Interferon and ribavirin for patients with chronic hepatitis C who did not respond to previous interferon therapy: a meta-analysis of controlled and uncontrolled trials

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Authors' objectives
To perform a systematic review of the literature evaluating the efficacy of interferon (IFN) combined with ribavirin for the treatment of patients with hepatitis C who failed to respond to initial IFN therapy.

Searching
MEDLINE was searched from 1966 to June 2000 using the keywords 'hepatitis C', 'IFN' and 'ribavirin'. Additional studies were identified from the bibliographies and text of relevant citations and from review articles. Preliminary studies were selected from abstracts of the American Association for the Study of Liver Diseases (1995 to 2000), and from the European Association for the Study of the Liver (1995 to 2000). No language restrictions were reported. The quality of each study was assessed by recording methodologic features most relevant to the control of bias. These related to randomisation, random allocation concealment, blinding and withdrawals.

Study selection
Study designs of evaluations included in the review
RCTs were used for the primary meta-analysis. Uncontrolled and preliminary studies were used to provide additional data for sensitivity analyses. The duration of follow-up was 24 weeks in all trials.

Specific interventions included in the review
IFN used in combination with ribavirin therapy versus IFN monotherapy. Only studies that used an IFN dose of at least 9 MU/week and a ribavirin dose of at least 800 mg/day, and had a treatment duration of at least 24 weeks, were included. The IFN dose used in the included studies ranged between 3 and 6 MU, three times per week. The type of IFN was alfa in 4 randomised controlled trials (RCTs), alfa-2b in 4 RCTs and alfa-n3 in one RCT. The ribavirin dose used in the included studies ranged between 800 and 1,200 mg/day. The control dose was 3 to 6 MU IFN, three times per week. The duration of therapy was 24 weeks in all trials.

Participants included in the review
Patients with chronic hepatitis C virus (HCV) who failed to respond to initial IFN therapy. The patients were considered nonresponders if they did not achieve a normal serum alanine transaminase level or an undetectable serum HCV RNA during a course of IFN therapy, which was given for a minimum duration of 3 months at a dose of 3 MU three times per week. Partial responders and breakthrough patients were excluded. However, prior nonresponse to IFN monotherapy was not explicitly defined in 2 studies.

Studies that included participants with co-existing disease were excluded. Such diseases included infection with human immunodeficiency virus, haemophilia or other forms of liver disease such as hepatitis B, hepatitis A, Epstein Barr virus, cytomegalovirus, alcoholic hepatitis/cirrhosis, autoimmune hepatitis, hepatocellular carcinoma, Wilson's disease, haemochromatosis and alpha-1 antitrypsin deficiency.

The majority of the patients were male. The mean age of the patients in the treatment and control groups was similar, ranging between 33 and 55 years. The majority of the patients were infected with genotype 1, and the proportion of patients with each genotype was similar between the treatment and control groups. Where stated, the mean viral load and mean histology activity index (HAI) score were similar between the treatment and control groups. Only four trials reported the proportion of patients with cirrhosis; this ranged from 20 to 86%.

Outcomes assessed in the review
The primary end points were biochemical and virologic response. Only studies that reported either the end-of-treatment (ETR) or a sustained biochemical or virologic response (SBR and SVR, respectively) were included in the review.
A biochemical ETR response was defined as a normal serum alanine transaminase level, while a virologic ETR response was defined as an undetectable serum HCV RNA at the end of the treatment period. A SBR or SVR was defined as a normal serum alanine transaminase and an undetectable serum HCV-RNA level 24 weeks or more after discontinuing therapy. The authors stated that these definitions were consistent with standards published in the literature.

How were decisions on the relevance of primary studies made?
The authors do not state how the papers were selected for the review, or how many of the reviewers performed the selection.

Assessment of study quality
The eligibility and exclusion criteria were pre-specified. The authors do not state how the papers were assessed for validity, or how many of the reviewers performed the validity assessment.

Data extraction
Two investigators extracted the data independently and consensus was achieved for all data. It was not stated whether the investigators were blinded.

Data were extracted for the following categories: the number of participants; definition of prior nonresponse; mean age; male gender; disease genotype; HCV-RNA detection method; mean viral load; mean HAI score; cirrhosis; type of IFN; IFN treatment dose; ribavirin treatment dose; IFN control dose; the duration of therapy; follow-up duration; dose reduction; randomisation method; allocation concealment; blinding; the number of withdrawals; biochemical ETR ; virologic ETR; SBR; and SVR.

Data from trials containing a mixed population of nonresponders and relapses were extracted and analysed separately from nonresponders.

The outcomes were analysed on an intention to treat basis.

Methods of synthesis
How were the studies combined?
To assess the public health impact of combination therapy in nonresponders, the pooled risk difference and 95% confidence interval (CI) were calculated for the SVR using the random-effects model of DerSimonian and Laird (see Other Publications of Related Interest). The number-needed-to-treat (NNT) was calculated by taking the inverse of the pooled risk difference. The response for each binary end point was estimated using standard techniques for binomial proportions. A pooled, overall weighted response for patients treated with combination therapy, based on the inverse of the variance for each study and the among-study variance, was calculated for each end point.

The authors performed sensitivity analyses by including uncontrolled trials and trials published as abstracts. They also examined the effect of the following covariates in a meta-analysis: RCTs with more than 50% genotype 1 patients; RCTs with less than 50% genotype 1 patients; RCTs with a baseline mean HCV RNA titre of at least 3 million; RCTs with a ribavirin dose of at least 1,000 mg/day; RCTs with a ribavirin dose of 800 mg/day; and uncontrolled and preliminary controlled trials with a treatment duration of at least 48 weeks.

How were differences between studies investigated?
Heterogeneity among studies was evaluated using the Q statistic (an approximate chi-squared test). It was considered significant for P-values of less than 0.10.

Results of the review
Nine RCTs were used for the primary meta-analysis, which included a total of 789 patients. There were 62 uncontrolled and preliminary studies that met the inclusion criteria and provided additional data for the sensitivity analyses.

The method used to randomise the patients was computer in 4 studies and random numbers table in one study; the
method was not stated in the remaining 4 studies. Allocation concealment was not stated in any of the studies and blinding was only stated in one study, where it was single.

A biochemical ETR could be evaluated in 7 trials with a total of 752 patients. Of these, 6 trials showed a significant improvement among patients treated with combination therapy in comparison with IFN monotherapy. The overall weighted response was 39.4% with a common odds ratio (OR) of 5.5 (95% CI: 3.7, 8.0) in favour of combination therapy.

A virologic ETR could be assessed in 7 trials with a total of 766 patients. Only 4 of these trials showed a significant improvement among the patients treated with combination therapy. The overall weighted virologic ETR was 23.1% with a common OR of 4.9 (95% CI: 2.9, 8.1) in favour of combination therapy.

A SBR could be assessed in 7 trials with a total of 700 patients. Only 2 of these trials showed a significant improvement among patients treated with combination therapy. The overall weighted SBR was 15.2% with a common OR of 3.8 (95% CI: 2.2, 6.7) in favour of combination therapy.

A SVR could be assessed in 8 trials with a total of 726 patients. Only 2 of these trials showed a significant improvement among patients treated with combination therapy. The overall weighted SVR was 13.2% with a common OR of 4.9 (95% CI: 2.1, 11.2) in favour of combination therapy. Of the 8 trials, 2 studies had a calculated risk difference of zero. The remaining 6 trials had NNTs that ranged between 7 and 28. The pooled risk difference for all 8 trials was 7% (95% CI: 2, 13) with a corresponding NNT of 14 (95% CI: 8, 50).

Overall, the response among the uncontrolled trials was higher than those from the randomised studies. For a treatment duration of 24 weeks, the overall weighted SVR of the combination treatment arms in uncontrolled trials and preliminary controlled trials was estimated to be 14.6% (95% CI: 11, 19.3). When adding the results of the published RCTs, the overall SVR was 14.0% (95% CI: 11, 18), suggesting that the eventual publication of the preliminary studies is unlikely to significantly influence the estimates in the primary analysis.

A number of viral-, patient- and treatment-related characteristics have been associated with a response in the individual clinical trials of IFN monotherapy or combination therapy. Favourable response characteristics include a lower baseline HCV-RNA titre, the absence of cirrhosis, infection with non-type 1 genotypes, non-black race, and treatment for at least 48 weeks. However, the influence of these predictors has varied among the different trials, and has not been well established among IFN nonresponders treated with combination therapy. Thus, the effect of these variables on the study end points in the published controlled trials where data were available was explored. Preliminary trials were used to examine the influence of 48 weeks of combination therapy, because the longest duration of treatment in the published controlled trials was 24 weeks. The SVRs of the combination treatment arms were determined after excluding studies containing the highest or lowest proportion of patients with various covariates. The overall weighted SVR for studies involving a treatment duration of 48 weeks was increased in comparison with the primary analysis: 21.3% (95% CI: 16.7, 26.9) versus 13.2% (95% CI: 10, 17.3). In contrast, the overall weighted SVR for trials that included more than 50% of patients with genotype 1 infection was decreased compared with the primary analysis: 7.9% (95% CI: 3.9, 15.5) versus 13.2% (95% CI: 10, 17.3). These findings suggest a possible advantage for longer treatment duration and for patients with non-type 1 genotypes. However, there were insufficient data to formally test these hypotheses. Minimal differences were detected when the sensitivity analysis was limited to trials with a mean baseline HCV-RNA level greater than three million copies/mL or trials using a dose of ribavirin greater than 1,000 mg/day.

The authors state that there was no significant heterogeneity among the trials within each meta-analysis, although the Q statistic was not reported.

Authors' conclusions
Combination therapy with IFN and ribavirin for 6 months was associated with a significantly higher SVR, compared with re-treatment with IFN alone, in patients with chronic hepatitis C who initially failed treatment with IFN monotherapy. However, the absolute response was low.

CRD commentary
The authors stated their review question clearly and the inclusion criteria were well defined. The literature search was clearly described but was not thorough, and there was no attempt to identify unpublished or grey literature, although preliminary studies were selected from abstracts of two sources. This narrow search strategy may have missed relevant studies, allowing the introduction of selection bias. A sensitivity analysis was performed to determine the extent to which data from identified preliminary and uncontrolled studies could influence the results of the meta-analysis of RCTs, although no analyses were conducted to assess publication bias. Further relevant literature may have been identified by searching other appropriate electronic databases, such as EMBASE, SIGLE and the National Research Register, and by contacting experts in the field.

The authors did not report how decisions were made in relation to the study selection and validity assessment processes, or whether the investigators extracting the data were blinded.

Details of the studies were tabulated clearly. These included most of the important information such as the sample size in each group, relevant participant characteristics, description of the interventions, follow-up and the number of withdrawals. The outcomes were displayed in a separate table and a forest plot of the sensitivity analysis was presented. These data were supplemented by a narrative discussion. However, there were typographical errors in the 'Results' section in relation to the number of trials where SVR was assessed.

Heterogeneity among the studies was assessed using the Q statistic, and considered significant for values less than 0.10. The authors stated that there was no significant heterogeneity but did not report the Q statistic.

The authors’ conclusions are justified and the review appears to be relevant to the topic area.

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

**Practice:** The authors state that although some authorities would argue that a 13% SVR cannot justify the cost and risk of treatment, others would advocate combination therapy as a relatively well-tolerated regimen, which can be effective in treating nonresponders who have factors predictive of a favourable response and in whom the disease appears to be progressing. Preliminary data suggest that a higher response can be achieved with longer duration of therapy.

**Research:** The authors did not state any implications for further research.

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