Cost-effectiveness of treatment for chronic hepatitis C infection in an evolving patient population

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 compared five strategies for the treatment of chronic hepatitis C infection:

- no treatment;
- monotherapy with interferon (IFN) alpha-2b;
- monotherapy with pegylated IFN alpha-2b;
- combination therapy with IFN plus ribavirin; and
- combination therapy with pegylated IFN plus ribavirin.

Type of intervention
Treatment.

Economic study type
Cost-utility analysis.

Study population
The study population comprised a hypothetical cohort of 40-year-old men and women with elevated levels of alanine aminotransferase, positive results on quantitative HCV RNA assays and serologic tests for antibody to HCV, and no histological evidence of fibrosis on liver biopsy.

Setting
The study 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 1990 and 2002. The resource use data were collected from two studies published in 1997 and 2000. The price year was 2001.

Source of effectiveness data
The effectiveness data were derived from published studies, supplemented by the authors’ assumptions.

Modelling
An epidemiologic model was first used to derive a range of natural history parameters that were empirically calibrated to provide a good fit to observed data on both prevalence of HCV seropositivity and time trends in outcomes related to
HCV infection. The results of this model were published elsewhere (Salomon et al., see Other Publications of Related Interest). Data from this model were then used in a Markov model to simulate disease progression in treated and untreated individuals who were seropositive for HCV, to estimate the costs and effects associated with the different treatment strategies for patients with HCV. The cycle of the model was 1 year. A lifetime horizon was used.

To be consistent with current US guidelines, the authors made some assumptions in their model. It was assumed that monotherapy was administered for 48 weeks, while combination therapy was administered for 48 weeks in patients with genotype 1 and 24 weeks in patients with other genotypes. Another assumption was that treatment was discontinued in patients with detectable HCV RNA levels, after either 12 weeks of receiving monotherapy or 20 weeks of receiving combination therapy.

In the base-case scenario, the authors assumed that chronic HCV infection could be resolved spontaneously or through successful treatment, in either case implying clearance of HCV RNA. In addition, spontaneous resolution occurred only in individuals without evidence of fibrosis. It was also assumed that patients with sustained response to treatment did not experience subsequent histological progression of fibrosis, and that patients who did not have sustained treatment response received no further treatment.

**Outcomes assessed in the review**
The outcomes derived from the epidemiologic model were:

- the annual remission rate per person;
- the annual rate of fibrosis progression in men and women;
- the annual progression rate from cirrhosis to decompensated cirrhosis and hepatocellular carcinoma;
- the annual mortality rate per person due to decompensated or hepatocellular carcinoma; and
- the proportion of patients who would not progress even if untreated.

The outcomes derived from the literature included:

- the treatment response probability with each of the four treatment strategies in patients with genotype 1 or other genotypes;
- the treatment mortality probability;
- the liver transplant probability; and
- the health-related quality of life weights associated with a number of health states. More specifically, mild and moderate chronic HCV, compensated cirrhosis, ascites, variceal haemorrhage, hepatic encephalopathy, hepatocellular carcinoma and liver transplant.

**Study designs and other criteria for inclusion in the review**
The estimates for treatment efficacy were based on results from randomised controlled trials.

**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**
Approximately 32 primary studies were included in the review. This number includes those studies used in the epidemiologic model.

**Methods of combining primary studies**
The authors reported that the estimates for treatment efficacy were based on the pooled results of randomised controlled trials.

**Investigation of differences between primary studies**
The authors did not report whether they had investigated any differences between the primary studies.

**Results of the review**
The ranges for natural history parameters from the epidemiologic model were as follows.

The annual remission rate per person was 0.012 (range: 0.007 - 0.017).

The annual rate of fibrosis progression in men ranged from 0.054 (range: 0.027 - 0.095) in men aged 40 to 49, to 0.301 (range: 0.152 - 0.478) in those aged 70 or over.

The annual rate of fibrosis progression in women ranged from 0.028 (range: 0.013 - 0.058) in women aged 40 to 49, to 0.210 (range: 0.085 - 0.355) in those aged 80 or over.

The annual progression rate from cirrhosis to decompensated cirrhosis was 0.040 (range: 0.032 - 0.052) and to hepatocellular carcinoma was 0.021 (range: 0.017 - 0.028).

The annual mortality rates per person due to decompensated or hepatocellular carcinoma were 0.306 (range: 0.129 - 0.395) and 0.433 (range: 0.319 - 0.499), respectively.

The proportion of patients who would not progress even if untreated was 0.242 (range: 0.096 - 0.741).

The results from the literature review were as follows.

The treatment response probability in those with genotype 1 (other genotypes) was 0.06 (0.26) for standard IFN monotherapy, 0.15 (0.47) for pegylated IFN monotherapy, 0.31 (0.67) for standard IFN plus ribavirin, and 0.42 (0.79) for pegylated IFN plus ribavirin.

The treatment mortality probability was 0.0005.

The liver transplant probability was 0.031.

The authors provided appropriate ranges for each of these parameters.

The health-related quality of life weights used in the analysis were:

0.98 (range: 0.92 - 1.00) for mild chronic HCV;

0.92 (range: 0.72 - 1.00) for moderate chronic HCV;

0.82 (range: 0.46 - 1.00) for compensated cirrhosis;
0.65 (range: 0.35 - 1.00) for ascites;
0.55 (range: 0.23 - 0.87) for variceal haemorrhage;
0.53 (range: 0.19 - 0.87) for hepatic encephalopathy;
0.55 (range: 0.15 - 0.95) for hepatocellular carcinoma; and
0.86 (range: 0.66 - 1.00) for liver transplant.

Methods used to derive estimates of effectiveness
The authors supplemented the data from the epidemiologic model and the effectiveness data from the literature review with their own assumptions.

Estimates of effectiveness and key assumptions
The authors assumed that a sustained virological response to treatment eliminated all decrements in health-related quality of life associated with living in the mild chronic HCV infection state. They also assumed that mild and moderate adverse effects of treatment reduced quality of life by 2% during the duration of therapy. Finally, the authors assumed that the consequences of severe adverse effects of treatment were captured as a small mortality risk.

Measure of benefits used in the economic analysis
The measure of benefits used was the quality-adjusted life-years (QALYs). The quality of life weights were derived from a published study using a panel of hepatologists and were assumed to be independent of the other co-morbidities. The health benefits were discounted at a rate of 3% per year.

Direct costs
The resource use quantities and the costs were not reported separately. The direct costs included in the analysis were those to the third-party payer. These consisted of the annual costs of care for patients in each of the clinical states in the model (including hospitalisations, outpatient visits, laboratory tests, medications and interventions) and the treatment costs. The annual costs of care were derived from a published study. The treatment costs were based on mean wholesale drug costs, combined with published cost estimates for clinic visits, laboratory tests and the treatment of adverse events. As the costs could be incurred over the lifetime of the patient, discounting was necessary and was appropriately performed at an annual rate of 3%. The study reported the mean costs. All the costs were adjusted to 2001 prices using the medical care component of the Consumer Price Index.

Statistical analysis of costs
The costs were treated as point estimates (i.e. the data were deterministic).

Indirect Costs
The indirect costs were not included in the analysis. The authors reported that the patients’ costs for time receiving medical care were not included in the model, and were assumed to be small relative to the health care costs.

Currency
US dollars ($).

Sensitivity analysis
The authors accounted for uncertainty around progression rates by using an array of natural history parameters that
provided a good fit to observed epidemiologic data. Sensitivity analyses on the costs, treatment efficacy, and health-related quality of life were also performed. The costs were varied from 50 to 150% of the base costs.

**Estimated benefits used in the economic analysis**
The QALYs gained were:

- 18.85 QALYs with no treatment;
- 18.94 QALYs with standard IFN;
- 19.09 QALYs with pegylated IFN;
- 19.28 QALYs with standard IFN plus ribavirin; and
- 19.40 QALYs with pegylated IFN plus ribavirin.

**Cost results**
The mean cost per patient was:

- $8,200 with no treatment;
- $10,200 with standard IFN;
- $13,300 with pegylated IFN;
- $17,700 standard IFN plus ribavirin; and
- $22,000 pegylated IFN plus ribavirin.

**Synthesis of costs and benefits**
The costs and benefits were combined using an incremental cost-utility ratio (i.e. the cost per extra QALY gained). Hence, the incremental ratio for a strategy was computed relative to the next most effective option after eliminating strategies ruled out by extended (weak) dominance (i.e. strategies having higher incremental cost-utility ratios than more effective options).

IFN therapy was weakly dominated by pegylated IFN therapy. The incremental cost-utility ratio of pegylated IFN was $21,000 per QALY gained compared with no treatment. The incremental cost-utility ratio of the combination therapies was $24,000 per QALY gained when standard IFN plus ribavirin was compared with pegylated IFN, and $35,000 when pegylated IFN plus ribavirin was compared with standard IFN plus ribavirin.

Among men, combination therapy with pegylated IFN compared with standard IFN had incremental cost-utility ratios ranging from $26,000 to $64,000 per QALY gained for genotype 1, and $10,000 to $28,000 per QALY gained for all other genotypes. Among women, these incremental cost-utility ratios ranged from $32,000 to $90,000 per QALY gained for genotype 1, and $12,000 to $42,000 per QALY gained for all other genotypes.

The results were most sensitive to assumptions about the gains and decrements in health-related quality of life associated with treatment.

**Authors' conclusions**
Even though newer treatment options for hepatitis C infection appeared to be reasonably cost-effective in a population with asymptomatic chronic hepatitis C, these results depended critically on assumptions about quality of life associated with mild hepatitis C virus (HCV) infection and treatment, and they varied widely across different patient sub-groups.
CRD COMMENTARY - Selection of comparators
The authors investigated the costs and effects of five available strategies for the treatment of chronic hepatitis C, with the baseline comparator being no treatment. All these treatment strategies appear to have been relevant to the study setting. You should decide if these represent current practice in your own setting.

Validity of estimate of measure of effectiveness
The authors reported that a systematic review of the literature was conducted to identify relevant research and minimise biases. The authors made use of a published model on the disease progression of HCV, presenting the key outcomes of the model, which they later used in a Markov model to identify the benefits of different treatment strategies. However, there were insufficient data in the article to judge the quality of the review, the study selection criteria, and the synthesis of the studies. On the other hand, appropriate details of the effectiveness estimates of each treatment were provided. These estimates were derived from randomised controlled trials which, if well conducted, represent the 'gold' standard study design. The authors combined estimates from these randomised controlled trials by pooling the results in a meta-analysis. The authors also made some assumptions in their model. All assumptions and estimates of effectiveness were appropriately varied in the sensitivity analysis.

Validity of estimate of measure of benefit
The estimation of benefits was modelled using a Markov model, which was appropriate. Assumptions used to derive some model parameters were referenced to the appropriate literature. An extensive sensitivity analysis, which strengthened the conclusions of the study, was performed. As the benefits could be incurred over the lifetime of the patient, the future benefits were appropriately discounted at an annual rate of 3%.

Validity of estimate of costs
Despite the authors reporting that a societal perspective was adopted, none of the indirect costs were included. Such indirect costs would include productivity losses in the form of foregone wages, owing to disease morbidity or premature death. The authors reported that patient time costs were not included, but that their omission would not have affected the results. The costs and the quantities were not reported separately, which will hamper generalisability to other settings. The costs were derived from published literature, and appropriate sensitivity analyses were undertaken. Since the costs were incurred over the lifetime of the patient, the future costs were appropriately discounted. The price year was reported, which will aid any possible inflation exercises.

Other issues
The authors made appropriate comparisons of their findings with those from other studies that compared the treatment of HCV with no treatment. The authors found that their model generated lower benefits and higher cost-utility ratios than those from these studies, with the differences ranging up to a factor of more than 40. The issue of generalisability to other settings was partially addressed in the sensitivity analysis. The authors did not present their results selectively and their conclusions reflected the scope of the analysis. The authors reported a number of further limitations to their study. First, their study did not address the possibility of retreating patients who relapsed, or pursuing more aggressive treatment for nonresponders. Second, other important issues regarding treatment of HCV infection in injection drug users, or in patients co-infected with human immunodeficiency virus, were not considered. Finally, this study did not intend to inform clinical decisions about the treatment of patients with advanced liver disease.

Implications of the study
The authors reported that it is imperative for patients and physicians to consider the assumptions very carefully when making individual-level treatment decisions.

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