Meta-analysis of factors associated with sustained viral response in patients on hemodialysis treated with standard or pegylated interferon for hepatitis C infection

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CRD summary
This review concluded that the additional benefit of monotherapy with pegylated interferon on viral response and adverse events in patients on haemodialysis with hepatitis C virus infection remained unclear; younger age was the only determinant of sustained viral response. These conclusions reflected the review findings, but limitations in the search and review process mean they should be interpreted with caution.

Authors' objectives
To evaluate factors associated with sustained virological response to pegylated or standard interferon monotherapy in patients on haemodialysis with chronic hepatitis C virus infection.

Searching
PubMed, Scopus, the Cochrane Central Register of Controlled Trials and the Science Citation Index were searched for peer-reviewed medical articles published in English between 1995 and September 2009. It was not clear if other databases were also searched. Search terms were reported. References of retrieved articles were also scanned.

Study selection
Studies of treatment for hepatitis C virus infection that included only patients on haemodialysis or peritoneal dialysis were eligible for inclusion. Included studies had to include at least nine patients in the treatment arm and have minimum treatment duration of at least 24 weeks. Eligible studies were required to report the dose and duration of therapy and sustained viral response as an outcome. Studies also had to define negative hepatitis C virus ribonucleic acid (RNA) by polymerase chain reaction at least six months after the conclusion of treatment. Studies that included patients with organ transplantation or renal graft, or patients with acute hepatitis C virus infection were excluded from the review. Also excluded were studies that used ribavirin in addition to interferon therapy.

Patients in included studies had mean ages that ranged from 31 to 56 years; the percentage of men ranged from 44 to 78%. Included patients with genotype 1 hepatitis C virus infection ranged from 56% to 100% and their mean alanine transaminase levels ranged from 42U/mL to 80U/mL. The mean duration of haemodialysis ranged from two to 11 years. In the two randomised controlled trials, the comparisons were pegylated interferon-alpha 2a versus interferon-alpha 2a, and interferon-alpha 2a versus albumin placebo. Other controlled studies used control groups that received either no treatment or a different dose or duration of treatment.

The authors did not state how the studies were selected for the review.

Assessment of study quality
There was no formal assessment of validity, but randomisation methods and blinding were discussed for the RCTs. The number of reviewers involved in this appraisal was not reported.

Data extraction
One reviewer extracted and double checked the data on an intention-to-treat (ITT) basis, and consulted with another reviewer in cases of lack of clarity or the need to make assumptions. Individual patient data (IPD) were combined where summary data were not reported. Only deaths or treatment withdrawals due to adverse events were included in the drop-out rate. Odds ratios (OR) with 95% confidence intervals (CI) were calculated.

Methods of synthesis
Pooled odds ratios with 95% confidence intervals were calculated using DerSimonian and Laird random-effects model meta-analyses. Mantel-Haenszel model analyses were used to generate estimates of heterogeneity using $X^2$ and $I^2$ statistics. This model was also used for sensitivity analyses which omitted individual studies.
Continuous variables were dichotomised to permit the use of data from the maximum number of studies reporting that variable in the regression analysis. The relationship of the following variables to sustained viral response was assessed: gender; hepatitis C virus RNA copies/mL; hepatitis C virus genotype; alanine transaminase pattern; duration of infection; liver fibrosis stage; and treatment duration.

Publication bias was assessed using the Begg and Mazumdar test and the Egger test.

Results of the review
Thirty-three studies (n=770 patients) were included in the review. Twenty-one studies (n=491 patients) assessed interferon-alpha 2a or 2b, and 12 studies (n=279 patients) assessed pegylated interferon-alpha 2a or 2b. Two studies were RCTs, the rest were described as retrospective evaluations (two studies), clinical trials (19 studies) or controlled clinical trials (eight studies).

Overall, 266 patients (44.5%) attained a sustained viral response and 174 patients (22.7%) discontinued treatment due to adverse events.

The rate of sustained viral response in standard interferon groups was 39.1% (95% CI 32.1 to 46.1), while in pegylated interferon the response was 39.3% (95% CI 26.5 to 52.1). The rates of treatment discontinuation were 22.6% (95% CI 10.4 to 34.8) for standard interferon and 29.7% (95% CI 21.7 to 37.7) for pegylated interferon.

The only variable that was significantly associated with sustained viral response was an age less than 40 years (OR 2.17, 95% CI 1.03 to 4.50). Treatment duration (24 weeks versus 48 weeks) was not associated with a statistically significant difference in response.

There was no evidence of publication bias.

Authors' conclusions
The additional benefit of monotherapy with pegylated interferon on viral response and adverse events in patients on haemodialysis with hepatitis C virus infection remained unclear; younger age (under 40 years) was the only determinant of sustained viral response.

CRD commentary
The review question and inclusion criteria were clear and explicit. The authors searched several relevant databases, but the limitation of the review to published peer-reviewed studies reported in English may have led to the omission of relevant studies and the introduction of selection biases. The potential for publication bias was assessed in the review and no evidence for it was found. The authors reported attempting to correct for errors in the extraction of data, but did not report using methods designed to reduce reviewer bias and error at any other stage of the review process.

The assessment of study quality was restricted to the two RCTs; this did not amount to a formal appraisal. The synthesis of studies appeared appropriate.

The authors' conclusions reflected the results of the review. However, the limitations of the search and the review process mean that some caution should be used in their interpretation.

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

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