Interferon and prevention of hepatocellular carcinoma in viral cirrhosis: an evidence-based approach
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Authors' objectives
To perform a meta-analysis of the available literature, in order to evaluate whether interferon (IFN) reduces the incidence of hepatocellular carcinoma (HCC) in patients with hepatitis B or C virus (HBV or HCV)-related cirrhosis (Child class A).

Searching
MEDLINE was searched from 1985 to 1999 using the following terms: 'hepatocellular carcinoma', 'interferon', 'cirrhosis', 'clinical trial' and 'cohort study'. Reference lists from review articles, primary studies, and proceedings of major meetings (1995 to 1999) were also examined. Data from an unpublished study were obtained from one of the reviewers. Studies reported in any language were considered.

Study selection
Study designs of evaluations included in the review
Randomised controlled trials (RCTs) and non-randomised controlled trials (prospective or retrospective) comparing IFN-treated and untreated cirrhotic patients were eligible for inclusion. The studies had to provide sufficient information on the treatment schedule, follow-up, and outcomes.

Specific interventions included in the review
IFN at doses ranging from 3 to 10 MU three times weekly, or a total dose of 102 to 780 MU. The duration of treatment ranged from 4 to 78 weeks.

Participants included in the review
Participants with HBV- or HCV-related cirrhosis were included. The proportion of men ranged from 46 to 86%, and the mean age ranged from 39 to 59 years.

Outcomes assessed in the review
Crude rates of HCC were assessed, i.e. the proportion of cancers observed in the IFN-treated and untreated groups, regardless of when these tumours were observed.

How were decisions on the relevance of primary studies made?
The studies were selected according to predefined criteria, although the authors do not state how many of the reviewers performed the selection.

Assessment of study quality
The authors do not state that they assessed validity. However, only controlled studies were included in the review.

Data extraction
Two reviewers independently performed the data extraction, and any discrepancies were resolved by discussion. Data were extracted for the following categories: study identification and year; type of study; follow-up period; dosage regimen; sample size; gender and mean age; and rate of HCC.

When not reported in the papers, the rate of HCC was calculated using an intention to treat method, i.e. all patients were evaluated according to their allocated treatment group and patients whose end point was unknown were considered failures. The risk difference (RD), i.e. the difference in the rate of HCC between the treated and untreated patients, was computed for each trial.
Methods of synthesis
How were the studies combined?
A meta-analysis was used to estimate the overall RD, and 95% confidence intervals (CIs), between the frequencies of events in both the treated and untreated control groups. This was performed using the random-effects model of DerSimonian and Laird (see Other Publications of Related Interest no.1). The overall OR and 95% CI also appear to have been calculated using a fixed-effect model, according to Mantel and Haenszel (see Other Publications of Related Interest no.2). The number of patients requiring treatment to prevent death, i.e. the number-needed-to-treat (NNT), was also evaluated.

How were differences between studies investigated?
The Q statistic (chi-squared) was used to test for heterogeneity, using a p-value of less than 0.05 as the significance level. A sensitivity analysis was conducted by examining all studies except for those with the lowest and highest therapeutic effect. The authors also conducted subgroup analyses for the following variables: study type (RCTs versus non-randomised controlled trials); the presence or absence of 'imbalance' in the baseline features between the treated and control patients; ethnic origin (European versus Oriental); the rate of HCC in untreated patients (below or above 20%); the duration of follow-up (below or above 60 months); the publication type (full papers versus abstracts); and the biochemical response to IFN. Heterogeneity was also explored using logistic regression.

Results of the review
Eighteen studies with 4,614 participants (1,782 received no treatment) were included in the review: 3 RCTs and 15 non-randomised controlled trials. Fourteen studies with 3,109 participants were concerned with HCV-related cirrhosis: 3 RCTs (246 participants) and 11 non-randomised controlled studies. Seven studies with 1,505 participants were concerned with HBV-related cirrhosis: all of these were non-randomised controlled trials; 3 trials also concerned HCV-related cirrhosis.

HCV-related cirrhosis.
The tests for heterogeneity were statistically significant (Q=58.16, d.f.=13, p<0.0001).

A difference in the incidence of HCC between the treated and untreated cirrhotic patients was observed. The pooled RD was 12.8 (95% CI: -8.3, -17.2, p<0.0001) when using a random-effects model.

Logistic regression analysis showed that cirrhotic patients treated with IFN have a lower likelihood of developing HCC (OR 0.28) after adjusting for covariates (IFN treatment, length of follow-up, cancer rate among untreated patients, design of study, type of publication and ethnic origin of patients).

When all studies except those demonstrating the highest and lowest therapeutic benefit were included in the meta-analysis, the RD was 12.5 (95% CI: -9.1, -15.1).

The authors conducted a number of subgroup analyses, and examined heterogeneity within each of these subgroups. They reported that 'consistent results' (i.e. no heterogeneity) were observed when assessing pooled data from RCTs, European reports, studies published as full papers, trials with a control rate less than 20%, and studies with a follow-up greater than or equal to 60 months.

Compared with untreated patients, the rate of HCC development was lower in both sustained responders to IFN (pooled RD 19.1, 95% CI: -13.1, -25.2, p<0.00001), and in non-responders (pooled RD 11.8, 95% CI: -6.4, -17.1, p=0.0001).

When only RCTs were pooled, there was a significant difference between the treated and untreated cirrhotic patients (RD 18.7, 95% CI: -3.9, -33.5).

The authors reported an NNT of 10 when using only those studies with 'consistent results'. When only patients from these studies who had a sustained response were evaluated, the NNT dropped to 5.2. HBV-related cirrhosis.

The tests for heterogeneity were statistically significant (Q=26.4, d.f.=6, p=0.0001).
The pooled estimate of the preventive effect of treatment was significantly in favour of IFN (RD 6.4, 95% CI: 2.8, -10, p<0.001) when using a random-effects model.

Subgroup analyses were only conducted in relation to the ethnic origin of the participants. ‘Consistent results’ were observed when assessing the data pooled from European studies. No preventive effect of IFN was shown in this subgroup.

The authors also briefly examined whether the preventive effect of IFN on HCC development was independent of the presence of cirrhosis. They found a preventive effect, but also discussed several confounding factors.

**Authors’ conclusions**
The pooled data suggested a slight preventive effect of IFN on HCC development in participants with HCV-related cirrhosis. The magnitude of this effect was low, and the observed benefit might be due to spurious associations. The preventive effect was more evident among sustained responders to IFN, which intrinsically represent a small proportion of all cirrhotic patients. IFN did not seem to affect the rate of HCC in HBV-related cirrhosis.

**CRD commentary**
The review question was well defined, although the inclusion and exclusion criteria were not detailed, e.g. the authors only specified that studies had to provide 'sufficient' analytical information. Only one database was searched over a relatively narrow time period; while there may have been a reason for this, it should be justified. It is possible that some studies may have been missed, even though there were no language restrictions and the authors conducted a reference search of review articles, primary studies and conference proceedings. The authors did not systematically assess the quality of the included studies. There was some discussion of the methodological downfalls of the non-randomised controlled trials, but there was no discussion of the quality of the RCTs, other than that they had small sample sizes. The authors conducted a number of tests to examine heterogeneity, and appeared to be very cautious about pooling. However, given the lack of any validity assessment, and the significant heterogeneity between all the studies, the overall results are not meaningful. The authors presented forest plots, but the units of analysis were not the same as those presented in the table. The authors also calculated the NNT, based on only those studies with ‘consistent results’. This is not a valid method for determining NNT. In addition, it may have been inappropriate to pool the RCTs and non-randomised controlled trials together.

The authors’ conclusions were, however, appropriately cautious.

**Implications of the review for practice and research**
Practice: There is no firm ground to recommend IFN for the prevention of HCC in HBV-related cirrhosis. INF treatment for patients with chronic hepatitis C without cirrhosis is not recommended if the specific aim of the treatment is to prevent HCC.

Research: The authors stress the need for RCTs with a long period of observation after the therapeutic intervention.

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