Cost effectiveness of combination therapy for hepatitis C: a decision analytic model
Stein K, Rosenberg W, Wong J

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
Combined therapy for the treatment of chronic hepatitis C (HCV) was compared with monotherapy. Monotherapy consisted of recombinant interferon-alpha (IFN-A). Combination therapy consisted of ribavirin used in conjunction with IFN-A.

Type of intervention
Treatment.

Economic study type
Cost-utility analysis.

Study population
The study population comprised a hypothetical cohort of patients with HCV. The analysis did not consider patients with persistent chaotic intravenous drug use, excessive alcohol consumption, psychiatric disorders (including depression), ischaemic heart disease, severe respiratory disease, or diabetic retinopathy.

Setting
The setting was secondary care. The economic analysis was carried out in the UK.

Dates to which data relate
The effectiveness data were collected from studies published between 1986 and 1997. The costs were estimated in 1998/9 pounds sterling. Some prices were estimated for 1997/8 and adjusted. The date to which the resource use related was not given.

Source of effectiveness data
The effectiveness data were derived from a review of completed studies and authors' assumptions.

Modelling
A Markov decision analytic model was used to depict patient progression through the various states of HCV. The model was created using DecisionMaker 7.07 (Pratt Medical Group). One cycle in the Markov model was used to represent one year of a patient's life. The model was used to estimate the average lifetime cost and utility for each treatment strategy. In addition, it allowed the marginal cost per quality-adjusted life-year (QALY) to be estimated. Further details of the model and parameter estimates were provided in a supplementary paper (see Other Publications of Related Interest).

Outcomes assessed in the review
None of the Markov transition probabilities, including the natural history and treatment response probabilities, were reported in the article. The authors stated that the model was presented in greater detail elsewhere (see Bennett et al., Other Publications of Related Interest).

**Study designs and other criteria for inclusion in the review**
Observational studies were used to estimate the natural history of disease. The response rates for antiviral treatment were derived from the results of clinical trials of patients with chronic HCV, which used the same treatment regime (recombinant IFN-A2b at a fixed dose of 3 million U, 3 times weekly for 6 months). The studies included in the review also had systematic follow-up, liver biopsy slides available for analysis, and study databases available for review. There was no indication that the review was systematic.

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

**Criteria used to ensure the validity of primary studies**
The authors used a single pathologist, who was blinded, to review the information and to establish the correlation between histologic findings and response.

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

**Number of primary studies included**
Eighteen primary studies were included in the review.

**Methods of combining primary studies**
The authors reanalysed pooled data from 5 clinical trials involving 287 patients to estimate treatment response. Transition probabilities for the natural history of chronic HCV were selected from the literature. The authors stated that this involved pooling the data where the follow-up was short or the sample size was small.

**Investigation of differences between primary studies**
The authors reported that likelihood estimates were reviewed by an expert panel of hepatologists and statisticians, and were modified where appropriate. This overcame some of the differences between the primary studies. The authors did not discuss differences or provide potential explanations for their existence.

**Results of the review**
None of the probabilities used in the model were reported. See the 'Estimate of Measure of Benefit' section for related effectiveness results.

**Methods used to derive estimates of effectiveness**
The authors made assumptions to supplement the results of the review.

**Estimates of effectiveness and key assumptions**
The authors assumed that recovery from decompensated states would only occur in the event of transplantation. They also assumed that a few treatment responders could experience ongoing progression after sustained viral clearance.
Measure of benefits used in the economic analysis
The summary measure of benefits was the QALYs. Utility values, which placed a weight on HCV states, were obtained from a group of American hepatologists using standard gamble and time trade-off methodology. The authors reported that these weights were checked with UK hepatologists.

Direct costs
The costing was carried out from the perspective of UK commissioning authorities and was reported to have been based on "typical UK management of HCV disease in each potential health state". The costs were discounted at 6%, which was appropriate for the long time horizon of the model. The analysis focused on the costs of hepatic complications and treatment. The unit costs were reported separately and were derived from actual data (e.g. drug costs from the British National Formulary) and other published tariffs. The Hospital and Community Health Services Index was used to adjust the estimates to 1998/9 values. The quantities were determined in the model.

Statistical analysis of costs
No statistical analysis of the costs was reported.

Indirect Costs
The indirect costs were not included in the analysis, but were not relevant given the main perspective of the study. However, the authors suggested that, where possible, a wider societal perspective was adopted. It was unclear which, if any, of the costs were estimated from such a perspective.

Currency
UK pounds sterling (€).

Sensitivity analysis
One-way sensitivity analyses were conducted to assess the impact of varying the cost of combination therapy, the cost of treating the consequences of HCV infection, and the annual likelihood of progressive liver disease.

Estimated benefits used in the economic analysis
In the analysis of combination therapy versus no treatment, no treatment gave 22.8 QALYs and combination therapy gave 27.6 QALYs. Therefore, the marginal effectiveness of combination therapy was 4.82.

In the analysis of combination therapy versus monotherapy, monotherapy gave 24.7 QALYs and combination therapy gave 27.6 QALYs. Therefore, the marginal effectiveness of combination therapy was 2.95.

Cost results
In the analysis of combination therapy versus no treatment, no treatment cost 13,729 and combination therapy cost 14,456. Therefore, the marginal cost of combination therapy was 523.47.

In the analysis of combination therapy versus monotherapy, monotherapy cost 14,363 and combination therapy cost 14,456. Therefore, the marginal cost of combination therapy was 93.93.

Synthesis of costs and benefits
In the analysis of combination therapy versus no treatment, the marginal cost-effectiveness (cost per QALY) of combination therapy was 151. The discounted marginal cost-effectiveness was 3,791. It increased because, comparatively, the benefits were spread over several years and the costs were not.
In the analysis of combination therapy versus monotherapy, the marginal cost-effectiveness (cost per QALY) of combination therapy was 32. The discounted marginal cost-effectiveness was 3,485.

The authors claimed that "the conclusions of the main analysis are not markedly sensitive to variation in key parameters".

In the analysis of combination therapy versus no treatment, the marginal cost-effectiveness within sub-group populations ranged from 1,646 per QALY (genotypes 2 or 3) to 9,170 per QALY (genotype 1).

In the analysis of combination therapy versus monotherapy, the marginal cost-effectiveness within sub-group populations ranged from 872 per QALY (genotypes 2 or 3) to 8,626 (genotype 1).

Authors' conclusions
Interferon (IFN) used in conjunction with ribavirin is "quite cost-effective". The authors suggested that, compared with accepted monotherapy, changing to combination therapy is cost-effective in most groups.

CRD COMMENTARY - Selection of comparators
The authors aimed to assess the cost-utility of combination therapy compared with no treatment and with monotherapy. They justified the use of monotherapy as a comparator on the basis that ribavirin had, relatively recently, been licensed for use in combination with IFN.

Validity of estimate of measure of effectiveness
The authors did not state that a systematic review of the literature had been carried out. In some cases the effectiveness estimates from the primary studies were combined. For instance, in estimating treatment response the authors reanalysed pooled data from 5 studies. The authors did not discuss differences in estimates between the primary studies or potential reasons for their existence. However, they did make efforts to ensure that when data from such studies were combined, the data related to groups of patients who had received comparable treatment experiences.

Validity of estimate of measure of benefit
The estimation of benefits was modelled using a Markov process to represent the stages of disease. This was appropriate for the objective of the paper and it enabled a realistic time horizon to be incorporated.

Validity of estimate of costs
The perspective of commissioning authorities was adopted, and for this perspective all the relevant cost categories appear to have been included. Given the relatively small difference in cost between the two strategies, any costs that may have been omitted could have had an impact on the authors' overall conclusions. The unit costs were reported separately and the quantities were determined in the economic model. Discounting was appropriately performed and the price year was reported, which helps with reflation exercises.

Other issues
The authors did not compare their results with the findings of published studies, neither did they address the issue of the generalisability of their results. The results from the study were not presented selectively and the conclusions drawn were an accurate reflection of these results. The authors discussed some limitations of their study. For example, the imprecise nature of the costs and the assumption of lifelong viral clearance for almost all patients. In some instances in this study, it was difficult to see where the model and analysis were identical to a prior analysis using the same model, and where the two analyses differed. This made it difficult for the reader to interpret the model and its results. In addition, it limits the extent to which the results can be reproduced by independent researchers.
Implications of the study
The authors did not make any recommendations for policy or practice as a result of their study. However, they did highlight that a better understanding of variation in the application of criteria for combination treatment would be important to inform future pragmatic trials.

Source of funding
Funded in part by Schering Plough.

Bibliographic details

PubMedID
11788569

Other publications of related interest


Indexing Status
Subject indexing assigned by NLM

MeSH
Adult; Aged; Antiviral Agents /economics /therapeutic use; Cohort Studies; Cost-Benefit Analysis; Decision Support Techniques; Drug Combinations; Female; Health Resources /utilization; Health Status; Hepatitis C, Chronic /drug therapy /economics; Humans; Interferon-alpha /economics /therapeutic use; Liver Transplantation /statistics & numerical data; Male; Markov Chains; Middle Aged; Quality-Adjusted Life Years; Ribavirin /economics /therapeutic use; Sensitivity and Specificity

AccessionNumber
22002000293

Date bibliographic record published
30/04/2004

Date abstract record published
30/04/2004