Cost-utility analysis of different peg-interferon alpha-2b plus ribavirin treatment strategies as initial therapy for naive Chinese patients with chronic hepatitis C

Lin W A, Tarn Y H, Tang S L

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 different treatment strategies with pegylated-interferon alpha-2b (peg-IFN-a2b) plus ribavirin (RIB) for the initial treatment of patients with different genotype chronic hepatitis C.

Strategy 1 was combination treatment with peg-IFN-a2b (1.5 microg/kg subcutaneously once a week) plus RIB (>10.6 mg/kg per day orally) for 24 weeks and follow-up of the therapeutic effect for another 24 weeks, no matter the genotype.

Strategy 2 was combination treatment with IFN-a2b (3 MU subcutaneously three times a week) plus RIB (>10.6 mg/kg per day orally) for 24 weeks and follow-up of the therapeutic effect for another 24 weeks in patients infected with non-genotype 1. The strategy was identical for patients infected with genotype 1, except that the combination treatment comprised peg-IFN-a2b (1.5 microg/kg subcutaneously once a week) plus RIB (>10.6 mg/kg per day orally).

Strategy 3 was combination treatment with peg-IFN-a2b (1.5 microg/kg subcutaneously once a week) plus RIB (>10.6 mg/kg per day orally) for 48 weeks and follow-up of the therapeutic effect for another 24 weeks in patients infected with genotype 1. The strategy was identical for patients infected with non-genotype 1, except that the duration of treatment was 24 weeks.

Type of intervention
Treatment.

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

Study population
The study population comprised a hypothetical cohort of 45-year-old patients with chronic hepatitis C. The patients had met the following criteria:

- positive anti-hepatitis C virus (HCV);
- positive serum HCV RNA;
- a serum alanine aminotransferase value of more than twice the upper limit of normal, twice in a year;
- liver tissue biopsy of hepatic portal and intraportal fibrosis, at or above the moderate stage in hepatic cell inflammation and necrosis;
- no cirrhosis;
- no concurrent infection with hepatitis B or human immunodeficiency virus; and
never received IFN, peg-IFN or RIB treatments.

**Setting**
The setting was secondary care. The economic analysis was carried out in Taipei, Taiwan.

**Dates to which data relate**
The effectiveness data were derived from studies published between 1998 and 2006. The resource use data were derived from a database that included resources utilised between 1996 and 2001. The price year was 2003.

**Source of effectiveness data**
The effectiveness data were derived from published studies, augmented with expert opinion when necessary.

**Modelling**
The authors generated a short-term decision tree model and a long-term deterministic Markov state transition model of chronic hepatitis C disease progression, reflecting various stages of HCV-associated liver disease. Graphical representations of both models were provided. A life-long time horizon was adopted for the long-term Markov model.

**Outcomes assessed in the review**
The outcomes assessed were:

- the end-of-treatment virological response (ETVR) and the sustained virological response (SVR) for each of the three treatment options;
- the annual transition probabilities from chronic hepatitis to cure, compensated cirrhosis and hepatocellular carcinoma;
- the annual transition probabilities from compensated cirrhosis to ascites, variceal bleeding, hepatic encephalopathy and hepatocellular carcinoma;
- the annual transition probabilities from ascites to death;
- the annual transition probabilities from variceal bleeding to death;
- the annual transition probabilities from hepatic encephalopathy to death;
- the annual transition probabilities from hepatocellular carcinoma to death;
- the annual transition probabilities from liver transplantation to death; and
- the quality of life estimates for the health states cure, during IFN/RIB treatment, during peg-IFN/RIB treatment, chronic hepatitis, compensated cirrhosis, hepatic encephalopathy, hepatocellular carcinoma, liver transplantation and death.

**Study designs and other criteria for inclusion in the review**
Not reported.

**Sources searched to identify primary studies**
Not reported.
Criteria used to ensure the validity of primary studies
Not reported.

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

Number of primary studies included
Approximately 16 primary studies were included in the review.

Methods of combining primary studies
The authors did not report how the effectiveness estimates for treatment response were combined.

Investigation of differences between primary studies
The authors did not report if differences between the primary studies were investigated.

Results of the review
The ETVR and SVR of peg-IFN-a2b plus RIB for 24 weeks were, respectively:

86.0% (range: 65.2 to 88.2) and 64.1% (range: 50 to 67.1) overall;

82.7% (range: 80.0 to 92.1) and 51.6% (range: 48.9 to 65.8) for genotype 1 patients; and

89.2% (range: 75.7 to 94.1) and 76.2% (range: 64.3 to 81.2) for non-genotype 1 patients.

For genotype 1 patients, the ETVR and SVR of peg-IFN-a2b plus RIB for 48 weeks were 65.7% (range: 53.9 to 93.3) and 56.2% (range: 41.1 to 80.0), respectively.

For non-genotype 1 patients, the ETVR and SVR of peg-IFN-a2b plus RIB for 24 weeks were 68.0% (range: 52.0 to 97.4) and 61.1% (range: 50.0 to 86.8), respectively.

The annual transition probabilities for the Markov model were presented in full in the paper.

The quality of life estimates for the health states considered were:

1.00 for cure,

0.95 during IFN plus RIB treatment,

0.90 during peg-IFN plus RIB treatment,

0.92 for chronic hepatitis,

0.89 for compensated cirrhosis,

0.81 for hepatic encephalopathy,

0.81 for hepatocellular carcinoma,

0.86 for liver transplantation, and

0.00 for death.
Methods used to derive estimates of effectiveness
The authors used expert opinion to supplement the effectiveness estimates derived from the review of the literature.

Estimates of effectiveness and key assumptions
The annual transition probability from ascites to liver transplantation was 3.1 (range: 2.9 to 3.3).

The annual transition probability from variceal bleeding to liver transplantation was 3.1 (range: 2.9 to 3.3).

The annual transition probability from hepatic encephalopathy to liver transplantation was 3.1 (range: 2.9 to 3.3).

The quality of life estimates for the health states ascites and portal variceal bleeding were both 0.81.

In addition, the authors assumed that transition probabilities between states and health state utility were identical for patients in Taiwan and patients in foreign countries.

Measure of benefits used in the economic analysis
The measures of benefits used were the SVR and the quality-adjusted life-years (QALYs) gained. Utility estimates were derived from the literature, augmented with expert opinion when required.

Direct costs
The direct costs to the BNHI were included in the analysis. These included the treatment costs incurred during combination treatment, along with all medical expenditures associated with the treatment of hepatitis C from the end of combination treatment to patient death. Annual medical costs of treating hepatitis C patients in each health status were taken from the analysis of a database from the BNHI. The BNHI database consisted of a randomly selected patient pool that comprised 200,000 patients from which all patients with hepatitis C were identified. Discounting was necessary, as the costs were incurred over the patients’ lifetime, and was appropriately performed at an annual rate of 3%. The study reported the average costs. The price year was 2003.

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

Indirect Costs
The indirect costs were not included in the analysis.

Currency
US dollars ($).

Sensitivity analysis
The authors performed a series of one-way sensitivity analyses to evaluate uncertainty in the model parameters. Treatment effectiveness, progression probabilities, discount rates, medical care costs and the price of peg-IFN-a2b plus RIB were varied.

Estimated benefits used in the economic analysis
In the short-term model, the SVR rate was:

0.641 for peg-IFN-a2b plus RIB for 24 weeks;
0.542 for peg-IFN-a2b plus RIB for 48 weeks for genotype 1 patients; and
0.622 for peg-IFN-a2b plus RIB for 24 weeks for non-genotype 1 patients.

In the long-term model, the QALYs gained with each strategy were:
29.2 for peg-IFN-a2b plus RIB for 24 weeks;
28.3 for peg-IFN-a2b plus RIB for 48 weeks for genotype 1 patients; and
29.1 for peg-IFN-a2b plus RIB for 24 weeks for non-genotype 1 patients.

Cost results
In the short-term model, the average cost per patient for each strategy was:
$6,000.50 for peg-IFN-a2b plus RIB for 24 weeks;
$5,562.50 for peg-IFN-a2b plus RIB for 48 weeks for genotype 1 patients; and
$9,591.00 for peg-IFN-a2b plus RIB for 24 weeks for non-genotype 1 patients.

In the long-term model the average cost per patient for each strategy was:
$10,647.69 for peg-IFN-a2b plus RIB for 24 weeks;
$11,463.31 for peg-IFN-a2b plus RIB for 48 weeks for genotype 1 patients; and
$14,578.63 for peg-IFN-a2b plus RIB for 24 weeks for non-genotype 1 patients.

Synthesis of costs and benefits
The costs and benefits were combined by means of an incremental cost-effectiveness ratio (i.e. the additional cost per
SVR) for the short-term model and an incremental cost-utility ratio (i.e. the additional cost per QALY gained) for the
long-term model.

In the short-term model, the incremental cost-effectiveness ratio of the strategy peg-IFN-a2b plus RIB for 24 weeks
was $141,565.70 per SVR in comparison with peg-IFN-a2b plus RIB for 48 weeks for genotype 1 patients. Also, when
compared with the latter, the incremental cost-effectiveness ratio of peg-IFN-a2b plus RIB for 24 weeks was
$1,611,400.00 for non-genotype 1 patients.

In the long-term model the intervention peg-IFN-a2b plus RIB for 24 weeks was found to be dominant over the two
other strategies, as it was both less costly and more effective. When comparing peg-IFN-a2b plus RIB for 24 weeks for
non-genotype 1 patients with peg-IFN-a2b plus RIB for 48 weeks for genotype 1 patients, the incremental cost-utility
ratio was $3,894.15 per QALY gained.

The main findings of the sensitivity analyses were that, when the SVR of peg-IFN plus RIB treatment for 48 weeks in
genotype 1 patients was higher than 67.8%, the best strategy of treating patients would be the peg-IFN plus RIB therapy
for 48 weeks in genotype 1 patients and for 24 weeks in non-genotype 1 patients.

Authors' conclusions
Combined treatment with pegylated-interferon alpha-2b (peg-IFN-a2b) plus ribavirin for 24 weeks in all genotype
patients would 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
Although no explicit justification was given for comparing the three different peg-IFN-a2b plus RIB treatment strategies, it would appear that these were selected because they formed part of the peg-IFN-a2b development programme in Taiwan.

Validity of estimate of measure of effectiveness
The authors did not report whether a systematic review of the literature had been undertaken to identify relevant research and minimise biases. Further, the authors provided only limited details of the methods used in the review of the literature. When data were unavailable from the literature, the authors used expert opinion to populate some of the model parameters. It was clear from their study which parameters were derived using data from the literature and which ones were derived from experts. However, the authors did not give details of the expert panel, such as background, number of experts and methods used to elicit opinions. The authors appropriately varied all major parameters in the model using a sensitivity analysis to ascertain the parameter uncertainty in the model.

Validity of estimate of measure of benefit
The estimation of benefits was obtained using decision analytic models. The authors used a simple decision tree model for the short-term period and a Markov model for the long-term period. Both models were appropriate for the study question. The benefit measures chosen were appropriate, with QALYs allowing comparisons across health technologies if required.

Validity of estimate of costs
The authors reported the use of two different perspectives in the study, a societal perspective being reported in the abstract and that of the National Insurance programme in the main text. However, given the categories of cost included in the economic analysis, the actual perspective appears to have been that of national insurance. All cost categories relevant to this perspective and all major costs appear to have been included.

The costs and the quantities were not reported separately, which will limit the generalisability of the authors’ conclusions. The costs were derived from the BNHI database. A sensitivity analysis of the costs was performed by varying the medical costs and the price of peg-IFN-a2b plus RIB over defined lower and upper limits. The authors converted costs from national currency to US dollars, although they did not provide the exchange rate used. Discounting was appropriately performed, as the costs could be incurred over the lifetime of the patient, and the price year was appropriately reported. These will assist any future inflation exercises.

Other issues
The authors reported that many studies showed that combination therapy was cost-effective in the treatment of naive hepatitis C patients. However, they also reported that none provided data on the most cost-effective way to treat Chinese patients. The issue of generalisability to other settings was partially addressed in the sensitivity analysis. The authors do not appear to have presented their results selectively and their conclusions seem to reflect the scope of the analysis. The authors reported a number of further limitations to their study. First, there were no data on the Chinese hepatitis C patient condition, probability of progression, or quality of life. Second, the study assumed that patients would have good compliance, which is not generally true in current settings. Finally, some transient probabilities used were based on expert opinion.

Implications of the study
The authors reported that for Chinese patients without genotyping, 24 weeks of peg-IFN-a2b plus RIB combination therapy was the most cost-effective in Taiwan.

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Other publications of related interest
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