Treatment of chronic hepatitis B with interferon-alpha: cost-effectiveness in developing countries
Aggarwal R, Ghoshal U C, Naik S R

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
The use of interferon (IFN)-alpha (IFN), at a dose of 5 million units/day for 16 weeks, for the treatment of hepatitis B virus (HBV).

Type of intervention
Treatment.

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

Study population
The study population comprised a hypothetical cohort of adult patients suffering from chronic HBV infection (hepatitis B surface antigen positive for 6 months). The patients had an elevated serum aminotransferase activity (more than 1.5 times the upper limit of normal) for at least 6 months and evidence of active viral replication (positive HBV DNA in the serum). They also had a histological diagnosis of chronic hepatitis, but no evidence of cirrhosis. Patients with coexistent hepatitis C virus, hepatitis D virus, or human immunodeficiency virus infection were excluded.

Setting
The setting was secondary care. The economic study was conducted in India.

Dates to which data relate
The effectiveness data were derived from studies published between 1993 and 2001. No dates for the resource use data were explicitly reported. The price year was not reported.

Source of effectiveness data
The effectiveness evidence was derived from a synthesis of published studies and assumptions.

Modelling
A Markov model was constructed to assess the costs and outcomes of two hypothetical cohorts of HBV patients, one that received IFN and one that did not. The cycle length was 1 year. The health states considered were chronic hepatitis B, compensated cirrhosis, decompensated cirrhosis, hepatocellular carcinoma (HCC) and death. The patients were followed for 30 years (time horizon of the model), or they died of decompensated cirrhosis or its complications before the end of that period.

Outcomes assessed in the review
The outcomes assessed in the review were:

- the disease progression rates,
- the death rates,
- the rate of remission with IFN compared with placebo, and
- the age-specific death rates in the Indian population.

**Study designs and other criteria for inclusion in the review**
The design of the primary studies was not explicitly reported, although one study was a meta-analysis and another was a statistical database of mortality.

**Sources searched to identify primary studies**
Not stated.

**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**
The effectiveness evidence was derived from 5 primary studies.

**Methods of combining primary studies**
Baseline primary estimates were selected from the ranges of values reported in the literature.

**Investigation of differences between primary studies**
Not stated.

**Results of the review**
The annual rates of progression were as follows:

- 0.02 (range: 0.01 - 0.03) from hepatitis to cirrhosis,
- 0.05 (range: 0.03 - 0.10) from cirrhosis to decompensated cirrhosis, and
- 0.02 (range: 0.01 - 0.03) from cirrhosis to HCC.

The death rates were 0.20 (range: 0.10 - 0.40) for patients with decompensated cirrhosis and 0.40 (range: 0.20 - 0.60) for patients with HCC.

The rate of remission with IFN, compared with placebo, was 0.30 (range: 0.10 - 0.40).

The death rates in the Indian population per 1,000 persons per year (for both genders) were:
3.4% in the age class 30 to 34 years;
3.7% in the age class 35 to 39 years,
4.9% in the age class 40 to 44 years,
7.7% in the age class 45 to 49 years,
13% in the age class 50 to 54 years,
13.5% in the age class 55 to 59 years, and
27.2% in the age class 60 to 64 years.

**Methods used to derive estimates of effectiveness**
The authors made some assumptions that were used in the decision model. In addition, the utility values associated with
model health states were based on expert opinion.

**Estimates of effectiveness and key assumptions**
The following assumptions were made:

no patient in the untreated cohort would lose serum hepatitis B e antigen (HbeAg);

the loss of HbeAg would eliminate the risk of cirrhosis, decompensated cirrhosis and death;

patients who were successfully treated with IFN would not suffer from relapse or reactivation of HBV infection;

patients who did not respond to IFN therapy would not receive a second course or another form of treatment;

liver transplantation was not available as a treatment modality;

the presence of HBV mutants, in particular the HbeAg-negative mutant, which was known to be associated with poorer
response to IFN therapy, was ignored.

The utility values were 0.95 (range: 0.9 - 1) for chronic hepatitis B, 0.9 (range: 0.8 - 0.95) for cirrhosis, 0.5 (range: 0.25
- 0.75) for decompensated cirrhosis, 0.5 (range: 0.25 - 0.75) for HCC, and 0.975 (range: 0.95 - 1) for successfully
treated hepatitis B.

**Measure of benefits used in the economic analysis**
The summary benefit measures used were the life-years gained and quality-adjusted life-years (QALYs). Both were
obtained through modelling. No discounting was applied in the base-case. The utility values were based on experts' assumptions.

**Direct costs**
No discounting was applied in the base-case analysis, even though it was relevant since the costs were incurred during a
long time. The unit costs were not presented separately from the quantities of resources used. The cost items were not
broken down since the costs were presented in macro-categories. More specifically, IFN therapy and the treatment of
disease and complications, such as HBV, cirrhosis, decompensated cirrhosis and HCC. The cost/resource boundary of
the patient or the employer was adopted. Resource use and the cost of treating complications was estimated from expert
assumptions. The cost of INF therapy was derived from retail prices indicated by the manufacturer. The price year was
not reported.
Statistical analysis of costs
The costs were treated deterministically.

Indirect Costs
The indirect costs were not considered.

Currency
Indian rupees (R). The exchange rate between Indian rupees and US dollars ($) was R48 = $1.

Sensitivity analysis
Univariate sensitivity analyses were conducted to assess the robustness of the cost-effectiveness ratios to variations in model inputs. The model inputs investigated included the disease progression rate, IFN efficacy, the cost of treatment, the discount rate and utility weights. The ranges used were derived from the literature, or were based on experts’ assumptions.

Estimated benefits used in the economic analysis
The undiscounted life-years were 25.14 with IFN and 24.54 with no treatment (difference 0.60). The undiscounted QALYs were 23.69 with IFN and 22.75 with no treatment (difference 0.94).

Cost results
The undiscounted costs were R300,000 with IFN and R40,700 with no treatment (difference R259,300).

Synthesis of costs and benefits
Incremental cost-effectiveness ratios were calculated to combine the costs and benefits of IFN in comparison with no treatment.

The incremental cost per life-year saved with IFN over no treatment was R432,500.

The incremental cost per QALY saved with IFN over no treatment was R276,900.

Since the annual per capita GNP of the Indian population was R21,120, the cost of each life-year gained was 20.5 times the annual per capita GNP. The cost of each QALY was 13.1 times the annual per capita GNP.

The sensitivity analysis showed that the use of lower estimates for rates of disease progression increased the cost-effectiveness and cost-utility ratios, while the use of higher estimates reduced them. Variations in other model inputs led to some changes in the estimated cost-effectiveness and cost-utility ratios. However, overall, even under favourable conditions, the incremental costs per life-year gained or per QALY were still too high, relative to the annual per capital GNP.

Only when the entire cost of IFN was below R23,000 (it was greater than R250,000 in the base-case) did the cost per QALY become lower than the annual per capita GNP in India.

Use of discounting made IFN therapy even less attractive.

Authors’ conclusions
Interferon (IFN) therapy for the treatment of adults with chronic hepatitis B virus (HBV) infection was not cost-effective in India under several scenarios. A similar conclusion might be valid for other developing countries with similar IFN costs and similar per capita gross national product (GNP).
CRD COMMENTARY - Selection of comparators
The choice of the comparator (no treatment) was appropriate as it reflected standard care in the authors’ setting, as well as in other developing countries where IFN treatment is not available. The authors stated that another drug currently available for the treatment of HBV infection, namely lamivudine, had several advantages over IFN (including lower cost), but it was associated with the development of lamivudine-resistant HBV mutants. Thus, it was not considered to be a valid comparator. You should decide whether this is a valid comparator in your own setting.

Validity of estimate of measure of effectiveness
The analysis of effectiveness used evidence derived mainly from published studies. However, it appears that a systematic review of the literature has not been undertaken. In addition, detailed information on the primary studies used to provide the data was not reported. The authors selected baseline estimates arbitrarily from the ranges of values observed in the literature. The comparability of primary studies and the methods used to extract the data were not reported. Some assumptions were also made when no published evidence was available. This introduced further uncertainty into the estimates. However, all of the inputs were varied in the sensitivity analysis, which enhanced the robustness of the results.

Validity of estimate of measure of benefit
Both benefit measures were appropriate for assessing the impact of the intervention on the patients' health in terms of quality of life and survival. Discounting was not applied in the base-case, but the impact of using several rates was investigated in the sensitivity analysis. The source of the utility data was reported and it reflected experts’ opinions. The use of alternative values was assessed in the sensitivity analysis. QALYs and life-years gained are easily compared with the benefits of other health care interventions.

Validity of estimate of costs
The authors stated that the perspective of the patient (or the employer) was adopted since, in India, there was no public health care system covering IFN costs. Accordingly, all relevant categories of costs were included in the analysis. However, a detailed breakdown of the cost items was not presented and the unit costs were not reported, thus limiting the possibility of replicating the study in other settings. The costs were treated deterministically, but the impact of variations in the costs was assessed in the sensitivity analysis. The discount rate was also varied. Most of the costs were based on experts’ opinions, which reflected local estimates. The costs were presented in the Indian currency, although a conversion rate into US dollars was reported.

Other issues
The authors did not compare their findings with those from other studies. The issue of the generalisability of the study results to other settings was addressed, as the authors stated that their results could be extrapolated to countries with similar IFN costs and similar per capital GNP. The external validity of the analysis was enhanced by the use of sensitivity analyses. The authors discussed some limitations of their analysis. First, rough estimates derived from the literature were used in the model (although the use of a sensitivity analysis increased the robustness of the analysis). Second, most of the assumptions were biased in favour of IFN because most of the data were derived from developed countries. Thus, the actual cost-effectiveness and cost-utility ratios could be even worse in real world settings.

Implications of the study
The authors suggested that their analysis should provide a guide to patients, their families and treatment providers, to assist in making more informed decisions. Future studies should assess the cost-effectiveness of preventive strategies, such as HBV vaccination of neonates, as the authors demonstrated in another study (Aggarwal et al., see Other Publications of Related Interest).

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Other publications of related interest

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