Cost-effectiveness of suppressing hepatitis B virus DNA in immune tolerant patients to prevent hepatocellular carcinoma and cirrhosis

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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
The study examined the use of lamivudine (100 mg once daily) for suppressing hepatitis B virus (HBV) DNA levels in immune tolerant patients. This strategy was compared with no treatment (standard care).

Type of intervention
Primary prevention.

Economic study type
Cost-utility analysis

Study population
The study population comprised a hypothetical cohort of patients with immune tolerant HBV, defined as hepatitis Be antigen (HBeAg) positive, normal serum alanine aminotransferase, and viral load of greater than 1,000,000 copies/mL of HBV DNA without cirrhosis or HCC. Males and females were considered as two separate cohorts. The base-case patient was 40 years of age.

Setting
The setting was outpatients. The economic study was carried out in the USA.

Dates to which data relate
The clinical data were derived from studies published between 1995 and 2006. Resource use and cost estimates were obtained from studies published between 1998 and 2005. The price year was 2006.

Modelling
A Markov model was developed to simulate the clinical and economic impact of the two strategies under examination. The model had a time horizon of the patients’ lifetime and cycles of one year. The health states considered were viral suppression, ongoing viremia, seroconversion, HCC, cirrhosis and death. Patients not achieving viral suppression within the first year of lamivudine treatment discontinued therapy, whilst those who achieved viral suppression continue treatment over time. First-order Monte Carlo micro-simulation was performed. A graphical representation of the model was provided.

Study designs and other criteria for inclusion in the review
The clinical data used in the decision model were:

- lamivudine efficacy (probability of viral suppression after one year of treatment);
- the rate of development of resistance on lamivudine while virally suppressed;
- the rate of spontaneous seroconversion (in men and women);
- the annual rate of development of HCC or cirrhosis;
- the survival rate of HCC by year after diagnosis; and
the death rates (all-cause mortality and liver-related mortality in cirrhotic patients).

**Sources searched to identify primary studies**
HCC survival data were obtained from the Surveillance Epidemiology and End Results database. Transition probabilities for developing HCC and cirrhosis with and without lamivudine treatment were derived from the REVEAL study. Information on the other studies was not given.

**Methods used to derive estimates of effectiveness**
MEDLINE was systematically reviewed in order to identify relevant sources of data. Details of the review were not provided. Most of the data were derived from the REVEAL study, this study being selected because of its large sample size and long follow-up.

**Measure of benefits used in the economic analysis**
The summary benefit measure used was the expected number of quality-adjusted life-years (QALYs). These were estimated using the decision model. The utility weights used to adjust survival were derived from published studies that used the time trade-off approach to elicit preferences for health states. Physician surveys were also used to estimate utility weights. A decrease in utility from taking a daily medication was assumed to be 0.01 and was subtracted from the utility associated with that health state. Future QALYs were discounted at an annual rate of 3%. Unadjusted life expectancy, lifetime risk of HCC and cirrhosis were also reported as further model outputs.

**Direct costs**
The analysis was carried out from the perspective of the third-party payer. The cost categories included were drugs, physician visits, laboratory tests, abdominal ultrasound, costs of cirrhosis and HCC. The unit costs and the quantities of resources used were not presented separately, but macro-categories were reported. A breakdown of items for the costs of cirrhosis and HCC was not given. The costs and quantities were derived from published costs in the medical literature. Discounting was relevant given that long-term costs were assessed, and an annual rate of 3% was applied. The costs were updated to 2006 values using the health care component of the Consumer Price Index.

**Statistical analysis of costs**
The costs and quantities were treated deterministically.

**Indirect Costs**
Productivity costs were not considered.

**Currency**
US dollars ($).

**Sensitivity analysis**
A univariate sensitivity analysis was carried out to investigate the robustness of the model results to variations in all model inputs. The results were presented using a tornado diagram. Ranges of values were derived from the literature, or were defined by the authors (by halving and doubling the point estimate). Base-case results were estimated using first-order Monte Carlo simulations.

**Estimated benefits used in the economic analysis**
In men, the expected QALYs were 16.09 with no treatment and 17.10 with lamivudine treatment (difference 1.01).

In women, the expected QALYs were 18.586 with no treatment and 19.130 with lamivudine treatment (difference 0.544).

The unadjusted survival was 68 years with no treatment and 72 years with lamivudine treatment in men. The corresponding figures in women were 76 years and 77 years.

**Cost results**
In men, the expected lifetime costs were $17,900 with no treatment and $23,700 with lamivudine treatment (difference $5,900).

In women, the expected lifetime costs were $12,500 with no treatment and $19,400 with lamivudine treatment (difference $6,900).

**Synthesis of costs and benefits**

Incremental and average cost-utility ratios were calculated in order to combine the costs and benefits of the alternative strategies.

In men, the average cost per QALY was $1,111 with no treatment and $1,388 with lamivudine treatment. The incremental cost per QALY gained with lamivudine treatment over no treatment was $5,784.

In women, the average cost per QALY was $675 with no treatment and $1,014 with lamivudine treatment. The incremental cost per QALY gained with lamivudine treatment over no treatment was $12,584.

The sensitivity analysis showed that lamivudine treatment was more cost-effective with longer time horizons. Overall, the model results were robust to variations considered in the sensitivity analysis and lamivudine remained cost-effective. The cost of lamivudine treatment was the most influential parameter. However, even with an annual drug cost of $10,000 per year (four times the base-case costs), lamivudine treatment remained cost-effective with an incremental cost-effectiveness ratio of $25,000 per QALY in males and $54,000 per QALY in females.

**Authors’ conclusions**

The authors concluded that lamivudine treatment for hepatitis B virus (HBV) DNA suppression was a cost-effective alternative to no treatment in immune tolerant patients, in order to prevent hepatocellular carcinoma (HCC) and cirrhosis. Treatment was particularly cost-effective in male patients.

**CRD COMMENTARY - Selection of comparators**

The authors provided a justification for their choice of the comparator (i.e. no treatment), which represented the standard of care recommended by the American Association for the Study of Liver Disease. You should decide whether this is a valid comparator in your own setting.

**Validity of estimate of measure of effectiveness**

The effectiveness data were derived from published sources, which were only described in part. Much of the data were derived from the REVEAL study, which involved a large number of patients. However, details of other sources of clinical estimates were not provided, which limits the possibility of judging the validity of these inputs. Furthermore, no information on the search methods and criteria used to select the primary studies was provided. Clinical data were varied in the sensitivity analysis to take account of their variability and uncertainty.

**Validity of estimate of measure of benefit**

The benefits were appropriately modelled. QALYs are a valid benefit measure in that they capture the impact of the interventions on both quality of life and survival, which are relevant dimensions of health for patients with HBV. Sources of utility data were provided, as well as the instrument used to elicit preferences. Appropriate discounting was performed. QALYs are comparable with the benefits of other health care interventions.

**Validity of estimate of costs**

The analysis of the costs was consistent with the authors’ stated perspective. The main costs included in the analysis were reported, but most of them were presented only as macro-categories. Furthermore, details of the unit costs and the quantities of resources used were not given separately, which reduces the possibility of replicating the analysis in other settings. The cost estimates were varied in the sensitivity analysis, but economic data were not analysed stochastically in order to consider the uncertainty surrounding some estimates. The price year was reported, which will facilitate reflation exercises in other time periods.
Other issues
The authors stated that their study was the first economic evaluation to examine the potential treatment of patients with immune tolerant HBV in order to prevent cirrhosis and HCC. Thus, comparisons with other studies were not made. The issue of the generalisability of the study results to other settings was implicitly addressed in the sensitivity analysis, which considered wide ranges of clinical and economic inputs. The authors noted some limitations to their analysis. For example, it was unclear whether the results of the REVEAL study could be applicable to immune tolerant patients, as the majority of patients enrolled in the REVEAL study were HBeAg negative. Furthermore, clinical estimates were derived from very heterogeneous studies in terms of sample size, enrolled population and quality of the evidence. Finally, the model did not consider the impact of future lamivudine resistance. The results of the base-case analysis and the sensitivity analysis were clearly presented.

Implications of the study
The study results support the use of lamivudine treatment as a preventive intervention for HBV DNA suppression in immune tolerant patients. The authors suggest that future clinical trials should be undertaken to confirm the current findings.

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Other publications of related interest
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MeSH
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