Introduction of lamivudine for the treatment of chronic hepatitis B: expected clinical and economic outcomes based on 4-year clinical trial data
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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 introduction of lamivudine as a treatment option for chronic hepatitis B (CHB) in a setting where either alpha-interferon (IFN-a) or no treatment were the options available for CHB patients (scenario A). Depending on whether the doctors decided the patients were eligible for treatment with lamivudine and/or IFN-a, and whether they accepted the treatment, the patients could receive either lamivudine (100 mg once daily), IFN-a (10 MU three times per week for 4 months), or no treatment.

Type of intervention
Treatment and secondary prevention.

Economic study type
Cost-effectiveness analysis and cost-utility analysis.

Study population
The study population comprised a hypothetical cohort of CHB patients who were representative of Australian clinical practice (70% men; average age at commencement of treatment 30 years), with HB antigen e (HBeAg) positive and alanine aminotransferase levels greater than or equal to twice the upper limit of normal. Patients with HBeAg negative HB virus or who had failed IFN-a treatment were excluded. Since lamivudine is better tolerated than IFN-a, this study population has a greater proportion eligible for lamivudine treatment than IFN-a treatment.

Setting
The setting was not reported, but it may have been either secondary and/or tertiary care. The economic study was performed in Australia.

Dates to which data relate
The effectiveness evidence was obtained from studies published between 1981 and 2000. The data from one of these studies corresponded to 1977 to 1996. The cost data were obtained from studies published between 1997 and 1999. The price year was not reported.

Source of effectiveness data
The evidence for the final outcomes was derived from a non-systematic review of published studies, experts’ opinions obtained from questionnaires, an expert panel of hepatologists, and authors’ assumptions.

Modelling
A two-step modelling approach was undertaken to estimate the costs and outcomes associated with the three scenarios considered at analysis. A decision tree model was used to estimate the results associated with the first year of treatment.
These results were then extrapolated using a Markov model that considered annual cycles and a 69-year period. The total timeframe considered for both models was 70 years.

**Outcomes assessed in the review**
The model parameters assessed were:

the HBeAg seroconversion rates at year 1, 2, 3 and 4 after treatment with lamivudine and IFN-a, and the spontaneous seroconversion rate for patients not receiving treatment; and

the rate of progression to cirrhosis after 12 months of treatment with lamivudine, IFN-a, and no treatment for patients who did not seroconvert.

Other epidemiological parameters were also assessed:

the reactivation rate back to non-seroconverted CHB state during the first year after seroconversion;

the annual progression rate to compensated cirrhosis for seroconverted patients and for patients with CHB;

the annual rate of progression to decompensated cirrhosis;

the annual progression rate to hepatocellular cancer for CHB patients who had not yet progressed to cirrhosis and for those with cirrhosis;

the annual mortality rate for patients with compensated cirrhosis, with decompensated cirrhosis, and those with liver cancer.

**Study designs and other criteria for inclusion in the review**
Not reported. Among the studies included, there was one meta-analysis, several clinical trials, one randomised clinical trial, a prospective study, a retrospective cohort study, and some studies of epidemiological and demographic data.

**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**
At least 29 studies appear to have been reviewed to obtain the effectiveness evidence.

**Methods of combining primary studies**
Not reported. Some effectiveness estimators (e.g. the HBeAg seroconversion rates at year 1) were calculated as a weighted average of the results obtained from several studies.
They provided explanations for some of the differences found between the primary studies. No statistical tests of homogeneity appear to have been performed.

**Results of the review**

The HBeAg seroconversion rates at year 1 after treatment were 28.7% for patients treated with lamivudine, and 28.7% for patients treated with IFN-a.

For patients treated with lamivudine the rates for later years were 18.7% at 2 years after treatment, 39.6% at 3 years after treatment, and 22.9% at 4 years after treatment.

At years 1, 2, 3, and 4 the spontaneous seroconversion rate was 9% for patients not receiving treatment.

The spontaneous seroconversion rate was also 9% at years 2, 3 and 4 for patients treated with IFN-a.

The rates of progression to cirrhosis after 12 months for patients who did not seroconvert were 2% with lamivudine, 14% with IFN-a and 14% with no treatment.

**Methods used to derive estimates of effectiveness**

Estimates of effectiveness were also derived from a panel of experts, experts' opinions obtained through a questionnaire, and authors' assumptions.

**Estimates of effectiveness and key assumptions**

A panel of experts estimated the likely percentages of patients receiving each kind of treatment in each of the scenarios:

- in scenario A, 65% of patients would receive lamivudine, 12% would receive IFN-a, and 23% would not be treated;
- in scenario B, 20% of patients would be treated with IFN-a, and 80% would not receive treatment;
- in scenario C, none of the patients would receive treatment.

The authors formulated assumptions about the treatments:

- the HBeAg seroconversion rate after year 4 was 9% for all patients in all scenarios; and
- treatment with lamivudine would have no benefit in the progression to cirrhosis after year 1.

**Measure of benefits used in the economic analysis**

The measures of health benefit used in the economic analysis were the number of life-years (LYs) and the number of quality-adjusted life-years (QALYs) gained under each of the scenarios during the 70-year period considered at analysis. Four members of the expert panel, using an Assessment of Quality of Life questionnaire, estimated quality of life utilities. These were combined with LYs in order to obtain the QALYs. The utility weights were not reported.

The authors also reported other intermediate model outcomes:

- the proportion of patients in each scenario that seroconverted;
- the proportion of patients who did not progress to cirrhosis during the fist year of treatment (within the short-term analysis); and
- the percentage reduction in the lifetime risk of developing compensated cirrhosis, decompensated cirrhosis, and hepatocellular carcinoma in scenario A compared with scenario B.
Direct costs

The direct costs included in the study were those of the Australian health system. These were for drugs, consultations (general practitioner, specialist and hospital outpatient), tests and hospitalisation related to compensated cirrhosis, decompensated cirrhosis and hepatocellular cancer. The tests comprised liver function tests, DNA testing, full blood count, HBeAg and HBsAg tests, alpha-fetoprotein, ultrasound, thyroid function test, endoscopy and computed tomography scan of abdomen. The direct costs came from published studies and the findings from the hepatologists’ questionnaire. The published studies included data from the Pharmaceutical Benefits Schedule, the Medicare Benefits Schedule, and the National Hospital Cost Data Collection, among others. The findings of the questionnaire were ratified by an expert panel (both the hepatologists’ questionnaire and the expert panel were the same as those used to derive the estimates of effectiveness). The authors also seem to have made some assumptions when estimating the costs. Therefore, the costs were estimated on the basis of actual data and a guess from experts.

The unit costs used in the economic analysis were reported. Some, but not all, of the resource quantities were reported separately from the costs. Discounting was performed at a rate of 5%. The price year was not reported. The study reported the average costs per patient and the incremental average costs per patient, according to each of the scenarios, for a timeframe of 70 years.

Statistical analysis of costs

No statistical analyses of the costs were performed.

Indirect costs

No indirect costs were reported.

Currency

Australian dollars (Aus$).

Sensitivity analysis

Sensitivity analyses were performed to assess the robustness of the results. The parameters varied were those related to the assumptions about the proportion of patients receiving treatments, seroconversion rates, progression rates to cirrhosis, costs and probabilities of disease progression. The area of uncertainty investigated was, therefore, variability in the data. One-way analyses used appear to have been used. The authors did not report the ranges over which the parameters were varied.

Estimated benefits used in the economic analysis

From the short-term analysis, the percentages of patients who seroconverted during the first year of treatment were 24.2% in scenario A, 12.9% in scenario B and 9.0% in scenario C. The percentage of patients who progressed to cirrhosis were 5.1% (scenario A), 12.2% (scenario B) and 12.7% (scenario C), respectively.

Starting from the least effective scenario, the results of the long-term analysis showed that the incremental LYs gained was 0.6 under scenario B when compared with scenario C, and 5 for scenario A versus B.

The incremental QALYs gained was 0.6 under scenario B when compared with scenario C, and 4.1 for scenario A versus B.

These benefits were estimated for a timeframe of 70 years. The benefits were discounted at a rate of 5%.

It was not stated whether the expert panel considered the side effects of the treatments when estimating the utilities used to calculate the QALYs.
Cost results
The undiscounted average costs per patient for the 70-year period considered in the economic analysis were Aus$40,131 for scenario A, Aus$39,390 for scenario B and Aus$38,848 for scenario C.

The discounted (5% rate) average costs per patient were Aus$21,692 for scenario A, Aus$22,240 for scenario B and Aus$21,767 for scenario C.

The authors reported that the costs of treating adverse effects associated with lamivudine or IFN-a, and the costs of symptomatic treatment for patients who did not receive antiviral treatment, were not considered in the economic analysis.

Synthesis of costs and benefits
In the short term, the costs and benefits were combined using incremental cost-effectiveness ratios (ICERs). These measured the incremental mean costs per additional case of seroconversion, and the incremental mean cost per additional case of cirrhosis avoided when scenarios A and B were compared.

The incremental cost per additional seroconversion in scenario A versus scenario B was Aus$3,341. The incremental cost per cirrhosis case avoided under scenario A, compared with scenario B, was Aus$5,272.

In the long term, scenario A proved to be the dominant strategy when compared with scenarios B and C, as it provided a higher number of LYs and QALYs at a lower cost.

The authors reported that the results were sensitive to changes in the proportion of patients eligible for each drug, and the HBeAg seroconversion rate in years 1 to 4. However, they stated that the ICER showed favourable results for scenario A, even when considering the worst-case scenarios for the assumptions modified in the sensitive analyses.

Authors’ conclusions
Scenario A, in which both therapies (lamivudine and alpha-interferon) were available, gave the best clinical outcomes. It was a cost-effective strategy in comparison with the alternative scenarios (B and C), as it achieved more seroconversions and lower progression to cirrhosis in patients with chronic hepatitis B (CHB) in the short term, while it was the dominant strategy in the long term.

CRD COMMENTARY - Selection of comparators
The two scenarios chosen as the comparators were justified because they represented current practice in the authors’ setting before the introduction of lamivudine as a treatment option for CHB patients (scenario B) or the natural progression of CHB without treatment (scenario C). A positive aspect of the selection of this health technology and these comparators is that they were intended to reflect actual clinical practice, as patients may receive any of the available options and some patients may not receive treatment. The objective of the analysis was to determine whether the availability (rather than use for specific sub-groups of patients) of lamivudine was cost-effective for the Australian health service.

Validity of estimate of measure of effectiveness
The authors did not state that a systematic review of the literature had been undertaken. The method used to combine most of the results of the primary studies was not reported, although it appears to have been mainly a narrative method. In addition, some estimates of effectiveness were obtained as the weighted averages of the results from several studies. The authors reported and explained some of the differences found in the effectiveness results obtained from some of the studies in the review.

Since lamivudine had only recently been approved, there must have been considerable uncertainty surrounding the prevalence of treatments. An expert panel of six hepatologists was assembled to derive some of the estimates of effectiveness. The panel members were selected on the grounds that they managed a significant proportion of CHB...
patients under treatment in Australia. The authors stated that details of the panel process had been published. The authors' assumptions about health state transition probabilities appear to have been justified by reference to the medical literature. The authors reported that the assumptions were conservative against lamivudine. The estimates of effectiveness were investigated in sensitivity analyses, but the ranges over which the effectiveness parameters were varied were not reported.

There were several anomalies in the data used. First, the probability of seroconversion was the same for no treatment and IFN-a for patients eligible for both lamivudine and IFN-a. Second, there was a reduction in the probability of seroconversion from 0.287 to 0.09 from the first year to succeeding years.

**Validity of estimate of measure of benefit**
The estimation of benefits was modelled. The models used appear to have been appropriate. However, quality of life was derived from experts' opinions rather than from patients' opinions. Therefore, the utilities obtained may not be representative of patient preferences associated with health states and treatments. The health benefits obtained were discounted at a rate of 5%, which was appropriate. It was unclear whether the expert panel considered the side effects of the treatments when estimating the utilities used to calculate the number of QALYs gained.

**Validity of estimate of costs**
Most of the cost categories relevant to the perspective adopted appear to have been included in the economic analysis. The authors did not justify the exclusion of the costs of treating adverse effects associated with lamivudine or IFN-a, and the costs of symptomatic treatment for patients receiving no antiviral treatment, which seem to have been relevant to the economic analysis. There was no discussion of how this exclusion may have affected the authors' conclusions. Some, but not all, of the resource quantities were reported separately from the costs. The price year was not reported, which will hinder reflation exercises to other settings. No indirect costs (i.e. productivity losses) or costs incurred by patients were reported, although they appear to have been relevant for the interventions considered at analysis. If these costs had been considered, it would have been possible to undertake an analysis from a societal perspective. The authors performed sensitivity analyses to assess the robustness of the results, but did not report the ranges considered for the parameters. Thus, it cannot be stated whether the ranges used were appropriate.

**Other issues**
The authors did not make appropriate comparisons of their findings with those from other studies, probably because, as they stated, there is a lack of research about the long-term effectiveness and cost effects of using lamivudine for CHB patients. They commented that the models developed in the study could easily be applied to many other countries, but they did not mention whether the results of this study could be generalised to other settings. The scope of the analysis was reflected by the authors' conclusions.

**Implications of the study**
The authors concluded that the use of lamivudine to treat CHB patients should not be limited for economic reasons, given its effectiveness and the savings in health care resources that it provides.

**Source of funding**
Funded by Glaxo Wellcome (now GlaxoSmithKline) Australia Limited.

**Bibliographic details**

**PubMedID**
Other publications of related interest


Indexing Status
Subject indexing assigned by NLM

MeSH
Antiviral Agents /economics /therapeutic use; Australia; Clinical Trials as Topic; Cost-Benefit Analysis; Decision Support Techniques; Disease Progression; Health Care Costs; Hepatitis B, Chronic /drug therapy /economics; Humans; Interferon-alpha /economics /therapeutic use; Lamivudine /economics /therapeutic use; Markov Chains; Models, Economic; Models, Statistical

AccessionNumber
22002000909

Date bibliographic record published
31/07/2004

Date abstract record published
31/07/2004