Economic and clinical effects of evaluating rapid viral response to peginterferon alfa-2b plus ribavirin for the 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
The use of rapid viral response assessment, to update treatment at various stages during initial antiviral therapy for the treatment of patients with chronic hepatitis C, was examined. Initial therapy was one of the three following strategies.

Strategy 1 was interferon (IFN) alpha-2b (3 million units given subcutaneously three times per week) plus ribavirin daily (the dosage of ribavirin was weight-based).

Strategy 2 was peginterferon alpha-2b (1.5 microg/kg per week subcutaneously) plus 800 mg/day ribavirin.

Strategy 3 was peginterferon alpha-2b plus weight-based ribavirin IFN.

Viral response to treatment was evaluated after 12, 24, and 48 weeks of treatment. A variety of management algorithms were compared (full details were provided in the paper).

Type of intervention
Treatment.

Economic study type
Cost-utility analysis.

Study population
The study population comprised untreated adult patients with chronic hepatitis C and elevated transaminases. The authors did not mention any further inclusion or exclusion criteria, but the reader was referred to the study of Manns et al. (see Other Publications of Related Interest).

Setting
The setting was not explicitly stated, although it is likely to have been secondary care. The economic study was carried out in the USA.

Dates to which data relate
The effectiveness data were derived from a trial published in 2001. All the costs were adjusted to the price year 2003.

Source of effectiveness data
The effectiveness data were derived from a single, international, randomised clinical trial (Manns et al., see Other Publications of Related Interest). The reader is referred to this trial for further details on the effectiveness data and the methods used to derive them.
Link between effectiveness and cost data
The costing was undertaken retrospectively on the same sample of patients as that used in the effectiveness study.

Study sample
The study sample in the randomised trial comprised 1,530 previously untreated adult patients with chronic hepatitis C and elevated transaminases. Overall, 511 patients received peginterferon plus ribavirin. Although a sub-group of 188 patients received more than 10.6 mg/kg ribavirin, the analysis of weight-based dose of peginterferon plus ribavirin was based on the entire group of 511 patients who received fixed ribavirin because different outcomes were higher than those for the sub-group of 188 patients. The reader is referred to the parent trial (Manns et al., see Other Publications of Related Interest) for further details on the appropriateness of the sample size and the number of patients allocated to each group.

Study design
The basis of the analysis was an international, randomised clinical trial that was conducted in 62 centres. The patients were stratified according to their genotype and the presence of cirrhosis, and then randomised to the treatment groups. Viral response was evaluated at 12, 24 and 48 weeks of treatment and the patients were followed up for 24 weeks after treatment interruption. The reader is referred to the parent trial (Manns et al., see Other Publications of Related Interest) for further details on the study design (e.g. method of randomisation, loss to follow-up, stratification method).

Analysis of effectiveness
The reference scenario for the analysis was based on intention to treat (ITT) for 48 weeks, accounting for dose reductions and discontinuation of treatment as they took place in the "parent" clinical trial. The main outcomes used in the analysis were the rates of sustained viral response (SVR), treatment duration, and adverse effects due to treatment (e.g. decompensated cirrhosis, hepatocellular carcinoma). To adjust for differences in the characteristics of the treatment groups at baseline, an identical cohort of patients (derived from the "parent" clinical trial) was used for each treatment path simulated in the model.

Effectiveness results
The rate of SVR relating to IFN plus ribavirin was 47% overall (for all patients), 33% in patients with genotype (GT) 1 and 79% in patients with genotype 2 or 3. For peginterferon plus fixed-dose ribavirin, the rates were 54% overall, 42% for GT 1 patients, and 82% for GT 2 or 3 patients.

For peginterferon plus weight-based ribavirin, the rate of SVR was 61% overall, 48% for GT 1 patients, and 88% for GT 2 and 3 patients.

Evaluation tests for response to antiviral therapy after 12 and 24 weeks' treatment reduced the sustained response rates by 2% at most for IFN plus ribavirin, and by 1% for peginterferon plus ribavirin.

The results for treatment duration were reported in detail for every treatment and management algorithm, but were too numerous to report here.

The reader is referred to two studies for a full report of the trial effectiveness results (Davis et al., see Other Publications of Related Interest).

Clinical conclusions
The authors concluded that their analysis demonstrated that "combination therapy with peginterferon plus ribavirin for treatment naive patients with chronic hepatitis C should reduce the lifetime risk of dying from liver disease and of developing decompensated cirrhosis or hepatocellular carcinoma". In addition, the use of 12- and 24-week treatment algorithms with ribavirin plus peginterferon can substantially reduce the mean duration of treatment and minimise the therapy-related morbidity.
Modelling
The authors used a reported Markov model to estimate the average life expectancy and lifetime cost for each treatment and each management strategy. According to the treatment received, each cohort of patients moved through various health states (i.e. clinical, histological and virological conditions). The cycles of the Markov model lasted for one year. During each cycle patients had four possibilities. They could remain in the same clinical health state, progress or regress to another clinical state, die because of liver disease, or die from other causes based on the patient's gender, race and age. Even patients who became viral negative could develop progressive disease. The model used the same cohort of patients with the average characteristics of the 1,530 patients from the international, randomised "parent" clinical trial to simulate each treatment and management algorithm. The characteristics and the initial health states of the cohort were well described. The time horizon of the model was equal to the patient's lifetime. The computations were carried out using DecisionMaker 7.0 software (Pratt Medical Group).

The model was based on several assumptions. First, it was assumed that patients who relapsed after initial treatment had no long-term benefits after relapse and received no further treatment. Second, spontaneous or treatment-induced loss of viremia was assumed to decrease the risk of developing progressive liver disease. Third, liver transplantation was not considered as an option for hepatocellular carcinoma, owing to the fact that it is inappropriate or unfeasible for most patients. Finally, patients with bridging fibrosis were classified as having moderate hepatitis, which is a more benign prognosis than is likely to be the case, thus treatment benefits for these patients might have been underestimated. These assumptions were based on data derived from the literature.

Measure of benefits used in the economic analysis
The measure of benefit used was the quality-adjusted life-years (QALYs) gained because of treatment. The utilities for each health state in the Markov model were assigned by experts with expertise in liver disease using a modified Delphi technique. For this purpose, time trade-off and standard reference gamble techniques were applied. It was assumed that combination therapy had a two-fold negative effect on quality of life compared with IFN alone. The assigned values were not reported.

Other outcomes from the model that were reported, but were not synthesised with the costs, were the life-years gained (changes in life expectancy). As the time horizon of the model was the patient's lifetime, all outcomes were appropriately discounted at an annual rate of 3%.

Direct costs
The health service costs included in the analysis were for drugs, laboratory tests (e.g. PCR, electrolytes, blood counts, liver and thyroid tests, qualitative pregnancy test), clinic visits, complications due to possible hepatitis C progression, other complications (e.g. liver transplantation), contraception (condoms), and post-treatment costs. While the unit costs of drugs were reported, non-drug costs were not described in detail and the quantities were not reported separately. The non-drug health service resources used were estimated from product label indications and not on evidence derived from the trial, owing to the fact that resource consumption was higher in the trial for safety-monitoring reasons. Post-treatment costs and the equivalent resources used were based on actual treatment costs and on the opinions of an expert panel (which had been published). The costs were appropriately discounted at an annual rate of 3%. All non-medication costs were adjusted to 2003 levels using the medical care component of the Consumer Price Index, while drug costs were based on the average wholesale costs of June 2003.

Statistical analysis of costs
The costs were treated deterministically.

Indirect Costs
The indirect costs were not included in the analysis.
Currency
US dollars ($).

Sensitivity analysis
One-way sensitivity analyses were carried out on all input parameters to investigate variability in the data. Multi-way sensitivity analyses were also conducted, but the authors only described the multi-way sensitivity analysis in which all the rates of histological liver disease progression were varied simultaneously so that the 20-year risk of cirrhosis decreased from 23 to 9%. The ranges and the methods used to select them were not described. A discount rate of 5% was also used in the sensitivity analysis.

Estimated benefits used in the economic analysis
Compared with no antiviral therapy, IFN plus ribavirin increased life expectancy by 3.1 years and added 4.0 QALYs. Peginterferon plus ribavirin increased life expectancy by 3.6 to 4.0 years and added 4.6 to 5.2 QALYs. The benefits of each treatment and evaluation strategy were not reported separately.

Cost results
The total lifetime costs (including adverse effects) were reported per patient for each treatment and management algorithm separately. Overall, the total lifetime costs with IFN alpha-2b plus ribavirin (strategy 1) ranged from $36,020 in the ITT algorithm to $30,061 in the 12-week test algorithm. With peginterferon alpha-2b plus 800 mg ribavirin (strategy 2), the total lifetime costs ranged from $45,226 (ITT algorithm) to $36,088 (12-week algorithm). With peginterferon alpha-2b plus weight-based ribavirin (strategy 3), the total lifetime costs ranged from $46,656 in the ITT algorithm to $36,331 in the 12-week algorithm.

For GT 1 patients, the total lifetime costs ranged:
from $40,350 in the ITT algorithm to $35,037 in the 12-week algorithm with strategy 1;
from $48,591 (ITT algorithm) to $41,586 (12-week algorithm) with strategy 2; and
from $53,301 (ITT algorithm) to $42,005 (12-week algorithm) with strategy 3.

For GT 2 or 3 patients, the total lifetime costs ranged:
from $28,218 in the ITT algorithm to $18,899 in the 12-week algorithm with strategy 1;
from $38,979 (ITT algorithm) to $23,909 (12-week algorithm) with strategy 2; and
from $40,599 (ITT algorithm) to $23,828 (12-week algorithm) with strategy 3.

Synthesis of costs and benefits
An incremental analysis was performed and all costs and QALYs were discounted. In the 12-week test algorithm, for all patients (regardless of genotype) compared with no antiviral therapy, strategy 1 incurred a cost of $1,500 per QALY gained, strategy 2 a cost of $4,400 per QALY gained, and strategy 3 a cost of $4,300 per QALY gained.

When compared with strategy 1, strategy 3 incurred a cost of $13,600 per QALY gained in the 12-week test algorithm and dominated treatment with strategy 2, which incurred a cost of $22,800 per QALY gained.

For GT1 patients, the 12-week algorithm was the most cost-effective for all treatment options. Compared with no therapy, strategy 1 incurred a cost of $4,400 per QALY gained, strategy 2 a cost of $7,700 per QALY gained, and strategy 3 a cost of $7,300 per QALY gained. Compared with strategy 1, strategy 2 incurred a cost of $19,300 per QALY gained and strategy 3 a cost of $13,500 per QALY gained.
For GT 2 or 3 patients, evaluation with the 12- and 24-week algorithms proved to be cost-saving. Similar results were obtained for all treatment options with these two management algorithms.

The one-way sensitivity analysis did not affect the main results. However, the multi-way sensitivity analysis had a great impact on the results, especially when all rates of histological liver progression were varied simultaneously. Specifically, in patients with GT 2 or 3, strategy 3 compared with strategy 1 incurred a cost of $100,000 per discounted QALY gained in the ITT algorithm. The cost-effectiveness ratios in the 12- and 24-week algorithms were lower but exceeded the cost-effective threshold of $50,000 per life-year saved.

**Authors’ conclusions**
The use of ribavirin plus peginterferon according to the 12- and 24-week treatment management algorithms "should reduce the cumulative incidence of liver complications, increase life expectancy, improve quality-adjusted life expectancy and be cost-effective". In particular, the 12-week management algorithm for patients with genotype (GT) 1 and the 24-week management algorithm for patients with GT 2 or 3 proved to reduce the costs of antiviral treatment.

**CRD COMMENTARY - Selection of comparators**
The authors provided a justification for their choice of the comparators, although there were some inconsistencies in the reporting of ribavirin dosages used in the various strategies. You should decide if these are widely used health technologies in your own setting.

**Validity of estimate of measure of effectiveness**
The analysis was based on an international, randomised clinical "parent” trial, which seems to have been appropriate given the study question. It is not possible to comment on the internal validity of the effectiveness results as the authors referred to a separate clinical paper for details of the clinical study. However, the authors carried out a number of sensitivity analyses relating to the efficacy estimates. These analyses improve both the internal validity and the generalisability of the study by demonstrating the robustness of the results to changes in the base-case estimates.

**Validity of estimate of measure of benefit**
The measure of benefit was the QALYs. The utilities were assigned by an expert panel according to a modified Delphi technique that used time trade-off and standard reference gamble techniques, both widely recognised and used techniques.

**Validity of estimate of costs**
The authors reported that the study had been conducted from a societal perspective, but the indirect costs (e.g. productivity loses or other non-medical costs) were not included. The costs and the quantities were not reported separately, thus impeding the reproducibility of the study in other settings. The resource quantities of non-drug health services were estimated according to product label indications and were not obtained from the parent clinical trial. This choice was justified. The post-treatment resources and costs were based on actual treatment costs and on the opinion of an expert panel, which had been published elsewhere. It is therefore difficult to comment on whether charges were used to proxy prices. The authors did not compute the total costs but variable costs (cost to treat one additional patient), while the omission of some costs (e.g. future liver biopsies, surveillance for hepatocellular carcinoma, and additional therapy for nonresponders) might have resulted in the underestimation of the actual total costs. The costs were appropriately discounted, inflation adjustments were carried out, and the price year was reported. In addition, the sensitivity analysis improved the generalisability of the findings.

**Other issues**
The authors did not compare their findings with those from other studies, thus it is not possible to comment on how far their results agree with other published studies. The issue of the generalisability of the results to other settings was not addressed. The study considered untreated hepatitis C infected adult patients and this was reflected in the authors'
conclusions. The authors reported a number of limitations to their study. First, the SVR rate of weight-based treatment with ribavirin was evaluated on a sub-group of patients from the “parent” clinical trial, as weight-based labelling of the drug is only approved in Europe and not in the USA. Second, the “parent” clinical trial started before the results of the IFN plus ribavirin treatment option were available. Therefore, all patients under study were handled with the intention of being treated for 48 weeks. In their conclusions the authors appeared to favour the peginterferon plus ribavirin treatment option over IFN plus ribavirin, although the cost-effectiveness results may indicate otherwise.

Implications of the study
The authors recommended that physicians, in making a decision on antiviral treatment, should consider the different sensitivities of different quantitative viral tests, patient preferences, and future results from ongoing studies on patients with advanced fibrosis. In addition, patients are recommended to weigh the risks and benefits of each treatment option, paying attention to particular side effects such as flu-like symptoms, depression, systemic symptoms haemolysis and teratogenic effects. Future research on whether GT 2 or 3 hepatitis C-infected patients should be treated for 48 weeks is proposed.

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Other publications of related interest


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