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

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CRD summary
This review concluded that adefovir dipivoxil and pegylated interferon alpha were beneficial for patients with Chronic Hepatitis B. Adefovir dipivoxil was beneficial for up to five years with relatively low risk of resistance. The authors’ conclusions reflect the evidence, but some included studies were small and there were no consistent statistically significant differences between treatments.

Authors’ objectives
To update and extend a previous report on the clinical effectiveness and cost-effectiveness of adefovir dipivoxil (ADV) and pegylated interferon alpha (PEG-α) for the treatment of chronic hepatitis B (see Other Publications of Related Interest). This abstract is focused on clinical effectiveness and mentions cost-effectiveness only briefly.

Searching
Thirteen bibliographic databases were searched (included MEDLINE, EMBASE and The Cochrane Library). Searches covered from the beginning of 2005 to September 2007. The search strategy was based on the previous report. All searches were limited to studies in English. Unpublished studies were ineligible for the review.

Study selection
Eligible studies had to be randomised controlled trials (RCTs) that compared adefovir dipivoxil, PEG-α-2a and PEG-α-2b with currently licensed treatments for chronic hepatitis B that included interferon alpha (IFN-α-2a or IFN-α-2b), lamivudine, adefovir dipivoxil, PEG-α-2a , PEG-α-2b, placebo and best supportive care. Treatment and comparators could be used alone or in combination with other treatments. Patients had chronic hepatitis B infection and included HBeAg-positive and HBeAg-negative with compensated or decompensated liver disease. Outcomes included survival, health-related quality of life, drug resistance, time to treatment failure, histological response, biochemical response, virological response, seroconversion and adverse effects.

Included studies compared adefovir dipivoxil to placebo or assessed adefovir dipivoxil versus adefovir dipivoxil plus lamivudine in patients with lamivudine resistance. Trial duration varied from 37.5 to 340 weeks. Most participants were male. Average age ranged from 32 to 56 years. PEG-α-2b plus lamivudine was compared to PEG-α-2b or lamivudine monotherapy or PEG-α-2b plus placebo. PEG-α-2b monotherapy was compared to IFN-α-2b. Most participants were male. Average age ranged from 31 to 43 years. Trial duration varied from 24 to 104 weeks. Trials varied in terms of aims, size and design characteristics. Most patients had received previous treatment for chronic hepatitis B.

Two reviewers were involved in study selection. Disagreements were resolved through discussion.

Assessment of study quality
Methodological quality was assessed by one reviewer using Centre for Reviews and Dissemination criteria of randomisation, allocation concealment, blinding, intention-to-treat (ITT) analysis, withdrawals, outcome reporting and comparability of groups at baseline. A second reviewer checked the assessment. Disagreements were resolved through discussion.

Data extraction
One reviewer extracted data using a standardised template which was checked by a second reviewer. Any disagreements were resolved through discussion.

Methods of synthesis
Trials were synthesised narratively.
**Results of the review**

Eight RCTs (13 publications) were included in the review.

**Adefovir dipivoxil**: There were three trials (647 participants). One trial became an observational study. One of the other two trials reported adequate randomisation, partial allocation concealment and similar baseline characteristics. This trial reported partial blinding; the other trial was open label. Reporting of outcomes and withdrawals was adequate in one trial and only partly so in second trial. ITT analyses were inadequate in one trial and adequate in the other.

Compared to controls, a greater proportion of patients who received adefovir dipivoxil reported a hepatitis B virus DNA (virological) response, but this was not confirmed statistically. Similarly, adefovir dipivoxil patients reported alanine aminotransferase normalisation (biological response), but this was not always confirmed statistically. The proportion of virological and biological responders was generally maintained in the long term. Two trials reported relatively low rates of adefovir dipivoxil resistance and this remained over the long term. Other results and findings from single trials were reported in the review.

**PEG-α-2b**: There were five trials (674 participants). Four out of five trials reported method of randomisation and three adequately reported allocation concealment. All trials reported patients' baseline characteristics and only one study reported statistically significant differences between groups at baseline. One study adequately described all blinding, the others were open-label with attempts to blind outcome assessors noted in two trials. Reporting of outcomes was variable and deemed adequate for two studies. ITT analysis was used in three studies and found to be inadequate in two. Reporting of withdrawals was adequate in two studies, partial in two and inadequate in one.

There were no significant differences between concurrent and staggered commencement of PEG-α-2b and lamivudine for hepatitis B virus DNA response and no consistently statistically significant differences for PEG-α-2b plus lamivudine versus PEG-α-2b monotherapy and PEG-α-2b versus IFN-α. PEG-α-2b plus lamivudine tended to show greater proportions with normalised alanine aminotransferase compared to either treatment as monotherapy. Proportions were generally similar for comparisons of different commencement regimens of PEG and lamivudine or PEG-α-2b and IFN-α. However, rates of normalisation generally decreased from the end of treatment to follow-up and few statistically significant differences were reported. Three trials showed mixed results for liver histological response and where statistical tests were reported there were no significant differences between treatments. Three trials reported viral resistance rates. Addition of lamivudine to PEG-α-2b was associated with lower rates of lamivudine resistance, but this was not confirmed statistically.

**PEG-α-2a**: No RCTs were identified.

**Cost information**

A systematic review of economic evaluations of antiviral treatments for chronic hepatitis B was conducted and the economic model constructed for the previous report was updated. Four full economic evaluations were identified in addition to one in the original report. The updated economic model found that adefovir dipivoxil as salvage became optimal above a willingness to pay threshold of £27,000 per quality-adjusted life-year (QALY). Incremental cost-effectiveness ratio (ICER) for PEG-α-2b compared with IFN-α-2b was £9,169 based on one trial with HBeAg-positive chronic hepatitis B patients. The probability of being cost-effective compared with IFN-α-2b was 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.

**Authors' conclusions**

Both adefovir dipivoxil and PEG-α were beneficial for patients with chronic hepatitis B in terms of suppressing viral load, reducing liver damage-associated biochemical activity, inducing HBeAg seroconversion and reducing liver fibrosis and necroinflammation. Benefits were durable when patients were treated with adefovir dipivoxil for up to five years with relatively low risk of resistance.

**CRD commentary**

This review had clear inclusion criteria for participants, interventions, outcomes and study designs. The search encompassed a range of databases. Unpublished studies and studies in languages other than English were not eligible for the review and this raised the possibility of publication and language biases. A validity assessment was conducted and
results presented in the context of study quality. Most studies were open label and were of mixed quality. Involvement of two reviewers in the processes of study selection, data extraction and validity assessment minimised the possibility of bias and error. A narrative synthesis was appropriate given the diversity of the studies. The authors highlighted that although both drugs appeared beneficial compared to controls, there were no consistent statistically significant differences and some trials were small and potentially underpowered.

The authors’ conclusions reflect the evidence but the highlighted limitations need to be taken into consideration when interpreting the findings.

Implications of the review for practice and research
Practice: The authors did not state any implications for practice.

Research: The authors stated that further high-quality trials were required to assess the durability of long-term antiviral treatment, optimum treatment of patients with lamivudine resistance and clinical effectiveness and cost effectiveness of initiating treatment with nucleoside combination therapy, including newer antiviral agents.

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Record Status
This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.