studies reported in the English language were included.

Study selection
Study designs of evaluations included in the review
Randomised controlled trials were eligible for inclusion.

Specific interventions included in the review
Studies comparing at least two different interferon formulations were eligible for inclusion in the review. Studies of monotherapy (peginterferon alpha-2a and b; pegylated interferon and standard interferon alpha-2a and b) and combination therapy (peginterferon plus ribavirin and standard interferon plus ribavirin), incorporating a range of doses, were included.

Participants included in the review
The inclusion criteria were not explicit. The majority of the included participants were Caucasian men. The mean age range was 40 to 47 years. The included studies looked at patients who had not been treated with interferon before, who had detectable serum antibody to hepatitis C virus (HCV) and HCV RNA, and who had persistently elevated alanine aminotransferase levels. Excluded patients were those with hepatocellular carcinoma, other liver disease, major psychiatric illness and some restrictive haematological exclusion parameters.

Outcomes assessed in the review
Studies that evaluated sustained virological response (SVR) as the primary end point were eligible for inclusion in the review. SVR was defined as an undetectable level of serum HCV RNA 24 weeks following the end of therapy. In addition, the review looked at histological or inflammatory scores (Knodell scoring system) and discontinuation rates due to treatment side-effects.

How were decisions on the relevance of primary studies made?
Two authors independently selected studies.

Assessment of study quality
The authors used the Jadad scale to assess the validity of the primary studies, based on the reporting of randomisation, blinding and loss to follow-up. Only studies with a quality score of 3 or more out of 5 were included in the analysis. The
studies were quality assessed. Any differences were adjudicated by consensus involving agreement of two authors.

**Data extraction**
Data extraction was carried out using a pre-designed form and consensus involving two authors. Data for the calculation of the percentage SVR in each treatment group were extracted.

**Methods of synthesis**
How were the studies combined?
The studies were combined in narrative according to several focused clinical questions. The questions related to SVR in patients with chronic hepatitis C.

Is peginterferon monotherapy more effective than standard interferon monotherapy or standard interferon plus ribavirin?

Is peginterferon plus ribavirin more effective than standard interferon plus ribavirin or pegylated interferon monotherapy?

Does weight-based dosing of peginterferon or ribavirin influence the SVR?

Does treatment with a peginterferon result in less discontinuation due to side-effects than treatment with standard interferon?

Each question was approached using a published level of evidence hierarchy to arrive at a graded recommendation: grade A (treatment is reliably superior) or grade B.

How were differences between studies investigated?
Differences between the studies were presented in tabular format, followed by a narrative summary according to each of the focused clinical questions addressed.

**Results of the review**
Seven studies met the inclusion criteria for the review, but only five of these met the quality criteria for inclusion in the analysis. A total of 4,672 participants were included in the studies.

The results are summarised below according to the predefined questions (see How Were the Studies Combined).

Is peginterferon monotherapy more effective than standard interferon monotherapy or standard interferon plus ribavirin?

The results from 3 studies showed that peginterferon was superior to interferon monotherapy in those patients who were new to treatment (grade A evidence), although these were derived from studies with variations in dosing schedules, drug formulations and patient inclusion criteria. The SVR rates were significantly higher (P<0.001) at 25% and 23% with peginterferon alpha-2b (1.0 and 1.5 microg/kg weekly, respectively) compared with 12% for standard interferon alpha-2b (3 MU, 3 times weekly). The rates were also higher (P<0.05) when peginterferon alpha-2a was given: 39% with peginterferon alpha-2a (180 microg weekly) versus 19% with standard interferon alpha-2a (6 MU 3 times weekly for 12 weeks followed by 3 MU for 36 weeks). The SVR rates were also significantly higher (no significance level stated) at 15% and 30% with peginterferon alpha-2a (90 microg and 180 microg weekly, respectively), compared with 8% for standard interferon alpha-2a (3 MU, 3 times weekly).

Standard interferon plus ribavirin was superior to peginterferon monotherapy in patients who were new to treatment (grade B evidence). The results from a single study found that standard interferon alpha-2b (3 MU, 3 times weekly) plus ribavirin (1,000 to 1,200 mg/day) produced a significantly higher SVR than peginterferon alpha-2a (180 microg weekly): 44% versus 29% (P<0.001).
Is peginterferon plus ribavirin more effective than standard interferon plus ribavirin or pegylated interferon monotherapy?

Peginterferon plus ribavirin was found to be superior to interferon plus ribavirin in patients new to treatment, and who were genotype 1 or had low HCV RNA levels (grade A evidence). The results were derived from 2 studies with variations in dosing schedules, drug formulations and patient inclusion criteria. The SVR rates with peginterferon alpha-2b (1.5 microg/kg weekly) plus ribavirin (800 mg/day) were significantly higher than those with standard interferon alpha-2b (3 MU, 3 times weekly) plus ribavirin (1,000 to 1,200 mg/day): 54% versus 47% (P<0.01). Peginterferon plus ribavirin was also superior to interferon plus ribavirin in patients with genotypes 1, 2 or 3 with high HCV RNA levels (grade B evidence). The SVR rates with peginterferon alpha-2a (180 microg weekly) plus ribavirin (1,000 to 1,200 mg/day) were significantly higher than those for patients receiving standard interferon alpha-2b (3 MU, 3 times weekly) plus ribavirin (1,000 to 1,200 mg/day): 56% and 44%, respectively (P<0.001).

A further study found that the SVR of 56% obtained with peginterferon alpha-2a (180 microg weekly) plus ribavirin (1,000 to 1,200 mg/day) was significantly higher (P<0.001) than the SVR of 29% found in those receiving peginterferon only (180 microg weekly).

Does weight-based dosing of peginterferon or ribavirin influence the SVR?

The results from 4 small studies suggested that higher doses of peginterferon (1.5 microg/kg weekly of alpha-2b and 180 microg weekly for alpha-2a at a fixed dose) and higher doses of ribavirin (greater than 10.6 mg/kg daily) (one study) produced better SVRs, but the results for ribavirin were based on a post hoc analysis and potential bias was acknowledged.

Does treatment with a peginterferon result in less discontinuation due to side-effects than treatment with standard interferon?

In all 5 studies, peginterferon (with or without ribavirin) had a similar tolerability profile and treatment withdrawal rate (range: 7 to 23%) to standard interferon (with or without ribavirin) (range: 6 to 27%), although the studies might have been underpowered to detect these outcomes.

The review failed to determine which peginterferon formulation was superior to standard interferon, owing to inherent differences between the trials. The validity assessment of the 5 included studies revealed that 3 studies had a Jadad score of 3 while 2 studies had a score of 4.

Authors' conclusions

Peginterferon-based therapies were superior to standard interferon-based therapies in patients with chronic hepatitis C, even in patients with advanced fibrosis. Peginterferon monotherapy was not, however, superior to any of the combination treatments.

CRD commentary

The questions and inclusion criteria were clearly stated for this review, with the exception of inclusion criteria for the participants. The fact that the included participants were largely Caucasian middle-aged men potentially limited the generalisability of the findings, and this was acknowledged by the authors' research recommendations. The searching of only one electronic database and the restriction to articles published in English meant that relevant studies might have been missed. Although disagreements in the review process were reported to have been resolved by consensus, it was unclear to what extent the data extraction and validity assessment were performed independently. The use of a published validity assessment tool and predefined quality threshold to exclude less reliable evidence added strength to the review (although there were debates about the usefulness of the particular assessment tool used). More detail on the consistency with which the definition of undetectable serum antibody to HCV was applied across the studies would have been useful. Given that the results of monotherapy and combination treatments were taken from a small number of trials with substantial heterogeneity, and because of the potential for publication and language bias, it is possible that the authors' conclusions were overstated.
Implications of the review for practice and research
Practice: The authors stated that peginterferon monotherapy should only be given to patients in whom ribavirin is contraindicated. It is not possible to distinguish the relative efficacy of different peginterferon formulations.

Research: The authors stated that more research is needed on different population subgroups. Such subgroups include African-American patients; hepatitis C patients with advanced fibrosis; those with co-infection with human immunodeficiency virus; patients with obesity; those with chronic HCV infection and constantly normal alanine aminotransferase levels; and patients with relapse or non-response to previous interferon-based treatment. The authors called for the measurement of longer term outcomes (such as morbidity and mortality) achieved by the extended follow-up of patients.

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