Meta-analysis: treatment of hepatitis B infection reduces risk of hepatocellular carcinoma

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CRD summary
This review compared risk of hepatocellular carcinoma in chronic hepatitis B patients who received interferon or nucleoside/tide analogue and concluded that both treatments significantly reduced risk. Generally this was a well-conducted review, but the paucity of randomised studies and a lack of good-quality data suggest that the conclusions should be interpreted with caution.

Authors' objectives
To compare the effects of interferon or nucleoside/tide analogue on risk of developing hepatocellular carcinoma (HCC) in chronic hepatitis B patients.

Searching
EMBASE, MEDLINE, Cochrane Central Register of Controlled Trials (CENTRAL), DARE and International Pharmaceutical Abstracts were searched for English-language studies up to the end of 2007; search terms were reported. Manual searches of abstracts published in six relevant international conferences for the previous 10 years and reference lists of included articles were undertaken.

Study selection
Randomised controlled trials (RCTs), case-control and cohort studies that compared either interferon/pegylated-interferon or nucleoside/tide analogue treatments against placebo or no anti-viral treatment in participants with confirmed chronic hepatitis B infection were eligible for inclusion. Eligible studies had to report cases of HCC during the follow-up period. The main outcome was the number of chronic hepatitis B-related HCC diagnoses. Included studies used lamivudine or adefovir. Mean age of participants in included studies ranged from 24.5 to 58.5 years. Mean alanine aminotransferase (ALT), where stated, ranged from 5.3 to 184.2. Males accounted for more than 70% of the study population.

Two reviewers independently selected studies for inclusion in the review. Disagreements were resolved through consultation with a third reviewer.

Assessment of study quality
For RCTs, study quality was assessed using five criteria: prospective design; randomisation by allocation concealment or computer generated allocation; exclusion criteria; clear virological or biochemical definitions of treatment response; and HCC diagnosis. For case-control studies, study quality was assessed using the same criteria except the design and randomisation method criteria were replaced by case-matching of participant characteristics.

The authors did not state how validity assessment was performed.

Data extraction
Dichotomous outcomes (number of HCC diagnoses) were extracted to calculate relative risks (RR) and their 95% confidence intervals (CIs).

The authors stated neither how data were extracted for the review nor how many reviewers performed data extraction.

Methods of synthesis
Pooled relative risks and their 95% CI were calculated using a fixed-effect model. A random-effects model was used if significant heterogeneity was detected. Heterogeneity was assessed using $X^2$ and $I^2$ tests. Significant heterogeneity was defined as $p<0.1$. 
Subgroup analyses were undertaken to explore variation across studies in relation to: HBeAg status; presence of early cirrhosis before treatment; response to anti-viral treatment; and resistance to anti-viral agents. One-way sensitivity analysis was carried out using study quality.

**Results of the review**

A total of 17 studies was included in the review (n=5,031, range 37 to 754): three RCTs; two case-controls; and 12 cohort studies. Study quality scores ranged from 1 to 4: one study scored 1; six scored 2; seven scored 3; and three scored 4. Duration of follow-up ranged 2.7 to 8.9 years.

**Interferon treatment (12 studies; n=2,742):** There was a significantly reduced risk of HCC for patients treated by interferon compared to controls (RR 0.66, 95% CI 0.48 to 0.89; 12 studies) and for patients with early cirrhosis (RR 0.53, 95% CI 0.36 to 0.78; six studies). There was no statistical heterogeneity for these comparisons.

**Nucleoside/tide analogue treatment (five studies; n=2,289):** There was a significantly reduced risk of HCC for patients treated by nucleoside/tide analogue compared with controls (RR 0.22, 95% CI 0.10 to 0.50; five studies).

Across subgroups there was a significantly reduced risk of HCC for: HBeAg-positive patients (RR 0.21, 95% CI 0.10 to 0.44; five studies); patients with early cirrhosis (RR 0.17, 95% CI 0.04 to 0.79; three studies); non-cirrhotic patients (RR 0.21, 95% CI 0.10 to 0.47; two studies); patients with drug resistance (RR 0.52, 95% CI 0.28 to 0.97; three studies); and those without drug resistance (RR 0.37, 95% CI 0.17 to 0.77; three studies). Statistical heterogeneity was absent.

Sensitivity analysis of higher-quality studies (score 3 to 4) demonstrated a significantly reduced risk of HCC when interferon was compared to no treatment.

**Authors' conclusions**

Risk of HCC was significantly reduced by interferon or nucleoside/tide analogue treatment.

**CRD commentary**

The review question and inclusion criteria were clear. The search strategy appeared reasonably thorough. The search was restricted to publications in English and there was no apparent search for unpublished studies; which introduced potential for language and publication biases. Study selection was undertaken in duplicate, which reduced potential for error and bias; it was uncertain whether this extended to data extraction. Appropriate criteria were used to assess study quality. Suitable methods were used for meta-analysis. Heterogeneity was assessed and found to be absent from analyses for significant outcomes. Generally this was a well-conducted review, but the findings were limited by a paucity of randomised studies and a lack of good-quality data. In light of these shortcomings, the authors' conclusion should be interpreted with caution.

**Implications of the review for practice and research**

**Practice:** The authors did not state any implications for practice.

**Research:** The authors recommended that studies that used more potent oral anti-viral therapy with long-term follow-up were required to assess their chemopreventive effects.

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None.

**Bibliographic details**


**PubMedID**
This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.