Economic evaluation for hepatitis C

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Abstract

This paper describes the methods used in economic evaluation and illustrates the challenges of assessing the cost-effectiveness of new interventions in Hepatitis C (HCV), where the impact of interventions needs to be assessed over the patient's lifetime.

This paper provides an example of an economic evaluation in HCV using a model estimating the cost-effectiveness of combination therapy (CMB) for patients with mild HCV. The preliminary results from the model suggested that for 1000 cases with mild disease CMB lead to 55 fewer deaths from liver disease compared to no treatment, an average gain of 1.2 life years. Although CMB lead to additional costs of 14,882 EURO's, the cost-effectiveness ratio was 8,490 EURO's per Quality Adjusted Life Year (QALY), which suggests the intervention is relatively cost-effective. The sensitivity analysis showed that the cost-effectiveness ratio was sensitive to the effectiveness of the intervention, and the progression rates between mild disease and cirrhosis.

A large UK study is collecting data on the effectiveness of CMB for patients with mild disease, and the costs and quality of life for patients at different stages of HCV. These data will be used to improve the projections of the model. In general, economic evaluations can provide information to help decide where priorities lie both in HCV, and other disease areas. (Acta gastroenterol. belg., **2002**, 65, **104-109**).

Key words : economic evaluation, cost and cost analysis, hepatitis C.

Introduction

Economic assessments of Hepatitis C (HCV) are required to provide information for decision-makers on the costs and consequences of different strategies to prevent and treat the disease. In this paper we briefly discuss the alternative forms of economic evaluation, the difficulties encountered in any economic assessment of HCV, then go on to outline a model to assess the cost-effectiveness of interventions for mild HCV and finally present a critique of the methodology used.

What is economic evaluation ?

Economic evaluation is a technique that has been developed to aid the process of efficient allocation of resources amongst alternative projects. All forms of economic evaluation require the comparisons of the costs and outcomes associated with two or more alternative programmes or interventions (1). Cost-benefit analysis (CBA) is the broadest form of economic evaluation and has the potential to compare the value for money of investment in public sector projects in different areas such as transport, health or education. CBA requires the benefits from projects to be valued in monetary units. Projects should then only be funded if the benefits are found to exceed the costs. In health care the difficulty of valuing benefits in CBA, have hindered its use (2).

A more popular approach to comparing projects in the health sector is cost-effectiveness analysis (CEA). In CEA outcomes from various interventions are usually measured in one-dimensional units such as life years gained. The costs of providing the alternative interventions are then compared in terms of their cost per unit of effect. One problem with this form of evaluation is that it ignores the relative effect of the interventions concerned on other dimensions of patients' health status, for example if the life year is the outcome measure only interventions which have an impact on mortality will be deemed worthwhile. One form of CEA, which aims to tackle this problem, is cost-utility analysis (CUA). Under CUA, the outcome measure used aims to capture the effect of various interventions on mortality and health related quality of life (HRQOL). The most common outcome measure used is the Quality Adjusted Life Year (QALY). In a CUA decision-makers are then presented with information on the cost per QALY of various interventions, with the suggestion that priority should be given to interventions with lower cost per QALY. However, difficulties are inherent in making comparisons of this nature, for example studies may differ in the range of costs included in the analysis, or different methods may be used to measure HRQOL, either will hinder the comparability of results.

Sometimes health planners wish to know just how many resources are absorbed by a disease : the burden of illness, so that they may make provision for treatment. Burden of illness studies do not attempt to assess the efficiency of an intervention (1). They may be used to ascertain how much the disease will cost over the lifetime of those now affected or the annual amount that is required to control and treat the disease at any point in time.

Economic evaluation for HCV

Attempts to conduct economic assessments in HCV pose a particular challenge as cases progress through a number of disease stages over a long time period. Attempts to evaluate interventions to prevent or interrupt progression or transmission of the disease involve

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estimation of the impact of the intervention at all stages of the disease. It is also necessary to take into account differential progression rates associated with different risk factors : co-morbidities, HIV or haemophilia, or life style attributes such as drug or alcohol abuse.

The use of data from randomised controlled trials does not resolve these difficulties of estimation as prospective studies cannot be sustained logistically or financially for the full course of the illness. In addition decision-makers require information on the costs and effects of new interventions sooner rather than later. Retrospective studies are affected by incomplete records, changes in diagnostic and treatment regimes, and staging classifications.

To tackle these problems decision-analytic models have been developed which synthesise information on the effectiveness of the intervention, natural history of the disease and long-term costs of treatment (3). These models have the potential to provide timely estimates to decision-makers of the relative costs and effectiveness of interventions. These techniques are especially useful in HCV, where estimates are needed of the impact of new anti-viral therapies over the patients' lifetime. To estimate the lifetime costs and consequences of therapies for hepatitis C, economic models need to extrapolate from trial results using the best available epidemiological data.

An early model for economic assessment in HCV was developed by G. Dusheiko and J. Roberts (1995) (4). Here the costs and outcomes of 1000 hypothetical chronic HCV cases treated with interferon alpha were compared to an untreated cohort. These hypothetical cohorts were processed through a Markov model, which divided the natural history of the disease into a series of health states. The probability of moving between the health states was taken from the literature, which at that time meant that progression rates for Hepatitis B were applied to HCV. Costs were based upon estimates of best practice. The model predicted that alpha interferon would save between 13 and 22 lives from the 1000 patient cohort. The discounted costs per life year saved ranged from £ 2,142 (3384 EURO's) to £ 17,128 (27,062 EURO's).

Several studies have assessed the cost-effectiveness of anti-viral therapies for patients with chronic HCV subsequently. The general conclusion from these studies was that anti-viral therapy was relatively cost-effective for cases with chronic HCV (5-9). In the UK recent recommendations have been made for the use of a combination of interferon and ribavirin for treating patients with HCV (5).

Aim of this paper

An outstanding issue is whether anti-viral therapy is effective and cost-effective for patients with mild HCV. In the UK, the NHS Health Technology Assessment (HTA) programme has commissioned a study, which aims to examine whether a combination of alpha interferon and ribavarin (CMB) is cost-effective for patients with mild HCV. The following sections present the decision-analytical model and early results from this study.

Methods and materials

The model structure was developed from the model previously outlined in Dusheiko and Roberts (1995) (4). However, certain changes to the original structure were undertaken to take account of the aim of this model, which was to evaluate anti-viral therapy for patients with mild rather than chronic HCV. Also a separate sub-stage was included for hepatocellular carcinoma (HCC). The structure of the model is illustrated in Figure 1. A literature review was undertaken to find the best available estimates of disease progression rates for patients with HCV. Although there appeared to be a general consensus in the literature about the transition probabilities between later disease states, such as cirrhosis and decompensated cirrhosis, there was much less agreement about the rate of progression between mild and moderate disease. The transition probabilities, which were felt to be most appropriate to the HCV population in the UK, were included in this version of the model, and are listed together with their sources in Table 1. The mortality rates for patients with decompensated cirrhosis, HCC, or following liver transplantation were also taken from published studies. The mortality rates in preceding health states were assumed to be the same as for the general population, and are taken from UK government official statistics (12).

As part of the UK HTA study, a large multi-centre RCT is being undertaken to assess the effectiveness of CMB for patients with mild HCV. Until the results from this study are available, the model uses data from trials on the effectiveness of CMB for cases with moderate HCV. In the baseline analysis of the model, CMB is assumed to be as effective for patients with mild disease

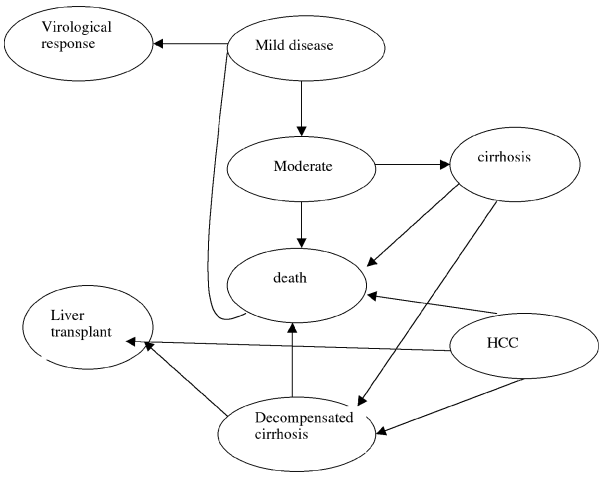

Fig. 1. — Markov model for HCV

Table 1. — Disease progression rates used in the model

Annual Transition probability	Value used in base-case	source
Mild-moderate HCV	0.06	Shepherd et al (2000) [5]
Moderate HCV-cirrhosis	0.06	Shepherd et al (2000) [5]
Cirrhosis-decompensated cirrhosis	0.04	Fattovitch et al (1997) [10]
Decompensated cirrhosis-HCC	0.01	Fattovitch et al (1997) [5]
Decompensated cirrhosis-liver transplant	0.03	Bennett et al (1997) [11]

as for those with moderate disease. In the mild HCV trial the ratio of cases with genotype 1 : genotype non-1 is 50:50. This ratio was used to extrapolate the results from the Poynard et al trial, which meant that 43% of cases were expected to have a sustained virological response (SVR) to therapy (11).

In our model we assumed that all cases were treated if they progressed to moderate disease or cirrhosis as recommended by UK guidelines. So, the economic assessment was addressing the question of whether cases should be treated early, while they have mild disease, rather than later when they have moderate disease or cirrhosis ([1]).

In this version of the model costs were taken from the literature (Table 2). The costs used in this analysis take a health service perspective so costs falling on social services, the patient and their carer are excluded from the analysis. None of the studies used for the costing collected detailed data on the specific resources and costs of managing cases at different stages of HCV. Instead, the use of resources was usually based on expert opinion of what was involved in providing care.

Measures of health related quality of life (HRQOL) were included for each of the health states included in the model. The values used were taken from the literature. These estimates were derived by asking health care professionals to state the utility associated with being in the health states of interest.

The incremental cost-effectiveness ratio (ICER) was calculated for CMB compared to no treatment, where :

$$ICER = \frac{\text{total cost treatment cohort} - \text{total cost no treatment cohort}}{\text{outcome treatment cohort} - \text{outcome no treatment cohort}}$$

In this example, the outcome measures used are life years and Quality Adjusted Life Years (QALYs). So the ICER is expressed in terms of costs per life year and costs per QALY for CMB compared to no treatment.

All costs were discounted at 6% and outcomes at 1.5% as recommended by recent guidelines from the UK Department of Health (14). All costs were converted from UK pounds into EURO's using official exchange rates (£ = 1.58 EURO's).

Sensitivity analyses were run to examine the impact of changing assumptions on the progression rates, and effectiveness of the intervention on the estimated cost-effectiveness of the intervention.

Results

The base case results are presented for a 40-year-old patient entering the model with mild HCV. The results compare the effect of treatment versus no treatment at the mild stage, on costs and outcomes over the cohorts' lifetime. The model predicted that on average the intervention will mean 55 fewer deaths from liver disease for 1000 cases, which will lead to an average gain of 1.2 life years (Table 3). Apart from the reduction in mortality, CMB also reduced morbidity, by preventing disease progression. So fewer life years were spent in disease states such as cirrhosis or decompensated cirrhosis, where quality of life is lower. The QALYs following treatment were therefore higher than following no treatment (28.2 compared to 26.4).

The average total lifetime costs for mild HCV were higher following treatment (33,228 EURO's) compared to no treatment for cases with HCV (18,346 EURO's) (Fig. 1). This is mainly because of the high treatment and monitoring costs associated with anti-viral therapy for mild HCV (21,534 EURO's). The costs associated with the intervention were partly offset by the lower costs of subsequent disease stages. For example if CMB is given to patients with mild disease fewer patients progress to moderate HCV or cirrhosis where they will require further treatment and monitoring. Nevertheless the average incremental lifetime costs of treatment for mild HCV with CMB were 14,882 EURO's.

The incremental cost-effectiveness ratio for the base case, was 12,089 EURO's per life year or 8,490 EURO's per QALY. The sensitivity analysis looked at the impact of changing various parameters on the cost per QALY. The analysis showed that the cost-effectiveness ratio varied widely according to certain parameters. For

(1) This means that when we refer to the no treatment cohort, it refers to patients who have no treatment as mild cases, they will go on subsequently to have treatment if they progress to moderate disease or cirrhosis.

Table 2. — **Costs and quality of life values used in the model**

Parameter	Value	source
Costs (EURO's)		
4 weeks alpha interferon	1,024	BNF (2001) [13]
4 weeks ribavirin	859	BNF (2001) [13]
Annual cost managing chronic HCV	454	Shepherd et al (2000) [5]
Annual cost managing cirrhosis	853	Shepherd et al (2000) [5]
Annual cost managing decompensated cirrhosis (1995) [4]	2,455	Duscheiko and Rober
Cost of transplant operation (1995) [4]	40,955	Duscheiko and Rober
Annual cost of managing HCC	21,046	Shepherd et al (2000) [5]
Utilities (0= dead, 1= perfect health)		
Following SVR to anti-viral therapy	1.00	Stein et al (2002) [8]
Mild HCV	0.98	Stein et al (2002) [8]
Moderate HCV	0.92	Stein et al (2002) [8]
Cirrhosis	0.82	Stein et al (2002) [8]
Decompensated cirrhosis	0.50	Kim et al (1998) [9]
HCC	0.25	Kim et al (1998) [9]

Table 3. — **The effect of CMB on outcomes for patients with mild HCV**

Health state CMB for mild	Treatment with treatment for mild HCV	No antiviral treatment HCV	Treatment-No
Total Liver deaths (for 1000 cases)	97	162	-55
Average life years	28.9	27.6	1.2
Without infection	17.0	7.7[1]	9.0
With chronic HCV	10.0	17.3	-7.3
Cirrhosis	1.5	2.5	-0.9
With decompensated cirrhosis	0.3	0.5	-0.2
Average QALYs	28.2	26.4	1.8

[1] Some cases in the no treatment group go onto have a response to treatment once they reach moderate disease or cirrhosis

example, for cases with genotype 1, the intervention was much less effective than for cases with genotype non-1 so the cost-effectiveness ratio was much higher (Table 4). Similarly for those cases who would progress from mild to moderate disease and then to cirrhosis at a fast rate (10% per year) without the intervention, then the cost-effectiveness ratio is more favourable than for those who would progress slowly through the illness. The results were relatively insensitive to changing most other parameters, for example reducing the transplantation rate from the base case estimate of 3% per year, to 1% only caused the cost-effectiveness ratio to fall from 8,490 to 8,397 EURO's per QALY.

Discussion

This study of the cost-effectiveness of interferon and ribavirin (CMB) for patients with mild HCV provides an illustration of how the techniques of economic evaluation can be applied to generate information for decision-makers. These preliminary results suggest that CMB for mild HCV is likely to prove a relatively cost-effective intervention. The projected cost per QALY for cases with mild HCV was 8,490 EURO's. This compares favourably with many other interventions which, are routinely provided. For example in the UK the cost-effectiveness of antiviral therapy for patients with modarate HCV was estimated at 11,850 EURO's, for coronary artery bypass grafts for coronary heart disease the estimated cost-effectiveness ratio has been estimated at 18,960 EURO's. However, before the results from our model are used to recommend that anti-viral treatment should be provided for patients with mild HCV certain concerns about the model need addressing.

Model critique

The model currently extrapolates data on effectiveness for patients with moderate HCV to cases with mild HCV. It may be that patients with mild HCV have lower (or higher) rates of response to antiviral therapy. The cost-effectiveness ratio is very susceptible to changes in the effectiveness of CMB, so until data are available from the mild HCV trial ([2]), the cost-effectiveness results can only be regarded as estimates.

The cost-effectiveness of CMB is also heavily dependent on the transition rates used in the model. In partic-

(2) Recruitment for this trial is now complete, with final results expected in July, 2003.

Table 4. **— Sensitivity analysis**

Scenario	Effectiveness of CNB (% SVR)	Progression rate: mild-moderate-cirrhosis	Cost/QALY (EURO's)
Base case	43	0.06	8,490
Sub group genotype 1	28	0.06	12,999
Sub group genotype non-1	66	0.06	5,969
Slow progression to cirrhosis	43	0.01	14,848
Fast progression to cirrhosis	43	0.10	6,194

ular, the cost-effectiveness ratio varies according to the transition rates that are assumed for moving between mild disease and cirrhosis. There is a lack of consensus in the literature about the rate at which patients move through the early stages of the disease. Studies such as Poynard *et al*. (15), suggest disease progression may vary depending on the characteristics of the patients. Nevertheless this and other studies base estimates of disease progression on cross-sectional data, whereas longitudinal data are required to estimate accurate rates of progression and establish how progression rates change according to disease stage. In the absence of such studies for HCV we have followed general advice on economic modelling in this area and assumed conservative rates of disease progression (16).

As part of the HTA study detailed information is being collected on the resources used, and costs in managing patients at different stages of HCV. A sample of cases at each stage of the disease has been recruited from three hepatology centres in the UK. The resources used at each stage are being recorded from medical records and by administering questionnaires. These data will be used to estimate the costs of mild and moderate disease, cirrhosis and decompensated cirrhosis. This approach provides more accurate costs than those used in previous models that had to rely on expert opinion and administrative databases to estimate disease costs.

Previous work has suggested that even cases with mild HCV may have considerable reductions in HRQOL compared with the general population (17). However, there is a lack of specific evidence on the HRQOL associated with different stages of HCV. In the HTA study standard questionnaires such as the Short Form 36 and the EuroQol 5D will be administered to patients, to derive estimates of the health related quality of life associated with being at different stages of HCV. These empirical estimates will be used to replace the current estimates of HRQOL that are based on expert opinion. Studies suggest that expert opinion is unlikely to represent the patients' own opinion of their quality of life accurately (18).

Finally, whilst in this paper the model was used to illustrate the cost-effectiveness of CMB for cases with mild HCV, the model can be adapted to provide information on the cost-effectiveness of new interventions for treating and preventing HCV. Examples of particular importance would be the evaluation of the cost-effectiveness of Pegylated interferon and ribavirin for treatment of different stages of HCV, and the use of screening and other strategies to prevent HCV.

To conclude, economic evaluations can provide decision-makers with useful information about the relative cost-effectiveness of various health care interventions. In HCV decision analytical models are often used to provide estimates of the cost-effectiveness of interventions, which have an impact over a lifetime. This paper provided an illustration of a model to assess the cost-effectiveness of combination therapy for cases with mild HCV. Although the model's estimates suggested the intervention was relatively cost-effective, the results should be treated with caution.

Further research is ongoing to empirically estimate the costs and quality of life associated with different stages of the disease, to improve the model's estimates. This and other studies can provide useful information for decision-makers on the cost-effectiveness of different strategies for treating and preventing hepatitis C.

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