Cost-utility analysis of tenofovir disoproxil fumarate in the treatment of chronic hepatitis B

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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
This study examined the cost-effectiveness of tenofovir disoproxil fumarate (TDF) in the treatment of chronic hepatitis B compared with other nucleosides or nucleotides. It assessed the optimal drug for patients who developed a resistance to first- or second-line treatment. The authors concluded that, from the perspective of the NHS, first-line TDF was the most cost-effective treatment, at a threshold of £20,000 per quality-adjusted life-year. The methods were robust and very well described and the authors’ conclusions appear to be valid.

Type of economic evaluation
Cost-utility analysis

Study objective
This study examined the cost-effectiveness of tenofovir disoproxil fumarate (TDF) in the treatment of adult patients with chronic hepatitis B (CHB), compared with other nucleosides or nucleotides. It also assessed the optimal drug for patients who developed resistance to first- or second-line treatment.

Interventions
The interventions were: best supportive care, lamivudine, TDF, adefovir, TDF and lamivudine, entecavir, adefovir and lamivudine, and entecavir and adefovir. Lamivudine was given at 100mg per day, TDF at 300mg per day, adefovir at 10mg per day, and entecavir at 0.5 or 1mg per day. Patients were assumed to receive sequences up to three nucleosides, nucleotides, or combinations. All sequences, except those in which patients were resistant to their third-line treatment before starting it, were considered, giving a total of 211 strategies; for simplicity, only 20 were reported.

Location/setting
UK/out-patient.

Methods
Analytical approach:
The analysis was based on a Markov model with a lifetime horizon. The model considered drug resistance and hepatitis B e antigen (HBeAg)-negative and HBeAg-positive patients. The authors stated that the perspective of the UK NHS was adopted.

Effectiveness data:
A systematic literature review was carried out to identify nucleoside and nucleotide inputs for the model. Additional searches were undertaken to retrieve data on the natural history of CHB. Most of the data on treatment effect and resistance were from a mixed-treatment comparison meta-analysis of RCTs, which synthesised the data to produce the key transition probabilities for the model. Other data were from clinical trials and natural history studies. Some assumptions were required, where there were no published data, particularly for the combination strategies. The key input of the model was drug resistance.

Monetary benefit and utility valuations:
Most of the utility values were from a study of 93 UK patients with CHB, which used the standard gamble approach. Other published studies were also used.

Measure of benefit:
Quality-adjusted life-years (QALYs) were the summary benefit measure and were discounted at an annual rate of 3.5%.
Cost data:
The economic analysis included two main cost categories, which were drug costs and the expenses associated with the long-term management of CHB. The expenses were presented as category totals and were derived from large, retrospective UK micro-costing studies on patients with hepatitis C, whose resource consumption was considered to be similar to that of CHB patients. The resource use for other disease states was based on expert opinion. All costs were in UK pounds sterling (£) and a 3.5% annual discount rate was applied. The reference year was 2006 to 2007.

Analysis of uncertainty:
A one-way sensitivity analysis was undertaken on all the model inputs except the unit costs. A probabilistic sensitivity analysis was performed, varying all the model parameters except the unit costs, over probability distributions defined by their mean and 95% confidence interval.

Results
After excluding 12 dominated strategies, the projected costs were £11,189 with best supportive care, £14,877 with lamivudine then best supportive care, £30,614 with lamivudine then TDF, £39,914 with TDF then lamivudine, £40,610 with TDF then TDF and lamivudine, and £40,612 with TDF then TDF and lamivudine then entecavir. The QALYs were 9.18 with best supportive care, 9.56 with lamivudine then best supportive care, 10.68 with lamivudine then TDF, 11.17 with TDF then lamivudine, 11.19 with TDF then TDF and lamivudine, and 11.19 with TDF then TDF and lamivudine then entecavir. The strategies with TDF as first-line therapy produced more QALYs than other options.

Compared with the next most effective strategy, the incremental cost per QALY was £9,636 with lamivudine then best supportive care, £14,064 with lamivudine then TDF, £19,084 with TDF then lamivudine, £24,992 with TDF then TDF and lamivudine, and £38,474 with TDF then TDF and lamivudine then entecavir.

At a ceiling ratio of £20,000 per QALY, strategies involving the first-line use of TDF produced the highest total net benefits. Adding in or switching to lamivudine was the best strategy for patients who developed TDF resistance. These results held in subgroups of HBeAg-positive and HBeAg-negative patients.

The sensitivity analysis confirmed that these finding were robust. Only when the probability of HBeAg-negative patients developing cirrhosis was reduced to its minimum (0.4% per annum), did the incremental cost per QALY of first-line TDF exceed a £30,000 threshold. The time horizon was an influential parameter. The probability of first-line TDF being cost-effective was 0.46 at a threshold of £20,000 per QALY and 0.78 at a threshold of £30,000 per QALY.

Authors' conclusions
The authors concluded that, from the perspective of the NHS, first-line TDF was the most cost-effective treatment for CHB patients at a threshold of £20,000 per QALY.

CRD commentary
Interventions:
The authors justified their selection of the comparators as the analysis focused on nucleosides and nucleotides, which were the most common treatments for CHB in the UK. The most plausible combinations for adefovir, entecavir, and TDF were considered. Interferon-alpha and pegylated interferon-alpha were not considered because they were short-term initial treatments for selected patients rather than maintenance treatments.

Effectiveness/benefits:
The approach used to identify the relevant sources of data was appropriate. The mixed-treatment comparison meta-analysis to synthesise the data on different drugs was a good method and, in general, RCTs, or meta-analyses of RCTs, were used for the data inputs, ensuring high internal validity. The details of sample sizes and the designs of source studies were reported in a companion paper and in an appendix. Some assumptions were required, but these were generally validated by experts and varied in the sensitivity analyses. The disease and its treatments have a substantial impact on both survival and quality of life, and QALYs were an appropriate benefit measure as they capture both these dimensions. The authors reported some key information on the derivation of the utility values and the patients’ preferences were elicited using the standard gamble method.
Costs:
The categories of costs were appropriate for the perspective of the NHS. The unit costs and resource quantities were not reported; most of the costs were presented as category totals. The key source for the economic inputs was explicitly stated and appears to have been appropriate, as it used a micro-costing approach. Other details, such as the price year and discounting, were clearly presented.

Analysis and results:
The results were presented in detail for the 20 strategies from the possible 211 combinations. The costs and benefits were synthesised using two valid approaches; an incremental analysis and a net benefit calculation. Both were appropriately carried out and reported. The uncertainty was satisfactorily investigated and was clearly discussed. Recommended discounting was applied to both the costs and the benefits. A clear description of the decision model was given. The authors stated that the analysis should be considered to be UK specific and not easily transferable to other settings.

Concluding remarks:
The methods were robust and very well described and the authors’ conclusions appear to be valid.

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