The cost-effectiveness of alternative therapeutic strategies for the management of chronic hepatitis B in Poland
Orlewska E

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
Four strategies for the treatment of chronic hepatitis B (CHB) were examined.

In strategy A, lamivudine was provided to all patients who were eligible, whilst other patients received interferon (IFN)-alpha, if possible, or no treatment.

In strategy B, IFN-alpha was provided if patients were eligible, whilst patients who were ineligible received lamivudine or no treatment.

In strategy C, patients received IFN-alpha if eligible and nothing if ineligible.

Strategy D was no treatment.

IFN-alpha is an established treatment for CHB, whilst lamivudine is a new and emerging treatment option. "Do nothing" was included in the analysis as a comparator.

Type of intervention
Treatment (management of symptoms and improvement of functioning).

Economic study type
Cost-effectiveness analysis.

Study population
The study population comprised patients with CHB who tested positive for hepatitis B e antigen (HBeAg), had moderately elevated alanine aminotransferase, had not yet progressed to cirrhosis, and were IFN-alpha-naive. Patients with the precore-mutant virus were excluded. For modelling purposes, it was assumed that the patients were aged between 30 and 50 years, and that 60% were female.

Setting
The setting was primary care. The economic study was carried out in Poland.

Dates to which data relate
The effectiveness data were gathered from literature published between 1995 and 2000. The cost data were obtained from databases available in 2002. The price year was 2002.

Source of effectiveness data
The effectiveness data were derived from a combination of published literature and expert opinion.
Modelling
A decision analysis model was designed to predict the pathways of hypothetical patients. The model used decision tree methods to determine the proportion of patients with each outcome. It calculated the cumulative costs and benefits associated with each strategy. Hypothetical patients began treatment with any of the four strategies. Therein, the patient moved through the model, dependent upon the probabilities described.

Outcomes assessed in the review
Several probabilities were used to populate the decision model:

- eligibility for lamivudine therapy,
- eligibility for IFN-alpha therapy,
- the likelihood of IFN-alpha intolerance,
- the likelihood of HBeAg seroconversion, and
- progression to cirrhosis.

For each potential outcome, the costs and benefits were calculated and summed for each treatment strategy.

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

Sources searched to identify primary studies
Not stated.

Criteria used to ensure the validity of primary studies
Not stated.

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

Number of primary studies included
The probabilities for the model were drawn from five different studies. In addition, two parameters were based on expert opinion.

Methods of combining primary studies
The author combined the findings from studies using a narrative method. The estimates based on expert opinion were derived from a questionnaire and a discussion panel.

Investigation of differences between primary studies
Not stated.

Results of the review
The following probabilities were included in the model:
eligibility for lamivudine therapy, 0.8;

eligibility for IFN-alpha therapy, 0.6;

the likelihood of IFN-alpha intolerance, 0.1;

the likelihood of HBeAg seroconversion, 0.18 for patients treated with lamivudine, 0.19 for patients treated with IFN-alpha, and 0.06 for untreated patients;

progression to cirrhosis, 0 for patients who seroconverted and for patients who did not seroconvert, 0.02 for patients treated with lamivudine, 0.12 for patients treated with IFN-alpha, and 0.12 for untreated patients.

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

Initially, the benefits were reported as the HBeAg seroconversion rates and non-progression to cirrhosis. However, these were later converted into life-years gained (LYG). The number of LYG was calculated using life expectancy tables, then adjusted for the increased risk of death due to the illness and/or adverse events.

**Direct costs**

The direct costs included in the model were drug costs, laboratory tests, abdominal ultrasonography, liver biopsy, ambulatory visits, specialist consultations and hospitalisation. The drug costs were for lamivudine, IFN-alpha, essentiale forte and lactulose. The laboratory tests included serologic examinations, DNA polymerase, blood cell counts, proteinogram, activated partial thromboplastin time, aminotransferases, bilirubin, proteinuria, blood urea nitrogen, creatinine and thyroid hormones. The drug costs were taken from the Pharmaceutical Wholesale Price List (2002), whilst the test costs were drawn from the Medical Services Schedule (2002). All the costs and the quantities were analysed separately. Discounting was not performed because the costs were calculated for the first year only. The price year was 2002.

**Statistical analysis of costs**

No statistical analysis of the costs was undertaken.

**Indirect Costs**

No indirect costs were included in the model.

**Currency**

Polish new zloty (PLN). The exchange rate was 4 PLN = 1 US dollar ($).

**Sensitivity analysis**

A one-way sensitivity analysis was undertaken on all probability parameters within the model. In most cases, the range was determined by the upper and lower limits found in the published literature. In addition, a one-way sensitivity analysis was carried out on the cost of routine medical management, both with and without hospitalisation.

**Estimated benefits used in the economic analysis**

In ascending order of effectiveness, the HBeAg seroconversion rates were 0.06 (strategy D), 0.13 (strategy C), 0.169 (strategy B) and 0.17 (strategy A).

In ascending order of effectiveness, the non-progression to cirrhosis was 0.89 (strategy D), 0.90 (strategy C), 0.93 (strategy B) and 0.97 (strategy A).

All the results referred to one year after treatment initiation.
It was suggested that progression to cirrhosis resulted in a loss of 40.76 life years for a 30-year-old woman, 33.26 years for a 30-year-old man, 22.31 years for a 50-year-old woman and 16.64 years for a 50-year-old man.

Cost results
The cost of each strategy was PLN 7,926 for strategy A, PLN 12,453 for strategy B, PLN 10,644 for strategy C and PLN 1,562 for strategy D. The costs included the likelihood of hospitalisation for related morbidities.

Synthesis of costs and benefits
The author combined the costs and benefits in two ways, as the cost per extra HBeAg seroconversion, and the cost per cirrhosis case avoided. In both cases, treatment strategies B and C were dominated by strategy A (i.e. they cost more and were less effective than A). Therefore, the incremental analysis was restricted to strategies A and D.

For strategy A compared with strategy D, the incremental cost per incremental HBeAg seroconversion was PLN 57,855. The incremental cost per incremental cirrhosis case avoided was PLN 79,550. The cost per LYG was PLN 2,105 for a population aged 30 years and PLN 3,978 for a population aged 50 years.

The sensitivity analysis showed that the model was fairly robust to most parameters. The least favourable incremental cost-effectiveness ratio (comparing strategy A against D) was observed when the probability of progression to cirrhosis in patients who were treated with lamivudine and who had failed seroconversion was 0.12 (base value 0.20). However, the cost-effectiveness ratio remained firmly within established acceptable values.

Authors' conclusions
Strategy A exhibited the greatest effectiveness. When considering this and that fact that strategy A was less costly than strategies B and C, the author suggested that it was the most appropriate method. When compared against strategy D, strategy A exhibited greater effectiveness, at a relatively modest incremental cost. The incremental cost-effectiveness ratio was well within established acceptable values.

CRD COMMENTARY - Selection of comparators
IFN-alpha is an established treatment for CHB, whilst lamivudine is a new and emerging treatment option. "Do nothing" was included in the analysis as a comparator. This suggests that the comparators were appropriate for the purposes of this study.

Validity of estimate of measure of effectiveness
Data for the population of the decision model were gathered from studies published in peer-reviewed journals. All of the data were relatively recent. Expert opinion was used to provide two estimates, although this was carried out appropriately (questionnaire followed by a discussion panel).

Validity of estimate of measure of benefit
The benefit measures were estimated in two ways. First, as the number of seroconversions, and second as the cases of cirrhosis avoided. Such outcome measures are not useful for policy decision-making, as they cannot be compared directly with results from other studies. However, the author provided estimates of the LYG. Whilst this is useful to some extent, it does not capture the full consequences of the treatment strategies because the quality of the patient's life is not accounted for. Future research should aim to use the quality-adjusted life-year as the summary outcome measure.

Validity of estimate of costs
The costs included within the model appeared to reflect the costs associated with each treatment strategy. However, the costs were only estimated for the first year after treatment initiation. It would have been more appropriate to have estimated the lifetime treatment costs associated with each strategy. It should be noted that the costs used in this study...
were representative of those for the study setting (i.e. Poland). Medication costs in Poland are not necessarily reflective of those elsewhere in the world. You should exhibit caution when applying these findings to your own setting.

Other issues
The costs were calculated for one year only, whilst the benefits (i.e. LYG) were accrued over the remainder of the patient's lifetime. Therefore, the cost per LYG is likely to have significantly underestimated the true values. It is likely that the lifetime costs were greater than those reported in this study (even if treatment was stopped after one year) due to further rehospitalisation and other factors. Therefore, the cost-effectiveness results should be treated with caution.

Implications of the study
The author suggested that the most appropriate strategy for treating patients with hepatitis B is to provide lamivudine to all patients who are eligible, whilst other patients receive IFN-alpha if possible, or no treatment at all if neither option is possible.

Source of funding
None stated.

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