Adefovir dipivoxil and pegylated interferon alpha for the treatment of chronic hepatitis B: an updated systematic review and economic evaluation

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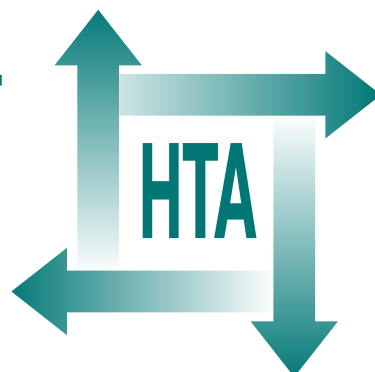[2]NIHR Evaluation, Trials and Studies Coordinating Centre (NETSCC), Southampton, UK

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Executive summary

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Executive summary

Background

This short report is an update and extension of a technology assessment report published in 2006 on the clinical effectiveness and cost-effectiveness of adefovir dipivoxil (ADV) and pegylated interferon alpha (PEG-α) for the treatment of chronic hepatitis B (CHB).

Hepatitis B is an infectious disease caused by the hepatitis B virus (HBV). If not successfully treated, it can lead to progressive liver damage, including cirrhosis, hepatocellular carcinoma and death. Patients with CHB may be HBeAg positive or HBeAg negative, depending on the presence or absence of the 'e' antigen. It is estimated that around 180,000 people (0.3%) in the UK are chronically infected, with around 7000 new cases each year, primarily from immigrants, most of whom are asymptomatic.

Methods

Assessment of clinical effectiveness

We searched for studies of the clinical effectiveness of adefovir dipivoxil, pegylated interferon alpha-2a (PEG-α-2a) and pegylated interferon alpha-2b (PEG-α-2b) (note that the latter was not included in the original report). Searches were run from the beginning of 2005 to September 2007. Thirteen bibliographic databases were searched, including MEDLINE, EMBASE and the Cochrane Library.

All studies were screened against a set of pre-specified inclusion criteria. For the clinical effectiveness review, we included randomised controlled trials (RCTs) which compared ADV, PEG-α-2a, and PEG-α-2b with currently licensed treatments for CHB, including the immunomodulatory drug non-pegylated interferon alpha (IFN-α) and the nucleoside analogue lamivudine (LAM).

Outcomes included biochemical (alanine aminotransferase, ALT), histological (liver fibrosis and necroinflammation) and virological [HBV deoxyribonucleic acid (DNA)] response to treatment, drug resistance and adverse effects. The trials were reviewed in a narrative synthesis but meta-analysis was not undertaken because of heterogeneity in the interventions and comparators evaluated.

Assessment of cost-effectiveness

A systematic review of economic evaluations of antiviral treatments for CHB was conducted. In addition, the economic model devised for our previous report was updated using utility values based on a recent study eliciting health-state valuations from CHB-infected patients. The model was also updated to account for changes in methodological guidance on discount rates for costs and outcomes. Health-state and treatment costs were inflated to 2006–7 prices. Evidence for the clinical effectiveness of PEG-α-2b was used in the model to estimate the cost-effectiveness of PEG-α-2b compared with IFN-α.

Results

Clinical effectiveness

Literature searches yielded a total of 735 articles. Of these, 653 were excluded on the basis of title and, where available, abstract. Eighty-two papers were retrieved for detailed screening and eight randomised controlled trials (RCTs) were included in the systematic review:

- Three evaluated ADV, one of which was a long-term follow-up of a trial included in our original assessment report. In two trials ADV was compared with placebo, and in a third ADV was compared with ADV added to LAM in patients with LAM resistance.
- Four evaluated PEG-α-2b. In two of these PEG-α-2b was combined with LAM and compared with either PEG-α-2b monotherapy or LAM monotherapy. Another compared three staggered regimens of PEG-α-2b combined with LAM. The fourth trial compared PEG-α-2b monotherapy with IFN-α.
- A further PEG-α-2b RCT was included from our original literature search database (but not included in the original assessment report as it was not in the scope of the review at that time). This RCT compared PEG-α-2b combined with LAM with PEG-α-2b monotherapy.
- No RCTs of PEG-α-2a were identified.

The trials varied in terms of aims, size and design characteristics. Five included only HBeAg-positive patients, with the remaining three including only HBeAg-negative patients.

Methodological quality also varied. Some trials reported adequate blinding, allocation concealment and randomisation methods, while other trials either failed to report such details or were judged inadequate.

ADV trials
In one trial there was a statistically significant difference between ADV and placebo in terms of ALT response and HBV DNA levels after 12 weeks, favouring ADV. Following withdrawal of ADV after 40 weeks, the proportion of patients exhibiting HBV DNA and ALT responses declined to levels similar to those experienced by patients who had received placebo. There was no viral resistance to ADV. The rate of adverse events and dose discontinuations was low and generally similar between study groups.

In the trial that compared switching to ADV versus adding ADV to LAM in patients with LAM resistance there was a statistically significant difference in favour of the combination treatment in terms of zero resistance to ADV. For the other outcomes there were no statistically significant differences between groups.

A follow-up publication of an RCT included in our original assessment report, comparing ADV with placebo in HBeAg-negative patients, reported generally sustained HBV DNA and ALT response rates among those treated with ADV for 5 years. Cumulative probabilities of resistance to ADV in the cohort varied from 11% to 29% depending on how resistance was defined.

PEG-α trials
Where statistical testing was reported, there were statistically significant differences favouring PEG-α-2b in combination with LAM compared with either one of the drugs given as monotherapy. This was the case for HBV DNA and ALT responses in two trials. However, another trial reported no significant differences between groups for these measures. There was a significant difference for HBeAg seroconversion, favouring combination therapy in one trial. For liver histology either there was no significant difference between groups or no statistical tests were performed.

For the comparison between PEG-α-2b and IFN-α and the comparison between different staggered regimens of the commencement of PEG-α-2b and LAM, there were no statistically significant differences between groups across the outcome measures where tests were reported.

Cost-effectiveness
The systematic review of cost-effectiveness studies identified four relevant full economic evaluations, in addition to one full economic evaluation identified and partially reviewed in our original assessment report. Two of the evaluations assessed PEG-α-2a; the remainder assessed ADV. Four of the five economic evaluations used Markov models, with lifetime horizons, while the other study used a decision tree with a 4-year time horizon. State-transition diagrams in the evaluations were similar, identifying the treatment aim as inducing HBeAg seroconversion for patients with HBeAg-positive CHB and viral suppression for patients with either HBeAg-positive or HBeAg-negative CHB.

Economic evaluations of PEG-α-2a found that it was associated with increased treatment costs but also gains in quality-adjusted life expectancy. In a UK study, the incremental cost-effectiveness ratio (ICER) for PEG-α-2a was £10,444 per QALY gained compared with LAM. Evaluations of ADV found that LAM monotherapy was dominated, while the ICER for ADV monotherapy compared with 'doing nothing' was $19,731($14,342–$24,224) at 2005 prices.

A review of health-state utility values used in economic evaluations of antiviral treatments for CHB showed that widely varying values were used, many of which were not specific to CHB patients. A recently published study reporting health-state utilities for patients with CHB infection and for non-infected general population samples, derived using the standard gamble technique, was identified and reviewed.

The ICERs generated by the update of our economic model were generally less favourable than those reported in the original assessment report. However, it appears that much of the difference arises from recent changes to methodological guidance (i.e. discounting costs and outcomes at 3.5% rather than 6% and 1.5% respectively) rather than from changes in costs or health-state utilities.

The sequential treatment strategies identified as optimal in our original report remained optimal in the updated model, i.e. interferon (pegylated or non-pegylated) followed by LAM, with ADV as salvage for patients who develop LAM resistance.

The results of the updated analysis were generally robust to changes in deterministic sensitivity analysis. The most notable changes were in the ICER for the strategy including ADV as salvage therapy for patients who develop resistance to LAM, in some cases increasing the ICER beyond the threshold conventionally used to indicate cost-effectiveness in the context of NHS decision making.

- The most influential structural assumption was excluding the possibility of HBeAg seroconversion (in HBeAg-positive CHB) in patients with compensated cirrhosis, which increased the ICER to £40,833 per QALY gained.
- In terms of the baseline characteristics of the treated cohort, decreasing the proportion with HBeAg-positive CHB and increasing age were associated with less favourable ICERs.
- The most influential parameter values related to the gain in utility associated with HBeAg seroconversion and loss of the surface antigen (HBsAg). This affected the ICERs for all strategies, but was most notable for the strategy including ADV as salvage for patients who develop resistance to LAM. If there is no utility gain for HBeAg seroconversion or loss of HBsAg, the ICER increases to £31,114.

In a probabilistic sensitivity analysis the same sequence of treatments was identified as optimal. However, the strategy including ADV as salvage becomes optimal only above a willingness-to-pay threshold of £27,000 per QALY. This is at the upper limit of the range of ICERs regarded as cost-effective from an NHS decision-making perspective. Interferon (conventional or pegylated) followed by LAM is optimal for a willingness to pay of £9000–£26,000, compared with a range of £5000–£11,500 in our previous report. As discussed, much of this difference arises from changes in the practice of discounting rather than changes to input values in the model.

The ICER for PEG-α-2b, compared with IFN-α-2b, in patients with HBeAg-positive CHB was £9169, based on the results of a clinical trial of 24 weeks of interferon treatment. The trial did not include a placebo arm, so no ICER for PEG-α-2b compared with best supportive care was estimated. Results were generally robust to changes in deterministic sensitivity analysis.

- Increasing age of the cohort and lower utility gains from HBeAg seroconversion or loss of HBsAg were associated with less favourable ICERs.
- Alternative discount rates (6% for costs and 1.5% for outcomes, as in our previous report,

or 0% for both costs and outcomes) and a reduction in cost for PEG-α-2b were associated with more favourable ICERs.
- All ICERs in the one-way sensitivity analyses were below the threshold conventionally deemed as cost-effective.

In a probabilistic sensitivity analysis, PEG-α-2b had a probability of being cost-effective (compared with IFN-α-2b) of 79% at a willingness-to-pay threshold of £20,000 per QALY, and 86% at a willingness-to-pay threshold of £30,000 per QALY.

Conclusions

Overall, the evidence from RCTs suggests that the effects of long-term treatment with ADV are generally durable, with relatively low rates of resistance. It is also apparent that beneficial effects are lost once ADV is withdrawn. Furthermore, in LAM-resistant HBeAg-negative patients there were no significant differences between adding ADV to ongoing LAM or switching from LAM to ADV, except for viral resistance where the combination was more favourable.

PEG-α-2a was associated with some benefit in terms of virological and biochemical response, HBeAg seroconversion and liver histology, relative to comparators. However, not all differences were statistically significant, and often significance tests were not reported at all. Consequently, there are uncertainties regarding the clinical effectiveness of this drug across different outcomes relevant to the control of CHB.

In terms of cost-effectiveness, optimum treatment strategies include IFN-α or PEG-α followed by LAM, with ADV used in patients who become resistant to LAM. In most cases, cost-effectiveness estimates were within acceptable ranges.

Further high-quality RCTs are required to assess the durability of long-term antiviral treatment, optimum treatment of patients with LAM resistance, and the clinical effectiveness and cost-effectiveness of initiating treatment with nucleoside combination therapy, including newer antiviral agents.

Publication

Jones J, Shepherd J, Baxter L, Gospodarevskaya E, Hartwell D, Harris P, *et al*. Adefovir dipivoxil and pegylated interferon alpha for the treatment of chronic hepatitis B: an updated systematic review and economic evaluation. *Health Technol Assess* 2009;**13**(35).

NIHR Health Technology Assessment programme

The Health Technology Assessment (HTA) programme, part of the National Institute for Health Research (NIHR), was set up in 1993. It produces high-quality research information on the effectiveness, costs and broader impact of health technologies for those who use, manage and provide care in the NHS. 'Health technologies' are broadly defined as all interventions used to promote health, prevent and treat disease, and improve rehabilitation and long-term care.

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First is the commissioned route. Suggestions for research are actively sought from people working in the NHS, from the public and consumer groups and from professional bodies such as royal colleges and NHS trusts. These suggestions are carefully prioritised by panels of independent experts (including NHS service users). The HTA programme then commissions the research by competitive tender.

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The research reported in this issue of the journal was commissioned by the HTA programme as project number 07/15/01. The contractual start date was in December 2007. The draft report began editorial review in July 2008 and was accepted for publication in October 2008. As the funder, by devising a commissioning brief, the HTA programme specified the research question and study design. The authors have been wholly responsible for all data collection, analysis and interpretation, and for writing up their work. The HTA editors and publisher have tried to ensure the accuracy of the authors' report and would like to thank the referees for their constructive comments on the draft document. However, they do not accept liability for damages or losses arising from material published in this report.

The views expressed in this publication are those of the authors and not necessarily those of the HTA programme or the Department of Health.