A health economic model to assess the cost-effectiveness of pegylated interferon alpha-2a and ribavirin in patients with moderate chronic hepatitis C and persistently normal alanine aminotransferase levels

Gerikens S, Nechelput M, Annemans L, Peraux B, Beguin C, Horsmans Y

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 study compared two different interventions for the treatment of patients with moderate chronic hepatitis C and persistently normal alanine aminotransferase (PNALT) levels. The two interventions under study were:

- Treatment of moderate chronic hepatitis C (METAVIR fibrosis scores of F2) and PNALT patients with pegylated interferon (IFN) alpha-2a ribavirin; and
- No treatment and only monitor patients with moderate chronic hepatitis C and PNALT levels.

Type of intervention
Treatment.

Economic study type
Cost-utility analysis.

Study population
The study population comprised a hypothetical cohort of patients with moderate chronic hepatitis C (i.e. METAVIR fibrosis scores of F2) and PNALT levels.

Setting
The study setting was secondary care. The economic study was carried out in Belgium.

Dates to which data relate
The effectiveness data were derived from studies published between 1987 and 2006. The cost data were derived from a study published in 2004 (Annemans et al. 2004). The price year was not explicitly reported.

Source of effectiveness data
The clinical and epidemiological data used in the economic evaluation included sustained viral response rates for each treatment arm and annual transition probabilities (e.g. fibrosis progression in men and women, cirrhosis progression, progression from carcinoma to death and progression from transplantation to death).

Modelling
A Markov decision analytic model representing the natural history of the disease was used to assess the cost-effectiveness of the two interventions under study. The model framework was adapted from a recently developed model for patients with chronic hepatitis C (Annemans et al. 2004, see ‘Other Publications of Related Interest’ below for
Sources searched to identify primary studies
The sustained viral response rates were derived from two randomised controlled trials that compared pegylated IFN alpha-2a with different combinations of ribavirin. The annual transition probabilities appear to have been derived from a series of longitudinal studies and from studies included in the model reported by Annemans et al. 2004. Mortality due to causes unrelated to hepatitis C was derived from routinely collected Belgian statistics on mortality.

Methods used to judge relevance and validity, and for extracting data
The authors obtained most of the clinical data from studies included in the model reported by Annemans et al. 2004. However, for other sources of model parameters such as sustained viral responses, the authors did not provide any details of how these studies were identified.

Measure of benefits used in the economic analysis
The measure of benefits used was the quality-adjusted life-years (QALYs) gained. Utility parameters for the model were derived from published studies. The utilities relating to the states of moderate chronic hepatitis C, severe chronic hepatitis C and compensated cirrhosis came from a study which distinguished between fibrosis scores (Bennett et al. 1997, see 'Other Publications of Related Interest’ below for bibliographic details). All other utility values were derived from sources used in the model reported in Annemans et al. 2004. As the benefits could be accrued over a period of 30 years, discounting was relevant, and was appropriately performed using an annual rate of 1.5% as recommended by Belgian guidelines.

Direct costs
The direct costs to the Belgian health care system were included in the study. These comprised the costs of chronic hepatitis C, compensated cirrhosis, decompensated cirrhosis, hepatocellular carcinoma, liver transplantation and drugs. The authors reported that cost estimates, excluding those for drugs, were derived from the model by Annemans et al. 2004, as it derived costs from a study published from a Belgian perspective. The drug costs were derived from current public prices as at January 2006. Discounting was relevant since the costs could be incurred over 30 years, and was appropriately performed at an annual rate of 3% as recommended by Belgian guidelines. The price year was not explicitly reported. The study reported the average costs.

Statistical analysis of costs
The costs were treated as point estimates (i.e. the data were deterministic).

Indirect Costs
Productivity costs were not included.

Currency
Euros (EUR).

Sensitivity analysis
The authors undertook a series of sensitivity analyses. First, univariate sensitivity analyses were performed to assess the effect on the results of changes in key parameters. Second, the elasticity of each decision parameter was calculated in order to identify which variables had an important impact on the results. Finally, a probabilistic sensitivity analysis was performed using a Monte Carlo simulation with 1,000 iterations. For this analysis, triangular distributions were introduced for each utility, beta distributions were introduced for viral response rates, and log normal distributions were used for costs.
Estimated benefits used in the economic analysis
For patients with Genotype 1, the QALYs gained were 19.11 with treatment compared with 16.63 with no treatment.

For patients with Genotypes 2-3, the QALYs gained were 20.51 with treatment compared with 16.63 with no treatment.

Cost results
For patients with Genotype 1, the mean cost was EUR 18,957.67 with treatment compared with EUR 5,760.04 with no treatment.

Synthesis of costs and benefits
The costs and benefits were combined using an incremental cost-utility ratio (i.e. the additional cost per QALY gained when treatment was compared with no treatment).

For patients with Genotype 1, the incremental cost-utility ratio was EUR 5,338 (95% confidence interval, CI: 3,199 to 8,972) per QALY gained.

For patients with Genotype 2-3, the incremental cost-utility ratio was EUR 1,080 (95% CI: 56 to 1,981) per QALY gained.

The results of the univariate sensitivity analyses showed that changes in model parameters did not alter the results substantially, with incremental cost-utility ratios not exceeding EUR 20,000 per QALY. The results of the Monte Carlo simulation showed that the probability of treatment being cost-effective was 100% when using a threshold of EUR 20,000 per QALY gained.

Authors' conclusions
Even though treatment of people with moderate chronic hepatitis C and persistently normal alanine aminotransferase (PNALT) levels generated costs in comparison with no treatment, treatment generated more quality-adjusted life-years (QALYs) at an acceptable cost (i.e. less than EUR 20,000 per QALY gained).

CRD COMMENTARY - Selection of comparators
A justification was given for using no treatment as the comparator, namely, the treatment of patients with PNALT is still under debate. You should decide if the comparator used represents current practice in your own setting.

Validity of estimate of measure of effectiveness
The parameters were derived from published research. Except for a few model parameters, the clinical data were derived from studies already included in a previous decision analytic model on the natural course of hepatitis C in Belgium (Annemans et al. 2004). For parameters not included in this model, the results were not synthesised and the authors obtained estimates based on the relevance of each study to the settings and treatments investigated in the model. The authors did not report any other methods relating to the literature search.

Validity of estimate of measure of benefit
The estimation of health benefit (i.e. QALYs) was derived appropriately using a Markov model. Since the QALYs could be accrued over the long term, they were appropriately discounted. The utilities were derived from the published literature, and some had already been included in a previous model of this disease (Annemans et al. 2004). No details of the valuation method were reported.

Validity of estimate of costs
The analysis of the costs was performed from the perspective of the national health care system paying for the treatment. Given this perspective, it appears that all the relevant cost categories have been included in the analysis. However, although the authors adequately reported the costs associated with each health state in the model (e.g.
cirrhosis, carcinoma, hepatitis C), they did not provide any details of the resource use categories included. The costs were derived from published studies undertaken in Belgium. Since the costs could be incurred in the future, they were appropriately discounted. The price year was not explicitly reported, which will hamper any future inflation exercises.

**Other issues**
The authors reported that their study was one of the first evaluating the cost-effectiveness of treatment for patients with PNALT levels. The issue of generalisability to other settings was addressed in the exhaustive sensitivity analyses performed. The authors do not appear to have reported their results selectively. However, as already reported, they do not appear to have captured the full uncertainty surrounding the model parameters. The authors reported a number of further limitations to their study. First, the extra-hepatic consequences of the disease were not taken into account in the study. Second, the costs were based on Belgian prices, which are lower than in other countries, therefore the results in other national settings could be more favourable than those presented here. Finally, the costs for different severity levels of cirrhosis were assumed to be the same.

**Implications of the study**
Based on their results, the authors would appear to recommend the use of pegylated IFN alpha-2a ribavirin in patients with moderate chronic hepatitis C and PNALT levels.

**Source of funding**
None stated.

**Bibliographic details**

**PubMedID**
17715631

**Other publications of related interest**
Because readers are likely to encounter and assess individual publications, NHS EED abstracts reflect the original publication as it is written, as a stand-alone paper. Where NHS EED abstractors are able to identify positively that a publication is significantly linked to or informed by other publications, these will be referenced in the text of the abstract and their bibliographic details recorded here for information.


**Indexing Status**
Subject indexing assigned by NLM

**MeSH**
Adult; Aged; Aged, 80 and over; Alanine Transaminase/blood; Antiviral Agents/administration & dosage /economics