The comparative efficacy and safety of peginterferon alpha-2a vs 2b for the treatment of chronic HCV infection: a meta-analysis
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CRD summary
This well-conducted review concluded that peginterferon alpha-2a was more effective than peginterferon alpha-2b in patients with chronic hepatitis C virus infection; it had a higher rate of sustained virological response and neutropenia. The authors’ conclusions reflected the evidence, but the limited quality of the included trials may weaken the strength of this evidence.

Authors’ objectives
To compare the efficacy and safety of peginterferon alpha-2a versus peginterferon alpha-2b in patients with hepatitis C virus infection.

Searching
MEDLINE, SCOPUS, the Cochrane Central Register of Controlled Trials (CENTRAL), and Web of Science were searched for studies in any language. No time restrictions were applied but search dates were not reported. Search terms were reported. Conference proceedings were excluded.

Study selection
Randomised controlled trials (RCTs) in adults with chronic hepatitis C virus infection were eligible if they compared peginterferon alpha-2a (180µg per week plus 800 to 1400mg riboflavin per day) with peginterferon alpha-2b (1.5µg/kg per week plus 800 to 1400mg riboflavin per day). Chronic hepatitis C virus infection was defined as a detectable hepatitis C virus-RNA value plus a duration of at least six months of infection. Eligible treatment had to last for at least 24 weeks in patients with hepatitis C virus genotypes 2 or 3 and for at least 48 weeks for genotypes 1 or 4. Eligible patients could have been previously treated, had dose modification or could be receiving growth factors and antidepressants. Trials were excluded if the included patients had positive seromarkers for HIV or hepatitis B virus infection, had decompensated liver disease or significant comorbidities, or were not all accounted for at the termination of the trial.

The primary review outcomes were sustained virological response (defined as undetectable hepatitis C virus-RNA at six months follow-up after treatment cessation) and measures of safety (withdrawals and drop-outs). Secondary outcomes were rapid virological response (defined as undetectable or a reduction of more than 2Log_{10} HCV-RNA after four weeks of treatment), early virological response (defined as undetectable or a reduction of more than 2Log_{10} hepatitis C virus-RNA after 12 weeks of treatment), end of treatment response (defined as undetectable hepatitis C virus-RNA immediately post-treatment), dose modifications, and adverse events (including flu-like syndrome and laboratory abnormalities).

Most included trials were in treatment-naive patients; other trials included a mix of treatment-naive patients, patient who had relapsed and those not responding to previous treatment. The mean age of patients across treatment groups ranged from 46 to 53 years; the percentage of males ranged from 27 to 71% (where reported). Participants' viral load ranged from 604x10$^3$ to 3.1x10$^6$ IU/mL; those with hard-to-treat genotypes (1/4) ranged from 52 to 100% (where reported). The proportion of patients with cirrhosis ranged from 15 to 21% (where reported). Most trials were conducted in Italy or the USA.

Two reviewers independently selected studies. All authors agreed upon studies to be included.

Assessment of study quality
Validity was assessed using the method of randomisation, adequacy of allocation concealment and blinding.

Validity was independently assessed by two reviewers and rechecked by a third reviewer. Disagreements were resolved.
Data extraction
Outcome data were extracted on an intention-to-treat basis using a worst case scenario in which missing data were treated as non-response. Odds ratios (ORs) with 95% confidence intervals (CIs) were calculated.

Data were extracted by two reviewers independently and re-checked by a third reviewer.

Methods of synthesis
Pooled odds ratios and 95% confidence intervals were calculated using a random-effects model. Heterogeneity was assessed using $X^2$ and $I^2$. Subgroup analyses were used to explore the influence of different hepatitis C viral genotypes (genotype 1/4, genotype 2 and genotype 3).

Results of the review
Seven RCTs were included in the review (n=3,518 patients). Treatment group size ranged from 37 to 1,035 patients. Four trials reported adequate randomisation methods, five reported adequate allocation concealment and one reported double-blinding. The reviewers stated that trials had similar inclusion and exclusion criteria.

Sustained virological response: Peginterferon alpha-2a plus riboflavin was associated with a statistically significantly greater rate of sustained virological response than peginterferon alpha-2b plus riboflavin (OR 1.39, 95% CI 1.02 to 1.89). Substantial heterogeneity was found ($I^2=55\%$). Compared with peginterferon alpha-2b plus riboflavin, peginterferon alpha-2a plus riboflavin was also associated with a significantly increased rate of sustained virological response in treatment-naive patients with genotype 1/4 infection (OR 1.36, 95% CI 1.01 to 1.88; n=2,715 patients) and genotype 2 infection (OR 4.06, 95% CI 1.67 to 9.86; n=242 patients). There was no significant difference in the sustained virological response rate between treatments in patients with genotype 3 infection (n=102 patients).

Safety: There was no significant difference between treatments for treatment discontinuation due to laboratory abnormalities or severe clinical adverse events. Substantial heterogeneity was found ($I^2=64\%$).

Virological response: Compared with peginterferon alpha-2b plus riboflavin, peginterferon alpha-2a plus riboflavin was associated with a statistically significantly greater rate of early virological response (OR 1.38, 95% CI 1.11 to 1.71; $I^2=29\%$) and significantly greater end-of-treatment virological response rate (OR 1.67, 95% CI 1.25 to 2.24; $I^2=47\%$). There was no significant difference between the two treatments in the rate of rapid virological response ($I^2=41\%$).

Adverse events: Compared with peginterferon alpha-2b plus riboflavin, peginterferon alpha-2a plus riboflavin was associated with a statistically significantly greater rate neutropenia (OR 1.50, 95% CI 1.25 to 1.79; $I^2=0\%$). There was no significant difference between the two treatments in rates anaemia ($I^2=0\%$), thrombocytopenia ($I^2=0\%$), depression or severe psychiatric complications ($I^2=0\%$) or flu-like syndrome ($I^2=85\%$).

Authors' conclusions
Peginterferon alpha-2a was more effective than peginterferon alpha-2b in patients with chronic hepatitis C virus infection and had a similar safety profile. Peginterferon alpha 2a had higher rates of sustained virological response and neutropenia.

CRD commentary
The review question was clearly stated and inclusion criteria were appropriately defined. Several relevant sources were searched. Attempts were made to minimise language bias, but unpublished studies (such as conference proceedings) were excluded, which increased the potential for publication bias. Methods were used to minimise reviewer errors and bias throughout the review process.

Trial quality was assessed and results were reported in full; trials were described as being of ‘modest’ quality. Appropriate methods were generally used for the meta-analyses; heterogeneity was assessed and a subgroup analysis was conducted. Some potential reasons for the heterogeneity in some analyses were discussed.
Overall, the review was well-conducted. The authors’ conclusions reflected the evidence, but the limited quality of the included trials may weaken the strength of this evidence.

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

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