Adefovir dipivoxil and pegylated interferon alfa-2a for the treatment of chronic hepatitis B: a systematic review and economic evaluation

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Aim

The aim of this systematic review and economic evaluation was to assess the clinical effectiveness and cost-effectiveness of adefovir dipivoxil (ADV) and pegylated interferon alfa-2a (PEG) for the treatment of adults with chronic hepatitis B (CHB) infection. This independent assessment was used by the National Institute for Health and Clinical Excellence (NICE) to issue guidance to the health service in England and Wales on treatment for patients with CHB.

Epidemiology and background

Hepatitis B is an infectious disease caused by the hepatitis B virus (HBV). Key routes of transmission include injecting drug use, sexual contact and from mother to child (particularly in South-east Asia).

Acute infection is largely asymptomatic, and is cleared by 95% of adults. Chronic disease results from an inadequate immune response to the primary infection, allowing continued viral replication and presence of the surface antigen (HBsAg). Those who develop chronic disease may remain asymptomatic for some time before developing symptoms of liver disease. Patients with CHB may be HBeAg positive or HBeAg negative, depending on the presence or absence of the e antigen.

There are approximately 156,000 people in England and Wales infected with CHB [180,000 (0.3%) in the UK], with around 7000 new cases every year (mostly from immigration of established HBV carriers). Intravenous drug use remains the single greatest risk factor for UK acquired acute HBV infection, with maternal transmission responsible for many of the chronic cases.

Methods

Electronic databases were searched from 1995–6 to April 2005 for studies of clinical effectiveness, cost-effectiveness, quality of life, resource use/costs and epidemiology/natural history. For the clinical effectiveness review, randomised controlled trials (RCTs) were included that compared PEG and ADV with currently licensed treatments for CHB, including non-pegylated (‘standard’) interferon alfa (IFN), lamivudine (LAM), and best supportive care. Short-term outcomes were biochemical, histological and virological response to treatment, drug resistance and adverse effects. The trials were reviewed in a narrative synthesis but meta-analysis was not undertaken owing to heterogeneity in the interventions and comparators evaluated.

A model was developed to estimate the cost-effectiveness (cost-utility) of PEG and of ADV compared with IFN, LAM and best supportive care in a UK cohort of adults with CHB. The perspective of the cost-effectiveness analysis was that of the NHS and personal social services.

A Markov state transition model was constructed, informed by a systematic search of the literature to identify source material on the natural history, epidemiology and treatment of CHB. In the state transition model, patients with CHB may remain in that state, may move on to more progressive stages of liver disease (such as cirrhosis or hepatocellular carcinoma) or may clear the disease spontaneously/move into remission. A cohort of treated and untreated patients pass through the eight disease states of the model at different rates:

- CHB
- HBeAg seroconversion/remission
- HBsAg seroconversion
- compensated cirrhosis
- decompensated cirrhosis
- hepatocellular carcinoma
- liver transplant
- death.

The model has a lifetime horizon and a cycle length of 1 year, with a half-cycle correction applied. For treated patients, clinical effectiveness results [HBeAg seroconversion rates and alanine aminotransferase (ALT) normalisation rates] were taken from the Phase II/III RCTs identified in our systematic review. Transition probabilities for untreated patients were taken from the published literature.
The baseline cohort comprised individuals with a median age of 31 years (HBeAg-positive CHB) and 40 years (HBeAg-negative CHB). About 70% of HBeAg-positive and 90% of HBeAg-negative patients are male. All have CHB, but have not progressed to cirrhosis.

To estimate changes in health-related quality of life (HRQoL) published age-specific quality of life weights for both CHB and chronic hepatitis C were taken from the literature. Resource and health state costs for assessment, investigation, treatment and monitoring were derived from the literature and from discussions with clinical colleagues and supplied by an English NHS Hospitals Trust. Costs are discounted at 6% and health outcomes at 1.5%.

Interventions were evaluated against their closest comparator (for PEG this is IFN, and for ADV this is LAM). In addition, the cost-effectiveness of sequential treatment scenarios was modelled. The results of these comparisons were reported in terms of the incremental gain in quality-adjusted-life years (QALYs) and the incremental costs determined in the cohort analysis.

Results

Clinical effectiveness

A total of 1086 references to clinical effectiveness studies were identified. After screening, seven fully published RCTs and one systematic review met the inclusion criteria. Four of the RCTs evaluated the effectiveness of ADV and three reported results for PEG. In addition, a conference abstract was reviewed which reported interim results from an on-going Phase II RCT of ADV in combination with LAM. The published trials were of good quality, although details of randomisation and allocation of concealment were poorly reported.

ADV

1. In terms of reductions in HBV DNA:
   (a) ADV was significantly more effective than placebo. Response rates were in the range 21–51% compared with 0%, respectively.
   (b) For patients resistant to LAM, response rates were significantly higher for those treated with ADV in addition to on-going LAM (35–85%) than for those who continued on LAM with placebo (0–11%).

2. Significant ALT reductions to normal levels were observed in all studies:
   (a) Response rates for ADV monotherapy after 1 year’s treatment were in the range 48–72%, compared with 16–29% for placebo.
   (b) In LAM-resistant patients, significantly higher response rates were observed for those given ADV in addition to LAM, compared with those who continued on LAM with placebo (37 versus 9%).

3. In terms of HBeAg loss and seroconversion:
   (a) For treatment-naïve patients, seroconversion rates were 12–14% for ADV compared with 6% for placebo (statistically significant).
   (b) Rates were higher for LAM-resistant patients who received ADV in addition to on-going LAM (8%) than for those who continued on LAM with placebo (2%). No significance value was reported.
   (c) Rates were higher for LAM-resistant patients who switched to ADV than for those who continued on LAM with placebo (11 versus 0%, respectively; not statistically significant).

4. HBsAg loss or seroconversion was observed in a minority of patients (<5%) taking ADV.

5. Two ADV studies reported changes in liver histology. In general, histological improvement and necroinflammatory activity/fibrosis scores were significantly better in ADV groups than in placebo groups.

6. Dose discontinuations for safety reasons were low for patients receiving ADV. With the exception of headache, the most commonly reported adverse events were often seen in the placebo groups in similar proportions to the ADV groups, with different trials reporting conflicting results.

PEG

1. PEG/LAM dual therapy and PEG monotherapy were similar in effect on HBV DNA and ALT levels, and both were significantly superior to LAM monotherapy. Response rates were higher for HBeAg-negative patients than for HBeAg-positive patients.
   (a) For HBeAg-positive patients, end of follow-up HBV DNA response rates were 32, 34 and 22%, respectively.
   (b) For HBeAg-negative patients, end of follow-up HBV DNA response rates were 43, 44 and 29%, respectively.
   (c) For HBeAg-positive patients, end of follow-up ALT response rates were 41, 39 and 28%, respectively.
   (d) For HBeAg-negative patients, end of follow-up ALT response rates were 59, 60 and 44%, respectively.
2. HBeAg seroconversion rates at follow-up were significantly higher for PEG monotherapy patients than for those receiving either a combination of PEG and LAM or LAM monotherapy (32%, 27% and 19%, respectively).

3. For the comparison between PEG-2a and IFN-2a, there was a significant difference in the combined outcome of ALT normalisation, HBV DNA response and HBeAg seroconversion at follow-up (24 versus 12%, respectively).

4. Changes in liver histology were reported by two studies. There was no statistically significant difference in histological improvement between the PEG monotherapy groups, the LAM monotherapy groups and the dual therapy groups.

5. Two PEG trials reported small percentages (up to 5%) of HBsAg loss or seroconversion among patients receiving PEG either as monotherapy or in combination with LAM, but no HBsAg loss or seroconversion was reported in those receiving LAM monotherapy.

6. HRQoL scores, as measured by the Short Form with 36 Items, decreased during treatment, but returned to at least baseline levels at follow-up (based on unpublished data). For HBeAg-positive patients, there were no significant differences in scores between treatment groups.

7. Dose discontinuations for safety reasons were significantly higher for patients receiving PEG than for patients receiving LAM monotherapy. The most commonly reported adverse events in the PEG studies were headache, pyrexia, fatigue, myalgia and alopecia.

Cost-effectiveness

Systematic review of cost-effectiveness studies

Only one fully published economic evaluation was identified, reporting a US cost-effectiveness study of ADV as salvage therapy for CHB with LAM resistance. A Markov model was used to estimate cost-effectiveness of interferon alfa (6–12 months), LAM and LAM followed by ADV when resistance occurs. ADV generated the most (undiscounted) life-years, but at highest costs, with an incremental cost-effectiveness ratio (ICER) of US$14,204 per life-year gained.

In addition to this study, six cost-effectiveness studies of existing treatments for CHB were identified, published between 1995 and 2002. There was little published literature on HRQoL in CHB.

Modelled cost-effectiveness analysis

From a model developed for this study by the authors, the incremental cost per QALY estimates (baseline cohort of all patients) were:

- £5994 – IFN compared with best supportive care
- £6119 – PEG compared with IFN
- £3685 – LAM compared with best supportive care
- £16,569 – ADV compared with LAM.

Incremental cost per QALY estimates (HBeAg-positive patients only) were:

- £7936 – IFN (24 weeks) compared with best supportive care
- £16,166 – PEG (48 weeks) compared with IFN (24 weeks)
- £3489 – LAM compared with best supportive care
- £15,289 – ADV compared with LAM.

Incremental cost per QALY estimates (HBeAg-negative patients only) were:

- £3922 – IFN (48 weeks) compared with best supportive care
- £2162 – PEG (48 weeks) compared with IFN (24 weeks)
- £4131 – LAM compared with best supportive care
- £18,620 – ADV compared with LAM.

For the sequential treatment strategies, incremental cost per QALY estimates ranged from £3604 (IFN followed by LAM versus IFN alone) to £11,402 (IFN followed by LAM with adefovir salvage versus IFN followed by LAM). Separating these results out for patients with HBeAg-positive and -negative disease reveals different patterns in the cost-effectiveness of these sequential treatment strategies. In all of these cases, the ICERs are well within the range that would conventionally be regarded as being cost-effective.

Deterministic sensitivity analysis showed that:

- Excluding transitions from the compensated cirrhosis health state to HBeAg seroconversion produces a substantial increase in the ICER for strategies including adefovir, whereas the results appear to be little influenced by variation in transitions from the HBeAg seroconverted state to hepatocellular carcinoma or to HBsAg seroconversion.
- The results appear to be robust to changes in the composition of the baseline cohort. However, reducing the proportion of the cohort that is assumed to be HBeAg positive dramatically reduces the ICERs for strategies that include PEG and ADV.
- Changing the discount rates applied to costs and health outcomes to 3.5% has a similar effect as in the pair-wise sensitivity analysis, greatly increasing the ICER for strategies including ADV.
• Changing the HBeAg seroconversion rate to carry forward the year 4 rate for all subsequent years in which a patient was treated, or to apply the spontaneous rate for years subsequent to year 4, had a dramatic effect on the ICER for ADV, which increased from £16,569 in the base case to £21,363 for the model that extrapolates beyond 4 years and to £50,168 for the model with no extrapolation (i.e. the spontaneous rate).
• The ICERs for PEG appear to be particularly sensitive to variations in the relapse rate for HBeAg-negative patients who achieve a response (by normalising ALTs) following treatment.

The probabilistic sensitivity analysis found that:

• LAM is a cost-effective option at lower willingness-to-pay thresholds for health outcomes, but as the threshold is increased ADV is increasingly likely to be the optimal intervention.
• Where a willingness-to-pay threshold of above £10,000 per QALY is employed, PEG is highly likely to be the optimal intervention compared with IFN (based on a cohort of HBeAg-positive and -negative patients).
• Interferon alfa (non-pegylated or pegylated) followed by LAM would be the optimal strategy at lower willingness-to-pay thresholds. As the threshold increases, the sequential treatment strategy of PEG followed by LAM with ADV added as salvage therapy is increasingly likely to be the optimal intervention.

Conclusions
ADV and PEG-2a are associated with significant improvements in a number of biochemical, virological and histological outcomes in both HBeAg-positive and -negative patients. For a small proportion of patients this is associated with resolution of infection. For another proportion it leads to remission and a reduced risk of progressing to cirrhosis, hepatocellular carcinoma, liver transplant and death. For others who do not respond or who relapse, retreatment with another agent is necessary.

The results of our cost-effectiveness analysis demonstrate that incremental costs per QALY for a range of comparisons were between £5994 and £16,569 and within the range considered by NHS decision-makers to represent good value for money. When subjected to sensitivity analysis, most costs per QALY estimates remained under £30,000.

Recommendations for further research
Further RCT evidence of the effectiveness of antiviral treatment is required, particularly for subgroups of patients with different genotypes, patients with cirrhosis, patients from different ethnic groups, patients with co-infections (e.g. HIV, HCV) and co-morbidities, liver transplant patients and children and adolescents.

Further published evidence is awaited on:

• the effectiveness of ADV in combination with LAM in treatment-naïve patients
• the long-term effectiveness of ADV
• the effectiveness of PEG in LAM non-responders and in interferon alfa non-responders
• long-term follow-up of PEG treatment
• HRQoL.

Publication
The research findings from the NHS R&D Health Technology Assessment (HTA) Programme directly influence key decision-making bodies such as the National Institute for Health and Clinical Excellence (NICE) and the National Screening Committee (NSC) who rely on HTA outputs to help raise standards of care. HTA findings also help to improve the quality of the service in the NHS indirectly in that they form a key component of the ‘National Knowledge Service’ that is being developed to improve the evidence of clinical practice throughout the NHS.

The HTA Programme was set up in 1993. Its role is to ensure that high-quality research information on the costs, effectiveness and broader impact of health technologies is produced in the most efficient way for those who use, manage and provide care in the NHS. ‘Health technologies’ are broadly defined to include all interventions used to promote health, prevent and treat disease, and improve rehabilitation and long-term care, rather than settings of care.

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Additionally, through its Technology Assessment Report (TAR) call-off contract, the HTA Programme is able to commission bespoke reports, principally for NICE, but also for other policy customers, such as a National Clinical Director. TARs bring together evidence on key aspects of the use of specific technologies and usually have to be completed within a short time period.

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Reviews in Health Technology Assessment are termed ‘systematic’ when the account of the search, appraisal and synthesis methods (to minimise biases and random errors) would, in theory, permit the replication of the review by others.

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