Pegylated interferon alpha-2a and -2b in combination with ribavirin in the treatment of chronic hepatitis C: a systematic review and economic evaluation

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CRD summary
This review assessed the effectiveness of pegylated interferon-alpha for treating chronic hepatitis C. Six good-quality studies found that the treatment was more effective than non-pegylated interferon-alpha, when given alone or with ribavirin. The review was well-conducted and the findings are likely to be reliable.

Authors' objectives
To assess the clinical- and cost-effectiveness of pegylated interferon (IFN)-alpha combined with ribavirin in the treatment of chronic hepatitis C.

Searching
The following electronic databases were searched from March 2000 to March 2003 for English language articles: MEDLINE, PubMed, EMBASE, the Cochrane Database of Systematic Reviews, the Cochrane Controlled Trials Register, BIOSIS Previews, Web of Science Proceedings, the Science Citation Index, DARE, HTA, NHS EED and the National Research Register. The search terms were reported. Pre-2000 studies were covered in a related review (see Other Publications of Related Interest). Internet sites were also searched and contact was made with experts in the field. Submissions made by drug companies to the National Centre for Clinical Excellence were also searched for relevant studies.

Study selection
Study designs of evaluations included in the review
Randomised controlled trials (RCTs) and systematic reviews of RCTs were eligible for inclusion in the review.

Specific interventions included in the review
Studies of pegylated IFN-alpha plus ribavirin compared with non-pegylated IFN-alpha plus ribavirin were eligible for inclusion in the review, as were studies of pegylated IFN-alpha compared with non-pegylated IFN-alpha.

Participants included in the review
Studies of people with moderate to severe chronic hepatitis C infection not previously treated with IFN-alpha were eligible for inclusion; patients with acute hepatitis C were not included in the report. The mean age of the participants in the included studies ranged from 40 to 47 years, and 63 to 79% were male.

Outcomes assessed in the review
Studies that reported the sustained viral response (as shown by the absence of viral RNA for at least 6 months after the end of treatment) and the adverse effects of treatment were eligible for inclusion.

How were decisions on the relevance of primary studies made?
Studies were selected for inclusion using a standardised inclusion form, with any uncertainties resolved by discussion. The authors did not state how many reviewers performed the selection.

Assessment of study quality
The studies were critically appraised using the following criteria: method of randomisation; concealment of treatment allocation; baseline comparability; specified eligibility criteria; outcomes reported; intention-to-treat analysis; and description of withdrawals and drop-outs. One reviewer assessed validity, while a second reviewer checked the assessment. Any disagreements were resolved through discussion.
Data extraction
One reviewer extracted the data into a standardised template, while a second reviewer checked the extraction. Any disagreements were resolved through discussion. Confidence Interval Analysis software was used to compute confidence intervals (CIs) where these were not provided by the study authors.

Methods of synthesis
How were the studies combined?
The trial results were summarised narratively. Meta-analyses were performed separately for combination therapy and monotherapy using a random-effects model.

How were differences between studies investigated?
The chi-squared test and the I-squared value were used to characterise between-study heterogeneity in the meta-analyses. Separate analyses were performed according to baseline viral load and genotype.

Results of the review
Two RCTs (n=2,651) investigated combination therapy and four RCTs (n=2,180) investigated monotherapy.

The trials were generally of a good quality, although their methodological details were not always thoroughly reported.

Combination therapy (2 RCTs).
The combined percentage of sustained virological response was 55% (95% CI: 52, 58) using pegylated IFN and 46% (95% CI: 43, 49) using non-pegylated IFN. The relative risk (RR) for remaining infected was reduced for pegylated in comparison with non-pegylated IFN (RR 0.83, 95% CI: 0.76, 0.91). There was no evidence of statistical heterogeneity (P=0.29; I-squared 12%).

Monotherapy (4 RCTs).
The combined percentage of sustained virological response was 31% (95% CI: 27, 34) for pegylated IFN and 14% (95% CI: 12, 17) for non-pegylated IFN. The RR for remaining infected was reduced for pegylated in comparison with non-pegylated IFN (RR 0.80, 95% CI: 0.76, 0.85). There was evidence of statistical heterogeneity (P=0.03; I-squared 66.6%).

For both combination and monotherapy, treatment response varied according to viral genotype and other prognostic variables, including baseline viral load. Adverse events with pegylated IFN were not substantially different from the rates of adverse events observed with non-pegylated IFN.

Cost information
A cost-effectiveness analysis was carried out. The incremental discounted cost per quality-adjusted life-year (QALY) for comparing 48 weeks of non-pegylated IFN plus ribavirin with 48 weeks of pegylated IFN plus ribavirin was £12,123. The incremental discounted cost per QALY when moving from 48 weeks of monotherapy with non-pegylated IFN to 48 weeks of monotherapy with pegylated IFN was £8,404.

Authors’ conclusions
Well-designed RCTs showed that patients treated with pegylated IFN, whether dual or monotherapy, had higher sustained viral response rates than patients treated with non-pegylated IFN.

CRD commentary
This review addressed a focused question with clearly specified inclusion criteria for primary studies. A comprehensive literature search was undertaken. However, since only English language literature was included, it was possible that some relevant studies might have been missed. The validity of the included studies was assessed using standard criteria, and steps were taken in the data extraction and validity assessment processes to reduce the possibility
of reviewer bias. It was unclear how many reviewers selected studies for inclusion in the review, making it possible that reviewer bias might have occurred at this stage. The specific nature of the review question meant that pooling data in a meta-analysis was appropriate. Heterogeneity was present in some of the pooled outcomes and did not seem to have been investigated. The authors' conclusions seem to follow from the evidence presented in the review.

**Implications of the review for practice and research**

Practice. The authors did not state any implications for practice.

Research: The authors stated that further trials are needed to compare pegylated IFN-alpha-2a and pegylated IFN-alpha-2b; to assess the re-treatment of nonresponders with pegylated IFN; to assess the treatment of patients with other co-morbidities with pegylated IFN; to assess other treatment combinations; to assess which treatment regimens achieved the best improvements in liver histology; and to test treatment stopping rules. Further research is also needed on: the treatment of acute infection; the appropriate treatment of patients with long-term complications such as vasculitis; the evaluation of additional psychological effects on quality of life; and the treatment of children and adolescents with hepatitis C.

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