A systematic review and economic evaluation of adefovir dipivoxil and pegylated interferon-alpha-2a for 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.

Health technology
The study examined several treatments for patients with chronic hepatitis B (CHB). These were best supportive care (BSC), conventional interferon-alpha (IFN-alpha), lamivudine (LAM), pegylated interferon-alpha-2a (PEG) and adefovir dipivoxil (ADV). The doses considered were 100 mg/day for LAM, 10 mg/day for ADV, 180 microg/week for PEG and 4.5 MIU 3 times per week for IFN-alpha.

Treatment schedules for PEG and IFN-alpha differed on the basis of patient characteristics. A course of treatment comprised 24 weeks of non-pegylated IFN-alpha for patients with hepatitis B e antigen (HBeAg)-positive disease, 48 weeks of non-pegylated IFN-alpha-2a for patients with HBeAg-negative disease, or 48 weeks of PEG for both HBeAg-positive and -negative patients.

Additional intervention strategies using IFN-alpha or PEG as first-line intervention, with LAM or ADV for those patients who did not respond to IFN-alpha, were also considered. In addition, the study included a strategy of "adefovir salvage", in which patients received IFN-alpha as first-line treatment followed by LAM for nonresponders, while patients who developed resistance to LAM then had ADV added.

Type of intervention
Treatment.

Economic study type
Cost-utility analysis.

Study population
The study population comprised a hypothetical cohort of adult patients with CHB infection. They could be HBeAg-positive or -negative, with compensated or decompensated disease.

Setting
The setting was secondary care. The economic study was carried out in the UK.

Dates to which data relate
The effectiveness data were derived from studies published between 1988 and 2005. No dates for the resource use and costs were given. The price year was not clear.

Source of effectiveness data
The clinical data used in the decision model were clinical effectiveness (reported as HBeAg loss or seroconversion), virological response, biochemical response and rates of adverse events. Patient characteristics at baseline were also derived from published evidence.
Modelling
A decision analytic Markov model was constructed to assess the clinical and economic impact of the different treatments for patients with CHB. The model was populated with data derived from the literature. A lifetime horizon was chosen with yearly cycles, and annual cycle correction was performed. Model health states were briefly described and transition probabilities were reported in detail, together with their sources. A graphical representation of the model was not provided.

Sources searched to identify primary studies
Treatment effect, tolerability and epidemiological data came from randomised clinical trials (RCTs) and systematic reviews of the literature. Disease progression was obtained from natural history studies as well as observational studies. Extensive details of RCTs were given, including the sample size and number of patients in each arm, dosages, follow-up and main clinical results.

Methods used to judge relevance and validity, and for extracting data
A systematic review of the literature was undertaken to identify relevant studies reporting clinical data required in the model. Extensive information on the review process was given. RCTs were chosen because of their high internal validity. However, the authors stated that the quality of most of these trials was relatively low and little information on the methods of randomisation was available. Thus, they considered that selection bias might have affected the trials. Also, heterogeneity was found amongst these trials and the studies were described in a narrative instead of the results being combined. Expert opinion was used to choose the most adequate estimates.

Measure of benefits used in the economic analysis
The summary benefit measure used was the quality-adjusted life-years (QALYs). These were derived by combining survival and quality of life data in the decision model. The utility values were derived from published studies based on the short-form 36-item questionnaire (SF-36). Other utility values were expressed as utility decrements for each health states and obtained from a published economic evaluation. Some assumptions were also made. The number of life-years (LYs) was also reported as a model output. The benefits were discounted at an annual rate of 1.5%.

Direct costs
The analysis of the costs was carried out from the perspective of the third-party payer (i.e. the NHS). The following health states were attributed a cost: HBsAg seroconverted, HBeAg seroconverted, ALT normalisation, CHB, compensated cirrhosis, decompensated cirrhosis, hepatocellular carcinoma, liver transplant and post-liver transplant. However, no breakdown of the cost items included in the analysis was given. The unit costs and quantities of resources were not reported. The authors stated that resource use and health state costs came from the published literature, discussion with experts, and figures supplied by an English NHS Hospital Trust. The price year was not reported. Discounting was relevant as the long-term costs were measured, and an annual rate of 6% was used.

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

Indirect Costs
Productivity costs were not considered.

Currency
UK pounds sterling (£).

Sensitivity analysis
Deterministic and probabilistic sensitivity analyses were carried out to determine the robustness of the cost-utility ratios to variations in clinical and economic model inputs. Little information on these analyses was provided.

**Estimated benefits used in the economic analysis**
The expected discounted LYs were 22.29 with BSC, 22.98 with conventional IFN-alpha, 23.51 with PEG, 23.36 with LAM and 24.55 with ADV.

The expected discounted QALYs were 17.07 with BSC, 17.75 with conventional IFN-alpha, 18.26 with PEG, 18.08 with LAM and 19.15 with ADV.

For sequences of treatments, the discounted LYs were 24.81 for conventional IFN-alpha followed by ADV, 25.00 for conventional IFN-alpha followed by LAM with ADV salvage, 25.13 for PEG followed by ADV, and 25.28 for PEG followed by LAM with ADV salvage. The corresponding discounted QALYs were 19.40, 19.56, 19.71 and 19.83, respectively.

**Cost results**
The expected costs were 8,555 with BSC, 12,609 with conventional IFN-alpha, 15,745 with PEG, 12,286 with LAM and 29,918 with ADV.

For sequences of treatments, the expected costs were 27,442 for conventional IFN-alpha followed by ADV, 27,740 for conventional IFN-alpha followed by LAM with ADV salvage, 28,907 for PEG followed by ADV, and 28,976 for PEG followed by LAM with ADV salvage.

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

The incremental cost per QALY gained was 5,994 with conventional IFN-alpha over BSC, 6,119 with PEG over conventional IFN-alpha, 3,685 with LAM over BSC, and 16,569 with ADV over LAM. The corresponding values were 7,936, 16,166, 3,489 and 15,289, respectively, in the sub-group of HBeAg-positive patients and 3,922, 2,162, 4,131 and 18,620 in the sub-group of HBeAg-negative patients.

The evaluation of alternative combined strategies suggested that sequential strategies using IFN (pegylated or non-pegylated) followed by LAM were cost-effective, with ADV reserved as a salvage strategy for patients who developed resistance to LAM. However, the use of PEG was more cost-effective in HBeAg-negative patients than in HBeAg-positive individuals.

The deterministic sensitivity analysis showed that the cost-effectiveness of ADV was sensitive to assumptions about the probability of HBeAg seroconversion for patients with compensated cirrhosis and HBeAg seroconversion rates with long-term treatment. The incremental cost per QALY with PEG was highly sensitive to variations in the relapse rate for HBeAg-negative patients who normalised ALT following treatment.

The probabilistic sensitivity analysis indicated that IFN-alpha (non-pegylated or pegylated) followed by LAM was the preferred strategy at low thresholds for the cost-utility ratio. The sequential treatment strategy of PEG followed by LAM, with ADV added as salvage therapy, became the optimal treatment option at higher thresholds (higher than 15,000 per QALY).

**Authors' conclusions**
Adefovir dipivoxil (ADV) and pegylated interferon-alpha-2a (PEG) were both clinically effective and cost-effective in the treatment of chronic hepatitis B (CHB), in comparison with current standard treatments and best supportive care (BSC).
CRD COMMENTARY - Selection of comparators
The rationale for the selection of the comparators was clear. The choice of the different treatments was appropriate as both conventional and new options were considered. The authors stated that LAM and IFN-alpha are the most common treatments for CHB, but they may have important adverse events. The inclusion of PEG IFN-alpha-2b was outside the scope of the analysis. You should decide whether they are valid comparators in your own setting.

Validity of estimate of measure of effectiveness
Clinical data were obtained from a systematic review of the literature, the methods and conduct of which were extensively reported. Details such as the databases, search procedures, inclusion criteria and review process were described. The authors included only RCTs for assessing treatment effect, which should ensure a high internal validity. The main characteristics of the studies were reported. However, when the quality of the primary studies was judged, poor reporting of details such as randomisation and concealment was observed.

Validity of estimate of measure of benefit
The estimation of health benefits (QALYs) was modelled using a Markov model. The methods used to estimate the utility weights were not fully described as they were taken from published studies. Some assumptions were also made. Discounting was performed in accordance with UK guidelines.

Validity of estimate of costs
There was little information on the analysis of the costs. The categories of costs included in the analysis were not broken down and few details of the sources used were given. This will limit the possibility of replicating the analysis in other settings. The costs were treated deterministically and the impact of using alternative cost estimates was not explicitly investigated. The price year was not reported, which will make reflation exercises in other time periods difficult.

Other issues
The authors did not compare their findings with those from other studies. They also did not explicitly address the issue of the generalisability of the study results to other settings, although sensitivity analyses were conducted.

The authors stated that caution will be required if extrapolating the study results to the general population of patients with CHB, given the peculiarities of the patient samples included in the RCTs used to derive treatment effectiveness. Further, it was acknowledged that treatment may vary across centres and countries. The importance of patient sub-groups was underlined by conducting separate analyses for HBeAg-negative and -positive patients.

Implications of the study
The study results support the use of ADV and PEG for the treatment of CHB. The authors stated "further data are required on the effects of long-term treatment, and durability of response following treatment cessation”.

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Bibliographic details

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Other publications of related interest

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Indexing Status

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MeSH

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