Effect of interferon therapy on the development of hepatocellular carcinoma in patients with hepatitis C virus-related cirrhosis: a meta-analysis
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Authors' objectives
To conduct a meta-analysis of all published studies, including interferon-treated and untreated patients with hepatitis C virus (HCV) cirrhosis, in order to review the subject in depth. In addition, to objectively evaluate whether interferon (IFN) therapy reduces the incidence of hepatocellular carcinoma (HCC).

Searching
MEDLINE was searched from 1990 to 2000 using the terms 'hepatocellular carcinoma', 'interferon' and 'hepatitis C'. The reference lists of all available review articles and original studies were checked for additional references. The search was restricted to full articles published in the English language.

Study selection
Study designs of evaluations included in the review
Randomised controlled trials and non-randomised studies (prospective and retrospective cohort studies) were included. Studies had to present data on the incidence of HCC in IFN-treated and untreated participants with HCV-related cirrhosis. The mean or median follow-up ranged from 2.7 to 6.9 years.

Specific interventions included in the review
IFN at doses ranging from 3 to 6 MIU three times weekly, or total dosages of 200 to 480 MIU. The duration of treatment ranged from 3 to 12 months. The mean age of the patients was greater than 50 years in those studies reporting such details.

Participants included in the review
Participants with HCV cirrhosis were included. Where the patients' characteristics were reported, the mean age ranged from 53 to 59 years, 50% were male, and 97% of them had HCV-related cirrhosis of Child class A.

Outcomes assessed in the review
The development of HCC was assessed.

How were decisions on the relevance of primary studies made?
At least two reviewers independently selected relevant articles.

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

Data extraction
Two reviewers independently extracted the data using a predefined review form, and any disagreements were resolved by consensus. Data were extracted for the following categories: study identification; study type, including how the control group was selected; sample sizes for the treatment and control groups; the inclusion criteria of the individual studies; the patients' characteristics, including mean age, gender, and Child class of HCV-related cirrhosis (A or B); the mean or median follow-up (years); IFN dose and duration; the definition of response; the procedure and schedule of screening for HCC; and the diagnosis of HCC. The authors also calculated the odds ratios (ORs) with 95% confidence intervals (CIs) for each study.
Methods of synthesis
How were the studies combined?
A meta-analysis was used to estimate the overall OR and 95% CI. This was performed using either a fixed-effect model, as described by Peto (see Other Publications of Related Interest no.1), or using the random-effects model of DerSimonian and Laird (see Other Publications of Related Interest no.2). The authors also calculated the number-needed- to-treat and examined publication bias.

How were differences between studies investigated?
A chi-squared test was used to examine heterogeneity using a p-value of less than 0.05 as the significance level. Sensitivity analyses were also conducted for the following variables: response to IFN treatment (sustained response, no sustained response or no treatment), study design (prospective or retrospective), duration of follow-up (less than or equal to 48 months), and origin of the study (Japan versus other countries).

Results of the review
Eleven studies with 2,178 participants (1,223 receiving IFN treatment, 955 receiving no treatment) were included in the review. There was 1 randomised controlled trial with 90 participants, 6 non-randomised retrospective studies, and 4 non-randomised prospective studies.

There was a 100% agreement between the reviewers for the selection of relevant articles.

HCC developed significantly more frequently in untreated than in IFN- treated participants; the OR was 3.0 (95% CI: 2.3, 3.9, p<0.001). There was no evidence of heterogeneity between the studies (p=0.57).

The number-needed-to-treat to prevent HCC in one patient was 9 (95% CI: 7, 11).

The assessment of publication bias showed that 171 null or negative studies would be needed to render the result of the analysis non significant.

Sensitivity analyses.
In the 5 studies reporting HCC incidence in patients with and without sustained response to IFN, HCC was detected at a much higher rate in patients without a sustained response (OR 3.7, 95% CI: 1.7, 7.8, p=0.001). There was no evidence of heterogeneity between the studies (p=1.00).

HCC developed significantly more frequently in the untreated participants than in the in non-sustained responders (OR 2.7, 95% CI: 1.9, 3.9, p<0.001). There was no evidence of heterogeneity between the studies (p=0.62).

The benefit of IFN on HCC was not influenced by study type, duration of follow-up, or the origin of the study (Japan versus other countries).

Authors’ conclusions
IFN therapy significantly reduced the risk of HCC in patients with HCV- related cirrhosis. The development of HCC became almost negligible among sustained responders, but a reduction in HCC incidence was also achieved in the non-sustained responders.

CRD commentary
The review question was clearly defined. However, the literature search was restricted to only one database with narrow search dates, and only full articles published in English were included in the review. It is likely, therefore, that some studies may have been missed. In addition, without a thorough literature search, the authors’ calculated publication bias assessment is not valid. The authors presented a number of tables with a good overview of information from the individual studies (two reviewers independently extracted the data). However, the review did not include an assessment of the quality of the studies. This is an essential step of a systematic review that helps to determine how the data are examined, and to convince the reader of the strength of the overall results. The authors examined heterogeneity and
performed sensitivity analyses. There were however, some sources of clinical heterogeneity; these were found in IFN regimens, as well as in the methods of screening for, and diagnosis of HCC. It may have been useful to conduct additional sensitivity analyses of these factors. The authors also presented forest plots, which could have shown more detail, e.g. sample size and weighting.

The authors’ conclusions follow the results, but should be interpreted with caution.

Implications of the review for practice and research
Practice: The presence of compensated cirrhosis should not be considered a reason for excluding patients with HCV-related liver disease from IFN therapy.

Research: More studies are needed to evaluate the effect of IFN therapy on the actual survival of patients with chronic hepatitis C.

Bibliographic details

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Other publications of related interest

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Subject indexing assigned by NLM

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