Cost-effectiveness of interferon-alpha-2b treatment for hepatitis B e antigen-positive 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
Treatment of hepatitis B e antigen positive chronic hepatitis B with interferon-alpha-2b.

Type of intervention
Treatment

Economic study type
Cost-effectiveness analysis and cost-utility analysis.

Study population
Hypothetical cohort of patients with chronic hepatitis B infection who are positive for hepatitis B virus e antigen (HBeAg).

Setting
The practice setting was secondary care. The economic study was carried out in Boston (New England Medical Centre and Tufts University School of Medicine), U. S. A.

Dates to which data relate
Effectiveness analysis data were taken from trials published in the period 1988-1993. There are no dates of prices or resource data.

Source of effectiveness data
The evidence for effectiveness was based on a synthesis of previously completed studies.

Modelling
A Markov model was used to estimate final outcomes and costs.

Outcomes assessed in the review
Disappearance of HBeAg and HBsAg (hepatitis B surface antigen), and the relative risk for developing cirrhosis.

Study designs and other criteria for inclusion in the review
All randomised trials involving interferon-alpha-2b. Primary studies were included if they met the following criteria: a) Did not include paediatric patients; b) Patients were HBeAg positive; c) Results were not superseded by later results. Patients were excluded who received less than the FDA approved 480 million units of interferon-alpha-2b or were
crossing over from a control group to a treatment group.

**Sources searched to identify primary studies**
Medline

**Criteria used to ensure the validity of primary studies**
Not stated.

**Methods used to judge relevance and validity, and for extracting data**
Not stated.

**Number of primary studies included**
Nine randomised controlled trials were included.

**Methods of combining primary studies**
Meta-analysis, overall odds ratios and rate differences for the disappearance of HBeAg were calculated using the DerSimonian and Laird method. The hazard rate for developing cirrhosis was calculated using the Cox proportional hazards model.

**Investigation of differences between primary studies**
Homogeneity of rates between studies was tested by Chi-square analysis. Test results of heterogeneity were not significant (P< 0.1) for overall pooled odds ratio and the absolute rate of causing disappearance of HBeAg.

**Results of the review**
The pooled odds ratio for interferon-alpha 2b therapy causing the disappearance of HBeAg was 7.4 (CI, 3.9 to 14.0; P < 0.001). Interferon-alpha 2b increased the absolute rate of causing disappearance of HBeAg by 36% (CI, 23.7% to 49.2%; P < 0.001) from 9.1% to 45.6%. The relative risk of developing cirrhosis for HBeAg patient was calculated to be 2.39. Assuming a constant hazard rate this was converted to an annual probability of 12.1%. Interferon-alpha 2b therapy increases the likelihood of becoming negative for HBsAg from 1.7% to 7.7% (difference, 6.0%; CI 2.8% to 9.3%) in the first year.

**Measure of benefits used in the economic analysis**
Life expectancy and quality adjusted life expectancy. The sickness health profile was used, and the expert panel assessed the utilities using the standard reference gamble and the time-trade off technique. A Markov model was used to estimate prognosis in a hypothetical cohort of patients since this allowed for patients to move between the health states, chronic hepatitis B, cirrhosis, hepatocellular carcinoma and death. Health state utilities were estimated by a panel of 7 experts using a modified Delphi method.

**Direct costs**
The discount rate was 5% for costs. Costs and quantities were analysed separately. Actual variable hospital costs or the cost to treat one additional patient with the same disease were obtained from the Clinical Cost Manager accounting system. These included laboratory costs. Physician fees for inpatient and outpatient care were estimated from multiplying the physician charges by the mean reimbursement-to-charge ratio for internal medicine services. Wholesale drug prices were used to represent drug costs. The expert panel estimated the frequency of hospitalisations, outpatient visits and laboratory test plus the choice and quantities of drugs used in each health state. Date of prices was not stated. A Markov model was used to estimate final costs.
Currency
American dollars ($)

Sensitivity analysis
Sensitivity analysis was carried out to assess the variability in the data. One way simple sensitivity analysis was carried out by varying: a) The age at inception, b) The probability of becoming HBeAg negative in the first year of interferon treatment, c) The probability of non-responders and patients treated with standard care becoming HBeAg negative after the first year, d) The probability of developing cirrhosis, e) The probability of reactivating HBeAg in the first year of interferon treatment, f) The probability of having cirrhosis before interferon treatment starts, g) The cost of interferon, h) The cost of treating cirrhosis, i) The discount rate. Multiway simple analysis was carried out by biasing all baseline values in favour of standard care.

Estimated benefits used in the economic analysis
Life-years were discounted at 5%. The incremental life years gained were estimated to be 3.1 (27.9-24.8) for a 35 year old male, HBeAg positive at the outset and the incremental quality adjusted life years gained were estimated to be 3.4 (25.8-22.4). These benefits refer to a simulated life time follow up for patients treated with either interferon or standard care.

Cost results
Estimated total lifetime costs per patient in the interferon group were $53 600 (discounted $30 600) and in the standard care group $60 200 (discounted $32 700). Thus the incremental costs were -$6600 ($-2100 discounted). The costs of adverse events were not considered.

Synthesis of costs and benefits
An incremental analysis was performed on undiscounted costs and benefits. Interferon-alpha-2b was estimated to save approximately US$6.6 million and 3137 years of life for every 1000 patients treated (incremental ratioUS$ 2103 per life year gained). Sensitivity analysis showed that even at the lower limit of the confidence interval for the risk difference between interferon and standard care of becoming HBeAg negative, treatment with interferon-alpha-2b would still increase quality adjusted life expectancy by 2.2 years saving US$2318 compared to standard care (US$-1053 per QALY gained). Interferon-alpha 2b is the dominant strategy.

Authors' conclusions
Interferon-alpha-2b should both prolong survival and diminish lifetime costs. Even if the benefit of interferon-alpha-2b beyond 10 years was zero it would still not be expensive compared to other therapies commonly in use in 1995.

CRD Commentary
The randomised controlled trials used in meta-analysis were assumed to reflect intention to treat and therefore assumed to include premature discontinuation of interferon treatment discussed in the reported results. Because the search strategy is not defined by the authors it is not clear the extent to which all relevant studies have been systematically included. The results of the analysis for final health outcomes (life years gained and QALYs gained) are largely dependant on expert opinion and projection from the intermediate outcome of HBeAg status and are thus subject to variability and uncertainty. Sensitivity analysis was undertaken in an attempt to investigate the reliability of these estimates. Overall a very detailed study.

Implications of the study
The data presented support the routine use of interferon-alpha-2b in chronic hepatitis-B for HBeAg positive patients only, until the results of a clinical trial with longer term follow up to assess effects on mortality and quality of life are
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