Watchful waiting with periodic liver biopsy versus immediate empirical therapy for histologically mild chronic hepatitis C: a cost-effectiveness analysis

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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 use of immediate antiviral combination therapy (IACT) of ribavirin and interferon for the treatment of patients with histologically mild chronic hepatitis who may progress to cirrhosis, was examined.

Type of intervention
Treatment.

Economic study type
Cost-utility analysis.

Study population
The study population comprised patients with chronic hepatitis C, elevated levels of serum aminotransferase, known genotype, and histologically mild liver inflammation.

Setting
The settings may have been secondary and/or tertiary care. The study appears to have been performed in Boston, USA.

Dates to which data relate
The effectiveness data were collected from studies published between 1985 and 1998. The cost data were collected from studies published between 1995 and 1999. The price year was 1998.

Source of effectiveness data
The effectiveness data were derived from published studies, some authors’ assumptions and data obtained from an expert panel, which had been published.

Modelling
A Markov simulation model was used to model the effectiveness and costs of the interventions, considering a lifetime horizon. The cycle length was one year.

Outcomes assessed in the review
The outcomes assessed in the review were mainly epidemiological data relating to the incidence and risks associated with histologically mild chronic hepatitis C patient. For example, mild and moderate hepatitis, cirrhosis and ascites. Only the transition probabilities between health states that related to the use of combination therapy were reported.
Study designs and other criteria for inclusion in the review
The main studies in the review were two randomised controlled trials (see Other Publications of Related Interest). The other studies were economic evaluations, observational studies and another randomised, multicentre clinical trial.

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
Some of the estimates of effectiveness obtained from the review were compared with those from more recent data, and similarities were found. Moreover, the model was validated by comparing its results with data from other published studies. Consistency in the results was obtained.

Number of primary studies included
At least 16 published studies were included in the review.

Methods of combining primary studies
Survival data were estimated using the pooled results from three large studies, while the response to treatment was estimated using the pooled results from two randomised trials. A multivariate logistic regression was used to pool the results. The methods used to combine the results of the other primary studies were not reported.

Investigation of differences between primary studies
Not reported. However, it may have been necessary to investigate differences between the studies since patients from several primary studies were pooled to obtain some of the effectiveness estimates.

Results of the review
There were several health state transition probabilities but only the probabilities for combination therapy were given in the paper.

Methods used to derive estimates of effectiveness
The authors made assumptions to derive some estimates of effectiveness.

Estimates of effectiveness and key assumptions
The authors assumed the following:

- there was perfect compliance with follow-up and future biopsy;
- biopsies had perfect sensitivity;
- IACT had twice the negative impact on quality of life in comparison with interferon therapy alone;
- mild hepatitis and viraemia did not affect quality of life;
- in the base-case analysis, the health-related quality of life weight for long-term mild chronic hepatitis, moderate chronic
hepatitis and viral positive were 1.

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

The summary measure of benefit used was the quality-adjusted life years (QALYs) gained with the strategies analysed. This measure of benefit was obtained from the Markov model, using utility weights to adjust life expectancies for quality of life. The utilities were derived from an expert panel, the results of which had been published. The QALYs were discounted using a discount rate of 3%. Other results obtained from the model were also reported. For example, the 20-year likelihood of developing cirrhosis and the 20-year likelihood of being treated with antiviral treatment with each of the alternatives evaluated.

**Direct costs**

The resource quantities were not reported separately from the costs. The direct costs considered in the economic analysis were those of the health service. These were for antiviral treatment-associated clinic visits, laboratory testing, adverse events, pregnancy tests, and contraception and abortion costs associated with ribavirin. The direct costs were obtained from the average wholesale costs of the drugs, and published costs and charges (which were adjusted with cost-to-charge ratios). Some cost estimates were derived from an expert panel and from authors' assumptions. Therefore, the costs were estimated on the basis of actual data and a guess. The price year was 1998. Discounting was performed using a 3% discount rate. The lifetime costs per patient were reported, both undiscounted and discounted. The Medical Care component of the Consumer Price Index was used to adjust for inflation.

**Statistical analysis of costs**

No statistical analyses of the costs were performed.

**Indirect Costs**

No indirect costs were reported.

**Currency**

US dollars ($).

**Sensitivity analysis**

One-way sensitivity analyses were performed to assess the robustness of the results when estimates of disease progression, effectiveness of IACT, and assumptions were varied. Clinical sub-groups stratified by age, gender or genotype were also considered. In addition, the discount rate was varied to 5% for both estimated the benefits and costs. Further, the authors stated that a Monte Carlo analysis was performed in which all the parameters were simultaneously varied over probability distributions defined by the 95% confidence interval (CI) or reasonable ranges. The areas of uncertainty investigated were, therefore, variability in the data and analytical methods.

**Estimated benefits used in the economic analysis**

The number of undiscounted QALYs gained was 30.7 with no antiviral treatment, 32.1 with WW+CT-MH, 33.1 with IACT and 30.9 with WW+CT-C. When a 3% discount rate was considered, these values were 19.0 (no treatment), 19.6 (WW+CT-MH), 20.1 (IACT) and 19.1 (WW+CT-C), respectively.

Adverse events appear to have been considered in the adjustments for quality of life.

**Cost results**

The undiscounted lifetime costs per patient were $17,714 with no antiviral treatment, $26,249 with WW+CT-MH, $21,073 with IACT and $33,288 with WW+CT-C. When discounting was performed, these lifetime costs per patient
were $8,237 (no treatment), $14,954 (WW+CT-MH), $15,238 (IACT) and $17,167 (WW+CT-C), respectively.

The costs related to adverse events were included in the economic analysis.

Synthesis of costs and benefits
The estimated benefits and costs were combined by calculating the incremental cost-effectiveness ratios (ICERs). These measured the additional cost per additional discounted QALY gained with IACT, WW+CT-MH and WW+CT-C in comparison with no antiviral treatment. The results indicated that IACT had extended dominance over WW+CT-MH (IACT was more effective than WW+CT-MH and its average cost per unit of effectiveness was lower than WW+CT-MH) and WW+CT-C, with an ICER of $7,000 per additional discounted QALY gained. If IACT were not an option, the most cost-effective strategy would be WW+CT-MH, with an ICER of $10,700 per QALY gained in comparison with no antiviral treatment.

One-way sensitivity analyses showed that the results did not change considerably when the parameters were modified. Sub-group analyses showed that higher benefits were obtained among younger patients, female patients and patients having genotype 2 or 3. The Monte Carlo analysis showed that IACT dominated WW+CT in 99.6% of the iterations, it was cost-saving in 37.5% of cases, and its ICER never exceeded $100,000 per discounted QALY gained.

Authors' conclusions
Compared with watchful waiting plus combination therapy (WW+CT), immediate antiviral combination therapy (IACT) may be cost-effective for patients with histologically mild hepatitis since it may increase survival and reduce the costs.

CRD COMMENTARY - Selection of comparators
A justification was given for the chosen comparators. WW+CT strategies were the suggested strategies for treating patients with histologically mild hepatitis. The choice of no antiviral treatment as another comparator allowed the active value of IACT to be evaluated. You must decide whether these are widely used health technologies in your own setting.

Validity of estimate of measure of effectiveness
The authors did not state that a systematic review of the literature had been undertaken. Some effectiveness estimates were derived from pooling the results of several studies and applying multivariate logistic regression. The differences between the primary studies were not analysed, although they would have been relevant. The authors also made some assumptions to derive the estimates of effectiveness. These assumptions were conservative and were justified with reference to the medical literature. The model was validated by comparing its results with the results from other studies. The parameters and assumptions were modified in the sensitivity analyses, showing that the effectiveness results obtained were quite robust.

Validity of estimate of measure of benefit
The estimation of benefits was modelled. A Markov model simulation was used to derive the number of QALYs gained (the summary measure of benefit), which appears to have been an appropriate instrument. This summary measure of benefit was appropriate since it allowed the cost-effectiveness results to be compared with those from other different interventions.

Validity of estimate of costs
The authors stated that a societal perspective was adopted, assuming that adjustments in quality of life account for the indirect costs. However, a health service perspective is more likely to have been adopted, as the authors did not report any estimation of productivity losses associated with histologically mild hepatitis and the alternative follow-up strategies considered at analysis. The fact that the resource quantities were not reported separately from the costs hinder reflation exercises to other settings. Adjustments for inflation were made and discounting was performed appropriately. The
price year was reported.

**Other issues**
The authors commented that the estimates of benefits obtained in this study were higher than those obtained by other studies. This introduces uncertainty into the reliability of the conclusions since this study may overestimate quality of life associated with histologically mild chronic hepatitis. The issue of the generalisability of the results was not addressed.

**Implications of the study**
The authors highlighted the lack of long-term randomised clinical trials demonstrating the benefits associated with sustained loss of viraemia in terms of increased survival and decreased liver complications. Moreover, they stated that further research is needed to find an inexpensive, noninvasive method to assess the extent of liver fibrosis and to identify patients that are likely to experience liver disease.

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**Other publications of related interest**


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