Long-term efficacy of interferon alpha therapy on hepatitis B viral replication in patients with chronic hepatitis B: a meta-analysis
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CRD summary
This review found that interferon alpha treatment increased hepatitis B e antigen and hepatitis B s antigen seroclearance in patients with chronic hepatitis B virus infection after long-term follow-up of three to seven years. Although this was a generally well-conducted review, the authors’ conclusions should be treated with caution as they are based mainly on observational studies of unknown quality.

Authors' objectives
To review the efficacy of interferon treatment in chronic hepatitis B virus infection.

Searching
PUBMED and EMBASE were searched between 1986 and May 2009; search terms were reported. Reference lists of reviews and primary studies plus proceeding of major meetings were searched. Studies published as full articles or meeting abstracts were included.

Study selection
Randomised or non-randomised controlled trials of patients with chronic hepatitis B who were treated with interferon, compared with patients who were not treated, were eligible for inclusion. Eligible studies were required to follow up patients for at least three years, and provide sufficient detail of treatment schedules, follow-up and outcomes. Studies had to use hepatitis B virus DNA seroclearance (undetectable hepatitis B virus DNA in the serum), hepatitis B e antigen seroclearance (disappearance of hepatitis B e antigen in the serum) or hepatitis B s antigen seroclearance (disappearance of hepatitis B s antigen in the serum) as outcome measures. Studies of patients with hepatitis C or D, or those receiving other antiviral drugs were excluded.

The interferon regimens in the included studies were between 2 and 10 million units (MU) given for between 11 and 52 weeks. Mean patient age in included studies ranged between 31 and 48.8 years; the proportion of males ranged from 53.2 to 94%.

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

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

Data extraction
The numbers of patients with each type of seroclearance were extracted and used to calculate relative risks (RR) with 95% confidence intervals (CI) on an intention-to-treat basis (patients with missing outcomes were considered to be failures).

Data were extracted by two independent reviewers with disagreements resolved by discussion.

Methods of synthesis
Individual study results were pooled using fixed-effect (in the absence of statistical heterogeneity) or random-effects (if significant heterogeneity was found) meta-analysis. Statistical heterogeneity was assessed using a \( \chi^2 \) test; a p-value less than 0.10 was considered statistically significant.

Sensitivity analyses were performed excluding the study with a baseline imbalance in alanine aminotransferase levels.

Funnel plots and Egger's regression test were used to assess publication bias.
Results of the review
Seven studies were included in the review (n=1,550 patients); these included one randomised controlled trial (n=64 patients), one case control study (n=466 patients) and five cohort studies (n=1,020 patients, range 62 to 404). There was no evidence of publication bias. Mean trial follow-up periods ranged from 3.2 to 7.2 years.

Hepatitis B virus DNA seroclearance (three studies): Two studies found that interferon treatment resulted in a significant increase in hepatitis B virus DNA seroclearance compared with no treatment. One study reported no significant difference.

Hepatitis B e antigen seroclearance: Interferon treatment significantly increased the incidence of hepatitis B e antigen seroclearance compared with no treatment (RR 0.66, 95% CI 0.44 to 0.99; four studies). There was significant heterogeneity (p=0.008).

Hepatitis B s antigen seroclearance: Interferon treatment significantly increased the incidence of hepatitis B s antigen seroclearance compared with no treatment (RR 0.28, 95% CI 0.17 to 0.46; six studies. There was no significant heterogeneity (p=0.77). One study in the hepatitis B s antigen analysis had a baseline imbalance in alanine aminotransferase levels, so the meta-analysis was repeated with this study excluded; this made little difference to the results.

Analyses were repeated using different models (fixed-effect if a random-effects model had been used originally and vice versa); this had little effect on the results.

Authors’ conclusions
Interferon treatment increased the incidence of hepatitis B e antigen and hepatitis B s antigen seroclearance after long-term follow-up of three to seven years.

CRD commentary
This review had clear inclusion criteria for study design, interventions, participants and outcomes. The authors searched for unpublished studies presented at conferences and included these in the review if they were eligible, which reduced the risk of publication bias. There was no mention of any language restrictions, which made it difficult to assess the risk of language bias. Data were extracted by two reviewers independently, but it was not reported whether the same method was used to select the studies for the review.

There was no assessment of study quality, which would have been useful given that most of the studies were observational in design and consequently at a greater risk of bias. The methods of meta-analysis seemed appropriate. The authors assessed heterogeneity, but the pooling of data from different study designs was questionable. Reporting the results of a case-control study as a risk ratio was incorrect.

Although the conduct of this review appears to be fairly good, the conclusions should be treated with caution as they are based mainly on observational studies without any consideration of their quality.

Implications of the review for practice and research
The authors did not make any recommendations for practice or research.

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