Prophylactic strategies for hepatitis B patients undergoing liver transplant: a cost-effectiveness analysis

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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
Adefovir dipivoxil, a rescue treatment for when lamivudine resistance develops, was the focus of the study. This treatment was offered in three different ways, defined within three potential treatment strategies. The three strategies were:

lamivudine monoprophylaxis pre-transplant, with adefovir dipivoxil rescue when lamivudine resistance developed (LAM/ADV);

combination prophylaxis with lamivudine pre-transplant and addition of indefinite high-dose hepatitis B immunoglobulin (HBIG) at transplant, with adefovir added when lamivudine resistance developed (LAM/HBIG);

combination prophylaxis with lamivudine pre-transplant, intravenous HBIG peri-transplant, and conversion to intramuscular HBIG for long-term maintenance, with adefovir added when lamivudine resistance developed.

Type of intervention
Treatment for lamivudine resistance following transplant in hepatitis B (HBV) patients.

Economic study type
Cost-utility analysis.

Study population
The hypothetical study population comprised a simulated cohort of 1,207 patients identical to the 1,207 patients who underwent orthotopic liver transplant for HBV cirrhosis from 1996 to 2004 in the United Network for Organ Sharing (UNOS) database. The median age was 52 years, and the median waiting time for treatment was 2.2 years.

Setting
The setting was secondary care. The economic study was carried out in Singapore.

Dates to which data relate
The effectiveness evidence was collated from studies published between 2000 and 2004. Resource use was determined by a decision model. The unit costs were taken from sources relating to 2003 and 2004 and were reflated to 2005 prices.

Source of effectiveness data
The effectiveness data were derived from a review and synthesis of studies.
Modelling
A Markov Model was used to simulate the costs and outcomes for the three treatment strategies. At any time point in the cycle the patients could be in one of the following Markov states: no recurrence, stable recurrence, viral resistance (sub-states: continue to remain stable, accelerated disease resulting in death, requiring re-transplant) or death. The analysis was conducted for 5 years post-transplant and for end of patient life expectancy of 15 years.

Outcomes assessed in the review
The following outcomes were assessed to ascertain probabilities for the model between 0 to 5 years and 5 to 15 years:

- the percentage of replicative patients (HBV DNA +ve);
- life expectancy;
- the incidence of HBV recurrence with LAM/HBIG and LAM/ADV at 1, 3, 5, 10 and 15 years;
- survival of HBV transplant with LAM/HBIG and LAM/ADV at 1, 3, 5, 10 and 15 years;
- the incidence of viral resistance with adefovir at 1, 3, 5, 10 and 15 years;
- the incidence of re-transplant for HBV recurrence;
- the incidences of renal impairment leading to ADV being stopped and leading to renal replacement therapy.

Study designs and other criteria for inclusion in the review
The authors reported that a systematic review of the literature was carried out. They aimed to extract data from the largest, most representative clinical trials identified that were published between 1996 and 2004 and that reported outcomes on the relevant treatments.

Sources searched to identify primary studies
The authors stated that PubMed was searched.

Criteria used to ensure the validity of primary studies
The authors aimed to include the largest and most representative clinical trial, but did not report how this was to be achieved.

Methods used to judge relevance and validity, and for extracting data
Not reported.

Number of primary studies included
Six primary studies published between 2000 and 2004 were included in the review.

Methods of combining primary studies
The authors used narrative methods, suggesting that variables from the largest trials were pooled.

Investigation of differences between primary studies
The authors reported that where clinical data were not available, they used the best available data favouring LAM/HBIG. Some differences between the studies, such as patient exclusions, were discussed.
Results of the review
The following variable estimates were used.

The percentage of replicative patients (HBV DNA +ve) was 55% for both analyses (0 - 5 years and 5 - 15 years).

Life expectancy was 15 years for both analyses (0 - 5 years and 5 - 15 years).

The incidence of HBV recurrence with LAM/HBIG was 0% at 1 year, 7% at 3 years, 11% at 5 years, 15% at 10 years and 17% at 15 years.

The incidence of HBV recurrence with LAM/ADV was 22% at 1 year, 38% at 3 years, 40% at 5 years, 55% at 10 years and 60% at 15 years.

Survival of HBV transplant with LAM/HBIG was 98% at 1 year, 93% at 3 years, 90% at 5 years, 85% at 10 years and 80% at 15 years.

Survival of HBV transplant with LAM/ADV was 93% at 1 year, 89% at 3 years, 83% at 5 years, 71% at 10 years and 65% at 15 years.

The incidence of viral resistance with adefovir was 0% at 1 year, 6% at 3 years, 10% at 5 years, 25% at 10 years and 40% at 15 years.

The incidence of re-transplant for HBV recurrence was 5% (estimated) for the 0 - 5 year analysis and 35% for the 5 - 15 year analysis.

The incidence of renal impairment leading to ADV being stopped was 2% per annum (estimated) for the 0 - 5 year analysis and 4% per annum for the 5 - 15 year analysis.

The incidence of renal impairment leading to renal replacement therapy was 1% per annum (estimated) for the 0 - 5 year analysis and 2% per annum for the 5 - 15 year analysis.

Methods used to derive estimates of effectiveness
The authors made some assumptions on the basis of the available evidence.

Estimates of effectiveness and key assumptions
The authors made assumptions to inform estimates on survival and the effectiveness of LAM/intramuscular (im)HBIG.

Measure of benefits used in the economic analysis
The incidence of HBV recurrence prevented and lives saved were used as summary measures of health benefit. Quality of life utility scores were adapted from the literature (Chong et al. 2004, see 'Other Publications of Related Interest' below for bibliographic details). The outcomes were discounted at a rate of 3%.

Direct costs
The authors reported that a societal perspective was adopted for the economic analysis. The analysis focused on the costs of prophylaxis and treatment. The cost of potential complications, such as renal impairment, regular screening liver biopsy for patients with HBV recurrence and accelerated disease, were also included. The unit costs were taken from the US Medicare fee schedule. Resource use was determined by the Markov model. The authors estimated all costs accrued until death and adjusted for inflation (2%) and discounting (3%). The price year was 2005.

Statistical analysis of costs
The costs were treated deterministically.
**Indirect Costs**
The authors stated that indirect costs to society and the individual encompassed the costs of follow-up, travelling and nursing care. It would appear that productivity costs were not included. These costs were adjusted for inflation and discounted in the same way as for the direct costs.

**Currency**
US dollars ($).

**Sensitivity analysis**
One- and two-way sensitivity analyses were carried out for each parameter to assess the robustness of the results and identify key drivers of cost-effectiveness. The ranges used in the analyses were informed by the ranges reported in the available literature. They also encompassed the costs of treatment in USA, Europe and Asia. The authors also investigated best- and worst-case scenarios.

**Estimated benefits used in the economic analysis**
The number of recurrences at 5 years was 506 (42%) for LAM/ADV, 121 (10%) for LAM/intravenous (iv)HBIG and 121 (10%) for LAM/imHBIG.

The number of recurrences at 15 years was 785 (65%) for LAM/ADV, 145 (12%) for LAM/ivHBIG and 145 (12%) for LAM/imHBIG.

The number of deaths at 5 years was 64 (5.3%) for LAM/ADV, 44 (3.7%) for LAM/ivHBIG and 44 (3.7%) for LAM/imHBIG.

The number of recurrences at 15 years was 173 (14%) for LAM/ADV, 81 (7%) for LAM/ivHBIG and 81 (7%) for LAM/imHBIG.

The number of life-years saved (LYS) per patient at 5 years was 4.02 for LAM/ADV, 4.18 for LAM/ivHBIG and 4.18 for LAM/imHBIG.

The number of LYS per patient at 15 years was 13.1 for LAM/ADV, 14 for LAM/ivHBIG and 14 for LAM/imHBIG.

The number of quality-adjusted life-years (QALYs) saved per patient at 5 years was 3.76 for LAM/ADV, 3.85 for LAM/ivHBIG and 3.85 for LAM/imHBIG.

The number of QALYs saved per patient at 15 years was 9.76 for LAM/ADV, 10.5 for LAM/ivHBIG and 10.5 for LAM/imHBIG.

**Cost results**
The total cost over 5 years was $31.4 million for LAM/ADV, $338 million for LAM/ivHBIG and $164 million for LAM/imHBIG.

The total cost over 15 years was $135 million for LAM/ADV, $814 million for LAM/ivHBIG and $303 million for LAM/imHBIG.

The total cost per patient over 5 years was $26,000 for LAM/ADV, $280,000 for LAM/ivHBIG and $136,000 for LAM/imHBIG.

The total cost per patient over 15 years was $112,000 for LAM/ADV, $674,000 for LAM/ivHBIG and $251,000 for LAM/imHBIG.
Synthesis of costs and benefits
The incremental cost over 5 years of LAM/ivHBIG over LAM/ADV was $796,000 per recurrence prevented, $15.3M per death prevented, $1.58 million per LYS and $2.8 million per QALY saved.

The incremental cost over 15 years of LAM/ivHBIG over LAM/ADV was $1.04 million per recurrence prevented, $7.4 million per death prevented, $624,000 per LYS and $760,000 per QALY saved.

The incremental cost over 5 years of LAM/imHBIG over LAM/ADV was $345,000 per recurrence prevented, $6.64 million per death prevented, $687,500 per LYS and $1.22 million per QALY saved.

The incremental cost over 15 years of LAM/imHBIG over LAM/ADV was $260,000 per recurrence prevented, $1.18 million per death prevented, $154,000 per LYS and $188,000 per QALY saved.

The sensitivity analysis revealed that the cost of HBIG had a significant impact on the incremental cost-effectiveness ratio.

Authors’ conclusions
The authors concluded "lamivudine prophylaxis followed by adefovir rescue is the most cost-effective strategy compared to either of the LAM/HBIG (lamivudine/hepatitis B immunoglobulin) combination strategies”, and that the cost of HBIG is the key cost-driver against the other two alternatives. However, treatment decisions may depend on the cost and willingness to pay for health outcomes associated with a specific setting.

CRD COMMENTARY - Selection of comparators
The authors compared three strategies for combating lamivudine resistance. The authors provided a thorough discussion of the increase in lamivudine resistance and the use of adefovir dipivoxil to combat this resistance. They then outlined three strategies for administering the technology of interest and compared their cost-effectiveness. You should decide if they represent valid comparators in your own setting.

Validity of estimate of measure of effectiveness
The authors carried out a systematic review of the literature, searching PubMed with clearly stated criteria to identify relevant literature. Further details on the review methodology (i.e. criteria to ensure the validity of the included studies, methods used to judge the relevance of the data extracted, and methods used to combine the primary data) might have been reported, further enhancing the internal validity of the study. In addition, it was unclear whether searching one source was sufficient to identify all of the relevant primary studies. The authors used extensive sensitivity analyses to explore the impact of parameter values on the results observed.

Validity of estimate of measure of benefit
The estimation of benefits was modelled with utility data taken from published sources. The use of QALYs provides a generic measure of health benefit that is widely comparable to other health technologies and across settings. The number of recurrences avoided provides a more specific comparator.

Validity of estimate of costs
The authors reported that a cost-effectiveness analysis was carried out from a societal perspective. Although they included costs to the patient, such as travel costs, the analysis should also have included broader economic costs to society, such as lost productivity due to illness and treatment. The authors provided a useful breakdown of the costs and reported the exact source for each estimate. This reporting improves the transparency of the analysis, enabling readers to better interpret the results and consider transferring the results to their own setting. An extensive sensitivity analysis further improves the generalisability of the results, and also demonstrates the robustness of the results observed and conclusions drawn.
Other issues
The authors were able to make extensive comparisons with results from related studies, drawing on the similarities but also explaining reasons for differences, where these existed. The issue of generalisability was considered at length and actions were taken to improve the generalisability to a wide range of settings. The conclusions drawn related well to the results presented and were an accurate reflection of the scope of the study. Several limitations were discussed. These focused on assumptions underlying the decision model, such as patients were assumed to be 100% compliant and that regular monitoring will identify in a timely fashion all patients who develop resistance.

Implications of the study
The authors did not make specific recommendations following their work, although the arguments they presented favoured lamivudine prophylaxis followed by adefovir when lamivudine resistance develops. Further work was suggested in the form of the need for longer term survival studies and prospective clinical trials.

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Other publications of related interest

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