Meta-analysis of interferon randomized trials in the treatment of viral hepatitis C: effects of dose and duration

Authors' objectives
To assess the level of efficacy of interferon in chronic hepatitis C in usual regimens, and at increased dose and duration.
To assess whether interferon is effective in treating acute hepatitis C.

Searching
MEDLINE using the keywords 'chronic hepatitis non-A, non-B, non-C clinical trials' and Current Contents (Clinical Medicine) were searched from 1985 to December 1995. Additional literature was located by manually searching general reviews and references from published studies, and by contacting pharmaceutical companies.

Study selection
Study designs of evaluations included in the review
Randomised controlled trials (RCTs) in which one intervention arm comprised a fixed dose of interferon. Only published studies were included.

Specific interventions included in the review
Standard regimen of interferon (3 MU, 3 times per week for 6 months) and higher doses.

Participants included in the review
Patients with acute or chronic hepatitis C were included. Trials that included previously treated patients, nonresponders or relapers were excluded.

Outcomes assessed in the review
Alanine transaminase (ALT) response during treatment, sustained ALT response in the months after treatment, and histological lesions assessed by biopsy.

How were decisions on the relevance of primary studies made?
Two independent researchers assessed each study, and conferred in cases of disagreement.

Assessment of study quality
Methodological quality was assessed using 'a previously validated questionnaire' (see Other Publications of Related Interest). Two researchers independently applied the questionnaire.

Data extraction
The authors do not state how the data were extracted for the review, or how many of the authors performed the data extraction.

Methods of synthesis
How were the studies combined?
The data were extracted from studies on an intention-to-treat basis. For each end point, the heterogeneity of results among the control groups was assessed. Fixed-effect and random-effects models were used to pool the data.

How were differences between studies investigated?
The heterogeneity of the control groups was assessed. Sensitivity analyses were conducted by comparing results when the following were included or excluded: studies published only as abstracts; studies scoring less than 10 on the quality
Results of the review
Seventeen RCTs comparing interferon with control in chronic hepatitis C (831 patients); 10 RCTs comparing different doses of interferon in chronic hepatitis C; 6 RCTs comparing different duration of treatment with interferon in chronic hepatitis C; and 4 RCTs comparing interferon with control in acute hepatitis C (134 patients).

Chronic hepatitis: the standard regimen was associated with an increase of the complete ALT response rate by 45% (95% confidence interval, CI: 35, 55, p<0.001); intervention and control group response rates were 47 and 2%, respectively. The standard regimen was associated with an increase of the sustained ALT response rate by 21% (95% CI: 13, 28, p<0.001); intervention and control group sustained response rates were 22 and 1% respectively. For the 2 RCTs using the standard regimen, which reported histological outcome data, 67% (33 out of 49 patients) in the intervention groups and 15% (7 out of 45 patients) in the control groups showed improvement. An increased dose of 6 MU for the same 6-month period was associated with non statistically-significant increases in both complete and sustained ALT response rates, compared with the standard regimen. A 6 MU dose for 12 months produced a higher rate of complete and sustained responses when compared with a 3 MU dose for 12 months, and these differences were statistically significant. Complete response rates: 6 MU for 6 months, 62%; 3 MU for 12 months, 54%; 6 MU for 12 months, 69%. Sustained response rates: 6 MU for 6 months, 28%; 3MU for 12 months, 28%; 6 MU for 12 months, 46%.

Acute hepatitis C: Complete response rates were 69% in the interferon group (3 MU, three times per week for 3 months) and 29% in the control group. The mean difference was 40% (95% CI: 25, 55, p<0.001). Sustained response rates were 53% in the interferon group and 32% in the control group. The mean difference was 21% (95% CI: 3, 39, p=0.02).

Reported side-effects included flu-like syndromes (reported in 41% of patients treated with a standard regime), alopecia (16%) and depression (7%).

Authors' conclusions
The best efficacy-risk ratio is in favour of 3 MU three times per week for at least 12 months in patients with chronic hepatitis C, not previously treated with interferon. Patients with acute hepatitis should be treated by interferon alfa, at least 3 MU three times per week for 3 months.

CRD commentary
The search strategy appears to be reasonably comprehensive. The decision to exclude unpublished studies may have left the review susceptible to the influence of publication bias. This review seems to have been conducted to good methodological standards, and the sensitivity analyses suggest the results are quite robust, although the total number of patients in the included studies is relatively small. A 12-month follow-up period may be regarded as short, particularly for chronic hepatitis C. Relapse and survival beyond 12 months are not considered.

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