Cost effectiveness of peginterferon alpha-2b plus ribavirin versus interferon alpha-2b plus ribavirin for initial treatment of chronic hepatitis C


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
Three strategies for treating chronic hepatitis C with interferon (IFN) alpha-2b (Intron) or pegIFN alpha-2b (PegIntron), plus ribavirin (Rebetol), were considered (all drugs manufactured by Schering-Plough and ESSEX Pharma GmbH). The three strategies were:

IFN, 3 million units (MU) taken subcutaneously three times a week, plus ribavirin (1,000 -1,200 mg/day) for 48 weeks;

pegIFN alpha-2b, 1.5 microg/kg per week for 4 weeks followed by 0.5 microg/kg per week for the next 44 weeks, plus ribavirin (1,000 - 1,200 mg/day) for 48 weeks; and

pegIFN alpha-2b, 1.5 microg/kg per week, plus ribavirin (800 mg/day) for 48 weeks.

For the first two groups, the ribavirin dose was based on weight (1,000 mg for weight less than 75 kg, or 1,200 mg otherwise).

Type of intervention
Treatment.

Economic study type
Cost-effectiveness analysis.

Study population
The study population comprised patients with chronic hepatitis C. The inclusion criteria specified no prior treatment, RNA positivity for the hepatitis C virus, and elevated transaminase levels.

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

Dates to which data relate
The effectiveness data were derived from studies published between 1989 and 2000. The resource data were modelled using the same information. The price year was 2000.

Source of effectiveness data
The effectiveness data were derived from a review or synthesis of completed studies, supplemented with estimates of effectiveness based on assumptions.
Modelling
A Markov model was used to extend the results of a clinical trial over a 20-year time span, and to assess resource use during this period. This Markov model was derived from published studies (Bennett et al. 1997 and Wong et al. 1998, see 'Other Publications of Related Interest' for bibliographic details). The health states were defined by clinical symptoms, liver histology, and virological condition. The cycle of the model was 1 year. A lifetime horizon was used. The authors also made assumptions in their model:

- there was no long-term benefit from antiviral treatment relapse;
- spontaneous or treatment-induced loss of viraemia greatly reduced, but did not eliminate, the risk of developing progressive liver disease; and
- serial liver biopsies, which would have increased the cost and morbidity for being viral positive, were not considered.

Outcomes assessed in the review
The outcomes derived from the single clinical trial were virological treatment response rates. The outcomes derived from the literature included the following transition probabilities:

from mild chronic hepatitis C to viral negative;
from mild chronic hepatitis C to moderate chronic hepatitis C;
from moderate chronic hepatitis C to compensated cirrhosis;
from moderate chronic hepatitis C to hepatocellular carcinoma;
from compensated cirrhosis to diuretic-sensitive ascites;
from compensated cirrhosis to variceal haemorrhage;
from compensated cirrhosis to hepatic encephalopathy;
from compensated cirrhosis to hepatocellular carcinoma;
from diuretic-sensitive ascites to diuretic refractory disease;
from diuretic-sensitive ascites to death from liver disease;
from diuretic refractory ascites to death from liver disease;
from variceal haemorrhage (first year) to death from liver disease;
from variceal haemorrhage (subsequent years) to death from liver disease;
from hepatic encephalopathy (first year) to death from liver disease;
from hepatic encephalopathy (subsequent years) to death from liver disease;
from hepatocellular carcinoma to death from liver disease;
from liver transplantation (first year) to death from liver disease; and
from liver transplantation (subsequent years) to death from liver disease.
Study designs and other criteria for inclusion in the review
The virological treatment response rates were derived from an international, randomised controlled clinical trial comparing pegIFN alpha-2b plus ribavirin with lpha-2b plus ribavirin, which enrolled 1,530 patients. Characteristics of the study population included a mean age of 44 years, 66% men, 32% genotype 2/3, 15% mild hepatitis, 78% moderate hepatitis or bridging fibrosis, and 7% cirrhosis.

The paper did not report any criteria used to assess primary studies for inclusion in the review of transition probabilities.

Sources searched to identify primary studies
Not stated.

Criteria used to ensure the validity of primary studies
Not reported.

Methods used to judge relevance and validity, and for extracting data
A German epidemiological expert panel reviewed transition probabilities for the appropriateness of applying them to the German health care context. They made alterations to the data where they were considered to deviate from current practice.

Number of primary studies included
Sixteen primary studies were included in the review.

Methods of combining primary studies
Not reported.

Investigation of differences between primary studies
Not reported.

Results of the review
The following treatment efficacies were used in the model:

IFN 3 MU per week plus ribavirin 1,000 - 1,200 mg/day, 47%;
pegIFN 0.5 microg/kg per week plus ribavirin 1,000 - 1,200 mg/day, 47%;
pegIFN 1.5 microg/kg per week plus ribavirin 800 mg/day, 54%; and
pegIFN 1.5 microg/kg per week plus ribavirin at more than 10.6 mg/kg per day, 61%.

The following transition probabilities were derived from the review of the primary studies:
from mild chronic hepatitis C to viral negative, 0.002;
from mild chronic hepatitis C to moderate chronic hepatitis C, 0.041;
from moderate chronic hepatitis C to compensated cirrhosis, 0.073;
from moderate chronic hepatitis C to hepatocellular carcinoma, 0.001;
from compensated cirrhosis to diuretic-sensitive ascites, 0.025;
from compensated cirrhosis to variceal haemorrhage, 0.011;
from compensated cirrhosis to hepatic encephalopathy, 0.004;
from compensated cirrhosis to hepatocellular carcinoma, 0.015;
from diuretic-sensitive ascites to diuretic refractory disease, 0.067;
from diuretic-sensitive ascites to death from liver disease, 0.110;
from diuretic refractory ascites to death from liver disease, 0.330;
from variceal haemorrhage (first year) to death from liver disease, 0.400;
from variceal haemorrhage (subsequent years) to death from liver disease, 0.130;
from hepatic encephalopathy (first year) to death from liver disease, 0.680;
from hepatic encephalopathy (subsequent years) to death from liver disease, 0.400;
from hepatocellular carcinoma to death from liver disease, 0.860;
from liver transplantation (first year) to death from liver disease, 0.210; and
from liver transplantation (subsequent years) to death from liver disease, 0.057.

Methods used to derive estimates of effectiveness
The panel of epidemiological experts reduced the annual likelihood of liver transplantation for decompensated cirrhosis to reflect the lower per capita liver transplantation rates in Germany compared with the USA.

To derive the quality of life weights, the authors conducted a cross-sectional interview-based quality of life study in 348 consecutive German patients with chronic hepatitis C at a single centre. Health state-specific quality of life weights were determined using multivariate regression analysis. For the base-case, quality of life was based on a transformed visual analogue scale. In addition, the authors assumed that ribavirin-treated patients with an unplanned pregnancy would have an elective abortion, so they decremented their quality of life by one week.

Estimates of effectiveness and key assumptions
The likelihood of liver transplantation for decompensated cirrhosis was reduced to 0.022 (from 0.031).

The health-related quality of life weights used in the analysis were:

0.95 for mild chronic hepatitis;
0.92 for moderate chronic hepatitis;
0.89 for compensated cirrhosis;
0.81 for decompensated cirrhosis and hepatocellular carcinoma;
0.86 for liver transplantation;
0 for death;
0.98 for utility multiplier viral positive;

0.95 for utility multiplier IFN plus ribavirin; and

0.90 for utility multiplier pegIFN plus ribavirin.

**Measure of benefits used in the economic analysis**
The measures of benefits used were the number of life-years saved and the number of quality-adjusted life-years (QALYs) gained. The quality of life weights were derived as described already. The health benefits were discounted at a rate of 3% per year.

**Direct costs**
The costs of the health care provider were included in this analysis. The direct costs included inpatient and outpatient visits, diagnostic and laboratory testing, medications and procedures. The costs of drug discontinuation, additional visits and blood tests due to adverse events, contraception and abortion were also included. Resource use was derived from the clinical trial and expert panel consensus. For example, the frequency of clinic visits and laboratory testing during antiviral therapy was based on product labelling and expert panel consensus. The drug dosage was as received in the trial. The unit costs for ambulatory care were taken from the reimbursement rates for social and private insurance in Germany. For hospital services, average per diem prices for different types of wards were used. The drug costs were based on wholesale prices. The annual cost of providing health care for each health state included in the model was taken from the GEHMO database. The price year was 2000. The costs were reflated to 2000 prices using the medical care component of the Consumer Price Index. The costs were discounted at a rate of 3% per annum.

**Statistical analysis of costs**
No statistical analysis of the costs was undertaken.

**Indirect Costs**
No indirect costs were included in this analysis.

**Currency**
Euros (Euro). All the costs were converted into Euros using the fixed conversion rate, Euro1 = 1.95583 German Mark.

**Sensitivity analysis**
One-way and multi-way sensitivity analyses were undertaken to assess the impact of variability in the data and the generalisability of the findings. Confidence intervals and maximum and minimum values found in the literature formed the ranges used in the sensitivity analysis. The costs were halved and doubled to obtain lower and upper limits. Antiviral treatment costs were inflated to consider additional costs for side effects and complications. EuroQoL and physician-based estimates for health utility weights were examined in the sensitivity analysis. In addition, the annual discount rate was varied from 0 to 5%.

**Estimated benefits used in the economic analysis**
The life expectancies were:

- 17 years with no antiviral treatment;
- 18.6 years with IFN plus ribavirin;
- 18.8 years with pegIFN plus fixed ribavirin; and
19.1 years with pegIFN plus weight-based ribavirin.

The discounted quality-adjusted life expectancies used in the economic analysis were:

- no antiviral treatment, 15.1 years;
- IFN plus ribavirin, 16.8 years;
- pegIFN plus fixed ribavirin, 17.0 years; and
- pegIFN plus weight-based ribavirin, 17.3 years.

Compared with standard combination therapy, pegIFN plus fixed ribavirin increased life expectancy by 0.5 years, while pegIFN plus weight-based ribavirin increased life expectancy by 1.0 year.

**Cost results**

The total costs included future costs due to hepatitis C complications.

The total undiscounted lifetime health care costs were:

- no antiviral treatment, Euro 25,500;
- IFN plus ribavirin, Euro 25,900;
- pegIFN plus fixed ribavirin, Euro 27,600; and
- pegIFN plus weight-based ribavirin, Euro 27,400.

The total discounted lifetime health care costs estimated were:

- no antiviral treatment, Euro 14,100;
- IFN plus ribavirin, Euro 19,300;
- pegIFN plus fixed ribavirin, Euro 21,800; and
- pegIFN plus weight-based ribavirin, Euro 22,400.

**Synthesis of costs and benefits**

PegIFN plus weight-based ribavirin and pegIFN plus fixed ribavirin had incremental cost-effectiveness ratios (ICERs) of 6,600 Euros and 11,800 Euros per QALY gained, respectively, compared with IFN plus ribavirin. Changing from fixed to weight-based dosing of ribavirin would cost 2,100 Euros per QALY gained.

Sub-group analyses by genotype, viral load, gender and histology showed that pegIFN plus weight-based ribavirin remained cost-effective in comparison with the other treatments. The sensitivity analysis indicated that pegIFN plus weight-based ribavirin remained cost-effective in comparison with standard combination therapy, even if the sustained response rate was only 50% or if the likelihood of liver disease progression was reduced such that the 20-year cirrhosis incidence was halved. PegIFN plus fixed ribavirin remained cost-effective for patients up to age 60 years, while pegIFN plus weight-based ribavirin remained cost-effective for patients up to age 69.

**Authors' conclusions**

Peginterferon (pegIFN) plus weight-based ribavirin is a cost-effective intervention for the treatment of chronic hepatitis C. PegIFN plus ribavirin should reduce the incidence of liver complications, prolong life, improve quality of life, and be cost-effective for the initial treatment of chronic hepatitis C.
CRD COMMENTARY - Selection of comparators
The authors investigated the costs and effects of three available strategies for the treatment of chronic hepatitis C. The baseline comparator was no treatment. All of these treatment strategies appear to have been relevant to the study setting. You should decide if these represent current practice in your own setting.

Validity of estimate of measure of effectiveness
The clinical effectiveness data were derived from a model. The input parameters for the model were taken from published primary studies. The authors did not indicate that a systematic review was undertaken to identify primary studies. This means that it is likely that there were biases in the search for appropriate material. In addition, there were insufficient data in the article to judge the quality of the review, the study selection criteria, and their synthesis. Consequently, it is difficult to comment on how this might have influenced the results of the study. The input parameters used in the study model were assessed and modified by a panel of epidemiological experts. Membership of the panel and the methods used to alter input parameters were not reported in the paper. The authors also made some assumptions in their model. However, most of the assumptions and all estimates of effectiveness were appropriately varied in the sensitivity analysis.

Validity of estimate of measure of benefit
The estimation of benefits was modelled using a Markov model, which was appropriate. Health benefit was measured in terms of quality of life-adjusted life expectancy. Quality adjustments were based on a visual analogue scale survey of patients with chronic hepatitis C, and a sensitivity analysis using physician-based estimates and EuroQoL was undertaken. This strengthened the conclusions of the study. As benefits could be incurred during the lifetime of the patient, future benefits were appropriately discounted at an annual rate of 3%.

Validity of estimate of costs
Although the paper stated that a societal perspective was adopted, only health care costs appear to have been included in the analysis. Such indirect costs would include productivity losses in the form of foregone wages, owing to disease morbidity or premature death. The authors reported that the indirect costs were not included so as to avoid double counting. This is not a relevant justification. The costs and the quantities were not reported separately, which will hamper generalisability to other settings. However, a comprehensive sensitivity analysis on the costs was undertaken, a clear price year was stated, and all of the costs were appropriately reflated to the single price year. These facts increase the generalisability of the study and will facilitate future reflation exercises. The costs were appropriately discounted to reflect the preference for current values.

Other issues
The authors did not compare their findings with other similar studies. They also did not directly consider their generalisability to other settings. The issue of generalisability to other settings was partially addressed in the sensitivity analysis. The authors presented their results in a comprehensive manner and their conclusions reflected the analysis presented. The authors reported a number of further limitations to their study. First, the study treatment regimen did not reflect current European pharmaceutical licensing (a 24-week treatment duration was not examined because the response rates were unknown). Second, they assumed that the efficacy of pegIFN plus ribavirin observed in a sub-group of individuals who received more than 10.6 mg/kg ribavirin daily would be achievable for the entire study population. Finally, they underestimated disease-related costs for several reasons (fixed costs, indirect and productivity costs, and cost of future liver biopsies and further therapy for nonresponders were not considered).

Implications of the study
The authors suggested that future studies are needed to determine the sustained response rates and cost-effectiveness of 24-weeks treatments. They did not make any direct recommendations for changes in practice.
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Other publications of related interest


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