Hepatitis B immunoglobulin and lamivudine improve hepatitis B-related outcomes after liver transplantation: meta-analysis


CRD summary
The review concluded that combination therapy reduced hepatitis B virus-related morbidity and mortality in hepatitis B virus-infected recipients of liver transplants when compared against treatment with hepatitis B immunoglobulin. The authors' conclusions should be interpreted with caution due to the poor reporting of the review methods and the methodological limitations of the included studies.

Authors' objectives
To compare combined therapy with hepatitis B immunoglobulin and lamivudine with hepatitis B immunoglobulin monotherapy in the prevention of hepatitis B virus-related morbidity and mortality.

Searching
MEDLINE, PubMed, EMBASE, TOXNET, Scopus and Web of Science were searched in all languages from inception to May 2007. Search terms were reported. Bibliographies of primary and review articles were searched for relevant studies. Only peer-reviewed articles and not conference abstracts were eligible for inclusion.

Study selection
Retrospective or prospective cohort studies with a control (or historic control) and controlled clinical trials that allowed assessment of hepatitis B recurrence after transplantation with more than five participants per treatment arm were eligible for inclusion. Eligible studies investigated hepatitis B immunoglobulin and lamivudine combination therapy compared with hepatitis B immunoglobulin alone. Studies needed to report at least one of the following outcomes: the primary outcome of hepatitis B virus recurrence (defined as the reappearance of HBsAg after transplantation); or the secondary outcomes hepatitis B virus-related death (death after a liver transplant attributed to hepatitis B virus). The baseline population had to be clearly defined regarding HBsAg positive status for included studies.

Studies that included rheumatologic diseases, human immunodeficiency virus (HIV), transplants other than the liver and cancer chemotherapy patients were excluded.

In included studies, participants studies ranged from 40 to 50 years old (median). The proportion of hepatitis B virus DNA positive participants varied from 0 to 100 per cent. Follow-up varied from seven to 98 months (median). Study populations were predominantly male. Most patients in the included studies received hepatitis B immunoglobulin IV 10,000 IU daily then reduced the frequency of this dose, and 150 mg lamivudine per day. Immunosupression used at the time of transplant varied (for example, azathioprine, cyclosporine, prednisone).

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

Data extraction
The cumulative rate of each outcome was calculated for each treatment arm and standardised by the total number of participants in each trial. Odds ratios and their corresponding 95% confidence intervals between treatment arms were calculated using the Peto method. The authors stated neither how the data were extracted for the review nor how many reviewers performed the data extraction.

Methods of synthesis
Odd ratios were pooled in a random-effects meta-analysis. Statistical heterogeneity was assessed with Cochran Q statistic and the Breslow and Day test. Funnel plots and Egger's test were used to evaluate publication bias.

Results of the review
Six studies were included in the meta-analysis (n=317): two prospective (n=79) and four retrospective (n=238). All used historical controls. Sample size ranged from 19 to 117 participants.

There was no evidence of statistical heterogeneity or publication bias.

Hepatitis B immunoglobulin combined with lamivudine was associated with reduced risk of: hepatitis B virus recurrence (six studies), odds ratio 0.08 (95% confidence interval: 0.03, 0.21, p<0.001); hepatitis B virus-related death (three studies), odds ratio 0.08 (95% confidence interval: 0.02, 0.33, P<0.001); and all-cause mortality (three studies), odds ratio 0.21 (95% confidence interval: 0.06, 0.82, p=0.02) compared with hepatitis B immunoglobulin alone.

The rate of recurrence of hepatitis B virus was 4.1 per cent with combination therapy compared with 36.1 per cent for hepatitis B immunoglobulin (number needed to treat was four). Hepatitis B virus-related death was 0.8 per cent compared with 15.1 per cent hepatitis B immunoglobulin (number needed to treat was seven). All-cause mortality was 5.1 per cent with combination therapy compared with 22.2 per cent with hepatitis B immunoglobulin (number needed to treat was six).

No studies reported harmful effects of combination therapy.

**Authors’ conclusions**
Combination therapy of hepatitis B immunoglobulin and lamivudine improved hepatitis B virus-related morbidity and mortality in hepatitis B virus infected recipients of liver transplants compared with hepatitis B immunoglobulin alone. However, the review was limited by small studies and varying levels of immunosuppression.

**CRD commentary**
The research question was well defined and supported by inclusion criteria for participants, intervention, outcomes and study design. Relevant databases were searched. But, the authors did not report any attempts to identify unpublished sources and this may have led to relevant studies being missed. Tests did not provide any evidence of publication bias, but the small number of studies may have made the tests unreliable. All languages were searched, which reduced the possibility of language bias. The review process was not described, so the reader did not know if any measures were taken to minimise the possibility of reviewer error and bias. Statistical heterogeneity between studies was assessed and no significant differences detected. The methodological quality of primary studies was not assessed, but the study designs of the included studies and small sample sizes suggested that the data (and the synthesis of the data) may not have been reliable. The authors’ conclusions should be interpreted with caution due to the poor reporting of the review methods and the methodological limitations of the included studies.

**Implications of the review for practice and research**
Practice: The authors did not state any implications for practice.

Research: The authors stated that future studies should examine duration, dose and route of administration of hepatitis B immunoglobulin and newer anti-hepatitis B virus agents in combination with hepatitis B immunoglobulin.

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