Cost-effectiveness of peginterferon alfa-2a (40 kDa) plus ribavirin in patients with HIV and hepatitis C virus co-infection

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 peginterferon (pegIFN) alpha-2a (40 kDa; 180 microg/week) plus ribavirin (RBV; 400 mg twice daily), a treatment for patients with human immunodeficiency virus (HIV) and hepatitis C virus (HCV) co-infection.

Type of intervention
Treatment.

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

Study population
The study population comprised patients with HIV-HCV co-infection. The analysis was stratified by HCV genotype (1 or 2/3). A combined genotype cohort was also considered. Patients with HCV genotypes 4-6 were excluded.

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

Dates to which data relate
The effectiveness data were derived from studies published between 1993 and 2004. No dates for resource consumption were explicitly reported. The price year was 2004.

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

Modelling
A published Markov model of chronic hepatitis C was modified to reflect the natural history of disease in patients with HIV-HCV co-infection. The impact of the alternative strategies was simulated. A simplified version of the model was provided. The nine health states in the model were no fibrosis, portal fibrosis (no septa), portal fibrosis (few septa), septal fibrosis (no cirrhosis), cirrhosis, hepatocellular carcinoma (HCC), decompensated cirrhosis, liver transplant, and mortality associated with HIV and HCV. Death due to HCV disease was related only to complications of liver disease such as cirrhosis and related complications. Treatments were discontinued if early virological response (EVR) was not achieved; otherwise treatment was continued for 48 weeks. Patients entered the model at age 40 years. The time horizon of the model was the patients' lifetime and a yearly cycle length appears to have been used.

Outcomes assessed in the review
The outcomes estimated from the literature were:

epidemiological data,
the rates of SVR and EVR (virological response at 12 weeks),
the rates of fibrosis progression,
the rates of liver complications,
mortality, and
the quality of life weights associated with model health states.

Study designs and other criteria for inclusion in the review
It was unclear whether a systematic review of the literature was undertaken to identify relevant studies. Thus, the studies might have been identified selectively. Clinical data on the effectiveness of treatments and epidemiological variables were mainly obtained from the APRICOT study, a multinational, randomised placebo-controlled trial. Rates of fibrosis progression were taken from epidemiological studies of HCV mono-infection. Age-specific death rates were derived from the National Center for Health Statistics. No information on the other sources of data was provided.

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
Nineteen primary studies provided the clinical data.

Methods of combining primary studies
Not reported.

Investigation of differences between primary studies
Not reported.

Results of the review
Age at initiation of treatment was 40 years. Sixty per cent of patients had genotype 1 infection while 40% had genotype 2/3.

For genotype 1, the probability of SVR was 29% with pegIFN alpha-2a (40 kDa) plus RBV and 7% with IFN-RBV.
For genotypes 2/3, the probability of SVR was 62% with pegIFN alpha-2a (40 kDa) plus RBV and 20% with IFN-RBV.
For genotype 1, the probability of EVR was 63% with pegIFN alpha-2a (40 kDa) plus RBV and 25% with IFN-RBV.
For genotypes 2/3, the probability of EVR was 88% with pegIFN alpha-2a (40 kDa) plus RBV and 69% with IFN-RBV.

The rate of spontaneous remission from the state of no fibrosis in the first year was 1.2% for both genotype groups.

The rate of fibrosis progression was age- and gender-dependent and was reported for age sub-groups.

The annual mortality rate was 0.218 (range: 0.129 to 0.306) for decompensated cirrhosis, 0.780 (range: 0.390 to 1) for HCC in the first year, and 0.300 (range: 0.15 to 0.45) for HCC after the first year.

The ratio of rate of fibrosis progression, HIV-HCV co-infection compared with HCV mono-infection, was 2 (range: 1 to 6).

The excess annual mortality due to HIV was 1.4% (range: 1.1 to 1.7).

The utility weights were:

0.87 (range: 0.74 to 1) for remission;
0.81 (range: 0.69 to 0.93) for no fibrosis, portal fibrosis (no septa), portal fibrosis (few septa), and septal fibrosis (no cirrhosis);
0.68 (range: 0.58 to 0.78) for cirrhosis;
0.48 (range: 0.41 to 0.55) for decompensated cirrhosis;
0.23 (range: 0.20 to 0.26) for HCC;
0.81 (range: 0.69 to 0.93) for liver transplant; and
0.93 (range: 0.93 to 0.98) with anti-HCV treatment.

Other probability values (rate of liver complications, distribution of histology) were also reported.

**Measure of benefits used in the economic analysis**

The summary benefit measure used was the quality-adjusted life-years (QALYs). These were estimated using the decision modelling approach. The utility weights were obtained from the literature but no further detail was given. The expected life-years (LYs) and the risk of cirrhosis after 30 years were also reported as model outputs, but were not combined with the costs. The benefits were discounted at an annual rate of 3%.

**Direct costs**

The analysis of the costs appears to have been carried out from the perspective of the third-party payer. The analysis included the costs of drugs and treatment of diseases at different stages, including liver transplant. The unit costs and the resource quantities were not presented separately, most of the costs being reported as macro-categories. Resource use and most costs were estimated on the basis of a published study. Drug costs were estimated using wholesale acquisition prices. Discounting was relevant, given that long-term costs were evaluated, and an annual rate of 3% was applied. The price year was 2004.

**Statistical analysis of costs**

The costs were treated deterministically.

**Indirect Costs**

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

Sensitivity analysis
An extensive univariate sensitivity analysis was carried out to identify the model inputs with the greatest impact on the cost-effectiveness results. The variables used in the analysis were patients' age, rate of SVR, rate of liver complications, mortality rates, rate of disease progression, values of quality of life, cost of liver disease, cost of anti-HCV treatment, cost of HIV care, discount rate and time horizon. Alternative values were based on published data or were determined by the authors.

Estimated benefits used in the economic analysis
In the sub-group of genotype 1, the expected 30-year risk of cirrhosis, was 55% with pegIFN alpha-2a (40 kDa) plus RBV, 70% with IFN-RBV and 75% with no treatment. The LYs and QALYs were, respectively, 23.74 and 12.47 with pegIFN alpha-2a (40 kDa) plus RBV, 22.61 and 11.74 with IFN-RBV, and 22.25 and 11.53 with no treatment.

In the sub-group of genotypes 2/3, the expected 30-year risk of cirrhosis, was 32% with pegIFN alpha-2a (40 kDa) plus RBV, 61% with IFN-RBV and 75% with no treatment. The LYs and QALYs were, respectively, 25.44 and 13.63 with pegIFN alpha-2a (40 kDa) plus RBV, 23.29 and 12.19 with IFN-RBV, and 22.25 and 11.53 with no treatment.

In the combined genotype group, the expected 30-year risk of cirrhosis, was 46% with pegIFN alpha-2a (40 kDa) plus RBV, 67% with IFN-RBV and 75% with no treatment. The LYs and QALYs were, respectively, 24.40 and 12.90 with pegIFN alpha-2a (40 kDa) plus RBV, 22.90 and 11.90 with IFN-RBV, and 22.25 and 11.53 with no treatment.

Cost results
In the sub-group of genotype 1, the expected costs were $43,042 with pegIFN alpha-2a (40 kDa) plus RBV, $38,613 with IFN-RBV, and $35,474 with no treatment.

In the sub-group of genotypes 2/3, the expected costs were $37,089 with pegIFN alpha-2a (40 kDa) plus RBV, $38,528 with IFN-RBV, and $35,474 with no treatment.

In the combined genotype group, the expected costs were $40,661 with pegIFN alpha-2a (40 kDa) plus RBV, $38,579 with IFN-RBV, and $35,474 with no treatment.

In general, the higher acquisition costs of pegIFN alpha-2a (40 kDa) plus RBV were totally or partially offset by a reduction in costs associated with the progression of HCV and HIV.

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

In the sub-group of genotype 1, the incremental cost per QALY gained was $14,873 with IFN-RBV over no treatment and $6,020 with pegIFN alpha-2a (40 kDa) plus RBV over IFN-RBV. In the sub-group of genotypes 2/3, the incremental cost per QALY gained was $4,631 with IFN-RBV over no treatment, while pegIFN alpha-2a (40 kDa) plus RBV dominated IFN-RBV. In the combined genotype group, the incremental cost per QALY gained was $8,392 with IFN-RBV over no treatment and $2,082 with pegIFN alpha-2a (40 kDa) plus RBV over IFN-RBV.

After removing IFN-RBV from the comparison because the comparison of pegIFN alpha-2a (40 kDa) plus RBV with IFN-RBV was more cost-effective than the comparison of IFN-RBV with no treatment, no treatment was considered as the reference strategy. Subsequently, the incremental cost per QALY gained with pegIFN alpha-2a (40 kDa) plus RBV over IFN-RBV was $7,993 in the sub-group of genotype 1, $769 in the sub-group of genotypes 2/3, and $3,786 in the combined genotype group.
The results of the sensitivity analysis showed that the base-case results were quite robust to variations in the model inputs, although changes in the discount rate and time horizon had a substantial effect on the cost-utility ratios. However, even under unfavourable scenarios, the incremental cost per QALY associated with pegIFN alpha-2a (40 kDa) plus RBV over no treatment did not exceed $20,000 for the sub-group of genotype 1, while pegIFN alpha-2a (40 kDa) plus RBV was often dominant or had a low cost-utility ratio in the sub-group of genotypes 2/3. Similarly, the incremental cost per QALY associated with pegIFN alpha-2a (40 kDa) plus RBV over IFN-RBV never exceeded $30,000 per QALY.

Authors' conclusions
The combination of peginterferon (IFN) alpha-2a (40 kDa) and ribavirin (RBV) for the treatment of patients with human immunodeficiency virus (HIV) and hepatitis C virus (HCV) co-infection was cost-effective in the USA.

CRD COMMENTARY - Selection of comparators
The authors provided a clear justification for the choice of the comparators considered in the study. The interventions under examination were described and dosages were based on a clinical trial. 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 the literature, although the conduct of a systematic review was not reported. Therefore, it was unclear whether the primary studies were identified selectively. Information on some primary sources of data was limited, which made it difficult to assess the validity of the clinical estimates. Treatment effectiveness was derived from a single clinical trial because of the heterogeneity among the available clinical studies. The use of this randomised trial should increase the internal validity of the analysis. Extensive sensitivity analyses were carried out to deal with the uncertainty surrounding some model inputs. The authors did not combine clinical estimates because of heterogeneity amongst the primary studies.

Validity of estimate of measure of benefit
QALYs are an appropriate measure of benefit as they incorporate two relevant dimensions of health, survival and quality of life. The utility values were reported for all health states, but little information on the sources of such data was provided. QALYs can be compared with the benefits of other health care interventions. LYs saved were also reported. The benefits were discounted, in accordance with recommendations for economic evaluations.

Validity of estimate of costs
The cost analysis was restricted to direct medical costs which, as the authors acknowledged, make the perspective of the third-party payer more relevant to the analysis than that of society. Nevertheless, the adoption of a societal perspective and the subsequent inclusion of indirect costs associated with productivity losses would have been interesting. A breakdown of the cost items was not provided and only few details of resource consumption were given. Thus, it may be difficult to replicate the whole analysis in other settings. Most of the costs were derived from a published study that was not described in detail. Statistical analyses of the costs were not carried out and only a limited number of cost items were varied in the sensitivity analysis. The price year was reported, which will facilitate reflation exercises in other time periods.

Other issues
The authors stated that their results were consistent with those reported in a previous economic evaluation. They also noted some limitations of their analysis. For example, the whole analysis relied on the key assumption that the effect of potent antiretroviral therapy would continue to benefit patients' HIV-related survival. Another important assumption was that patients who achieved an SVR remained free of HCV infection. However, the impact of this assumption was modest, as demonstrated in the sensitivity analyses. Further, the latter assumption was common to other studies of treatments for HIV-HCV co-infection. The issue of the generalisability of the study results to other settings was not
explicitly addressed, although alternative scenarios were considered in the sensitivity analysis. The authors noted that a suboptimal RBV dose was used in the APRICOT study (and thus assumed in this analysis), but higher doses might be associated with better SVR, thus increasing the cost-effectiveness of pegIFN alpha-2a (40 kDa) plus RBV.

Implications of the study
The study results supported the use of pegIFN alpha-2a (40 kDa) plus RBV for the treatment of patients with HIV-HCV co-infection.

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