Effectiveness and cost-effectiveness of initial combination therapy with interferon/peginterferon plus ribavirin in patients with chronic hepatitis C in Germany: a health technology assessment commissioned by the German Federal Ministry of Health and Social Security

Siebert U, Sroczynski G

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
Several treatments for patients with chronic hepatitis C (CHC) were examined. The treatments were:

- no antiviral therapy;
- interferon monotherapy (3 x 3 MU/week) for 48 weeks;
- combination therapy with interferon (3 x 3 MU/week) and ribavirin (1,000 to 1,200 mg/day) for 48 weeks; and
- combination therapy with peginterferon (180 microg/week peginterferon alpha-2a or 1.5 microg/kg for peginterferon alpha-2b) plus ribavirin (800 to 1,200 mg/day) for 48 weeks.

Interferon monotherapy was stopped after 12 weeks and combination therapies after 24 weeks if no virological response was observed.

Type of intervention
Treatment.

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

Study population
The study population comprised a hypothetical cohort of naive patients with CHC and elevated ALT 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 1995 and 2003. No dates for the costs or resource use were reported. The price year was 2002.

Source of effectiveness data
The effectiveness evidence was derived from a synthesis of published studies.
Modelling
A modified version of the published German Hepatitis C Model (GEHMO) was used to assess the cost-effectiveness of
the four treatment options in a hypothetical cohort of patients with CHC. A 20-year time horizon was chosen. The state-
transition (Markov) model was depicted. Target populations were defined by histological states and were separated by
viral-positive and viral-negative status. Histology-specific rates for no response, relapse after response, and sustained
response after antiviral treatment were applied to the three viral-positive health states (i.e. mild hepatitis, moderate
hepatitis and compensated cirrhosis). Separated health states were considered for liver diseases from decompensated
cirrhosis: variceal haemorrhage, hepatic encephalopathy and liver transplant, which were separated into the first year
and subsequent years, and ascites, which was separated into diuretic-sensitive and diuretic-refractory ascites. Patients
could die from causes related to their age and gender as would occur in the general population of Germany. Individuals
with decompensated cirrhosis, hepatocellular carcinoma, or liver transplantation could die from liver-related causes.

Outcomes assessed in the review
The outcomes estimated from the literature were:
clinical inputs related to the natural history of CHC; and
the impact of the four treatments on short- and long-term end points, such as the utility values and rates of sustained
virological response (SVR).

Study designs and other criteria for inclusion in the review
A systematic review of the literature was undertaken to identify the primary studies. Randomised controlled trials, meta-
analyses, or HTA reports were included in the review.

Sources searched to identify primary studies
Electronic databases, HTA-information networks and bibliographic sources were systematically searched from 1990 to
2002.

Criteria used to ensure the validity of primary studies
The authors stated that study quality was evaluated using specific tools developed by the German Scientific Working
Group Technology Assessment for Health Care. Quality of life data were taken from a survey of 428 patients suffering
from CHC.

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

Number of primary studies included
Nineteen primary studies provided clinical data.

Methods of combining primary studies
Whenever necessary, the primary estimates were pooled in a meta-analysis. In particular, a meta-analysis of clinical
trials on the medical effectiveness of combination therapy with peginterferon plus ribavirin was performed using both
random-effects and fixed-effect models.

Investigation of differences between primary studies
Not stated.
Results of the review
With respect to utility values, the reduction in the short-term quality of life was 2% due to positive hepatitis C virus status, 5% due to adverse events associated with interferon plus ribavirin therapy, and 10% due to adverse events associated with peginterferon plus ribavirin therapy.

The SVR rates were significantly higher for combination therapy with interferon and ribavirin than for interferon monotherapy (38 to 54% versus 11 to 21%).

For peginterferon combined with ribavirin, two multi-centre clinical trials reported SVRs of 54% versus 47%, (p=0.01), and 56% versus 44%, (p<0.001), compared with standard combination therapy.

The pooled relative risk for the outcome "no SVR" for peginterferon plus ribavirin versus interferon plus ribavirin was 0.83 (95% confidence interval: 0.76 - 0.91 for fixed-effect model; 0.75 - 0.91 for random-effects model).

Other clinical inputs used in the decision model were not reported.

Measure of benefits used in the economic analysis
The summary benefit measures used were life expectancy and quality-adjusted life-years (QALYs). Both were derived from the decision model. An annual rate of 3% was applied to discount future benefits.

Direct costs
The perspective adopted in the study was unclear. The health services included in the economic evaluation were inpatient and outpatient visits, diagnostic and laboratory tests, medications, and procedures related to specific health states. The unit costs were not presented separately from the quantities of resources used, as most costs were presented as macro-categories. Resource use was estimated using data derived from a German expert panel (n=10) and an economic survey of a sample of 196 patients with CHC. The costs were derived from health care databases and current pharmaceutical prices for interferon alpha, peginterferon alpha and ribavirin. A 5% deduction in drug prices was applied for persons insured by the social health insurance in Germany. Discounting was relevant, because of the long time horizon of the model, and an annual rate of 3% was applied. The price year was 2002. Prices estimated in other fiscal years were converted to 2002 using the medical care component of the Consumer Price Index in Germany.

Statistical analysis of costs
The costs were treated deterministically in the base-case analysis.

Indirect Costs
The indirect costs were not taken into consideration.

Currency
The costs were estimated in German marks (DM) and then converted to Euros (Euro). The conversion rate was DM 1 = Euro 1.95583.

Sensitivity analysis
Univariate sensitivity analyses were performed on all model inputs to assess the robustness of the base-case results of the model. Clinical data were varied within published confidence intervals. The cost estimates were halved and doubled to obtain lower and upper limits. Multivariate sensitivity analyses were also carried out on all variables related to disease progression rates. Further, a worst-case scenario was assessed using extremely conservative estimates for the benefits and costs for the peginterferon and ribavirin combination therapy.
Estimated benefits used in the economic analysis
The estimated life expectancy was 17.97 years with no antiviral therapy, 18.45 years with interferon, 19.19 years with interferon plus ribavirin, and 19.90 years with peginterferon plus ribavirin.

The estimated QALYs were 16.07 years with no antiviral therapy, 16.60 years with interferon, 17.38 years with interferon plus ribavirin, and 18.13 years with peginterferon plus ribavirin.

Cost results
The estimated costs were Euro 14,800 with no antiviral therapy, Euro 17,600 with interferon, Euro 26,600 with interferon plus ribavirin, and Euro 32,500 with peginterferon plus ribavirin.

Synthesis of costs and benefits
Incremental cost-utility and cost-effectiveness ratios were calculated to combine the costs and benefits of the alternative treatment strategies.

The incremental cost per life-year saved was Euro 5,800 with interferon versus no therapy, Euro 12,300 with interferon plus ribavirin versus interferon, and Euro 10,300 with peginterferon plus ribavirin versus interferon.

The incremental cost per QALY saved was Euro 5,300 with interferon versus no therapy, Euro 11,600 with interferon plus ribavirin versus interferon, and Euro 9,800 with peginterferon plus ribavirin versus interferon.

The sensitivity analysis showed that base-case results were robust to most of the variations in model inputs. Peginterferon plus ribavirin remained the most cost-effective strategy, even in the worst-case scenario, with an incremental cost per QALY of Euro 27,300 over the next best non-dominated strategy (i.e. interferon monotherapy).

Authors’ conclusions
Combination treatment with peginterferon and ribavirin was the most effective and cost-effective treatment strategy for patients with chronic hepatitis C (CHC) and elevated alanine amino transferase (ALT) levels in Germany.

CRD COMMENTARY - Selection of comparators
The selection of the comparators was appropriate, as the health interventions examined in the study were all available strategies for the treatment of patients with CHC. The authors stated that recommended dosages were used. You should decide whether they are valid comparators in your own setting.

Validity of estimate of measure of effectiveness
The clinical evidence came from a review of the literature, the methods and conduct of which were reported. Inclusion criteria were not stated, but the use of clinical trials and meta-analyses ensured a high internal validity. The method used to pool the primary estimates was provided. The issue of homogeneity across the primary studies was addressed using fixed-effect and random-effects models. The results of the review were reported selectively since some estimates were not provided. For other estimates, only published ranges of values were given. The authors stated that validated methods were used to assess the validity of the data. The issue of uncertainty was tested in the sensitivity analysis.

Validity of estimate of measure of benefit
The benefit measures used in the analysis were appropriate as QALYs and survival capture the impact of the interventions on the most relevant dimensions of care (i.e. survival and quality of life). Further, both survival and QALYs are comparable with the benefits of other health care interventions. Discounting was applied and the impact of alternative discount rates was assessed in the sensitivity analysis. The source of the utility weights was provided, but there was limited information on the approach used to calculate the QALYs.
Validity of estimate of costs
The perspective adopted in the study was unclear. Only the direct medical costs were considered in the analysis. The source of the data was reported for all items. A breakdown of the costs was not provided since most costs were presented as macro-categories, thus limiting the possibility of replicating the results of the analysis in other settings. Further, the unit costs were not provided separately from the quantities of resources used. No statistical analyses of the costs were carried out, but all economic inputs were varied in the sensitivity analysis. The price year was reported, which aids reflation exercises in other time periods. The authors noted that some costs, such as those associated with future liver biopsies and further therapies to nonrespondents, were not included in the study. Since disease-related costs were likely to have been underestimated, potential cost-savings associated with more effective strategies were not considered.

Other issues
The results of the current study were compared extensively with those from other studies since a systematic review of the literature had been undertaken to identify published cost-effectiveness studies. Details of the country, therapy duration, patients’ characteristics, and other data were reported for each economic evaluation found in the literature. The authors noted that the main drawback of the study was the uncertainty surrounding data on the natural history of CHC, owing to the controversial evidence found in the literature. However, this issue was addressed in the sensitivity analysis. It was also noted that the results could be different for patients with normal ALT levels, with acute hepatitis C, or in populations in which a systematic screening for hepatitis C virus was performed. In terms of the issue of the generalisability of the study results to other settings, the authors stated that caution is required when extrapolating the findings of the current study to other countries, owing to differences in sociodemographic structure, patients’ characteristics and resource use patterns across countries.

Implications of the study
The study results supported the use of combination peginterferon and ribavirin treatment for patients with CHC and elevated ALT. The authors suggested that future studies should investigate the natural progression of the disease considering different prognostic factors. Further research on the efficacy and the need for antiviral therapy in patients with normal ALT levels, with histological mild hepatitis C and with certain risk and co-morbidity profiles, should also be carried out.

Source of funding
This work was commissioned and funded by the German Agency for Health Technology Assessment at the German Institute for Medical Documentation and Information, German Federal Ministry of Health and Social Security.

Bibliographic details

PubMedID
15736515

Other publications of related interest


**Indexing Status**
Subject indexing assigned by NLM

**MeSH**
Antiviral Agents /economics /therapeutic use; Cost-Benefit Analysis; Drug Therapy, Combination; Germany; Hepatitis C, Chronic /drug therapy /economics; Humans; Interferon-alpha /economics /therapeutic use; Markov Chains; Polyethylene Glycols /economics /therapeutic use; Quality-Adjusted Life Years; Randomized Controlled Trials as Topic; Recombinant Proteins; Ribavirin /economics /therapeutic use; Technology Assessment, Biomedical

**AccessionNumber**
22005008097

**Date bibliographic record published**
31/03/2006

**Date abstract record published**
31/03/2006