Lamivudine for the treatment of hepatitis B virus-related liver disease after renal transplantation: meta-analysis of clinical trials

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CRD summary
This review evaluated the efficacy and safety of lamivudine for the treatment of hepatitis B following renal transplantation. The authors found that rates of virological and biochemical response to lamivudine were high and the drug was well tolerated, but lamivudine resistance was frequent after prolonged therapy. The conclusions are based on evidence from uncontrolled studies and, therefore, may not be reliable.

Authors' objectives
To evaluate the safety and efficacy of initial lamivudine monotherapy in renal transplant recipients with hepatitis B.

Searching
The authors searched MEDLINE, Current Contents and selected specialty journals were searched from 1990 to July 2002; the three keywords used were reported. No language restrictions were imposed. The reference lists from qualitative reviews and published clinical trials were also checked.

Study selection
Study designs of evaluations included in the review
Inclusion criteria for the study designs were not specified. All of the included studies were prospective cohort studies.

Specific interventions included in the review
Studies of primary lamivudine therapy were eligible for inclusion. In the included studies, the dose of lamivudine ranged from 50 to 150 mg/day and the duration of lamivudine therapy from 4 to 35 months.

Participants included in the review
Eligible participants were renal transplant recipients with hepatitis B. Studies that included patients on maintenance haemodialysis or peritoneal dialysis were excluded, as were studies that included patients infected with the human immunodeficiency virus, haemophilia or liver diseases other than hepatitis B. The mean age of participants in the included studies ranged from 30 to 52 years and 54 to 100% were men. The mean time from transplantation to the start of treatment, where reported, ranged from 8 to 156 months.

Outcomes assessed in the review
The primary efficacy outcomes eligible for inclusion were hepatitis B e antigen (HBeAg) and/or hepatitis B virus DNA (HBV-DNA) clearance after lamivudine therapy. The secondary outcomes included drop-out rate and lamivudine resistance as measures of tolerability, and biochemical response (normalisation of alanine aminotransferase (ALT) levels at the end of treatment).

How were decisions on the relevance of primary studies made?
The authors did not state how the papers were selected for the review, or how many reviewers performed the selection. There was 100% agreement between reviewers with respect to the final inclusion or exclusion of studies.

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

Data extraction
Two reviewers independently extracted the data and consensus was achieved for all data. The data were extracted on an intention-to-treat basis. Data on HBV-DNA and HBeAg clearance, lamivudine resistance and ALT normalisation from the included studies were used to calculate pooled summary estimates.

**Methods of synthesis**

**How were the studies combined?**
The studies were combined by meta-analysis using the DerSimonian and Laird random-effects model. Ninety-five per cent confidence intervals (CIs) for summary estimates were computed using non-parametric (bootstrap) methods, each with 1,000 re-samples.

**How were differences between studies investigated?**
Chi-squared tests were used to test for homogeneity across the studies. Spearman correlation coefficients were used to assess associations between outcomes and variables thought to be potential sources of heterogeneity. P-values of less than 0.05 were considered statistically significant.

**Results of the review**

Fourteen studies (n=184) were included.

The mean overall estimate for HBV-DNA clearance (14 studies) was 91% (95% CI: 86, 96). For HBeAg clearance (12 studies) the pooled estimate was 27% (95% CI: 16, 39), while for ALT normalisation (9 studies) the estimate was 81% (95% CI: 70, 92).

None of the above meta-analyses tested significant for heterogeneity (P>0.05), suggesting that the studies were homogeneous for the primary outcomes.

The overall estimate for lamivudine resistance (8 studies) was 18% (95% CI: 10, 37). Two studies reported any drug-related drop-outs. HBV-DNA and HBeAg clearance were not associated with percentage of male patients, percentage with cirrhosis, race, age or lamivudine dose.

**Authors' conclusions**
The majority of the patients had a high virologic and biochemical response to lamivudine therapy and the drug was well tolerated. Lamivudine resistance was frequent with prolonged therapy, potentially limiting its long-term efficacy.

**CRD commentary**
The review addressed a clear question with explicit inclusion criteria, although no criteria were specified for the study designs. The search had no language restrictions, but the number of sources searched was limited and only three keywords were used, so it is possible that relevant studies were missed. Some measures were taken to reduce the risk of reviewer errors during the review process (duplicate data extraction). The methods used to select studies for the review were not reported clearly, so it is difficult to comment on the risk of errors or bias being introduced at this stage. Validity was not assessed and all the included studies were uncontrolled case series, which are a poor source of evidence for effectiveness. The authors investigated heterogeneity between the pooled studies but the risk of bias and confounding in uncontrolled studies is high, therefore the results of the meta-analyses may not be reliable. The risk of publication bias was not assessed. In view of the weakness of the evidence and the methodological weaknesses of the review, the authors' conclusions may not be reliable.

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

**Bibliographic details**

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Record Status
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.