The importance of baseline viral load when assessing relative efficacy in treatment-naive HBeAg-positive chronic hepatitis B: a systematic review and network meta-analysis


CRD summary
This review's conclusions emphasised the importance of adjusting for baseline viral load when assessing the relative efficacy of chronic hepatitis B treatments in achieving an undetectable viral load. These conclusions are likely to be reliable.

Authors' objectives
To evaluate the importance of variation in initial viral load when assessing the relative efficacy of treatments for chronic hepatitis B.

Searching
EMBASE, MEDLINE, and Cochrane Central Register of Controlled Trials (CENTRAL) were searched to April 2011 for studies published in English. A search strategy was presented in an appendix. Abstracts from the European Association for the Study of the Liver, and the American Association for the Study of Liver Diseases, 2010 and 2011 annual conferences, were searched.

Study selection
Randomised controlled trials (RCTs) of adults with hepatitis B e antigen (HBeAg)-positive chronic hepatitis B were eligible if they studied a licensed-dose monotherapy of interferon alpha, pegylated interferon alpha-2a or 2b, lamivudine, adefovir, dipivoxil, entecavir, tenofovir, or telbivudine. Trials could be head-to-head comparisons, or versus placebo. Outcomes could be: alanine transaminase normalisation, histological improvement, HBeAg seroconversion, or the achievement of undetectable viral load at one year.

The most common treatments, in the included trials, were entecavir, lamivudine, adefovir and telbivudine. Patient mean age ranged from 28 to 40 years, and around three-quarters of them were male. Initial viral load ranged from 1.8 to 10.3 log_{10} copies per mL. Where stated, the lower quantification level for undetectable viral load ranged from 200 to 400 copies per mL.

Two reviewers independently selected studies, with disagreements resolved by a third reviewer.

Assessment of study quality
Trial quality was assessed using questions from the Cochrane Handbook, covering the description of randomisation and allocation concealment, baseline characteristics, treatment blinding, eligibility criteria, and the use of intention-to-treat data.

The authors did not state how many reviewers assessed quality.

Data extraction
Three reviewers independently extracted the data to calculate relative risks. Disagreements were resolved by two other reviewers.

Methods of synthesis
Network meta-analyses were performed and the results were presented as relative risks with 95% credible intervals. A fixed-effect model was used for unadjusted data, and a fixed-effect and a random-effects model were used when adjusting by baseline viral load. A Bayesian approach was used, with uninformative priors for the unadjusted analyses, for all model parameters. For the adjusted analyses, individual patient data from an entecavir clinical trial were used to inform the prior distributions on the regression coefficient associated with baseline viral load. The efficacy estimates were presented relative to 0.5mg entecavir. Sensitivity analyses were performed by adding or removing individual trials because of heterogeneity.
**Results of the review**

Fourteen RCTs (4,253 patients) were included in the network meta-analysis. In half the trials, the allocation concealment method was not described. The details of blinding were ambiguous; only four trials adequately described treatment blinding, but 10 trials were reported as double blind and one was reported as single blind. All but one of the trials used intention-to-treat data.

For the unadjusted analysis, tenofovir was significantly more effective than entecavir for undetectable viral load (RR 1.43, 95% CrI 1.30 to 1.54) and all other treatments were significantly less effective than entecavir, except telbivudine where there was no statistically significant difference.

For the random-effects adjusted analysis, entecavir produced significantly increased risk ratios for undetectable viral load at one year, compared with all interventions, except telbivudine (RR 0.64, 95% CrI 0.18 to 1.19) and tenofovir (RR 1.21, 95% CrI 0.48 to 1.51). Similar results were seen in the sensitivity analyses.

**Authors’ conclusions**

This study demonstrated the importance of adjusting for baseline viral load when assessing the relative efficacy of chronic hepatitis B treatments in achieving an undetectable viral load.

**CRD commentary**

This review addressed a clear question and was supported by reproducible eligibility criteria. Several relevant electronic databases were searched, and attempts were made at identifying recent unpublished trials. The restriction to articles published in English means that some relevant trials may have been missed. Appropriate methods were reported to reduce the risks of reviewer error and bias for most parts of the review.

Trial quality was assessed, but the results were not used to inform the network meta-analyses, nor the discussion of the results (the authors did suggest further research exploring the impact of study design). Appropriate methods were used to pool the data in network meta-analyses, which utilised both direct and indirect evidence.

A potential conflict of interests existed for two of the review authors, who were employees of Bristol-Myers Squibb, the manufacturer of entecavir, but the authors’ conclusions are likely to be reliable.

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

**Practice:** The authors stated that reimbursement agencies should only use covariate-adjusted relative efficacy estimates for making decisions on treatments for chronic hepatitis B.

**Research:** The authors stated that research was needed to explore the impact of other potentially clinically-relevant covariates on the relative effects of comparators and the probability of achieving undetectable viral load.

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