Pretreatment evaluation of chronic hepatitis C: risks, benefits, and costs
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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 administration of alternative pre-treatment management strategies for patients with chronic Hepatitis C.

Type of intervention
Treatment.

Economic study type
Cost-utility analysis.

Study population
A hypothetical population that has evidence of chronic hepatitis distributed among 3 histological stages with serum alanine aminotransferase (ALT) levels persistently above 1.5 times the upper limit of normal for at least 6 months, HCV antibody reactive on second-generation enzyme-linked immunosorbent assay testing, and viremia confirmed by qualitative polymerase chain reaction. The authors used a mean age of 40 years. Baseline values for histology, genotype, HCV viral load, liver biopsy complications and disease progression were provided.

Setting
The study was carried out in a secondary care setting in Boston (New England Medical Centre and Tufts University School of Medicine), USA.

Dates to which data relate
Effectiveness data were based on a decision model previously published in 1997 and a literature search which spanned the period 1966-1996. The authors used previously published variable cost estimates (1997). The price year was 1995.

Source of effectiveness data
The evidence for effectiveness was based on a synthesis of previously completed studies.

Modelling
A Markov model was used to examine the prevalence of genotypes, viral load, and histological characteristics in relation to the sustained response rate with treatment.

Outcomes assessed in the review
The review first identified those factors on which the prognosis following decompensation depended, which factors served as predictors of a sustained response, and the risk of hospitalisation and complications due to liver biopsy. The review assessed outcomes including the proportion of the population who would be treated, the probability of sustained response to interferon treatment among all patients and among patients treated, the number of patients needed to treat
with interferon to achieve 1 sustained response, the number of missed sustained responders, the lifetime incidence of cirrhosis, of decompensated cirrhosis, of hepatocellular carcinoma and of liver transplantation and life expectancy.

**Study designs and other criteria for inclusion in the review**
Not stated.

**Sources searched to identify primary studies**
Medline was searched for the period 1966-1996 and a study previously published in 1997 was also used.

**Criteria used to ensure the validity of primary studies**
Not stated.

**Methods used to judge relevance and validity, and for extracting data**
Not stated.

**Number of primary studies included**
The number of studies included in the review was approximately 77.

**Methods of combining primary studies**
The distribution of pre-treatment predictors of response was obtained by pooling published studies with a fixed-effects model. The probability of a sustained response based on pre-treatment predictors was calculated by logistic regression. Odds ratios were calculated for biopsy findings, HCV RNA viral load and genotype.

**Investigation of differences between primary studies**
As previous studies probably overestimated the likelihood of hospitalisation, the authors adjusted the risk of complications to bias the analysis toward liver biopsy. The authors assumed that a short-term response only, or the absence of a response, conveys no long-term benefits, even if this does not conform with the results of previous studies. If improvement does lead to improved prognosis, then this assumption biases against interferon treatment.

**Results of the review**
The prognosis following decompensation depended on the mode of presentation: diuretic-sensitive ascites, diuretic-refractory ascites, variceal hemorrhage, and hepatic encephalopathy. The odds ratio (OR) for mild or moderate hepatitis biopsy findings was 4.94 (p=0.16), the OR for HCV RNA viral load of no more than 3.5x10^5 was 17.8, the OR for HCV RNA viral load of more than 3.5x10^5 and no more than 32x10^5 was 3.24 (p<0.001), and the OR for genotype 3a was 29.7 and for genotype not 1b or 3a was 8.20 (p<0.001). Whilst the review suggested a risk of hospitalisation of 4.7% (95%CI: 0 - 17.1%), the authors, in order to bias the review toward liver biopsy, adopted a value of 0.3% as the risk of complications. A mortality risk of 0.018% or 18 deaths per 100,000 liver biopsies was found. The proportion of the population who would be treated varied between 0% and 100%. The sustained response to interferon would range from 7.9% for empirical treatment of all patients to 23% for highly selective pre-treatment strategies.

The probability of sustained response among all patients varied between 0% and 7.9%, and among patients treated varied between 0% and 23.3%. More selective strategies have a lower number of patients needed to treat with interferon to achieve 1 sustained response. In general, this number ranged from 4.5 to 12.6. But these selective strategies also withhold treatment from 36% to 85% of patients who could have had a sustained response if treated. This number of patients ranged from 0% to 100%. The model estimated that treatment of all patients with CHC would reduce their lifetime incidence of cirrhosis from 66% to 60%, of decompensated cirrhosis from 46% to 43%, of hepatocellular carcinoma from 18% to 17%, and of liver transplantation from 6.3% to 5.9%. It also estimated that
40-year-old patients with mild or moderate CHC, or compensated cirrhosis should have life expectancies without (with) treatment of 33.5 (33.9), 26.4 (27.5), and 18.8 (19) years respectively, compared with a normal life expectancy of 37.6 years. Among sustained responders, interferon would increase average life expectancy by 4 to 11 years. Nearly all strategies involving testing should increase life expectancy by 9 months compared with conservative management.

Methods used to derive estimates of effectiveness
An expert panel of senior hepatologists familiar with liver disease and interferon therapy assessed their own utilities for being in each health state using the standard reference gamble and the time trade-off technique.

Estimates of effectiveness and key assumptions
The quality-of-life adjustments based on the expert panel assessments ranged from 0.52 to 0.98.

Measure of benefits used in the economic analysis
The measure of benefits was life expectancy and quality adjusted life years (QALYs). Health state utilities were assessed by an expert panel of senior hepatologists using the standard reference gamble and the time trade-off technique. A Markov simulation was used to estimate prognosis by following identical cohorts over time for each strategy.

Direct costs
1995 costs or adjusted charges were used. Taking a societal perspective, the authors used previously published variable cost estimates for actual CHC patients, including inpatient, outpatient, and drug costs for each state of health. Future expenditures were discounted at 5% and 3%. Quantities and costs were not reported separately. Although the authors reported that they adopted a societal perspective, the quantity/cost boundary adopted was, rather, that of the health service. The price year was 1995, but the cost data were retrieved from a study published in 1997.

Statistical analysis of costs
Not reported.

Indirect Costs
No indirect costs were included.

Currency
US dollars ($).

Sensitivity analysis
The authors varied the likelihoods of different histologies, viral loads, and genotypes for a 40-year-old. The assumptions regarding the likelihood of histological progression, of sustained response, the distribution of genotypes, the duration of interferon treatment and the quality of life values were altered.

Estimated benefits used in the economic analysis
Life expectancy and QALYs were estimated to be:

- conservative management, 25.9 years and 21.2 QALYs;
- quantitative HCV RNA testing for those patients with a level of viremia <= 3.5x10^5, 26.4 years and 21.8 QALYs;
quantitative HCV RNA testing for those patients with a level of viremia <=32x10^5, 26.7 years and 22.1 QALYs;
empirical interferon treatment, 26.7 years and 22.2 QALYs.

Cost results
Lifetime discounted costs at 5% for the above pre-treatment strategies amounted to $12,490, $12,530, $12,840 and $13,160.

Synthesis of costs and benefits
Using conservative management as the comparator, quantitative HCV RNA testing for those patients with a level of viremia less than 3.5x10^5 and less than or equal to 32x10^5 genomes per ml, and empirical interferon treatment yielded an incremental cost-effectiveness ratio of $300, $4,400 and $12,400 per discounted QALY gained, respectively. All other strategies were dominated. During the sensitivity analysis, the marginal cost-effectiveness ratio of interferon treatment remained under the $50,000 per discounted QALY gained mark. When the authors examined 12 months of therapy, the marginal cost-effectiveness ratio of the empirical treatment fell to $4,300 per discounted QALY gained.

Authors’ conclusions
Routine liver biopsy before treatment with interferon increases the cost of managing patients with CHC without improving health outcomes. Using quantitative HCV RNA testing to guide therapy misses some potential sustained responders. Empirical interferon treatment has a marginal cost-effectiveness ratio that is within the bounds of other commonly accepted therapies.

CRD COMMENTARY - Selection of comparators
The rationale for the choice of the comparator is clear.

Validity of estimate of measure of benefit
The measure of benefit would appear to be valid. However, patients may assess the process and outcome utility differently than physicians. The utility results may also depend on the method used to elicit them. The authors acknowledged that their utility values bias the analysis against the empirical interferon treatment.

Validity of estimate of costs
The authors could have tried to include indirect costs and time costs in the analysis. It is difficult to assess to what extent these cost figures are generalisable to other settings.

Other issues
A comprehensive sensitivity analysis was undertaken in an attempt to examine the robustness of the results. More details could have been provided on how the literature search was conducted. Overall, a very detailed study.

Implications of the study
Empirical interferon treatment has a marginal cost-effectiveness ratio within the bounds of other commonly accepted therapies and misses none of the sustained responders.

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Other publications of related interest


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