Cost-effectiveness of growth factors during hepatitis C anti-viral therapy
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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 types of growth factors, erythropoietin (EPO) and granulocyte colony-stimulating factor (G-CSF), were examined. These were used to treat, respectively, anaemia (EPO) and neutropenia (G-CSF) in patients with hepatitis C virus (HCV) who had previously been treated with ribavirin (RBV) and pegylated interferon (pIFN). EPO was administered at a dose of 40,000 units per week, and G-CSF at 300 microg 2 days per week.

Type of intervention
Treatment.

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

Study population
The study population comprised HCV patients with anaemia or neutropenia that had developed after receiving RBV and pIFN.

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

Dates to which data relate
The effectiveness data were retrieved from studies published between 1993 and 2005. The dates for the resource use data were not reported. The price year was 2004.

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

Modelling
Two decision tree models were constructed to assess the costs and benefits of the alternative treatments for the management of HCV treatment-related complications in a hypothetical 45-year-old patient who could develop either neutropenia or anaemia after 4 weeks of therapy. Dose reduction in RBV and pIFN was compared with EPO in the case of anaemia and with G-CSF in the case of neutropenia. The duration of treatment was 48 weeks for patients with genotype 1 HCV and 24 weeks for patients with genotype 2/3 HCV. The decision trees were identical for either complication (anaemia or neutropenia). Regardless of the treatment, the complication could either be controlled or persist. If the complication was controlled, treatment continued; if the complication persisted, treatment was discontinued. Patients who continued treatment could either have an early virological response (EVR, defined as at least a 2 log decrease in viral load at the end of the first 12 weeks of treatment) or not. In the latter case (no EVR), antiviral and anaemia treatments were discontinued. Finally, patients with an EVR could experience an SVR or not. A schematic
representation of the model was reported. The time horizon of the model was unclear.

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

- the duration of antiviral therapy,
- the week when treatment for anaemia or neutropenia started,
- the time when ineffective dose reduction was stopped,
- the time when ineffective growth factor was stopped,
- the time when EVR was assessed,
- the drug doses and dose reductions,
- the rate of anaemia or neutropenia controlled by growth factor,
- the rate of anaemia or neutropenia controlled by dose reduction,
- the EVR with growth factor and with dose reduction,
- the absolute reduction in SVR resulting from dose reduction, and
- the quality-adjusted life-years (QALYs) associated with the condition of achieving an SVR with antiviral treatment.

Most outcomes were stratified by complication and genotype.

**Study designs and other criteria for inclusion in the review**
A review of the literature was undertaken to identify the primary studies. However, no information on the review was provided. There was also little information on the designs of the studies from which the model parameter estimates were obtained.

**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**
Twenty-three primary studies provided the clinical data.

**Methods of combining primary studies**
A narrative approach appears to have been used to combine the primary estimates. The authors stated that the two best designed studies were used to estimate the relationship between dose reduction and SVR.
Investigation of differences between primary studies
Not reported.

Results of the review
The duration of antiviral therapy was 48 weeks for genotype 1 and 24 weeks for genotypes 2/3.

Treatment for anaemia or neutropenia started at week 4.

Ineffective dose reduction or ineffective growth factor was stopped at week 8.

EVR was assessed at week 12.

The proportion of patients with anaemia or neutropenia controlled by growth factor was 96%.

The proportion of patients with anaemia or neutropenia controlled by dose reduction was 96%.

The percentages of patients who achieved EVR with growth factor and with dose reduction were 81% for genotype 1 and 97% for genotypes 2/3, regardless of the complication.

The absolute reduction in SVR resulting from dose reduction was 0.12 for genotype 1 and 0.01 for genotypes 2/3 in patients with anaemia.

The corresponding values in patients with neutropenia were 0.13 with genotype 1 and 0.06 with genotypes 2/3.

Over a lifetime, the QALYs associated with the condition of achieving an SVR with antiviral treatment were 7.13 higher than those in patients who did not experience an SVR.

Drug doses and dose reductions were also reported.

Measure of benefits used in the economic analysis
Two summary benefit measures were used in the economic analysis and were combined with the costs. These were the QALYs and global SVR. Both measures were estimated using the modelling approach. No information was given on the sources of the utility weights or on the methods used to convert SVR to QALYs. It was unclear whether future benefits were discounted to present values.

Direct costs
The cost/resource boundary of the analysis was unclear. The analysis included only the costs associated with the drugs and the future cost of treatment for the consequences of HCV if antiviral therapy failed.

Weekly drug costs of medications, as well as dosages, were reported. The costs of antiviral therapy failure were derived from a published study and were presented as macro-categories. The costs of medication were derived from a national retailer of pharmaceutical products in the USA. It was unclear whether discounting was applied to future medical costs. All costs were projected to November 2004, which was the price year.

Statistical analysis of costs
Statistical analyses of the costs were not performed.

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

Sensitivity analysis
A univariate deterministic sensitivity analysis was undertaken to assess the robustness of the cost-effectiveness and cost-utility ratios to variations in:

- the medication costs (alternative values were based on prices from the Veteran Affairs pharmacy);
- the future costs of hepatitis C care if antiviral therapy was not effective in achieving SVR (alternative range: 50% lower and 400% higher than baseline);
- a change in QALYs gained from eliminating the virus (20% lower and 20% higher than baseline); and
- the probability (range: 0.85 to 1.00) that growth factor use or dose reduction would control anaemia or neutropenia.

Estimated benefits used in the economic analysis
The expected benefits of the interventions were not reported.

Cost results
The total costs were not reported.

Synthesis of costs and benefits
Incremental cost-effectiveness ratios and cost-utility ratios were calculated in order to combine the costs and benefits of the alternative strategies for either type of complication.

In the cost-effectiveness analysis, the cost per added SVR of using G-CSF instead of pIFN dose reduction was $115,870 for genotype 1 patients with neutropenia and $134,628 for genotype 2/3 patients with neutropenia.

The cost per added SVR of using EPO instead of RBV dose reduction was $164,029 for genotype 1 patients with anaemia and $1,037,471 for genotype 2/3 patients with anaemia.

In the cost-utility analysis, the cost per QALY of using G-CSF instead of pIFN dose reduction was $16,247 for genotype 1 patients with neutropenia and $18,877 for genotype 2/3 patients with neutropenia.

The cost per QALY of using EPO instead of RBV dose reduction was $22,999 for genotype 1 patients with anaemia and $145,468 for genotype 2/3 patients with anaemia.

The two most striking results of the sensitivity analysis were as follows. First, the use of drug prices from the Veteran Affairs pharmacy reduced both the cost-effectiveness ratios and the cost-utility ratios. Second, when dose reduction had a smaller effect on SVR, both the cost-effectiveness ratios and the cost-utility ratios increased substantially. For example, the cost per QALY of using G-CSF instead of dose reduction for genotype 2/3 patients with neutropenia increased from $6,757 if dose reduction resulted in a 15% reduction in SVR to $22,916 if dose reduction resulted in a 5% reduction in SVR and to $119,872 if dose reduction resulted in a 1% reduction in SVR (it was 12% in the base-case analysis). Changes in other parameters had only a minimal effect on the results of the base-case analysis.

Authors' conclusions
The cost-effectiveness of growth factors was sensitive to the effect of pegylated interferon (pIFN) or ribavirin (RBV) dose reduction on sustained virological response (SVR), hepatitis C virus (HCV) genotype, and the cost of medications. Under base-case assumptions, the analysis showed that granulocyte colony-stimulating factor (G-CSF) may be cost-effective for genotype 1 patients, while erythropoietin (EPO) was probably not cost-effective for genotype 2/3 patients.
Given the uncertainty in some model inputs, a conclusion about the cost-effectiveness of EPO for genotype 1 patients or G-CSF for genotype 2/3 patients could not be drawn.

CRD COMMENTARY - Selection of comparators
The rationale for the choice of the comparators was clear. The dosages were accurately reported. The authors noted that alternative strategies of growth factor use, such as short-term use, were not considered. 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 a review of the literature, the details of which were not reported. Inclusion and exclusion criteria were not given and there was no information on the designs of the primary studies and patient characteristics. Therefore, it was not possible to assess the validity of the primary estimates. The authors did not address the issue of heterogeneity across the primary studies, and the sensitivity analysis investigated the uncertainty surrounding only one clinical input. These issues could limit the robustness of the effectiveness estimates.

Validity of estimate of measure of benefit
Both a generic and a disease-specific benefit measure were used in the economic evaluation. The use of QALYs has the advantage of not only being comparable with the benefits of other health care interventions, but also of capturing the impact of the treatments on survival and quality of life, which are two relevant dimensions of health in patients with HCV experiencing treatment-related adverse events. The QALYs were derived from a published study, details of which were not provided.

Validity of estimate of costs
The analysis of the costs included only the costs of medication and cost-savings associated with future costs of disease. Extensive information on the calculation of medication costs was provided, the authors reporting weekly dosages and unit costs. In addition, alternative sources of costs were considered in the sensitivity analysis, which will assist with replicating the analysis in other settings. However, the future cost-savings were derived from a published study and were presented as macro-categories of costs. Therefore, in effect, no breakdown of the cost items was provided. Further, it was not clear whether future costs were discounted. The costs were treated deterministically since no statistical analysis was performed. The price year was reported, which will facilitate reflation exercises in other time periods.

Other issues
The authors discussed the results from some published studies, but did not make explicit comparisons. The issue of the generalisability of the study results was implicitly addressed in the sensitivity analysis, although this focused mainly on the cost side of the analysis that might be specific of the USA. Therefore, caution will be required if extrapolating the results of the analysis to other settings. The authors noted some limitations of their analysis. For example, the availability of newer and well-tolerated antiviral therapies was not considered. Also, the model did not consider patient level characteristics that could impact on the effect of treatments. Finally, the analysis did not consider further laboratory and diagnostic costs associated with dose reduction or the use of growth factors.

Implications of the study
The study results suggest that the cost-effectiveness of using G-CSF or EPO as an alternative to dose reductions in antiviral therapies is highly dependent on genotype, effect of dose reductions on SVR, and medication costs. The authors pointed out the importance of running randomised studies to assess the impact of growth factors on HCV patients experiencing side effects related to antiviral therapies.

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