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
Pegylated (polyethylene glycol) interferon (IFN) alpha-2b combined with the oral antiviral drug ribavirin (RBV) (PEG+RBV) was compared with non-pegylated INF plus RBV (INF+RBV) for the treatment of patients with moderate to severe chronic hepatitis C (HCV). The recommended dosages were 1.5 microg/kg per week for PEG-2b (based on an average patient weight of 79 kg), 3 million international units 3 times per week for IFN-2b, and 1,200 mg/day for RBV. Both treatments were administered for 48 weeks.

Type of intervention
Treatment.

Economic study type
Cost-utility analysis.

Study population
The study population comprised a hypothetical cohort of patients with moderate to severe chronic HCV infection who had not been treated with IFN before. Moderate to severe chronic HCV was defined as histological evidence of significant scarring (fibrosis) and/or significant necrotic inflammation.

Setting
The setting was secondary care and a hospital. The economic study was carried out in the UK.

Dates to which data relate
The effectiveness data were derived from studies published between 1996 and 2004. No dates for resource use were explicitly reported. The price year was 2002.

Source of effectiveness data
The effectiveness evidence was derived from a synthesis of completed studies and experts' opinions.

Modelling
A state-transition Markov model was constructed to examine the clinical and economic impact of the two alternative treatments for HCV in a hypothetical cohort of 1,000 patients with moderate to severe chronic disease. The time horizon of the model was 30 years. The average age at diagnosis was 36 years. The health states considered in the model were chronic HCV, progression to cirrhosis, development of ascites, development of variceal bleeds, development of hepatic encephalopathy, progression to hepatocellular cancer, liver transplantation, and death. Annual cycles were considered.
Outcomes assessed in the review
The outcomes considered were:

- the probabilities of disease progression across health states;
- the probabilities of patients achieving a sustained virological response (SVR);
- adverse events; and
- utility values associated with model health states.

SVR was defined as the absence of viral ribonucleic acid (RNA) for at least 6 months after the end of treatment (proxy for cure).

Study designs and other criteria for inclusion in the review
A systematic review of the literature was carried out to identify relevant studies providing data on the effectiveness of treatment (SVR) using specific inclusion criteria. Only randomised, clinical trials published in English were included. Other data used in the model (i.e. progression rates and utility values) were derived from the literature, but it was unclear whether a systematic review had been undertaken.

Sources searched to identify primary studies
MEDLINE and the Cochrane Library were searched up to March 2003. Experts were contacted and relevant Internet sites were searched. Documents made available by drug manufacturers were also reviewed.

Criteria used to ensure the validity of primary studies
The validity of the primary studies was ensured by the use of criteria devised by the UK NHS Centre for Reviews and Dissemination.

Methods used to judge relevance and validity, and for extracting data
One reviewer extracted and appraised the data and a second reviewer checked them. Any disagreements were resolved by discussion.

Number of primary studies included
Nine primary studies provided the data for the base-case. Two additional studies provided effectiveness data for the sensitivity analyses.

Methods of combining primary studies
The effectiveness data were combined in a meta-analysis using a random-effects model.

Investigation of differences between primary studies
The two clinical trials were similar in terms of patient populations, drug doses and methodological aspects. A test for heterogeneity was carried out. The issue of the comparability of the other primary studies was not explicitly addressed.

Results of the review
The pooled SVR was 55% (95% confidence interval, CI: 52 - 58) for PEG+RBV and 46% (95% CI: 43 - 49) for IFN+RBV.
The pooled relative risk for remaining infected was 0.83 (95% CI: 0.76 - 0.91).

The values of the other data derived from the literature (utility values and probability of disease progression) were not reported.

The sub-group analysis revealed that patients treated with PEG+RBV had generally better outcomes than those treated with IFN+RBV across all genotypes, although there were some small differences between the two trials. In general, patients with a low viral load (≤ 2 million copies per mL) had higher SVR than those with a higher viral load (> 2 million copies per mL), although some differences across the trials were observed.

Side effects were similar between the groups.

**Methods used to derive estimates of effectiveness**
Experts' opinions on disease progression and utility values were derived using a Delphi consensus-based exercise. Such values were integrated with published evidence.

**Estimates of effectiveness and key assumptions**
The utility values and probability of disease progression values were not reported.

**Measure of benefits used in the economic analysis**
The summary benefit measure was the number of quality-adjusted life-years (QALYs) associated with each treatment strategy. QALYs were estimated using the modelling approach and were discounted at an annual rate of 1%. Quality of life estimates came from the literature.

**Direct costs**
Discounting was relevant because of the long time horizon of the study and an annual rate of 6% was applied. The unit costs were not presented separately from the quantities of resources used. The health services considered in the economic evaluation were investigation, monitoring, treatment and drugs. Capital and overhead costs were not included. A detailed breakdown of the cost items was not provided. The cost/resource boundary of the NHS was adopted. The estimation of costs came from an English NHS Hospitals Trust and the British National Formulary. Drug use was based on recommended dosages. The source of the other resources was not explicitly reported. The price year was 2002.

**Statistical analysis of costs**
The costs were treated deterministically.

**Indirect Costs**
The indirect costs were not included.

**Currency**
UK pounds sterling ( £ ).

**Sensitivity analysis**
Univariate sensitivity analyses were performed to examine the robustness of the estimated cost per QALY to variations in SVR (using data derived from the clinical trials), discount rate (0 to 6% for both costs and benefits) and drug costs (+/- 50%). Sub-group analyses were also carried out. The analysis investigated the impact of stopping treatment after 12 weeks in patients who had achieved a viral response at that time, using values that were derived from alternative studies.
Estimated benefits used in the economic analysis
In the cohort of 1,000 patients, the estimated discounted QALYs were 23,098 with IFN+RBV and 23,417 with PEG+RBV. The QALYs gained with PEG+RBV were 320.

Cost results
In the cohort of 1,000 patients, the discounted costs were 9,987,505 with IFN+RBV and 13,862,982 with PEG+RBV. The additional costs associated with PEG+RBV were 3,875,478.

Synthesis of costs and benefits
An incremental cost-utility ratio was calculated to combine the costs and benefits of the two interventions. The incremental cost per QALY gained with PEG+RBV relative to IFN+RBV was 12,123.

In the sub-group analysis, the incremental cost per QALY gained was 10,848 for genotype 1, 7,051 and 37,578 for genotype 2/3 (using data from two separate clinical trials), and 8,946 for genotype 4/5/6. When patients were stratified according to viral load and genotype group, the incremental cost per QALY gained ranged from 4,624 to 13,701. In general, lower incremental cost-effectiveness ratios were associated with low baseline viral load.

The cost-utility ratios were most sensitive to variations in SVR (the highest cost per QALY was 37,611) and discount rate (the highest cost per QALY was 23,357). Changes in drug prices had a small effect on the base-case results.

Stopping treatment after 12 weeks in patients who had achieved a viral response at that time led to cost-savings of around 16%.

Authors’ conclusions
Dual therapy with pegylated interferon (PEG) and ribavirin (RBV) was a cost-effective alternative to standard interferon (IFN) plus RBV for the treatment of patients with moderate to severe chronic hepatitis C (HCV) infection that had not been treated with IFN before. It represented good value for money from the perspective of the UK National Health Service (NHS). Genotype was a strong predictor of outcome, and sustained virological response (SVR) was higher for patients with genotypes 2 and 3.

CRD COMMENTARY - Selection of comparators
The selection of the comparators was appropriate. The authors stated that IFN+RBV represented the usual care in their own setting for patients with chronic HCV. The use of PEG+RBV was an alternative option. Treatment dosages were reported. You should decide whether they are valid comparators in your own setting.

Validity of estimate of measure of effectiveness
The analysis of effectiveness came mainly from published studies. The methods and conduct of the review of the literature, which aimed to identify effectiveness evidence, were reported satisfactorily. The inclusion criteria, search methods, quality of the primary studies, data extraction and synthesis of the primary estimates were clearly described. However, the information on the sources used to derive the other model inputs was limited. Experts’ opinions were also required and the authors reported that a Delphi approach was used. The sensitivity analysis investigated only the impact of variations in SVR, which was derived from the clinical trials. The issue of uncertainty in other estimates, such as transition probabilities among health states, was not investigated.

Validity of estimate of measure of benefit
The use of QALYs as the summary benefit measure was appropriate, as it captures the impact of the interventions on survival and quality of life. The utility values, which were derived from the literature and experts’ opinions, were not reported. The authors stated that the time trade-off approach was used but such values were not varied in the sensitivity analysis. QALYs are comparable with the benefits of other health care interventions. Discounting was applied, as
recommended in UK guidelines.

Validity of estimate of costs
The authors stated explicitly the perspective adopted in the study. However, limited information on the cost analysis was provided. A detailed breakdown of the items was not reported and the costs were presented as macro-categories. The unit costs and the quantities of resources used were not presented. The source of the costs was given, but the source of resource use data was unclear. The price year was reported, which will facilitate reflation exercises in other settings. The costs were specific to the study setting and only drug costs were varied in the sensitivity analysis.

Other issues
The authors stated that their findings were comparable with those from other published economic evaluations. The issue of the generalisability of the study results to other settings was not explicitly addressed, although some sensitivity analyses were carried out, which enhanced the external validity of the study. The authors noted some potential limitations of their study. First, the evidence on the natural progression of disease was limited due to the recent identification of the disease. Second, there were some differences between the two clinical trials used to provide effectiveness data.

Implications of the study
The study results suggested that health care providers are likely to face an increase in direct health care costs because of the growing demand for PEG therapy, especially in settings with large numbers of previously injecting drug users. The National Institute of Clinical Excellence recommend that patients with genotype 2 and 3 only receive 24 weeks of treatment, while patients with genotypes 1, 4, 5 and 6 are tested at 12 weeks for an early viral response, and treatment is only continued for the remaining 36 weeks in those who have responded at that time. The authors stressed that additional economic evaluations should be carried out to that takes emerging evidence for the treatment of HCV into consideration.

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Other publications of related interest


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