Peginterferon alfa-2a versus peginterferon alfa-2b as initial treatment of hepatitis C virus infection: a cost-utility analysis from the perspective of the Veterans Affairs health care system

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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
The study examined two types of peginterferon (PEG-IFN), peginterferon alpha-2a and peginterferon alpha-2b, for treating patients with chronic hepatitis C virus (HCV). Both treatments were administered in combination with ribavirin (RIB). A strategy of no treatment was also considered for comparative purposes. PEG-IFN alpha-2a was given at a dosage of 180 micro g/week and PEG-IFN alpha-2b at 120 microg/week, both with RIB at a dose of 1,200 mg/day. The duration of treatment was 48 weeks for HCV genotype 1 patients and 24 weeks for HCV genotype 2 or 3 patients.

Type of intervention
Treatment.

Economic study type
Cost-utility analysis.

Study population
The study population comprised a hypothetical cohort of men with chronic HCV. The patients had evidence of liver fibrosis but not cirrhosis.

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 1989 and 2005. The resource use data were derived from studies published mainly in 1997. The price year was 2005.

Source of effectiveness data
The clinical data used in the decision model were:

- the transition probabilities across health states (moderate HCV, compensated cirrhosis, decompensated cirrhosis, ascites, variceal haemorrhage, encephalopathy, haapatocellular carcinoma, liver transplantation, and HCV-unrelated and related death),
- the rate of sustained virological response (SVR),
- the rate of early virological response (EVR), and
- the probability of SVR after EVR.
Modelling
A Markov model was constructed to simulate disease progression and treatment under the three treatment options. Possible complications due to HCV progression were included in the model. A lifetime horizon was used and yearly cycles appear to have been selected. The patients were followed until death or age 90 years. The two cohorts of patients with chronic HCV considered were 45- and 55-year-old men. A schematic representation of the decision model and the health states was provided. The authors described the transitions between health states.

Sources searched to identify primary studies
The treatment effects for EVR and SVR were derived from large-scale clinical trials. In particular, two clinical trials were used for PEG-IFN alpha-2a plus RIB, while one trial was used for PEG-IFN alpha-2b plus RIB. The rates of HCV-unrelated mortality came from 2002 US life tables. Transition probabilities among health states were estimated from several published studies which were not described.

Methods used to judge relevance and validity, and for extracting data
No systematic search for data was reported. It is therefore possible that the primary studies might have been identified selectively. However, treatment effect data were obtained only from large clinical trials.

Measure of benefits used in the economic analysis
The summary benefit measure used was the expected number of quality-adjusted life-years (QALYs). These were estimated using the decision modelling approach. Survival was combined with data on quality of life, which were derived from a published study based on standard gamble techniques. The disutility associated with adverse drug events came from two published studies that were not described. Life-years (LYs) were also reported, but were not combined with the costs. The benefits were discounted at an annual rate of 3%.

Direct costs
The analysis of the costs was carried out from the perspective of the VA health care system. It included two main categories of costs, treatment costs (drugs, blood tests, and other laboratory tests) and annual HCV-related direct medical costs (outpatient visits, laboratory tests, medical support). The unit costs and the resource quantities were not presented separately for all items. Annual resources and costs related to HCV were derived from a published study, supported by expert opinion. The resource use data for treatment costs came from published clinical trials, while the drug costs were estimated from the Pharmacy Benefit Management national database and Medicare payment rates. Discounting was relevant, given that the long-term costs were evaluated, and an annual discount rate of 3% was applied. The costs were inflated to 2005 prices using the Consumer Price Index.

Statistical analysis of costs
The costs were treated deterministically in the base-case analysis but statistical tests were performed in the sensitivity analysis.

Indirect Costs
Productivity costs were not considered.

Currency
US dollars ($).

Sensitivity analysis
A sensitivity analysis was carried out to evaluate the robustness of the cost-utility ratios to variations in the model.
inputs. Specifically, a univariate sensitivity analysis was performed by varying the costs, probabilities and utility values. Published ranges of values were used for probabilities and utility values, whilst a range of 50 to 200% was selected for costs. In addition, utility values obtained using alternative instruments and methods (e.g. visual analogue scale, the Health Utility Index Mark 3 and the EuroQol) were considered. A Monte Carlo simulation with 3,000 hypothetical patients was also carried out to generate 95% confidence intervals (CIs) for the costs, benefits and incremental net monetary benefits (INMBs).

**Estimated benefits used in the economic analysis**

In the cohort of 45-year-old men, the expected mean QALYs (LYs) were:

- for genotype 1, 14.77 (27.81) with PEG-IFN alpha-2a + RIB, 14.74 (27.74) with PEG-IFN alpha-2b + RIB, and 12.39 (22.74) with no treatment; and

In the 55-year-old men cohort, the expected mean QALYs (LYs) were:

- for genotype 1, 12.09 (20.89) with PEG-IFN alpha-2a + RIB, 12.07 (20.84) with PEG-IFN alpha-2b + RIB, and 10.15 (17.34) with no treatment; and
- for genotypes 2 and 3, 13.45 (23.04) with PEG-IFN alpha-2a + RIB, 13.83 (23.68) with PEG-IFN alpha-2b + RIB, and 10.15 (17.34) with no treatment.

The 95% CI around QALY mean point estimates showed that both PEG-IFN treatments were significantly more effective than no treatment, but no statistically significant differences were found between the two PEG-IFN strategies.

**Cost results**

In the 45-year-old men cohort, the expected mean costs per patient were:

- for genotype 1, $31,719 with PEG-IFN alpha-2a + RIB, $30,777 with PEG-IFN alpha-2b + RIB, and $41,302 with no treatment; and

In the 55-year-old men cohort, the expected mean costs per patient were:

- for genotype 1, $30,920 with PEG-IFN alpha-2a + RIB, $29,967 with PEG-IFN alpha-2b + RIB, and $39,748 with no treatment; and
- for genotypes 2 and 3, $14,933 with PEG-IFN alpha-2a + RIB, $10,925 with PEG-IFN alpha-2b + RIB, and $39,748 with no treatment.

**Synthesis of costs and benefits**

INMBs were calculated in order to combine the costs and benefits of the alternative strategies using a threshold of $50,000 per QALY gained. Thus, incremental QALYs for one strategy over another were multiplied by $50,000. The incremental costs were then subtracted from the value obtained.

In the cohort of 45-year-old, the INMBs were:

- for genotype 1, $558 (95% CI: -27,159 to 29,148) with PEG-IFN alpha-2a + RIB over PEG-IFN alpha-2b + RIB, $128,583 (95% CI: 79,279 to 117,308) with PEG-IFN alpha-2a + RIB over no treatment, and $128,025 (95% CI:
80,425 to 173,448) with PEG-IFN alpha-2b + RIB over no treatment, and for genotypes 2 and 3, -$27,646 (95% CI: -65,966 to 9,359) with PEG-IFN alpha-2a + RIB over PEG alpha-2b + RIB, $225,527 (95% CI: 154,253 to 297,019) with PEG-IFN alpha-2a + RIB over no treatment, and $253,173 (95% CI: 169,469 to 342,957) with PEG-IFN alpha-2b + RIB over no treatment.

In the cohort of 55-year-old men, the INMBs were:

for genotype 1, $47 (95% CI: -22,723 to 22,890) with PEG-IFN alpha-2a + RIB over PEG-IFN alpha-2b + RIB, $105,828 (95% CI: 66,961 to 148,213) with PEG-IFN alpha-2a + RIB over no treatment, and $105,781 (95% CI: 68,377 to 146,440) with PEG-IFN alpha-2b + RIB over no treatment; and for genotypes 2 and 3, -$23,008 (95% CI: -55,284 to 7,334) with PEG-IFN alpha-2a + RIB over PEG-IFN alpha-2b + RIB, $189,815 (95% CI: 130,886 to 250,707) with PEG-IFN alpha-2a + RIB over no treatment, and $212,823 (95% CI: 144,716 to 284,415) with PEG-IFN alpha-2b + RIB over no treatment.

The 95% CIs showed that there was no statistically significant difference between the two PEG-IFN regimens. The sensitivity analysis showed that the utility estimates and treatment effectiveness had a substantial impact on the results of the analysis. However, the use of alternative utility estimates did not alter dramatically the INMB.

Authors' conclusions
Both combined peginterferon (PEG-IFN) treatments for chronic hepatitis C virus (HCV) were cost-effective from the perspective of the Veterans Affairs (VA) health care system.

CRD COMMENTARY - Selection of comparators
The authors justified the choice of the comparators in that the two PEG-IFN treatments were the two marketed PEG-IFN products in the USA. Dosages were reported. You should decide whether they are valid comparators in your own setting.

Validity of estimate of measure of effectiveness
The authors did not state whether a systematic review of the literature was undertaken to identify the primary studies. Treatment effect came from individually selected clinical trials, which usually represent a valid source of data. However, more information on the other primary studies would have been helpful. It is therefore difficult to judge the validity of most of the transition probabilities. The authors stated that some of these studies were case-control studies, which are usually associated with some limitations.

Validity of estimate of measure of benefit
The benefits (QALYs) were modelled using a Markov model. Discounting was applied in accordance with US guidelines. Some information on the sources of the utility weights was given, and the impact of alternative sources of quality of life data using different instruments was investigated in the sensitivity analysis. The authors stated that the use of patient-reported utility scores was a strong feature of the analysis.

Validity of estimate of costs
The analysis of the costs appears to have been consistent with the perspective stated in the study. A breakdown of cost items was not reported and there was no information on the quantities of resources; this limits the possibility of replicating the analysis in other settings. The sources of the costs were reported but there were few details of the main study from which the HCV-related costs were derived. Other costs were derived from typical US sources. An extensive sensitivity analysis was performed to address the issue of variability in the cost data. The price year was reported, which will help with reflation exercises in other time periods.
Other issues
The authors stated that their findings were in line with previous economic evaluations and made some direct comparisons with the results from other studies. However, they stated that this was one of the few studies comparing the two PEG-IFN options. The issue of the generalisability of the study results to other settings was addressed in the sensitivity analysis, which considered the impact of variation in all model inputs. The results of the base-case and the sensitivity analysis were extensively presented. The authors discussed some potential limitations of their analysis. For example, it was assumed that patients reaching SVR from PEG-IFN treatments were free from disease in the following years. In addition, the additional costs associated with PEG-IFN-related adverse events were not modelled. Finally, clinical data on treatment effectiveness came from clinical trials but no head-to-head study showing differences between the two PEG-IFN regimens was available.

Implications of the study
The study results support the use of both PEG-IFN regimens for patients with chronic HCV. The authors stated that large-scale studies should be undertaken to provide patient-reported health status utilities in HCV patients.

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None stated.

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Other publications of related interest
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