Treatment of chronic hepatitis C with alpha-interferon: an analysis of the literature

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Authors' objectives
To evaluate whether the type, dose, and duration of interferon treatment affect its short- and long-term responses, and to analyse whether the presence of liver cirrhosis predicts response rates.

Searching
MEDLINE was searched from 1986 to 1993; no search terms are given. Additional material was located by searching articles and abstracts published in the journals of the American and European Associations for the Study of Liver Diseases, and the proceedings of recent international meetings referring to research in viral hepatitis.

Study selection
Study designs of evaluations included in the review
Randomised controlled trials, except those with a crossover design, were included.

Specific interventions included in the review
Recombinant interferon alpha-2a (dosages vary from 3 to 28 MU/week), recombinant interferon alpha-2b (dosages vary from 0.75 to 35 MU/week), recombinant interferon alpha-2c (dosages vary from 12 to 36 MU/week), and lymphoblastoid (natural) interferon alpha-n (dosages vary from 4.5 to 31.5 MU/week).

Participants included in the review
Patients with biopsy-proven chronic hepatitis and elevated serum transaminases for at least 6 months, where other chronic liver diseases had been excluded.

Outcomes assessed in the review
Short-term response rate, defined as normalisation of serum alanine aminotransferase (ALT) at the end of interferon treatment.

Long-term response, defined as normalisation of serum ALT for at least 3 months after the end of interferon treatment.

Relapse rate, defined as the rate of patients in whom transaminases had become normal after the end of interferon treatment but were again elevated 3 months after the end of treatment.

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 authors performed the selection.

Assessment of study quality
The authors do not state that they assessed validity.

Data extraction
The data extraction was performed blindly by two of the authors, and results reached by consensus.

Methods of synthesis
How were the studies combined?
Response rates in cirrhotic versus noncirrhotic patients were compared after various doses, durations and types of interferon, using chi-squared tests. Regression analyses of the effect dose, total dose and duration of treatment on
response rates was undertaken.

How were differences between studies investigated?
Separate analyses were undertaken for studies published in full and as abstracts.

Results of the review
Fifty-two studies, enrolling 3,749 patients: 2,927 patients received interferon and 822 had either not been treated or had received placebo.

Twenty-nine studies evaluated interferon alpha-2b, 12 studies evaluated interferon alpha-2a, 11 studies evaluated interferon alpha-n, 1 study evaluated interferon alpha-2c, and in 1 the type of interferon is not given; 2 studies evaluated 2 types of interferon.

Interferon-alpha therapy caused a normalisation of serum transaminases in 51.2% of patients (1,499 out of 2,927).

Only 21.7% of patients (482 out of 2,218) still had normal serum transaminases for at least 3 months after discontinuation of therapy. Spontaneous long-term normalisation was 2.7% (22 out of 822) in untreated or placebo patients. Long-term benefit of interferon therapy is more than 8-fold higher than in the control group (chi-squared=156.1, p<0.00001).

Short-term responses were approximately doubled when weekly doses of 9 MU or more were compared to doses of 6 MU or less. Doses of 12 MU or more did not show an increase compared to 9 MU. Response rates were 25.8% for 6 MU or less, 53.7% for 9 MU, and 57.1% for 12 MU or more (Pearson's chi-squared=87.2, p<0.00001).

The long-term response gradually increased with increasing doses of interferon, with response rates of 9.2% for 6 MU or less, 16.7% for 9 MU and 31.3% for 12 MU or more (Pearson's chi-squared=59.9, p<0.00001).

Treatment for 9 months or more doubled the long-term response rate (29.4%), compared to treatment for 6 months or less (14.6%; chi-squared=64.0, p<0.00001).

Similarly, the long-term response was approximately 3-times better for patients receiving a total dose of more than 240 MU (30.6%), compared to those receiving less than 240 MU (10.8%), (chi-squared=103.3, p<0.00001).

There was no significant association between the long-term response rate and the type of interferon given.

There was no significant difference in the results from studies published in full and abstracts, or between escalating or constant dose.

Identifying the effects of cirrhosis as a pre-treatment selection criterion, both short- (28.9%) and long-term (12.2%) response rates were significantly lower in patients with cirrhosis present, compared to those without cirrhosis (59.8 and 31.5% respectively; chi-squared=59.1 and 12.1, p<0.00001 and p=0.00013, respectively).

Authors' conclusions
The data suggest that widely-used dose schedules such as subcutaneous injections of 3 MU interferon-alpha thrice weekly for 4 to 6 months induce insufficient long-term responses, which could be better with higher doses and in particular with longer treatment periods. Future studies should focus on comparative studies with higher interferon doses and longer duration of therapy, preferably in noncirrhotic patients.

CRD commentary
The potential for publication bias exists since only published studies were considered (both articles and abstracts) and, although no language restrictions are stated in the search details, there are no non-English studies included in the review. The rationale for, and details of, the statistical analyses are unclear.
The authors' conclusion that future studies should focus on noncirrhotic patients does not follow from the results of the review, what is important is that the cirrhotic status of patients be recorded.

Short- and long-term response rates are intermediate outcomes, and the extent to which they are correlated with patient outcomes is unclear from the review. The review does not address the issue of side-effects; another review comparing relatively low doses of interferon reported serious side-effects such as flu-like syndromes, alopecia and depression (see Other Publications of Related Interest).

**Bibliographic details**

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**Other publications of related interest**

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