Interferon and ribavirin vs interferon alone in the re-treatment of chronic hepatitis C previously nonresponsive to interferon: a meta-analysis of randomized trials.


Authors' objectives
To assess the efficacy and safety of interferon (IFN) and ribavirin, versus IFN alone, for treatment of patients with chronic hepatitis C who previously did not respond to IFN monotherapy.

Searching
MEDLINE (from 1966 to December 1999) and the Science Citation Index were searched using the keywords 'hepatitis C AND interferon AND ribavirin' and the publication type 'clinical trial'. Additional studies were located by examining the references of selected articles, and by reviewing major journals on internal medicine, gastroenterology, hepatology and infectious diseases from January 1999 to August 1999. The authors also contacted clinical hepatology experts. No restrictions on publication language were reported.

Study selection
Study designs of evaluations included in the review
Randomised controlled trials (RCTs) with a study size ranging from 14 to 303 participants were included. None of the studies were placebo-controlled.

Specific interventions included in the review
IFN alfa-n/n3 or alfa-2a/2b monotherapy compared with the combination of ribavirin (600 to 800 mg/day or 1,000 to 1,200 mg/day) and IFN therapy.

Participants included in the review
Patients with clinically and histologically confirmed chronic hepatitis C who previously did not respond to IFN monotherapy.

Outcomes assessed in the review
Virological response, defined as the absence of hepatitis C virus RNA levels in serum, and biochemical response, defined as the normalisation of serum alanine aminotransferase concentration; both were measured at 24 weeks. Studies that did not report data for these end points at the end of a follow-up period were excluded.

How were decisions on the relevance of primary studies made?
Two investigators independently reviewed the trials for inclusion, and any disagreements were resolved by discussion.

Assessment of study quality
A quality evaluation questionnaire was used to score studies. The questionnaire contained sections on study population, bias and confounding, and description of therapy based on suggested RCT quality assessment questions. Questions regarding the outcomes reported, the follow-up time, and crossover were added for completeness. For each of the 17 questions, studies were assigned a score of 0 (inappropriate), 1 (fair) or 2 (appropriate). Two investigators independently performed the quality assessment, each of whom was blinded to the other's evaluation. Any disagreements were resolved by discussion.

Data extraction
Two investigators independently performed the data extraction, and any disagreements were resolved by discussion. Data were extracted for the categories of: study characteristics (location, year, blinding, dose and schedule), patient characteristics (percentage male, risk factors for hepatitis C and percentage with cirrhosis), and the total number of
responders at the end of follow-up for the virological and biochemical outcomes. The recorded histological outcomes were the total number of participants with pre-treatment and post-treatment biopsy specimens, the number of patients with post-treatment biopsy specimens showing improvement, and the modified Knodell histologic activity index score before and after treatment. Data on treatment groups other than those of interest were excluded. The authors also recorded the number of patients having their dose reduced, or withdrawing from the study, on account of adverse events. The number of symptoms reported for each group was recorded by symptom category whenever possible. When this data were unavailable, the authors of the original studies were contacted for additional information.

**Methods of synthesis**

**How were the studies combined?**

Pooled risk differences with 95% confidence intervals (CIs) were calculated for the biochemical and virological outcomes, and the discontinuation of treatment data, using fixed-effect and random-effects models. When the results of the models differed, the results of the random-effects model were reported.

The data regarding adverse effects for each treatment group were compared using Poisson regression. Funnel plots were used to investigate publication bias in small studies reporting negative results.

**How were differences between studies investigated?**

Heterogeneity was assessed using L'Abbe plots and Q-statistics.

Sensitivity analyses of study characteristics were performed to identify potential sources of heterogeneity. Stratified analyses were performed using the variables found to be statistically significant in the meta-regressions.

**Results of the review**

Twelve RCTs with 941 participants were included in the review.

Quality of studies: none of the studies were placebo-controlled. Quality scores ranged from 20 to 28 with a mean of 24.3 (95% CI: 22.8, 25.7).

Funnel plots revealed that most smaller studies found no significant difference between IFN monotherapy and combination therapy.

The pooled virological response rate for combination therapy was 14% (95% CI: 11, 17), with a risk difference of 7% (95% CI: 2, 13) in favour of combination therapy.

Use of IFN alfa-2a/2b and 1000 to 1200 mg/day ribavirin was associated with a pooled virological response rate of 18% and a risk difference of 16% (95% CI: 11, 21). The risk difference was 0% (95% CI: -7, +7) when IFN alfa-n/n3 and a lower dose of ribavirin (600 to 800 mg/day) were used.

Combination therapy was associated with more adverse effects (9 studies) with a risk difference of 4% (95% CI: 1, 7, p=0.01). The pooled withdrawal rate was 9% (95% CI: 7, 12) for combination therapy, compared with 4% (95% CI: 3, 7) for monotherapy. No treatment-related deaths were reported.

**Authors' conclusions**

The authors state that results suggest that combination therapy incorporating recombinant IFN and higher-dose ribavirin (1000 to 1200 mg/day), for at least 24 weeks, is more effective than IFN alone in the re-treatment of IFN nonresponders. However, the response rates remain low (less than 20%) regardless of IFN type or ribavirin dose. While combination therapy is tolerable in most cases, the fact that the vast majority will not benefit highlights the urgent and ongoing need for more effective therapies for the treatment of chronic hepatitis C.

**CRD commentary**

The authors have clearly stated the research question as well as their predetermined inclusion and exclusion criteria.
The literature search was fairly limited, although it was not restricted to only English language publications, and whilst it was limited to published data, there were tests for publication bias.

The quality of the included studies was assessed using a quality questionnaire, and the authors have reported how the articles were selected and who performed the selection, quality assessment, and data extraction.

The data extraction is reported in tables and discussed in the text of the review. The studies were statistically combined, and heterogeneity was assessed and taken into account when reporting the results. Further sensitivity and stratified analyses were performed to evaluate the effects of study and patient characteristics on the results of the meta-analysis. The authors’ conclusions appear to follow from the results.

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

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