Evaluation of the cost-effectiveness of entecavir versus lamivudine in hepatitis BeAg-positive chronic hepatitis B patients
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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.

CRD summary
The objective was to examine the cost-effectiveness of entecavir in comparison with lamivudine in patients who were positive for hepatitis B e antigen and had not received a nucleoside before. The authors concluded that entecavir given for up to 10 years was a cost-effective alternative to lamivudine from the perspective of the US third-party payer. The analysis appears to have been carried out using valid methodology, which makes the authors’ conclusions more robust.

Type of economic evaluation
Cost-effectiveness analysis, cost-utility analysis

Study objective
The objective was to examine the cost-effectiveness of entecavir in comparison with lamivudine in patients who were positive for hepatitis B e antigen (HBeAg) and had not received a nucleoside before.

Interventions
The two strategies were one year of treatment with entecavir (0.5mg once daily) or lamivudine (100mg once daily) with the addition of adefovir (10mg once daily) if patients developed resistance to lamivudine or entecavir.

Location/setting
USA/secondary care.

Methods
Analytical approach:
This economic evaluation was based on a decision tree model with a 10-year time horizon. The authors stated that the perspective of the third-party payer was taken.

Effectiveness data:
The clinical data came from a selection of known, relevant studies. The treatment effect came from a phase III, double-blind, randomised controlled trial (RCT), namely the Benefits of Entecavir for Hepatitis B Liver Disease (BEHoLD) trial, which compared the efficacy and safety of entecavir and lamivudine in 709 patients over one year. Long-term data and the risk of events came from a longitudinal cohort study, with a mean follow-up of 11.4 years. This included community residents, who were seropositive for the hepatitis B surface antigen and was called the Risk Evaluation of Viral Load Elevation and Associated Liver Disease/Cancer-Hepatitis B Virus (REVEAL-HBV) study. Additional published sources were used for other clinical inputs. The main clinical endpoint was the treatment efficacy.

Monetary benefit and utility valuations:
The utility data were derived from a published survey of 100 uninfected individuals using the standard gamble method.

Measure of benefit:
Quality-adjusted life-years (QALYs) and life-years (LYs) were the summary benefit measures and were discounted at an annual rate of 3%. Other model outputs related to liver complications were reported.

Cost data:
The economic analysis considered two main cost categories: study drugs and treatment of complications related to the
hepatitis B virus (HBV). The drug-related resource consumption was based on actual dosages administered in the clinical trial. Drug costs were calculated using wholesale acquisition costs. The annual medical costs of disease came from two published studies, which used the reimbursed costs from third-party payers. The costs of out-patient visits and laboratory tests incurred in the clinical trial were excluded from cost estimates, because it was assumed that they would be equivalent in both groups. All costs were in US dollars ($) and a 3% annual discount rate was applied to future costs. The price year was 2006.

Analysis of uncertainty:
A set of univariate sensitivity analyses was carried out for the clinical and economic inputs as well as for the utility valuations. Alternative published sources of data were used together with authors’ assumptions. Alternative treatment durations of three, five, and 10 years were also investigated. A comprehensive probabilistic sensitivity analysis was undertaken with 1,000 iterations on two key parameters: viral rebound rates after treatment cessation and the time to the first event.

Results
Entecavir led to a gain of 0.728 QALYs and 0.817 LYs at an incremental cost of $2,350 over lamivudine. Thus, the incremental cost per QALY gained with entecavir was $3,230 (95% confidence interval: $2,312 to $4,528) and the incremental cost per LY gained was $2,877.

The probabilistic sensitivity analysis showed that 99.3% of simulations were below the value of $5,000 per QALY. The most influential model inputs were the efficacy parameters, drug costs, and treatment duration. Increasing the treatment duration increased the cost-utility ratio ($12,233 per QALY at 10 years), but all estimates were well below the threshold of $50,000 per QALY.

Authors’ conclusions
The authors concluded that entecavir, given for up to 10 years, was a cost-effective alternative to lamivudine for the treatment of HBeAg-positive patients from the perspective of the US third-party payer.

CRD commentary
Interventions:
The authors described the available treatments and the selection of entecavir and lamivudine was based on a recent head-to-head RCT, which compared the efficacy and safety of the two drugs. At the time of the study, no clinical trial directly comparing entecavir with other treatments was available. Dosages and length of treatment were reported.

Effectiveness/benefits:
The sources of data appear to have been appropriate. RCT data were combined with long-term data from the cohort study to simulate the management of patients over time. This approach is quite common in studies with a long time horizon. The authors provided some key details of the two primary sources of data, such as the study sample, follow-up, missing data, and location. Both studies had specific strengths, which made them valid sources of data. The utility valuations, used to calculate the QALYs, were derived from a sample of individuals from the general population using a validated approach. Due to the uncertainty underlying the estimation of the utilities, an alternative source of data was also considered in the sensitivity analysis. QALYs are a valid measure of benefit, not only because they capture the impact of disease on a patient's health, but also because they are generalisable across diseases.

Costs:
The categories of costs were relevant to the perspective. The drug costs were presented in detail, while those of complications were reported as macro-categories and were not broken down into individual items. This was due to the fact that these costs were derived from previous studies, the methodologies of which were not described. Other details of the analysis such as the price year and use of discounting were reported. The uncertainty surrounding the cost estimates was investigated in the deterministic sensitivity analysis.

Analysis and results:
The costs and benefits were clearly presented and the use of an incremental analysis was appropriate. The issue of uncertainty was satisfactorily addressed using both a deterministic and a probabilistic approach. The authors justified...
their selection of a specific modelling framework, which allowed a better simulation of the disease management. Some potential methodological limitations were pointed out, for example: the possible demographic and clinical differences between the patient samples in the two studies; the paucity of reliable long-term data on the rebound rates after treatment discontinuation; or the appropriateness of extrapolating Chinese data to the US population. The authors pointed out that their analysis referred to patients without co-infections and these findings should be restricted to this specific sub-group of HBV (mono-infected) patients. The authors noted that their results were conservative.

Concluding remarks:
In general, the analysis appears to have been carried out using valid methodology, which makes the authors’ conclusions more robust.

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