Cost-effectiveness of ribavirin plus interferon alpha-2b for either interferon relapsers or non-responders in chronic hepatitis C: a Japanese trial

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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
Two treatments for patients with hepatitis C virus (HCV) were examined. The treatments were combination therapy with ribavirin plus interferon (IFN) alpha-2b and monotherapy with IFN alpha-2b.

Type of intervention
Treatment.

Economic study type
Cost-utility analysis.

Study population
The study population comprised a hypothetical cohort of patients who had relapsed or who were nonresponders to prior IFN monotherapy.

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

Dates to which data relate
The effectiveness data were derived from studies published from 1990 to 2002. No dates for when the resource use data were collected were explicitly reported. No price year was given.

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

Modelling
A published Markov model was used to simulate the natural history of HCV, and to determine the long-term impact of the two treatment strategies on costs and clinical benefits in a cohort of patients in Japan. The model followed all patients until they died. The cycle length was one year. Thirteen health states were considered:

- viral positive and negative mild chronic hepatitis,
- viral positive and negative moderate chronic hepatitis,
- viral positive and negative compensated cirrhosis,
- decompensated cirrhosis (ascites, first year or subsequent years following hepatic encephalopathy, first year or
subsequent years following variceal hemorrhage),

hepatocellular carcinoma (HCC), and
dead.

Patients who remained viral positive after 12 weeks of therapy continued treatment, as suggested in Japan guidelines.

Outcomes assessed in the review
The outcomes estimated from the literature were the response rates and annual probabilities of disease progression. The response rates were also assessed in the sub-group of patients with genotype 1b and high viral load. High viral load was defined as a viral titre exceeding 100k copies/mL by the RT-PCR assay and 1 Meq/mL by the branched DNA assay.

Study designs and other criteria for inclusion in the review
The authors did not state whether a systematic review was undertaken to identify relevant studies. The majority of the evidence used in the decision model was derived from a double-blind, randomised, placebo-controlled trial that involved 126 patients. However, the designs of the other primary studies were not described.

Sources searched to identify primary studies
Not stated.

Criteria used to ensure the validity of primary studies
The authors stated that the studies providing the data were considered to be the best currently available.

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

Number of primary studies included
Four primary studies provided the evidence.

Methods of combining primary studies
The primary estimates appear to have been combined using narrative methods.

Investigation of differences between primary studies
Not stated.

Results of the review
The sustained response rate (24 weeks after treatment discontinuation) was 9.4% in the monotherapy group and 35.5% in the combination therapy group.

The rate of remission-relapse (defined as temporarily viral negative but viral positive again 24 weeks after treatment) was 46.9% in the monotherapy group versus 48.4% in the combination therapy group.

The withdrawal rate was 9.4% (monotherapy) versus 8.1% (combination therapy).

In the sub-group of patients with genotype 1b and high viral load, the sustained response rate (24 weeks after treatment discontinuation) was 0% with monotherapy and 10.8% with combination therapy. The rate of remission-relapse was
47.2% (monotherapy) versus 67.6% (combination therapy), and the withdrawal rate was 8.3% (monotherapy) versus 8.1% (combination therapy).

The annual probabilities of disease progression were as follows:

from mild hepatitis, 0.002 to spontaneous remission and 0.041 to moderate hepatitis;
from moderate hepatitis, 0.073 to cirrhosis and 0.03 to HCC;
from cirrhosis, 0.025 to ascites, 0.011 to variceal haemorrhage, 0.004 to hepatic encephalopathy, and 0.079 to HCC;
from ascites, 0.110 to death and 0.079 to HCC;
from variceal haemorrhage, 0.4 to death in the first year, 0.130 to death in subsequent years, and 0.079 to HCC;
from hepatic encephalopathy, 0.680 to death in the first year, 0.400 to death in the subsequent years, and 0.079 to HCC; and
from HCC, 0.3 to death.

Methods used to derive estimates of effectiveness
Some estimates of effectiveness were used as model inputs. The estimates were derived from assumptions made by the authors or a modified Dephi panel (including family practice doctors). The latter approach was used only to derive utility weights (time trade-off and standard gamble methods).

Estimates of effectiveness and key assumptions
The following utility weights were estimated:

0.87 and 0.92, respectively, for viral positive and viral negative in mild hepatitis;
0.80 and 0.84, respectively, for viral positive and viral negative in moderate hepatitis;
0.65 for both viral positive and viral negative in cirrhosis;
0.52 for ascites;
0.40 for hepatic encephalopathy;
0.33 for variceal haemorrhage;
0.38 for HCC;
0.97 for IFN therapy; and
0.94 for combination therapy.

Quality of life was decreased by one week for patients undergoing an elective abortion for an unplanned pregnancy.

It was also assumed that the subsequent prognosis of patients who did not respond (nonresponders), or who only temporarily responded (relapers) to initial treatment was identical to those who had never had any antiviral treatment at all, except for those who responded temporarily and relapsed after antiviral treatment. These patients were assumed to have a prognosis between that of patients with complete remission and that of nonresponders. The risk of occurrence of HCC was reduced among patients in whom sustained or temporary viral eradication had been achieved by IFN therapy or combination therapy. Patients who "lose" HCV either spontaneously or from treatment had a greatly reduced, but non-zero, likelihood of developing progressive liver disease compared with those who were not treated. Liver
transplantation for HCC or decompensated liver cirrhosis was not considered in the model. The model did not consider any quality of life decrements for treatment discontinuation.

**Measure of benefits used in the economic analysis**
The summary benefit measure used was the number of quality-adjusted life-years (QALYs). These were derived from the decision model. The utility weights were derived from a Delphi panel. A 3% discount rate was applied to future benefits.

**Direct costs**
An annual discount rate of 3% was applied because of the long-term timeframe of the analysis. The unit costs were not reported separately from the quantities of resources used and a detailed breakdown of the cost items was not given. The health services included in the economic evaluation were the direct medical resources associated with each health state. These included inpatient and outpatient costs, medications, screening with tumour markers, abdominal ultrasonography, and computer tomography. The cost/resource boundary of the insurance system was adopted in the study. The resource use data were estimated according to expert opinion, guidelines from the Japan Society of Hepatology, and authors' assumptions. Drug dosage was estimated from the clinical trial. The costs were mainly estimated from reimbursement rates. The price year was not reported.

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

**Indirect Costs**
The indirect costs were not included in the economic evaluation.

**Currency**
Japanese yen (Y). The exchange rate from Japanese yen into US dollars ($) was Y120 = $1.

**Sensitivity analysis**
One- and two-way sensitivity analyses were carried out to investigate uncertainty due to variability in the data. The model inputs varied were the progression rate, sustained viral negative response, ribavirin cost, and age at start of treatment. No justification was provided for the choice of the alternative values. Alternative scenarios, based on sub-group analyses and different discount rates, were also considered.

**Estimated benefits used in the economic analysis**
In the base-case (3% discount rate), the estimated QALYs were 11.73 (no discounting: 17.10; 5% discount: 9.57) with monotherapy and 13.37 (no discounting: 20.20; 5% discount rate: 10.71) with combination therapy. The difference was 1.64 (no discounting: 3.10; 5% discount rate: 1.14).

In the sub-group analysis the estimated QALYs were 11.26 (no discounting: 16.17; 5% discount: 9.25) with monotherapy and 12.22 (no discounting: 18.02; 5% discount rate: 9.91) with combination therapy. The difference was 0.97 (no discounting: 1.85; 5% discount rate: 0.67).

**Cost results**
In the base-case (3% discount rate), the estimated lifetime costs were Y4,992,000 (no discounting: Y6,734,000; 5% discount: Y4,296,000) with monotherapy and Y4,871,000 (no discounting: Y6,325,000; 5% discount: Y4,301,000) with combination therapy. The difference was -Y121,000 (no discounting: -Y409,000; 5% discount rate: Y5,000).
In the sub-group analysis, the estimated lifetime costs were ¥5,210,000 (no discounting: ¥7,075,000; 5% discount: ¥4,465,000) with monotherapy and ¥5,390,000 (no discounting: ¥7,095,000; 5% discount: ¥4,717,000) with combination therapy. The difference was ¥181,000 (no discounting: ¥21,000; 5% discount rate: ¥252,000).

Synthesis of costs and benefits
An incremental cost-effectiveness ratio was calculated to combine the costs and benefits of the treatment strategies. A threshold of ¥6.0 million ($50,000) per QALY was considered as the threshold for cost-effectiveness.

The incremental analysis showed that with 0% and 3% discount rates, combination therapy dominated monotherapy, which was both less effective and more costly.

With an annual discount rate of 5%, the incremental cost per additional QALY with combination therapy over monotherapy was ¥4,530.

In the sub-group analysis, the incremental cost per additional QALY with combination therapy over monotherapy was ¥111,000 with no discounting, ¥187,000 with a 3% annual discount rate, and ¥377,000 with a 5% discount rate.

Other sub-group analyses revealed that combination therapy was dominant regardless of gender, in patients with moderate hepatitis, in genotypes other than 1b, and in patients with low viral load.

Positive incremental cost-utility ratios were observed for patients with moderate mild hepatitis (¥564,000), genotype 1b (¥25,000), and high viral load (¥26,000).

The sensitivity analysis showed that variations in model inputs affected the estimated cost-utility ratios. However, even under the worst scenario, the incremental cost per QALY of combination therapy over monotherapy remained below the critical threshold.

The survival benefit and cost-effectiveness of combination therapy decreased with age at the start of treatment, and the incremental cost-effectiveness ratio also increased. However, at an annual discount rate of 3%, combination therapy for all patients up to 63 years was cost-saving.

Authors' conclusions
Combination therapy for the treatment of individuals infected with hepatitis C virus (HCV) decreased the lifetime risk of progression from chronic hepatitis to cirrhosis and hepatocellular carcinoma (HCC) for relapsers or nonresponders. Combination therapy was cost-effective in comparison with monotherapy in Japan. This conclusion held under a variety of scenarios.

CRD COMMENTARY - Selection of comparators
The choice of the comparators appears to have been appropriate. Monotherapy represented the standard care in the authors' setting, while combination therapy was a new promising approach for the treatment of HCV-infected patients. You should decide whether they are valid comparators in your own setting.

Validity of estimate of measure of effectiveness
The analysis of effectiveness was based on published studies. However, it was not stated explicitly whether the authors had undertaken a systematic review of the literature to identify the primary studies, which appear to have been included selectively. The design of the primary studies was only described in detail for the clinical trial used as the main source of efficacy data. Some data were obtained from studies that the authors considered to be the best available, although no information on such studies was provided. The utility weights were based on assessments made by a panel of experts using a modified Delphi technique (no information on the approach used was given). Other assumptions were based on authors' opinions and were conservative (i.e. the result were biased against combination therapy). Uncertainty around some cost estimates was investigated in the sensitivity analysis.
Validity of estimate of measure of benefit
The summary benefit measure was appropriate for capturing the impact of the interventions on survival and quality of life. The methods used to derive the utility weights were described. The authors noted that utility values should have been derived from the general population, as recommended in recent guidelines. However, such estimates are likely to be lower than those obtained from experts, leading to even more favourable results for the combination therapy. Discounting was also performed, and the impact of varying the discount rate was examined. QALYs are easily compared with the benefits of other health care interventions.

Validity of estimate of costs
The authors stated explicitly which perspective was adopted in the study. As such, it appears that all the relevant categories of costs have been included in the analysis. However, the costs were presented as macro-categories and a detailed breakdown of the cost items was not provided. The authors noted that the estimation of true costs was difficult on account of the Japanese insurance system. Therefore, reimbursement rates were used as proxies for costs. The costs were calculated for each health state. Resource use was estimated from several sources and reflected treatment patterns in the authors' setting. However, only the price of ribavirin was varied in the sensitivity analyses. The investigation of other categories of costs or resources used would have been helpful. The price year was not reported, which makes reflation exercises in other settings difficult. No statistical analyses of the costs were performed. Caution is required when extrapolating some of the costs to other settings.

Other issues
The authors reported that a number of studies had shown the cost-effectiveness of combination therapy in the USA and Europe. The issue of the generalisability of the study results to other settings was implicitly addressed in the sensitivity analyses, where alternative values were used to calculate the cost-effectiveness. The authors noted some drawbacks of their study. First, the follow-up for trial-based data was relatively short and modelling was required to extrapolate long-term data. Second, caution is required when extrapolating the trial data to real-world contexts. Third, it was necessary to make some assumptions about the natural history of HCV and IFN treatment, owing to the uncertainty surrounding some estimates. The cost-effectiveness of the interventions under evaluation was examined in several sub-group analyses, which enhanced the robustness of the conclusions.

Implications of the study
The authors suggested that combination therapy with IFN alpha-2b and ribavirin for the treatment of HCV should be offered to patients with demographic and clinical characteristics similar to those included in the Japanese trial.

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None stated.

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