Cost-efficacy analysis of peginterferon alfa-2b plus ribavirin compared with peginterferon alfa-2a plus ribavirin for the treatment of chronic hepatitis C

Malone D C, Tran T T, Poordad F F

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 examined two combination therapies with pegylated interferon (Peg) and ribavirin (RBV) for the treatment of chronic hepatitis C virus (HCV) infection. One was Peg interferon alpha-2b (1.5 microg/kg per week) plus RBV (800 mg/day) (Peg-2b+RBV). The other was Peg interferon alpha-2a (180 microg per week) plus RBV (1,000 - 1,200 mg/day) (Peg-2a+RBV). A third strategy, the so-called weight-based dosing regimen, was also considered. This consisted of 1.5 microg/kg per week Peg-2b plus 10.6 mg/kg per day RBV.

Type of intervention
Treatment.

Economic study type
Cost-effectiveness analysis.

Study population
The study population comprised a hypothetical cohort of chronic HCV patients, including 75% of genotype 1. The average weight of the patients was 80 kg.

Setting
The setting was a hospital. The economic study was carried out in the USA.

Dates to which data relate
The effectiveness and resource use data were derived from studies published between 2001 and 2003. The price year was 2004.

Source of effectiveness data
The effectiveness evidence was derived from a synthesis of published studies.

Modelling
A decision tree model was constructed to simulate the costs and benefits of the three alternative combination therapies for the treatment of a hypothetical sample of 100 patients with chronic HCV infection. The time horizon of the model was one year. The model accounted for the ratio of genotype 1 to genotype 2 or genotype 3, and the positive predictive value (PPV) in response to treatment for persons with genotype 1. Treatment lasted 24 weeks for those persons non-genotype 1, while viral response was assessed at 12 weeks for genotype 1 patients. Those patients who had a decrease of 2 logs or more in viral load received an additional 36 weeks of therapy, for a total of 48 weeks. Treatment was stopped at 12 weeks for patients who did not show a viral response.
Outcomes assessed in the review
The outcomes estimated from the literature were:

- the SVR for all HCV genotypes and for HCV genotype 1 only with the three combination treatments,
- the EVR at 12 weeks for HCV genotype 1 only with the three combination treatments, and
- the PPV of the three treatments for genotype 1 patients only.

Study designs and other criteria for inclusion in the review
The primary studies providing the clinical data appear to have been identified selectively rather than through a systematic review of the literature. However, the three studies selected were randomised, multi-centre, multinational, registration trials. Details of patient characteristics, dosages, follow-up, withdrawals and key efficacy results were given for each study. No direct comparison of the three combination treatments was available, thus the analysis was based on an indirect comparison (the three Peg combinations were compared with standard interferon combination therapy in three separate trials).

Sources searched to identify primary studies
Not relevant.

Criteria used to ensure the validity of primary studies
The use of international clinical trials ensures a high internal validity.

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

Number of primary studies included
Three primary studies provided the clinical evidence.

Methods of combining primary studies
The primary studies were not combined.

Investigation of differences between primary studies
To show the baseline comparability of the patient groups, the authors reported some demographic and clinical characteristics of the three patient populations considered in the primary studies. Only the weight of the patients was slightly different.

Results of the review
The rate of SVR for all HCV genotypes was 56% with Peg-2a+RBV, 54% with Peg-2b+RBV, and 61% with the weight-based dosing regimen with Peg-2b+RBV.

The rate of SVR for HCV genotype 1 only was 46% (95% confidence interval, CI: 40 to 52) with Peg-2a+RBV, 42% (95% CI: 37 to 47) with Peg-2b+RBV, and 48% (95% CI: 39 to 57) with the weight-based dosing regimen with Peg-2b+RBV.

The rate of EVR at 12 weeks for HCV genotype 1 only was 81% (95% CI: 77 to 85) with Peg-2a+RBV, 71% (95% CI: 66 to 76) with Peg-2b+RBV, and 74% (95% CI: 66 to 82) with the weight-based dosing regimen with Peg-2b+RBV.
The PPV for HCV genotype 1 only was 0.57 (95% CI: 0.51 to 0.63) with Peg-2a+RBV, 0.63 (95% CI: 0.58 to 0.68) with Peg-2b+RBV, and 0.65 (95% CI: 0.63 to 0.79) with the weight-based dosing regimen with Peg-2b+RBV.

**Measure of benefits used in the economic analysis**
The summary benefit measure was the proportion of patients having an SVR, which was defined as the absence of detectable hepatitis C ribonucleic acid at least 20 weeks after completion of therapy. It was estimated directly from the clinical trials.

**Direct costs**
The analysis of the costs took the perspective of a managed care organisation. It included only the costs associated with Peg and RBV. The costs of adverse events were not considered as clinical studies had shown that the safety profiles of the two therapies were similar. Likewise, the costs of monitoring were not considered because of their similarity for the three treatment strategies. The unit costs were presented separately from the quantities of resources used. Resource use was derived from drug dosages observed in the clinical trials. The drug costs were obtained from average wholesale prices in October 2004, which was also the price year. Discounting was not relevant as 1-year costs were estimated.

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

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

**Currency**
US dollars ($).

**Sensitivity analysis**
Univariate and threshold analyses were carried out to assess the robustness of the cost-effectiveness ratios to variations in the PPV and drug costs. Specifically, the effects of a reduction of 17% in the drug prices and an alternative source for costs were investigated. The alternative values for the PPV were based on published CIs. Alternative values for the costs came from official sources.

**Estimated benefits used in the economic analysis**
The proportion of patients having an SVR was 53.63% with Peg-2a+RBV, 53.80% with Peg-2b+RBV, and 61.41% with the weight-based dosing regimen with Peg-2b+RBV.

**Cost results**
The total costs in a hypothetical cohort of 100 patients were $2,505,317 with Peg-2a+RBV, $2,024,846 with Peg-2b+RBV, and $2,397,529 with the weight-based dosing regimen with Peg-2b+RBV.

The number of weeks of therapy in a hypothetical cohort of 100 patients was 3,687 with Peg-2a+RBV, 3,417 with Peg-2b+RBV, and 3,498 with the weight-based dosing regimen with Peg-2b+RBV.

The Peg-2b combinations were less expensive on account of a higher PPV that suggested the discontinuation of therapy for a higher percentage of patients that could not benefit from treatment.

**Synthesis of costs and benefits**
Average and incremental cost-effectiveness ratios (i.e. the cost per SVR), which reflect the cost per successfully treated patient, were calculated in order to combine the costs and benefits of the alternative strategies.

The average cost-effectiveness ratio was $46,717 with Peg-2a+RBV, $37,638 with Peg-2b+RBV, and $39,045 with the weight-based dosing regimen with Peg-2b+RBV.

The incremental cost-effectiveness ratio for the weight-based dosing regimen with Peg-2b+RBV over Peg-2b+RBV was $48,989. Peg-2a+RBV was dominated by the Peg-2b+RBV treatments.

The sensitivity analysis showed that unrealistic values of PPV were required for Peg-2a+RBV to be cost-effective (lower average cost-effectiveness ratio) in comparison with the two Peg-2b+RBV regimens. A similar conclusion was achieved when alternative drug prices were used. For example, the threshold analysis showed that, only when the price of Peg-2a was reduced by 34% was the cost per successfully treated patient identical for Peg-2a and Peg-2b dosing.

**Authors’ conclusions**
Pegylated interferon alpha-2b (Peg-2b) plus ribavirin (RBV) was a cost-effective treatment in comparison with pegylated interferon alpha 2a (Peg-2a) plus RBV for the treatment of patients with chronic hepatitis C virus (HCV) in the USA. The main advantage of Peg-2b plus RBV was the difference in early virologic response (EVR) and positive predictive value (PPV), which led to fewer genotype 1 patients in the Peg-2b cohort continuing treatment when there was a very low likelihood of benefiting from it.

**CRD COMMENTARY - Selection of comparators**
The authors justified the choice of the comparators, which were appropriate. The dosages were reported and these reflected treatment patterns observed in the clinical trials. You should decide whether they are valid comparators in your own setting.

**Validity of estimate of measure of effectiveness**
The effectiveness data were derived from three published studies. The authors did not report details of any systematic review of the literature. Therefore, the primary studies might have been identified selectively. However, all the data came from well-conducted clinical trials, which should ensure a high validity of the clinical inputs. Confidence intervals for the most relevant inputs were reported. The authors showed that the patient populations were quite comparable, which strengthens the robustness of the comparison. In particular, the authors reported the inclusion and exclusion criteria used in the primary trials. However, efficacy results were obtained from these trials which did not directly compare the strategies under analysis. Thus, the analysis was based entirely on indirect comparisons, and the possibility that the differences in efficacy results were due to differences in the original studies cannot be ruled out. Moreover, the CIs for SVR, EVR and PPV between the three combinations overlapped.

**Validity of estimate of measure of benefit**
The summary benefit measure was specific to the disease considered in the study. It will not be comparable with the benefits of other health care interventions. The impact of the interventions on quality of life was not explicitly addressed, but was probably not relevant given the objective of the study.

**Validity of estimate of costs**
The cost analysis was restricted to the cost of the drugs under examination. The authors justified their exclusion of other categories of costs. Extensive information on the unit costs and quantities of resources used was provided, which will help in replicating the analysis in other settings. Data on resource use were based on treatment patterns observed in the clinical trials, which might not reflect real-world dosages and patient compliance. The costs were based on typical US sources. Deterministic costs were used in the study, but the issue of variability around the drug prices was appropriately addressed in the sensitivity analysis. The price year was reported, which will facilitate reflation exercises in other time periods.
Other issues
The authors compared the results of their study with published findings that appear to have been quite consistent, although different time-horizons and different outcome measures (quality-adjusted life-years) were generally used. The issue of the generalisability of the study results to other settings was not explicitly addressed, and only limited sensitivity analyses were carried out. The analysis focused on a short-term time horizon, which was appropriate given the pattern of disease. The authors noted that the analysis did not consider adverse events associated with treatment since they are likely to be very similar. This assumption appears to have been supported by the existing literature, unless different data on safety becomes available from a direct comparison of the two treatments.

Implications of the study
The study results support the use of Peg-2b+RBV for the treatment of chronic HCV patients. However, these results should be confirmed by head-to-head comparisons of the combination treatments under analysis.

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