Effects of interferon treatment on development and progression of hepatocellular carcinoma in patients with chronic virus infection: a meta-analysis of randomized controlled trials

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CRD summary
The review found that interferon therapy may reduce the risk of hepatocellular carcinoma in patients with chronic hepatitis C infection but evidence was lacking on its use in other subpopulations. The authors noted limitations in their review and the included studies and appropriately advised caution when interpreting their conclusions.

Authors' objectives
To evaluate the effect of interferon on hepatocellular carcinoma risk in patients with chronic hepatitis B or C virus infection and assess the efficacy of interferon on local tumour progression and survival of patients with advanced hepatocellular carcinoma.

Searching
Searches were made of PubMed, EMBASE, The Cochrane Library and Web of Science to July 2010. Search terms were reported. Bibliographies of reviewed manuscripts were handsearched. Only studies published in English were eligible.

Study selection
Randomised controlled trials (RCTs) that compared interferon with no antiviral agent (placebo, systematic or no treatment) were eligible for inclusion. Study inclusion criteria differed for three research questions:

Non-maintenance interferon therapy in patients with hepatitis B or C infection: Eligible studies had to assess the effect of up to two years initial interferon treatment on hepatocellular carcinoma risk and have a minimum of two-year mean/median follow-up period. Studies could include any dosage regimen of interferon and include patients who achieved sustained virologic response (hepatitis C infection), virologic response (hepatitis B infection) or neither.

In the included studies of hepatitis C infection, mean age ranged from 52 to 58 years, 49% to 73% of patients were male and all patients in all but one study had cirrhosis at baseline. Treatments included interferon alpha, alpha-2a, alpha-2b, and beta.

In the included studies of hepatitis B infection, mean age ranged from 32 to 41 years, 71% to 100% of patients were male and in one study 11% had cirrhosis at baseline and the other study no patients had cirrhosis at baseline. Treatments were interferon alpha for three to six months.

Maintenance interferon therapy in patients with hepatitis C infection: Eligible studies had to assess the effect of a minimum of two years interferon re-treatment on hepatocellular carcinoma risk in patients with hepatitis C infection who had failed to achieve sustained virologic response in initial interferon-based antiviral therapy. Studies had to have a minimum of two years mean or median follow-up.

In the included studies, mean age ranged from 50.1 to 60.5 years, 45% to 71% of patients were male and between 40% and 100% had cirrhosis. Treatments were interferon alpha-2a, three million International Units three times weekly for two years or peginterferon alpha-2a, 90μg weekly for 3.5 years.

Therapeutic effect of interferon therapy on patients with hepatocellular carcinoma: Eligible studies had to compare first-line interferon treatment against no anti-tumour treatment and assess survival in patients with advanced primary hepatocellular carcinoma who were not suitable for potentially curative treatment.

In the included studies, mean age ranged from 60 to 62 years, 80% of patients were male and (in the one study where this was reported) 84% had cirrhosis. In one study, 94% of patients had Hepatitis B infection; in the other study 78% had Hepatitis C infection. In the one study where reported, 60% of patients had disease stage A and the rest B (Child-Pugh classification). One study used interferon alpha-2a and the other used interferon alpha-2b, both at a dose of three...
million International Units three times weekly.

The authors did not state how many reviewers performed the study selection.

Assessment of study quality
Validity was assessed using the five-point Jadad scale of randomisation, blinding and description of withdrawals and drop-outs during follow-up. Studies that scored 3 or more were considered high-quality and those that scored less than 3 were classed as low quality.

Two reviewers independently assessed study quality. Disagreements were resolved by consensus.

Data extraction
Data were extracted to calculate pooled relative risks (RR) and 95% confidence intervals (CI). The authors of the original papers were contacted for any missing key data. In the analysis of overall survival in patients with hepatocellular carcinoma, where the absolute number surviving was not reported it was estimated from the survival curves according to the method proposed by Parmar (1998).

The authors did not state how many reviewers performed data extraction.

Methods of synthesis
Studies were pooled in meta-analyses using a fixed-effect model. Heterogeneity was assessed using the X² test and I² statistic. The authors stated that they would use meta-regression to investigate reasons for heterogeneity, but this was not done as no heterogeneity was detected.

Sensitivity analyses were conducted using random-effects rather than fixed-effect models and by excluding low quality studies. Publication bias was assessed using Egger's test. These two analyses were performed only for results that were statistically significant in the main analysis.

Results of the review
Eleven RCTs (1,772 patients) were included in the review. The authors stated that eight studies were classed as good quality (Jadad score details for one of these was missing from the table).

Non-maintenance interferon treatment was associated with a reduction in the overall risk of hepatocellular carcinoma in hepatitis C infected patients when compared with no antiviral treatment (RR 0.39, 95% CI 0.26 to 0.59; four studies). The results were unchanged after excluding the low quality study. Subgroup analysis showed a similar effect in patients with hepatitis C related cirrhosis (RR 0.44, 95% CI 0.28 to 0.68). There was no difference in effect of interferon treatment compared to no treatment among patients with a sustained virologic response versus non-responders (two studies). Maintenance interferon treatment was not associated with a reduction in the overall risk of hepatocellular carcinoma in hepatitis C infected patients compared to no antiviral treatment (two studies).

Non-maintenance interferon treatment was associated with a reduction in overall risk of hepatocellular carcinoma in hepatitis B infected patients when compared to no treatment, although the effect was not statistically significant (RR 0.23, 95% CI 0.05 to 1.04; two studies).

Interferon treatment was associated with an improvement in overall one-year survival in patients with advanced hepatocellular carcinoma compared to no treatment, but the results did not quite reach statistical significance (RR 1.61, 95% CI 0.96 to 2.69; two studies).

The authors stated that there was no evidence for significant publication bias (p=0.594), but it was not clear which set of studies this analyses was based on.

Authors' conclusions
The authors stated that their results suggested that non-maintenance interferon treatment can reduce the risk of hepatocellular carcinoma in patients with chronic Hepatitis C infection and that maintenance therapy with interferon did not reduce the risk in non-responders to initial antiviral therapy.
CRD commentary
The review had clearly specified inclusion criteria. The search was of several databases and used appropriate search terms. The search was restricted to studies published in English so the review may have been affected by language and publication biases; Egger's test suggested no publication bias, but it is of limited value when based on a small number of studies. It was unclear whether methods to reduce error and bias were used in study selection and data extraction processes.

Study quality was assessed by more than one reviewer; quality was accounted for in the sensitivity analysis by assessing the effect of excluding studies classified as poor quality. The Jadad scale does not assess allocation concealment, so the possibility of selection bias affecting the results of the trials included in the review could not be ruled out. Appropriate methods were used to pool the results, although the authors made no attempt to group studies according to the type of interferon treatment that was used. No statistical heterogeneity between studies was found but it was likely that there was some clinical heterogeneity in the results; the main results were based on four studies, and the largest of these had higher rates of hepatocellular carcinoma compared to the others.

The authors noted limitations in their review and the included studies and appropriately advised caution when interpreting their conclusions.

Implications of the review for practice and research
Practice: The authors stated that using interferon therapy in patients with chronic hepatitis C infection may reduce hepatocellular carcinoma.

Research: The authors stated that further studies were required to investigate the effect of interferon on the risk of hepatocellular carcinoma in patients with hepatitis B infection and on tumour progression and survival in patients with advanced hepatocellular carcinoma.

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