Conversion from intravenous to intramuscular hepatitis B immune globulin in combination with lamivudine is safe and cost-effective in patients receiving long-term prophylaxis to prevent hepatitis B recurrence after liver transplantation

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 intramuscular hepatitis B immune globulin (IM HBIG) in combination with lamivudine, for the prevention of recurrent hepatitis B virus (HBV) infection after liver transplantation.

Type of intervention
Secondary prevention.

Economic study type
Cost-effectiveness analysis.

Study population
The study population comprised patients who had undergone OLT for HBV. The authors did not report any exclusion criteria.

Setting
The setting was secondary care. The economic study was carried out in Los Angeles (CA), USA.

Dates to which data relate
The effectiveness data related to 1993 to 2000. Some of the resource use data also related to 1993 to 2000, but the dates to which the rest of the cost data related were unclear. The price year was not stated.

Source of effectiveness data
The effectiveness data for the treatment of interest (i.e. IM HBIG combined with lamivudine) were derived from a single study. The effectiveness estimates for the other comparators were derived from a review of completed studies.

Link between effectiveness and cost data
Some of the resource use data were derived from the same study used as a source of effectiveness evidence.

Study sample
The study size was not determined in the planning phase of the study. The participants were selected consecutively as they underwent OLT for HBV. The study question addressed patients undergoing OLT for HBV, so the study sample appears to have been suitable for the study question. However, some of the patients initially received IV HBIG before being converted to IM HBIG, while others received only IM HBIG. The inclusion of patients who were previously maintained on IV HBIG may impact on the applicability of the results to patients who will only be maintained on IM
HBIG. The final study sample comprised 59 patients. The authors did not report any exclusions or refusals to participate.

**Study design**
The study was a case series that was conducted in a single centre. The median follow-up was 1,051 days. The authors did not report any loss to follow-up.

**Analysis of effectiveness**
All of the patients included in the study were accounted for in the analysis. The primary health outcome was recurrence of HBV. Recurrence of HBV was defined as the reappearance of hepatitis B surface antigen in serum after its initial disappearance following OLT.

**Effectiveness results**
Fifty-six patients (94.9%) survived at a median follow-up of 1,051 days.

At a median follow-up of 1,051 days after beginning treatment with IM HBIG and lamivudine, 58 patients (98.3%) did not have recurrent HBV infection, but this number included 3 patients who had died.

**Clinical conclusions**
The authors concluded that IM HBIG combined with lamivudine is of similar efficacy to IV HBIG combined with lamivudine in preventing the recurrence of HBV infection.

**Modelling**
A Markov model was used estimate the cost-effectiveness of IM HBIG combined with lamivudine, and to extrapolate the trial data to 5 years. The model had four possible scenarios:

- no recurrence of HBV on IM HBIG and lamivudine;
- no recurrence of HBV but requirement for supplementary IV HBIG;
- recurrence of HBV requiring re-transplantation; and
- death from other causes.

**Outcomes assessed in the review**
No details of the parameters derived from the literature were provided.

**Study designs and other criteria for inclusion in the review**
Not reported.

**Sources searched to identify primary studies**
Not reported.

**Criteria used to ensure the validity of primary studies**
Not reported.
Methods used to judge relevance and validity, and for extracting data
Not reported.

Number of primary studies included
Not reported.

Methods of combining primary studies
Not reported.

Investigation of differences between primary studies
Not reported.

Results of the review
Not reported.

Measure of benefits used in the economic analysis
The measure of health benefits used was number of cases of recurrent HBV infection prevented.

Direct costs
Some resource use quantities were reported separately from the costs. The study included the direct costs to a third-party payer. These comprised the costs of lamivudine, IM HBIG, IV HBIG, re-transplantation, death, liver biopsy and laboratory tests. The cost data were derived from published studies and the Medicare fee schedule. Discounting was relevant as the model extrapolated the data to 5 years, but it does not appear to have been applied. The study reported the average costs. The price year was not given.

Statistical analysis of costs
Some patient level data were available, but these were treated as point estimates. The study presented median quantities with the range.

Indirect Costs
The indirect costs were not included.

Currency
US dollars ($).

Sensitivity analysis
Sensitivity analyses were not performed.

Estimated benefits used in the economic analysis
The precise application of the study results to the Markov model was unclear. The reader is referred to the 'Effectiveness Results' section. The effectiveness parameters used for the comparators were not reported.

Cost results
The annual cost per patient of IM HBIG combined with lamivudine was $13,500 without supplementary IV HBIG, or $28,500 with supplementary IV HBIG.

The annual cost per patient of lamivudine monotherapy was $1,380.

The annual cost per patient of IV HBIG monotherapy was $180,000. This rose to $181,130 when combined with lamivudine.

**Synthesis of costs and benefits**
The costs and health outcomes were combined to calculate the average cost-effectiveness ratios.

The cost per recurrence prevented for the alternative strategies was:

- $52,600 for IM HBIG combined with lamivudine,
- $558,000 for IV HBIG monotherapy,
- $172,000 for lamivudine monotherapy, and
- $371,000 for IV HBIG combined with lamivudine.

**Authors' conclusions**
Intramuscular hepatitis B immune globulin (IM HBIG) combined with lamivudine is superior to HBIG monotherapy and lamivudine monotherapy. The authors argued that IM HBIG plus lamivudine is of similar efficacy to intravenous (IV) HBIG plus lamivudine, but is much cheaper.

CRD COMMENTARY - Selection of comparators
The comparators were selected to represent alternative methods of prophylaxis that had already been studied in the literature. You must decide whether these comparators are relevant in your own setting.

Validity of estimate of measure of effectiveness
The study design may not have been appropriate for the study question. The case series included an unspecified proportion of patients who had been maintained on IV HBIG combined with lamivudine prior to converting to IM HBIG, and the impact of this on the subsequent effectiveness was not discussed. The study also included a patient who switched to IV HBIG as IM HBIG was not effective enough. The study sample was, therefore, not representative of the study population of patients maintained only on IM HBIG combined with lamivudine (with potential supplementary IV HBIG). The analysis of effectiveness does not appear to have been handled credibly. Three patients who died during follow-up and one patient who converted to IV HBIG after IM HBIG was found to be ineffective were included in the calculation of recurrent HBV prevented. The source of effectiveness data for the comparators was unclear, and the point estimates were not reported. The study was not transparent in its use of effectiveness estimates and this prevents comparisons with other studies.

Validity of estimate of measure of benefit
The application of the effectiveness results from the case series to the Markov model was unclear. The authors stated that the costs and health outcomes were assessed over 5 years in the model, but only the number of patients who remained free of recurrent HBV infection at the end of the trial were reported. This prevents a clear interpretation of the study results.

Validity of estimate of costs
All the costs relevant to the perspective adopted were included in the analysis. Some quantities were reported separately.
from the costs. Where resource use estimates were estimated from the same study used to provide the effectiveness estimates, no statistical analysis was conducted. Other resource use data were based on the authors’ opinions. A sensitivity analysis was not used to explore uncertainty in resource use. The cost data were derived from the Medicare fee schedule and published studies. The references for the cost data were not clearly indicated, so their source remains unknown. The price year was not given, which hinders the generalisability of the study results. Although the costs were incurred during 5 years, discounting was not applied.

Other issues
The authors compared their findings with those from other studies, but the comparisons were unclear since the authors failed to clearly report the effectiveness results they applied in their model. The lack of transparency in the study makes generalisation difficult, and the authors did not address this issue. The authors appear to have presented the results selectively. The use of average cost-effectiveness ratios does not permit statements about one comparator being more or less cost-effective than another. The authors’ conclusions were not fully supported by the data they reported.

Implications of the study
The authors recommended that a controlled trial should be conducted to determine the optimal treatment strategy, including issues on the length of treatment and potential new comparators.

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