Economic analysis of early serum hepatitis C virus RNA testing in patients with chronic hepatitis C on interferon therapy


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 use of hepatitis C virus (HCV) viral-load measurement early in the course of interferon (IFN) therapy, to inform subsequent treatment decisions in patients with chronic HCV. Doses of IFN ranged from 1 to 10 MU and were taken at frequencies of one or three times per week. Under this intervention, the decision of whether or not to continue IFN therapy was based on the results of an HCV RNA test at 3 months after the initiation of IFN therapy, with patients with an HCV RNA test result below 0.75 MEq/mL continuing and completing the full course of IFN therapy. For patients with a result above this threshold, therapy was discontinued.

Type of intervention
Diagnosis.

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

Study population
The study population comprised non-cirrhotic patients with chronic HCV infection. To be included in the study, the patients had to have a positive HCV antibody test, as confirmed by RIBA HCV 2.0 SIA or Abbot MATRIX, and persistently elevated serum alanine aminotransferase (ALT) levels for at least 6 months prior to the start of treatment. They also had to have had a baseline liver biopsy within 2 years prior to the start of treatment, and completed the course of treatment and follow-up to at least 9 months, with a baseline and end of follow-up specimen available for testing. The study excluded patients who had been on IFN or immunosuppressive therapy in the 3 months preceding the study and those who were pregnant. Also excluded were patients with decompensated liver disease, those who were positive for human immunodeficiency virus, and those taking immunosuppressive medication. The baseline characteristics of the study population were 63% male, mean age 42 years, mean serum ALT ratio 3.2, and mean serum HCV RNA level 5.8 MEq/mL.

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

Dates to which data relate
The effectiveness and cost data were derived mainly from a study published in 1997. Other effectiveness data were derived from studies published between 1996 and 1998.

Source of effectiveness data
The clinical consequences of IFN treatment strategies were derived using clinical data from a cohort of 274 non-cirrhotic patients with chronic HVC and an adaptation of a published Markov simulation model (Bennett et al., see Other Publications of Related Interest).
Modelling
The natural history of chronic HVC progression was modelled using an adaptation of a published Markov simulation model (Bennett et al., see Other Publications of Related Interest) in which patients move through various clinically and histologically defined disease states. The movement between states was defined in annual cycles during which patients remained in the same state, progressed to another state, or died of a liver-related disease or other causes.

The basic decision model represented the probability of response to IFN therapy at the end of a 6-month posttreatment observation period, based on the response rates for the study population. Three categories of response were considered, complete sustained response (CSR), complete response and relapse (CRR), and non-response (NR). In the comparative model, a hypothetical treatment decision of whether or not to continue IFN therapy was based on the results of an HCV RNA test at 3 months after the initiation of IFN therapy, with patients with an HCV RNA test result below 0.75 MEq/mL continuing and completing the full course of IFN therapy. For patients with a result above this threshold, therapy was discontinued. The response distribution at the end of follow-up for the group of patients who continued IFN therapy was based on the same probabilities as those in the decision with no HCV RNA test. Patients for whom IFN therapy was discontinued were assumed to be non-responders at one year.

CSR was defined as a normalised ALT ratio of 1.0 at the end of therapy and at the follow-up visit 6 months after the end of treatment, and an undetectable HCV RNA (<0.0350 MEq/mL) at the follow-up visit 6 months after the end of treatment. CRR was defined as normalised ALT at the end of treatment and at least one elevated ALT measurement at some point during follow-up. NR was defined as elevated ALT at the end of treatment.

Variations of the basic decision tree analytic model, such as the impact of HCV RNA test results at 1 month from the start of therapy and two different retreatment strategies, were investigated. In the retreatment model, patients who did not achieve a CSR at 1 year from the start of treatment were retreated with high-dose IFN (5 MU three times per week) or combination therapy (3 MU IFN three times per week plus 1,200 mg ribavirin per day).

Outcomes assessed in the review
The outcomes assessed were:

the transition probabilities of chronic hepatitis C disease progression;

the utility weights for each disease state; and

the retreatment response rates.

The authors also obtained the sensitivity, specificity, positive and negative predictive values, and the accuracy of the HCV RNA test used from the clinical data for the study population.

Study designs and other criteria for inclusion in the review
The transition probabilities of chronic hepatitis C disease progression were derived from those reported by Bennett et al. (see Other Publications of Related Interest). These were derived from published studies, and were reviewed and modified by an expert panel of hepatologists and statisticians.

The retreatment response rates with combination therapy were estimated from the results of randomised controlled trials for the FDA approval of REBETOL (a combination therapy).

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
The study by Bennett et al. (see Other Publications of Related Interest) was used to derive the transition probabilities and utility weights. A further 6 studies were used to derive estimates of retreatment response rates.

Methods of combining primary studies
Not necessary.

Investigation of differences between primary studies
Not necessary.

Results of the review
The Markov model transition probabilities between the various health states were as follows.

Remaining in the CSR, CRR and NR health states was 100 (CSR), 95.9 (CRR), and 95.7 (NR), respectively.

Moving from the CRR and NR to the chronic hepatitis health state was 4.1 in both cases.

Moving from the NR to the CSR health state was 0.2.

Moving from the chronic to the hepatocellular and cirrhosis health states was, respectively, 0.1 and 7.3.

Moving from cirrhosis to the hepatocellular health state was 1.5, to ascites 2.5, to variceal bleeding for one year 1.1, and to hepatic encephalopathy for one year 0.4.

Moving from the hepatocellular to death health state was 86.

Moving from ascites to refractory ascites was 6.7, to transplant within the first year 3.1, and to death 11.

Moving from the refractory ascites to the death health state was 33.

Moving from variceal bleeding for one year to transplant within the first year was 3.1, to variceal bleeding for more than one year 56.9, and to death 40.

Moving from variceal bleeding for more than one year to transplant within the first year was 3.1, and to death 13.

Moving from hepatic encephalopathy for one year to transplant within the first year was 3.1, to hepatic encephalopathy for more than one year 28.9, and to death 68.

Moving from hepatic encephalopathy for more than one year to transplant within the first year was 3.1, and to death 40.

Moving from transplant within the first year to transplant in subsequent years was 79, and to death 21.

Moving from the transplant in subsequent years to the death health state was 5.7.

The quality of life utility estimates were:

0.82 for mild chronic hepatitis disease state,

0.78 for moderate chronic hepatitis disease state,
0.35 for ascites and refractory ascites disease states,

0.28 for variceal haemorrhage disease state in year 1 and subsequently,

0.30 for hepatic encephalopathy disease state in year 1 and subsequently,

0.10 for hepatic cancer disease state,

0.50 for liver transplant in year 1,

0.70 for liver transplant after year 1, and

0.70 for cirrhosis health state.

Thirty-five per cent of CRR patients and 15% of NR patients retreated with high-dose IFN for 24 weeks achieved a sustained response.

Forty-six per cent of CRR patients retreated with combination therapy achieved a sustained response.

The test characteristics of HCV RNA at 3 months for predicting sustained response at 6 months post-treatment for the cohort were sensitivity 100%, negative predictive value 100%, specificity 38%, positive predictive value 19%, and accuracy 46%.

**Methods used to derive estimates of effectiveness**
The authors made several assumptions, based on the literature.

**Estimates of effectiveness and key assumptions**
The authors assumed that a sustained response at 6 months post-IFN treatment was essentially equivalent to being cured of HCV disease and life expectancy restored. The authors also assumed that 20% of NR patients retreated with combination therapy would achieve a sustained response.

**Measure of benefits used in the economic analysis**
The measures of benefits used were the life-years and quality-adjusted life-years (QALYs). Quality of life utility estimates were derived from Bennett et al. (see Other Publications of Related Interest).

**Direct costs**
The resource quantities and the costs were not reported separately. The direct costs included were those of the health service. For the base-case (standard 6-month course of IFN therapy) it was assumed that one counselling visit and two additional visits plus laboratory evaluations would be required. One HCV RNA test and one additional counselling visit were added to this for the model variation where HCV RNA was tested during IFN therapy. The retreatment models assumed similar resource use, except for the additional cost of IFN at higher doses or the cost of combination therapy with IFN and ribavirin.

Patient resource use and associated costs during IFN therapy were derived from Bennett et al. (see Other Publications of Related Interest), as were the costs for each disease state in the model. However, the costs for cirrhosis were estimated from Kim et al. (see Other Publications of Related Interest), based on a ratio of costs from Kim et al. and Bennett et al. Discounting was relevant, as the costs were incurred over the lifetime of the patient, and was carried out at a rate of 3% per annum. The study reported the average costs. The price year was not reported.

**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.

**Currency**
US dollars ($).

**Sensitivity analysis**
A sensitivity analysis was performed to estimate how the results would be affected if the input values for the model were changed. The variables examined were the sensitivity of the HCV RNA test for identifying CSR, the threshold value used to categorise responses to IFN, the cost of the HCV RNA test, and the cost of IFN therapy.

**Estimated benefits used in the economic analysis**
The discounted (undiscounted) life-years gained with and without HCV RNA testing at 3 months post-IFN therapy were 19.54 (31.81) for both.

The discounted (undiscounted) QALYs gained were 15.87 (25.61) with no HCV RNA testing and 15.88 (25.63) with HCV RNA testing at 3 months post-IFN therapy.

The discounted (undiscounted) life-years gained in the retreatment models with no HCV RNA testing were 19.73 (32.29) when patients were retreated with high-dose IFN, and 19.79 (32.45) when patients were retreated with combination therapy. The corresponding discounted (undiscounted) QALYs gained were 16.82 (27.74) for retreatment with high-dose IFN and 17.13 (27.99) for retreatment with combination therapy.

The discounted (undiscounted) life-years gained in the retreatment models with HCV RNA testing were 19.77 (32.39) when patients were retreated with high-dose IFN, and 19.84 (32.58) when patients were retreated with combination therapy. The corresponding discounted (undiscounted) QALYs gained were 16.99 (27.73) for retreatment with high-dose IFN and 17.34 (28.39) for retreatment with combination therapy.

**Cost results**
The total discounted (undiscounted) costs per patient were $41,500 ($82,600) in the no HCV RNA test model, compared with $41,300 ($82,300) in the HCV RNA test at 3 months model.

The total discounted (undiscounted) costs per patient in the retreatment models with no HCV RNA testing were $37,200 ($70,000) when patients were retreated with high-dose IFN, and $37,900 ($68,100) when patients were retreated with combination therapy.

The total discounted (undiscounted) costs per patient in the retreatment models with HCV RNA testing were $35,700 ($66,900) when patients were retreated with high-dose IFN, and $36,100 ($64,300) when patients were retreated with combination therapy.

**Synthesis of costs and benefits**
The costs and benefits were not combined, as the strategies involving HCV RNA testing at 3 months were found to be at least equally effective and less costly than strategies with no HCV RNA testing.

The model was highly sensitive to the performance characteristics of the HCV RNA test in identifying CSR, and the threshold value used for categorising patients into response categories based on HCV RNA test results. It was also found that if the HCV RNA test cost less than $428, then the strategy of HCV RNA testing at 3 months cost no more than the strategy without testing. In addition, as the costs of IFN therapy increased, management strategies using HCV RNA became more economically attractive.
Authors' conclusions
Measuring hepatitis C virus (HCV) RNA early in the course of interferon (IFN) therapy could allow clinicians to provide better care by identifying non-responders earlier, in order to tailor subsequent therapy and avoid unnecessary IFN therapy.

CRD COMMENTARY - Selection of comparators
Although no explicit justification was given for the comparator used, it would appear to represent current practice in the authors' setting. You should decide if the comparator represents current practice in your own setting.

Validity of estimate of measure of effectiveness
The authors evaluated the clinical consequences of IFN treatment strategies using clinical data from a cohort of 274 non-cirrhotic patients with HCV and a Markov model, based on transition probabilities derived from one study. The transition probabilities from this one study were based on published studies, and were reviewed and modified by an expert panel of both hepatologists and statisticians. The authors did not provide any more details of this study. It would have been desirable if the authors had given a brief summary of the different health states comprising the Markov model, as no mention was given of what each health state entailed or what they represented. Other effectiveness measures (i.e. retreatment response rates) were derived from a review of the literature, in particular, randomised controlled trials and earlier reports. The authors varied several inputs in the sensitivity analysis, such as the sensitivity of the HCV RNA test and the threshold value used to categorise responses to IFN. However, the authors did not vary any of the transition probabilities in the study used, even though this would have desirable, as these were obtained from a literature review and expert opinion.

Validity of estimate of measure of benefit
The estimation of benefits was modelled. The quality of life estimates were obtained from the literature. The benefits were appropriately discounted at 3% per annum.

Validity of estimate of costs
All the categories of cost relevant to the perspective adopted were included in the analysis. As such, all the relevant costs appear to have been included. The costs and the quantities were not reported separately, which will limit the generalisability of the authors' results. The costs were derived from published sources and appropriate sensitivity analyses were carried out to test for uncertainty in these estimates. As all the costs were incurred over the lifetime of the patient they were discounted at 3% per annum. However, the price year was not reported.

Other issues
The authors did not make appropriate comparisons of their findings with other studies estimating the cost-effectiveness of HCV RNA testing. This was because these studies focused primarily on the saving that would be generated by discounting IFN treatment in non-responders, but not the long-term consequences of such decisions on the life-years and costs over the lifetime of chronic HCV patients. The issue of generalisability to other settings was partly addressed in the sensitivity analysis. The authors do not appear to have presented their results selectively and their conclusions reflected the scope of the analysis. The authors reported no limitations to their study.

Implications of the study
The authors reported that their findings could be used to inform practice, following validation of the model with comprehensive clinical data.

Source of funding
None stated.
Bibliographic details

Other publications of related interest


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Subject indexing assigned by CRD

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