Pegylated interferons for chronic hepatitis C virus infection: an indirect analysis of randomized trials
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CRD summary
The authors concluded that there was insufficient evidence to conclude that one pegylated interferon (alfa 2a or 2b) was superior to another for the treatment of chronic hepatitis C virus infection. There were limitations in the search and reporting of review methods, but overall the authors’ conclusions reflected the evidence and are likely to be reliable.

Authors’ objectives
To use indirect analysis to compare dual therapy with pegylated interferon alfa-2a versus dual therapy with pegylated interferon alfa-2b for chronic hepatitis C virus (HCV) infections.

Searching
MEDLINE, Cochrane Central Register of Controlled Trials, the Cochrane Database of Systematic Reviews and DARE were searched for studies published between 1980 and 2005. Search terms were reported. In addition, reference lists and selected dossiers from pharmaceutical companies were screened. Only studies that had been published in full in peer-reviewed journals were eligible.

Study selection
Randomised controlled trials (RCTs) that compared dual therapy with pegylated interferon alfa-2a or alfa-2b plus ribavirin versus each other or versus non-pegylated interferon plus ribavirin in non-pregnant adult outpatients with chronic hepatitis C virus infection were eligible for inclusion. Eligible subgroups of patients were listed.

Studies had to assess sustained virological response (SVR), improvement in inflammation or fibrosis on liver biopsy, overall adverse events, withdrawals due to adverse events or serious adverse events. The primary review outcome was sustained virological response defined as the absence of hepatitis C virus RNA in the serum six months after the end of treatment.

The included studies evaluated pegylated interferon alfa-2a (180μg weekly) and pegylated interferon alfa-2b (mostly 1.5μg/kg once weekly). Ribavirin dose ranged from 600mg to 1,200mg daily. Some studies used amantadine as a co-intervention. Most studies were in treatment naïve patients. Some studies were in human immunodeficiency virus (HIV) co-infected patients and some only included hepatitis C virus genotype 4 or genotype 1 patients. None of the studies were in patients with decompensated cirrhosis.

Two reviewers independently screened titles and abstracts. One reviewer selected studies from full publications. Inclusions and exclusions were checked by a second reviewer. Disagreements were resolved by consensus.

Assessment of study quality
Validity was assessed using randomisation, allocation concealment, blinding and use of intention-to-treat analysis.

The authors did not state how many reviewers assessed validity.

Data extraction
Where possible, data were extracted on an intention-to-treat basis.

The authors did not state how many reviewers performed the data extraction.

Methods of synthesis
Pooled relative risks (RR) and 95% confidence intervals (CIs) were calculated using the random-effects DerSimonian
and Laird model.

Direct meta-analysis was used to compare dual therapy with pegylated interferon alfa-2a versus non-pegylated interferon and dual therapy with pegylated interferon alfa-2b versus non-pegylated interferon. Heterogeneity was assessed using the Q and the $I^2$ statistics. L’Abbe plots were used to detect outliers and examine the influence on treatment effects of sustained virological response rates in the control group. Publication bias was assessed using funnel plots and Egger’s test. The influence of the following variables was explored: quality items; HIV status; hepatitis C virus genotype; dose of pegylated interferon and ribavirin; and amantadine co-therapy.

Adjusted indirect analysis methods described by Butcher et al were used to calculate indirect relative risks of dual therapy with pegylated interferon alfa-2a versus dual therapy with pegylated interferon alfa-2b. Analyses were adjusted by results of direct meta-analyses. Assumptions about the consistency of treatment effects across studies were tested (such as sustained virological response rates in control groups, HIV co-infected patients, hepatitis C virus genotype, study-quality items, ribavirin dose, pegylated interferon dose, use of amantadine and outliers). When funnel plots were asymmetrical, sensitivity analyses were performed, adjusted for potential publication bias using the trim-and-fill method.

**Results of the review**

Sixteen RCTs were included (n=5,080). Sample size ranged from 21 to 1,530. Eight studies reported adequate methods of randomisation, six described adequate allocation concealment, two reported blinding of outcome assessors and 14 reported intention-to-treat analysis.

**Direct meta-analyses:**

Dual therapy with pegylated interferon alfa-2a was associated with a statistically significant increase in sustained virological response compared to non-pegylated alfa-2a or -2b (RR 2.03, 95% CI 1.36 to 3.03; six studies). Heterogeneity was high ($I^2=86\%$). There was no statistically significant difference between non-pegylated alfa-2a regimes and pegylated interferon alfa-2a regimens (five studies, n=1,157) or alfa-2b regimens (one study, n=897).

Dual therapy with pegylated interferon alfa-2b was associated with a statistically significant increase in sustained virological response compared to non-pegylated alfa-2b (RR 1.28, 95% CI 1.11 to 1.48; 10 studies). Heterogeneity was moderate ($I^2=39\%$).

Withdrawal/treatment discontinuation rates ranged from 6% to 16% with pegylated interferon therapy. There were no statistically significant differences in rates of withdrawal or treatment discontinuation between non-pegylated interferon regimes and either pegylated alfa-2a regimens (five studies) or alfa-2b regimens (seven studies).

L’Abbe plots did not suggest any outliers or any influence on treatment effect of sustained virological response rates in the control group. Funnel plots and Egger’s test showed no evidence of publication bias for pegylated interferon alfa-2a, but there was evidence of publication bias for pegylated alfa-2b ($p$ for Egger’s test 0.018). There were no significant differences in sustained virological response rates when studies were stratified by quality items.

**Indirect meta-analysis:**

There were no significant differences among studies in sustained virological response rates for groups treated with non-pegylated interferon.

There was no significant difference in sustained virological response between pegylated interferon alfa-2a and pegylated alfa-2b regimens (RR 1.59, 95% CI 0.07 to 4.46). Confidence intervals were wide.

**Subgroup analysis:**

Results were similar when only studies that compared pegylated interferon with no pegylated alfa-2b were analysed and when studies were stratified by HIV status, hepatitis C virus genotype, higher doses of ribavirin, use of FDA-approved dose of pegylated interferon, amantadine co-therapy and using the trim-and-fill method to account for publication bias.
Using indirect meta-analyses, there were no significant differences between pegylated alfa-2a and alfa-2b in adverse events, anaemia, neutropenia, depression or flu-like symptoms.

Results for further subgroup analyses were reported.

Authors' conclusions
There was insufficient evidence to conclude that one pegylated interferon (alfa 2a or 2b) was superior to another for the treatment of chronic hepatitis C virus infection. Confidence intervals were wide and so significant treatment differences could not be ruled out. Further head-to-head trials were recommended.

CRD commentary
The review question was clearly stated and inclusion criteria were appropriately defined. Several relevant sources were searched, but no attempts were made to minimise publication and language biases. The potential for publication bias was assessed. Analyses adjusted to take account of potential publication bias did not change the review findings. Methods were used to minimise reviewer errors and bias in the selection of studies, but it was not clear whether similar steps were taken in the assessment of validity and extraction of data study selection. Only RCTs were included, validity was assessed and results were reported and taken into account in analyses. Appropriate methods were used for the indirect analyses and assumptions about the method tested. Heterogeneity was assessed and various predefined subgroup analyses conducted. Many aspects of the review were well-conducted and limitations were discussed. There were limitations in the search and reporting of review methods, but overall the authors' conclusions reflected the evidence and are likely to be reliable.

Implications of the review for practice and research
Practice: The authors did not state any implications for practice.

Research: The authors stated that there was a need for head-to-head studies to verify the findings of this indirect meta-analysis and directly compare dual therapy with pegylated interferon alfa-2a versus dual therapy with pegylated interferon alfa-2b for chronic hepatitis C virus infections. Research should include use of different ribavirin dosing regimens and use of pragmatic trials in community settings.

The authors stated that results of a large individualised dosing efficacy therapy versus flat dosing to assess optimal pegylated interferon regimens (IDEAL) study were expected in late 2008.

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