An efficacy and cost-effectiveness analysis of combination hepatitis B immune globulin and lamivudine to prevent recurrent hepatitis B after orthotopic liver transplantation compared with hepatitis B immune globulin monotherapy


**Record Status**
This is a critical abstract of an economic evaluation that meets the criteria for inclusion on NHS EED. Each abstract contains a brief summary of the methods, the results and conclusions followed by a detailed critical assessment on the reliability of the study and the conclusions drawn.

**Health technology**
The use of two strategies for long-term immunoprophylaxis of hepatitis B virus (HBV) in patients who had undergone orthotopic liver transplantation (OLT). The strategies examined were hepatitis B immune globulin (HBIG) monotherapy versus a combination of HBIG and lamivudine. Lamivudine (150 mg/day) was administered orally while HBIG was administered under a standard protocol. The standard protocol was 10,000 IU intravenously during the anhepatic phase, 10,000 IU/day intravenously for one week, then 10,000 IU intravenously every month.

**Type of intervention**
Secondary prevention.

**Economic study type**
Cost-effectiveness analysis.

**Study population**
The study population comprised patients who had undergone OLT and received long-term immunoprophylaxis.

**Setting**
The setting was secondary care. The economic study was conducted in California, USA.

**Dates to which data relate**
The effectiveness data were gathered from 1991 to 1998. The dates relating to resource use were not reported. The price year was not given.

**Source of effectiveness data**
The effectiveness evidence was derived from a single study and authors’ assumptions.

**Link between effectiveness and cost data**
The costing was not conducted on the same sample of patients as that used in the effectiveness study.

**Study sample**
The use of power calculations was not reported. A sample of 71 patients who received immunoprophylaxis therapy at the study centre was considered for the analysis. Patients that received HBIG alone between February 1991 and December 1995 were included in the monotherapy group, while those that received both HBIG and lamivudine between February 1994 and November 1998 were included in the combination group. There were 12 patients (8 men) in the
monotherapy group and 59 (47 men) in the combination group. The median age at OLT was 44 years in the monotherapy group (age range: 23 - 59) and 50 years in the combination group (age range: 18 - 67 years). All of the patients had undergone OLT for HBV-related liver disease before the immunoprophylaxis therapy.

**Study design**
This was a retrospective comparative study with historical controls that was conducted in a single centre, the Dumont-University of California at Los Angeles Liver Transplant Center. For the assessment of HBV recurrence, the median follow-up was 663 days (range: 10 - 2,590) in the monotherapy group and 459 days (range: 30 - 1,855) in the combination group. For the assessment of HBV DNA, the median follow-up was 416 days (range: 65 - 1,855) in the combination group. The follow-up was initially weekly (from discharge to stable) then biweekly or monthly. Standard biochemical tests of liver function were performed at each follow-up visit. It appears that no patient has been lost to follow-up.

**Analysis of effectiveness**
All the patients included in the initial study sample were considered in the effectiveness analysis. The health outcomes used were the HBV recurrence rate post-OLT, the overall patient survival rate and the allograft failure rate. The baseline comparability of the two groups of patients was not commented upon.

**Effectiveness results**
The HBV recurrence rate post-OLT was 25% with monotherapy. No patient had HBV recurrence with combination therapy (0%).

The overall patient survival rate was 83.3% in the monotherapy group after a mean follow-up of 15.1 months (range: 1 - 86.3), and 98.3% in the combination group after a mean follow-up of 15.3 months (range: 1 - 61.8).

The overall allograft failure rate was 16.7% in the monotherapy group and 10.2% in the combination group.

**Clinical conclusions**
The effectiveness study showed that combination therapy was associated with better outcomes, such as overall patient survival and a reduction in HBV recurrence, than standard monotherapy.

**Modelling**
A decision analytic model was developed to assess the long-term costs and benefits of combination therapy versus monotherapy for the immunoprophylaxis of HBV in OLT patients. Details of the model, which appears to have been deterministic, were not provided.

**Methods used to derive estimates of effectiveness**
The authors made some assumptions that were used in the decision model.

**Estimates of effectiveness and key assumptions**
It was assumed that monthly laboratory assessments were obtained from each patient and a liver biopsy was performed when abnormal clinical or laboratory parameters were identified. In addition, all patients who developed recurrent HBV despite prophylaxis would undergo re-transplantation within the 2-year time horizon of the model. The authors also assumed that one in 60 patients had an HBV recurrence that required re-transplantation (1.6%). This assumption was made to bias the analysis against combination therapy, as no patient in the authors' series developed recurrent HBV.

**Measure of benefits used in the economic analysis**
The summary benefit measure used in the economic analysis was the rate of HBV recurrence prevented. This was derived from the effectiveness study. No discounting was applied.

**Direct costs**
Discounting was not relevant since the costs per patient were incurred within a timeframe of 2 years. The unit costs were presented separately from the quantities of resources used. The health services included in the economic evaluation were HBIG, lamivudine, liver biopsy, re-transplantation and laboratory tests. The cost of HBIG included nursing time, methylprednisolone infusion, and recovery room time. The cost/resource boundary of the study was that of the third-party payer. The costs were estimated from actual Medicare fees. Resource use appears to have been mainly derived from the authors' assumptions. The price year was not reported.

**Statistical analysis of costs**
The costs were treated deterministically in the base-case.

**Indirect Costs**
The indirect costs were not considered.

**Currency**
US dollars ($).

**Sensitivity analysis**
Threshold analyses were conducted to address the issue of uncertainty in the data. Several cost and probability estimates were varied.

**Estimated benefits used in the economic analysis**
The rate of HBV recurrence prevented was 75% with monotherapy and 98.4% with combination therapy. Therefore, combination therapy led to a marginal gain of 23.4% in terms of HBV recurrence prevented.

**Cost results**
The estimated cost was $272,863 with monotherapy and $248,077 with combination therapy. This led to an incremental cost of $24,786 per patient in favour of combination therapy.

**Synthesis of costs and benefits**
Average and incremental cost-effectiveness ratios were calculated to combine the costs and benefits of the two immunoprophylaxis strategies.

Combination therapy was both more effective and less costly than monotherapy, it was therefore considered dominant.

The average cost per HBV recurrence prevented was $362,570 with monotherapy and $252,111 with combination therapy.

The sensitivity analysis showed that monotherapy would become the most cost-effective strategy if the recurrence rate of combination therapy reached 24% or greater, or the cost of lamivudine exceeded $4,640 per month (the base-case estimate was $111 per month). In addition, the recurrence rate with monotherapy would have to decrease to less than 2% before both strategies could be considered equally cost-effective.

Due to the low acquisition price of lamivudine and a study showing that lamivudine monotherapy resulted in a
recurrence rate of 29%, the authors calculated the average cost-effectiveness ratio for lamivudine monotherapy to be $50,490 per recurrence prevented. Under this scenario, the incremental cost per recurrence prevented with combination therapy relative to lamivudine monotherapy was $831,571. However, it was highlighted that lamivudine monotherapy cannot be considered comparable to the combined therapy because it is characterised by a substantial higher HBV recurrence rate.

Authors' conclusions
Combination prophylaxis with hepatitis B immune globulin (HBIG) and lamivudine represented a cost-effective strategy, in comparison with HBIG monotherapy alone, for the prevention of hepatitis B virus (HBV) infection after orthotopic liver transplantation (OLT).

CRD COMMENTARY - Selection of comparators
The authors justified their choice of the comparators. HBIG represented the standard prophylactic approach before the introduction of lamivudine. The potential use of lamivudine monotherapy was considered only for comparative purposes, although it did not represent an actual comparator due to the superior efficacy of combination therapy. You should decide whether HBIG monotherapy represents a valid comparator in your own setting.

Validity of estimate of measure of effectiveness
The effectiveness evidence was derived from a retrospective comparative study. The groups were evaluated in two different time periods (albeit with a short overlap), which represented two eras of transplantation. Therefore, two different prophylactic strategies were compared. The main limitation associated with this design is the potential impact of factors other than the study interventions on the results of the analysis. The baseline comparability of the two groups of patients was not discussed, and it was not stated whether treatment patterns were similar. The authors admitted that the two groups were studied in two different periods and noted that some changes in treatments occurred. For example, most of the monotherapy patients received cyclosporine while the combination therapy patients were predominantly administered tacrolimus. However, the authors stated that this change in treatment patterns was unlikely to have affected the incidence of outcomes.

No statistical test was conducted in the effectiveness analysis and there was no evidence that the size of the sample was appropriate. The sample size appears to have been relatively low, in particular in the monotherapy arm. Consecutive patients were included in the analysis and the study sample was likely to have been representative of the study population. However, the study was conducted in a single centre and might not reflect epidemiologic and treatment patterns across the USA. These issues tend to limit the internal validity of the analysis. Some assumptions were also made and uncertainty was investigated in the sensitivity analysis.

Validity of estimate of measure of benefit
The benefit measure was derived directly from the effectiveness study. Since it represented a measure specific to the disease under evaluation, it could be difficult to compare it with the benefits of other health care interventions. The impact of the treatment on quality of life was not investigated.

Validity of estimate of costs
The authors reported explicitly which perspective was adopted in the study. It appears that all the relevant categories of costs have been included in the analysis. The indirect costs, which were irrelevant from the perspective of the health care system, were not considered. However, the authors noted that their inclusion would have favoured combination therapy, therefore resulting in an even more favourable cost-effectiveness ratio. The unit costs and the source of the cost data were reported. However, the price year was not given, which makes reflation exercises in other settings difficult. Resource use was mainly derived from the authors’ assumptions. Statistical tests on the costs were not conducted, but sensitivity analyses were performed on the cost estimates.
Other issues
The authors made a few comparisons of their findings with those from other studies. They did not, however, address the issue of the generalisability of the study results to other settings. Sensitivity analyses were performed, which partially enhance the external validity of the analysis. The authors noted that the cost-effectiveness of combination therapy could have been underestimated, as conservative assumptions favouring monotherapy were made and the re-transplantation costs could be far higher than those considered in the study.

Implications of the study
The authors stressed that longer follow-up would be helpful and further clinical trials should investigate the cost-effectiveness of combination therapy.

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