Lamivudine or lamivudine combined with hepatitis B immunoglobulin in prophylaxis of hepatitis B recurrence after liver transplantation: a meta-analysis

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CRD summary
This review concluded that lamivudine plus hepatitis B immunoglobulin effectively reduced hepatitis B virus recurrence and YMDD mutant incidence in liver transplant patients, but did not improve patient or graft survival compared with lamivudine monotherapy. Limitations with the included trials, such as trial quality and the data synthesis, suggest that the authors’ conclusions should be interpreted with caution.

Authors’ objectives
To assess the effects of lamivudine monotherapy and lamivudine combined with hepatitis B immunoglobulin in the prevention of hepatitis B virus recurrence in patients who have received liver transplant.

Searching
The following databases were searched up to April 2008 without language restrictions: EMBASE, MEDLINE, BIOSIS Previews, CINAHL, the China National Knowledge Infrastructure (CNKI) and DERWENT. Search terms were reported. In addition, eleven journals were manually searched for published articles between 1988 and April 2008.

Study selection
Case-control and cohort studies randomising allogeneic liver transplant patients to the intervention arm (lamivudine plus hepatitis B immunoglobulin) or control arm (lamivudine monotherapy) for prevention of hepatitis B virus recurrence were eligible for inclusion.

The majority of included studies administered lamivudine 100mg per day and intramuscular hepatitis B immunoglobulin 400 to 800 IU per month. The majority of studies included patients who were identified as hepatitis B virus-DNA positive before liver transplantation.

Two reviewers independently screened studies for inclusion.

Assessment of study quality
Two reviewers independently assessed study quality on the following criteria: randomisation, allocation concealment, blinding, sample size, and completeness of follow-up. No other details were provided.

Data extraction
Two reviewers independently extracted data on: hepatitis B virus recurrence; YMDD mutants (i.e. patients on lamivudine therapy who tested hepatitis B virus DNA negative initially and became DNA positive subsequently); patient and graft survival; and disease related death (hepatitis B virus recurrence and hepatocellular carcinoma). Relative risks (RRs) and their 95% confidence intervals (CIs) were calculated. Data on hepatitis B recurrence in hepatitis B virus DNA positive patients before liver transplantation were also extracted.

Methods of synthesis
Relative risks and their 95% confidence intervals were combined using a fixed-effect model. Statistical heterogeneity was assessed using the Cochrane Q and $I^2$ tests.

Publication bias was assessed using a funnel plot.

Results of the review
Six trials were included in the review (n=551 patients); one was prospective and five were retrospective. Sample sizes ranged from 29 to 165 patients. All trials randomised patients to treatment groups, but only one reported methods for
randomisation. All trials had complete follow-up, but none were double blind. Follow-up ranged between 60 and 104 months.

Patients receiving lamivudine plus hepatitis B immunoglobulin showed a significant reduction in the rate of hepatitis B recurrence (RR 0.38, 95% CI 0.25 to 0.58; six trials), and YMDD mutants (RR 0.40, 95% CI 0.23 to 0.72; five trials) compared with patients receiving lamivudine monotherapy. Lamivudine plus hepatitis B immunoglobulin also had a significant reduction in hepatitis B recurrence in hepatitis B virus DNA positive patients before liver transplantation (RR 0.31, 95% CI 0.21 to 0.45; five trials).

No significant differences in patient and graft survival or disease related death were observed between the two treatment groups. There was no evidence of significant statistical heterogeneity for any comparisons, and no evidence of publication bias using a funnel plot.

Authors' conclusions
Lamivudine in combination with hepatitis B immunoglobulin effectively reduced hepatitis B virus recurrence and the incidence of YMDD mutant, but did not improve patient and graft survival compared with lamivudine monotherapy. Further research is warranted.

CRD commentary
The review question and inclusion criteria were clearly stated. Several appropriate databases and sources were searched without language restrictions, minimising the potential for language bias. There was no apparent attempt to identify unpublished papers to reduce the potential for publication bias, but assessment of publication bias indicated no evidence of bias. The authors went some way to reduce reviewer error and bias by undertaking each step of the review process in duplicate.

Trial validity was assessed using appropriate criteria, but the quality of the trials appeared to be fairly low. Details on patient characteristics were lacking, which meant that it was unclear whether patients were comparable at baseline and whether it was appropriate to combine the trials. In addition, sample sizes were generally small and confidence intervals appeared very wide for some comparisons, reducing the robustness of the results.

Given the above limitations, the authors' conclusions should be interpreted with caution, although their recommendation for further research appears appropriate.

Implications of the review for practice and research
Practice: The authors stated that as the combination therapy showed no improvement in the survival rate of patients, hepatitis B immunoglobulin should not be administered at a high dose of 10,000 IU per month.

Research: The authors stated that further large, well-conducted trials are needed to assess the efficiency of lamivudine plus hepatitis B immunoglobulin for the prevention of hepatitis B virus recurrence in liver transplant patients.

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