Treatment alternatives for chronic hepatitis B viral infection: a cost-effectiveness analysis

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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
Five treatment strategies for chronic hepatitis B virus (HBV) infection were compared:

- no HBV treatment ("do nothing" strategy);
- interferon monotherapy, (10 million units subcutaneously 3 times per week);
- lamivudine monotherapy, (100 mg orally once daily);
- adefovir monotherapy, (10 mg orally once daily); and
- a hybrid strategy of up-front lamivudine followed by adefovir salvage if lamivudine-related viral resistance developed ("adefovir salvage" strategy).

Type of intervention
Treatment.

Economic study type
Cost-utility analysis.

Study population
The hypothetical population comprised a cohort of patients of 40 years of age with chronic HBV infection, elevated aminotransferase levels, and no clinical or histological evidence of cirrhosis. To emulate the case-mix in clinical practice in the USA, the study assumed that 55% of the cohort was hepatitis B e antigen (HBeAg)-negative.

Setting
The setting was primary care. The economic study was carried out in Los Angeles (CA), USA.

Dates to which data relate
The studies used for the effectiveness evidence dated from January 1970 to February 2005. For the cost data, the studies dated from 1997 and 2004. The price year was 2004.

Source of effectiveness data
The evidence was derived from a review or synthesis of completed studies and estimates based on experts' opinions.

Modelling
A Markov (state transition) decision model was used and described in detail. Since the clinical course, prognosis and response to therapy varied in patients with HBeAg-positive and HBeAg-negative HBV, the analysis was stratified by
HBeAg status and separate probability estimates were assigned to each group. Patients entering the model received either no treatment ("do nothing" strategy) or one of the comparators. Then, the cohort was followed yearly over a lifetime horizon. During each 1-year cycle, individual patients either remained in their assigned health state or progressed to a new health state. Patients achieving virologic response (either spontaneously or after treatment) were assumed to not develop cirrhosis and to have a normal life expectancy. The model also included two sub-models that simulated pre-cirrhosis and cirrhosis health states. It was assumed that patients achieving initial virologic response might subsequently relapse, in which case they re-entered the original state of chronic HBV infection. Patients with viral resistance maintained during long-term therapy were eligible to achieve virologic response. All the data across studies were combined by calculating a weighted mean, using study sample size as the weight.

Outcomes assessed in the review
The parameters used in the model included:

natural history estimates considering the effect of chronic HBV infection on survival, and the relationship between virologic response and viral resistance with subsequent health;

the treatment efficacy estimates; and

the effect of treatment-related adverse events.

The utilities for different health states were also incorporated.

Study designs and other criteria for inclusion in the review
A systematic review was performed. The authors reported that they used randomised controlled trials (RCTs), cohort studies, meta-analyses, observational studies and published literature. The criteria for the search were relevant English-language studies published from January 1970 to February 2005. Studies that addressed either the natural history of chronic HBV infection, or the efficacy of interferon, lamivudine or adefovir in treating chronic HBV infection, were targeted. The keywords and search strings used for the systematic review are available from the authors on request.

Sources searched to identify primary studies
Published abstracts from three major sub-specialty journals, as identified via MEDLINE, and the bibliographies of key review articles were reviewed.

Criteria used to ensure the validity of primary studies
The authors relied on summary estimates derived from published systematic reviews and meta-analyses where available.

Methods used to judge relevance and validity, and for extracting data
Three independent reviewers assessed titles and followed explicit rules (described in detail in an appendix) for the inclusion of final articles. They also assessed the relevance of the articles to their model.

Number of primary studies included
The search strategy identified 4,811 titles, 150 of which met the explicit inclusion criteria. Of these studies, 91 addressed natural history estimates, 33 addressed lamivudine efficacy estimates, 15 addressed interferon efficacy estimates, and 11 addressed adefovir efficacy estimates.

Methods of combining primary studies
Weighted means of the estimates were calculated where possible, otherwise individual study results were used.
Investigation of differences between primary studies
The authors investigated differences between the primary studies and used such differences for the ranges selected for the sensitivity analysis.

Results of the review
The base-case rates for selected outcomes for HBeAg-positive and -negative patients were as follows.

The probabilities of spontaneous virologic response were 6.9% and 1.6%, respectively;
the probability of developing adverse events during a course of interferon was 26% for both sub-groups; and
the probabilities of durable virologic response were 33% and 20%, respectively, in adherent patients receiving interferon, and 7% and 0% in non-adherent patients.

For the lamivudine monotherapy strategy:
the probability of durable virologic response after initial 18 months of therapy was 20% for HBeAg-positive patients and 10% for HBeAg-negative patients;
the yearly probability of developing resistance while receiving long-term lamivudine was 23% for both groups; and
the yearly probabilities of durable virologic response while receiving long-term lamivudine without resistance were 24% and 10%, respectively.

For adefovir-based strategies:
the probability of durable virologic response after initial 18 months of therapy was 12% for HBeAg-positive patients and 10%* for HBeAg-negative patients;
the yearly probability of developing resistance while receiving long-term adefovir was 1.3% for both groups;
the yearly probabilities of durable virologic response while receiving long-term adefovir without resistance were 17.5% and 10%*, respectively; and
the yearly probabilities of durable virologic response following crossover from lamivudine to adefovir were 12% and 10%, respectively.

(* denotes cases were no data to support the base-case estimates were found; therefore, the estimate was an assumption).

Some of the natural history variables were as follows:
the probability of HBeAg-negative chronic HBV was 55%;
the probability of HBeAg-positive chronic HBV was 45%;
progression from chronic hepatitis to hepatocellular cancer was 1.5%;
progression to compensated cirrhosis was 4.6% in HBeAg-negative patients and 3.0% in HBeAg-positive patients;
progression from compensated to decompensated cirrhosis was 7.3%;
progression from cirrhosis to hepatocellular cancer was 3.4%;
the rate of mortality in compensated cirrhosis was 4.9%;
the rate of mortality in decompensated cirrhosis was 19%; and

the rate of mortality in hepatocellular cancer was 43.3%. The probabilities of developing other complications in cirrhosis, and receiving a liver transplant and its prognosis, were also reported.

The utility estimates used were:

0.99 for chronic HBV without cirrhosis;

0.80 for compensated cirrhosis;

0.6 for decompensated cirrhosis;

0.86 after successful liver transplantation;

0.73 for hepatocellular cancer; and

1.0 for durable virologic response.

Methods used to derive estimates of effectiveness
This analysis was based on published data and authors’ assumptions.

Estimates of effectiveness and key assumptions
Key model assumptions were reported in an appendix. These considered base-case patient characteristics, survival assumptions, definition of virologic response, relationship between virologic response or resistance and subsequent health, and effect of treatment-related adverse events.

The authors stated that when published estimates were not available, they assumed an estimate of the parameter, based on literature of a similar value. They did not find any studies that reported data on the long-term durability of virologic response in HBeAg-negative patients receiving adefovir. Without data, they assumed that the rate of durable virologic response was the same between lamivudine and adefovir. Therefore, they set the rate for adefovir at 10% per year in HBeAg-negative patients.

Without long-term durability data on this response, the authors assumed that the annual durable response rate among HBeAg-negative patients receiving long-term adefovir therapy was similar to the corresponding estimate for long-term lamivudine therapy. They based the annual rate of durable virologic response after crossover from lamivudine to adefovir on data reported in RCTs of adefovir. Thus, they assumed that the efficacy of adefovir was the same, regardless of whether the patients had developed lamivudine resistance.

Measure of benefits used in the economic analysis
The measure of benefits was the quality-adjusted life-years (QALYs).

Several studies in hepatitis C virus have measured patient health preferences, or utilities, for complications of chronic liver disease such as compensated cirrhosis, decompensated cirrhosis, hepatocellular cancer and liver transplantation. According to the authors, there are no similar studies in HBV. Therefore, established utilities for cirrhosis and related complications that relied on standard-gamble elicitation in patients with chronic hepatitis C virus infection (Chong et al. 2003, see ‘Other Publications of Related Interest’ below for bibliographic details) were used. All utilities were discounted at a rate of 3% per year.

Direct costs
The direct health care costs for each therapy covered drugs, physician visits, diagnostic tests and complications of chronic liver disease. The costs for physician services and procedures were obtained from the 2004 American Medical
Association Current Procedural Terminology codebook and the 2004 Medicare Fee Schedule. The base-case pharmaceutical costs were derived from the average wholesale prices listed in the 2004 Red Book. The cost estimates for cirrhosis and related health states were obtained from a published study of detailed, itemised inpatient and outpatient direct costs incurred by patients with cirrhosis (Bennett et al. 1997, see 'Other Publications of Related Interest' below for bibliographic details). All the costs were discounted at a rate of 3% per year. All cost estimates were updated to 2004 US dollars using the medical care component of the Consumer Price Index. The price year was 2004. The authors did not report the quantities and the costs separately. The estimations of the quantities and the total costs were derived using modelling.

**Statistical analysis of costs**
The costs were included as parameters in the model. No statistical analysis of the costs was reported.

**Indirect Costs**
The indirect costs were not reported.

**Currency**
US dollars ($).

**Sensitivity analysis**
The authors reported the base-case probability estimates with respective ranges. To test the influence of all variables on the model results, they performed a multivariable sensitivity analysis ("tornado analysis") and rank-ordered the most influential variables. Thus, they performed one-way sensitivity analyses on the most influential variables. A Monte Carlo simulation was also conducted, assuming that all variables followed a triangular distribution with base-case, minimum and maximum values reported. The authors simulated 1,000 trials and plotted the results on cost-effectiveness acceptability curves, stratified by willingness-to-pay thresholds. They analysed the base-case cohort (55% HBeAg-negative) to find the 2.5th and 97.5th percentiles for their estimate of incremental cost per QALY gained among competing strategies. A further sensitivity analysis was performed, using the acquisition costs of the Veterans Administration as a proxy for the discounts achieved by large third-party payers.

**Estimated benefits used in the economic analysis**
The benefit results were just presented graphically by cohort and can be seen in the paper, assuming that the entire cohort is HBeAg-negative or HBeAg-positive. The graphics displayed the lifetime cumulative cost and the number of QALYs gained.

**Cost results**
The total intervention costs for lifetime treatment strategies were not reported in the text.

**Synthesis of costs and benefits**
The "do nothing" strategy was the least expensive and least effective strategy. Compared with doing nothing, using interferon cost an incremental $6,337 per QALY gained (2.5th and 97.5th percentiles: $4,123 and $8,992, respectively). Compared with interferon, the adefovir salvage strategy cost an incremental $8,446 per QALY gained (2.5th and 97.5th percentiles: $6,031 and $11,542, respectively). Both the lamivudine and adefovir monotherapy strategies were more expensive and less effective than the alternative strategies and, therefore, were dominated. The base-case analysis revealed that the restricted use of adefovir as salvage therapy was more cost-effective than both lamivudine and adefovir monotherapies.

The adefovir salvage strategy was more effective and less expensive than the four competing strategies. It became the dominant strategy in the HBeAg-positive cohort.
Compared with the base-case analysis, in the HBeAg-negative cohort, all the strategies became more expensive and more effective, thereby reflecting the difficulties and expense of treating HBeAg-negative patients. The incremental cost of using interferon decreased from $6,337 per QALY gained in the base-case analysis to $2,280 per QALY gained in the HBeAg-negative cohort. Compared with interferon, the adefovir salvage strategy cost an incremental $16,593 per QALY gained. In contrast, the use of up-front adefovir showed diminishing returns, costing an incremental $90,983 per QALY gained versus the adefovir salvage strategy. The lamivudine monotherapy strategy was dominated.

The tornado analysis revealed that the model was most sensitive to six variables. These were the monthly costs of adefovir, lamivudine and interferon, the annual incidences of viral resistance on lamivudine and on adefovir, and the annual incidence of cirrhosis in HBeAg-negative patients with viral resistance. The thresholds of these variables were reported. The results of the sensitivity analysis using Veterans Administration acquisition costs for pharmaceuticals did not differ qualitatively from those of the base-case analysis.

Together, the results indicated that of the four active therapy strategies, the interferon and adefovir salvage strategies were potentially cost-effective. To determine which comparator to use under different budgetary restraints, the authors performed three Monte Carlo analyses to compare interferon and adefovir salvage across a range of willingness-to-pay thresholds.

The cost-effectiveness acceptability curves reflecting 1,000 hypothetical patients in each cohort revealed that the use of the adefovir salvage strategy instead of interferon was the most cost-effective strategy in HBeAg-positive patients. In contrast, interferon was the most cost-effective in health care systems with tight budgetary constraints (i.e. low willingness-to-pay) and high prevalence of HBeAg-negative patients.

Authors’ conclusions
The analysis revealed that the use of either lamivudine or adefovir monotherapy was not cost-effective in the treatment of chronic hepatitis B virus (HBV) infection. Of the active therapeutic strategies currently available for chronic HBV infection, only interferon monotherapy and adefovir salvage therapy were potentially cost-effective. Whereas adefovir salvage was likely to be highly cost-effective across most health care settings independent of hepatitis B e antigen (HBeAg) status, interferon might be preferred in health care systems with limited resources, especially in those serving populations with a high prevalence of HBeAg-negative chronic HBV.

CRD COMMENTARY - Selection of comparators
The authors justified their choice of the comparators. Current treatment options for chronic HBV infection have varying effects and costs and, given the uncertainty on how best to initiate therapy in HBV, this study might assist clinicians in everyday clinical decision-making. You should judge whether these treatment strategies are relevant in your own setting, or whether other comparators from other drugs could also be relevant.

Validity of estimate of measure of effectiveness
The authors reported that a systematic review of the literature had been undertaken, therefore it ensured that the best data available were used in the model. The estimates of effectiveness were derived credibly from the studies identified. The authors used data from published sources, and the inclusion and exclusion criteria were clearly reported. The authors also made some assumptions that were justified with reference to the medical literature. The methodology for selecting and reviewing the literature used was reported. The effectiveness evidence was derived from meta-analyses and RCTs, which are adequate sources to estimate effectiveness. The authors provided the base-case value and the range tested in the sensitivity analysis around each point estimate, and the sources were adequately referenced.

Validity of estimate of measure of benefit
The authors used QALYs as a measure of benefits. The estimation of quality-adjusted utility weights was taken from the literature, and details were provided in an appendix. The estimation of benefits was modelled and only incremental results were reported; the reporting of total strategy benefits could have helped to evaluate their magnitude.
Validity of estimate of costs

The authors reported that the costs were estimated from a third-party payer perspective. All the relevant cost categories appear to have been included. Although some costs were taken from different sources and years, they were discounted at a rate of 3% per year and adjusted using the medical care component of the Consumer Price Index. This will aid any future reflation exercise. The prices were taken from published sources and the price year was reported. The resource use quantities were not reported separately, nor were the total costs of the treatment strategies. These factors may limit extrapolation exercises to other settings. Sensitivity analyses of selected direct costs, to assess the robustness of the estimates used, were conducted and reported.

Other issues

The authors did not make appropriate comparisons of their findings with those from other studies. Mainly because they stated that their study was the first decision analysis to compare all three currently approved agents for chronic HBV infection, as no model had examined the role of adefovir or adefovir salvage strategies.

The authors explicitly addressed the generalisability of the results and they considered assessing the impact of population heterogeneity. The reasons stated were that their model acknowledged the increasing prevalence of HBeAg-negative chronic HBV infection, and that it was stratified by HBeAg status. The model also attempted to reflect the everyday challenges in treating chronic HBV infection, accounting for non-adherence to medical therapy, non-adherence to physician follow-up visits, virologic recurrence after initially successful HBV therapy, various treatment durations according to HBeAg status, and poor availability of donor organs for eligible patients. The authors’ conclusions reflected the scope of the analysis.

The authors stated that the principal limitations of the model were that several of their estimates were based on studies of varying design, patient population, follow-up and quality. Also, the estimates of patient health preferences might be limited, because they adopted utilities for cirrhosis and related complications resulting from hepatitis C. The utilities for non-cirrhosis health states were derived from expert opinion. In addition, they did not evaluate the potential strategy of up-front treatment with interferon followed by crossover to lamivudine or adefovir in case of interferon treatment failure. Finally, their analysis applied only to a narrow patient population. Therefore, their results might not apply to alternative populations. In all these cases, the authors provided reasonable commentaries on how they tried to overcome these limitations, and provided valid alternative explanations about the strengths of the study.

Implications of the study

Future research should prospectively measure the cost-effectiveness of these competing treatment strategies in representative samples of community-based patients with chronic HBV infection.

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Bibliographic details


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Other publications of related interest


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