

LIVER DISEASE

Cost effectiveness of combination therapy for hepatitis C: a decision analytic model

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Objective: To estimate the cost utility of treatment with combination therapy (ribavirin and interferon α) for hepatitis C compared with no treatment or monotherapy (interferon α) based on UK costs and clinical management.

Design: Decision analysis model using a Markov approach to simulate disease progression.

Setting: UK secondary care.

Participants: Hypothetical cohort of patients with hepatitis C.

Main outcome measures: Cost per quality adjusted life year (QALY) gained.

Results: Discounted cost per QALY for combination therapy over no treatment was £3791. Cost per QALY varied between £1646 and £9170 according to subgroup, with the lowest ratios being for genotype 2 or 3, women, those aged less than 40 years, and those with moderate hepatitis. The discounted cost per QALY of the combination over monotherapy was £3485. Similar findings were shown for subgroups as for the comparison with no treatment. One way sensitivity analysis showed that while drug costs were more important in the analysis than assumptions about disease progression or costs of treating hepatitis C disease, the results were robust to large changes in underlying assumptions.

Conclusions: Combination therapy for hepatitis C is a cost effective treatment option and is superior to monotherapy. Considerable uncertainties remain over the appropriate management strategies in the populations excluded from randomised controlled trials and in whom treatment is currently being considered in the UK.

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Hepatitis C (HCV) is an important public health problem, characterised by prevalence, chronicity, and latency. Prevalence estimates vary with the population studied.¹ Prevalence in blood donors may be as low as 0.04%.² A UK community based survey showed seroprevalence of 0.7% in 1994³ and a more recent antenatal clinic based survey showed seroprevalence of 0.8%.⁴ Rates among intravenous drug users may be at least 60%.⁵ Infection persists in the majority of infected cases⁶ with a clinical latency of decades before a wide range of hepatic manifestations of which the most important are cirrhosis and hepatocellular carcinoma.^{6,7} Approximately 30% of those with chronic infection develop cirrhosis within 20 years,⁸ and these are at risk of developing hepatocellular cancer at a rate of 3% per annum.

HCV accounts for 30% of liver transplants in the USA.⁹ Data on HCV related transplants have been collected centrally by the UK Transplant Support Services Authority (UKTSSA) since 1995. In the UK, the number of liver transplants increased from 315 to 632 between 1990 and 1998. HCV related cirrhosis has been recorded as the primary disease leading to transplantation in 11% of transplants since then, with a near doubling in the number of HCV related transplants from 44 to 79 between 1995 and 1998 (UKTSSA, personal communication, September 1999).

Recombinant interferon α (IFN- α) therapy was licensed in the UK for the treatment of HCV infection in 1995. Sustained viral response, defined by viral clearance six months after the end of therapy, is observed in approximately 15% of treated patients but not in untreated patients. Ribavirin was licensed in 1999 for use in combination with IFN- α . Evidence from randomised controlled trials shows that combination therapy results in eradication of virus and normalisation of liver function in 40% of treated subjects, which is 25% more patients than with interferon monotherapy given for 48 weeks.^{10,11} The higher response rates observed with combination therapy are accompanied by increased costs of treatment attributable to ribavirin. Commissioners of health care and clinicians have

expressed considerable interest in the balance between cost and benefit of treatment.

Given the long clinical course of HCV infection, it is not feasible to use randomised controlled trials to investigate the extent to which these intermediate outcomes translate into improvements in survival or quality of life gains in the long run. Furthermore, it is not known whether the short term costs of treatment may be offset by savings on health care budgets, such as that saved by avoidance of liver transplantation. This prompted us to use a decision analysis model¹² to investigate the value of combination therapy in UK practice. The National Institute for Clinical Excellence recently recommended that combination therapy should be offered to patients with moderate to severe HCV on the basis that it is clinically and cost effective (<http://server1.nice.org.uk/nice-web/Article.asp?a=11676>).

We addressed the following questions:

- (1) What is the cost utility of combination therapy for chronic HCV infection in UK patients compared with no treatment?
- (2) What is the cost utility of combination therapy compared with interferon monotherapy in those with chronic HCV infection being treated in the UK?
- (3) Is combination therapy more cost effective than no treatment or monotherapy in certain groups of patients with chronic HCV infection?

METHODS

General approach

We used a Markov model to simulate progression through the various states of ill health involved in progressive HCV disease,

Abbreviations: HCV, hepatitis C virus; QALY, quality adjusted life year; UKTSSA, UK Transplant Support Services Authority; HRG, Healthcare Resource Group; IFN- α , interferon α .

including death (from hepatic and other causes), using DecisionMaker 7.07 (Pratt Medical Group, Boston, USA). In this approach a cohort of hypothetical patients move between specified health states on an annual basis according to probabilities for progression based on best available evidence. For each annual cycle, the model tracks how many patients are in each state so that, given estimates for the quality of life and resource use associated with the health states, the model yields an average lifetime cost utility for each strategy and allows estimation of the marginal cost per quality adjusted life year (QALY) gained. This approach to modelling HCV disease progression performs well when compared with existing cohort data.¹³⁻¹⁵ The model was originally developed by one of us (JW) to investigate aspects of management of HCV disease in a North American setting. In this study we adapted the model for the UK. The analysis is undertaken primarily from the perspective of UK commissioning authorities (primary care groups/trusts and district health authorities). Where possible, information is included that allows a wider societal perspective to be taken.

Parameters used in the analysis

Patient population

At the start of the model, patients are in one of several states of compensated chronic HCV infection defined by sustained abnormal liver function and histological status. These states also summarise the populations studied in the two clinical trials of combination and monotherapy.^{10, 11} Three variables have been consistently identified as predicting improved sustained response to antiviral therapy¹⁶⁻²² and these are considered when calculating the cost effectiveness of targeted treatment strategies: histological type (mild hepatitis, moderate hepatitis, or cirrhosis); level of viraemia; and viral genotype (1 and 4, or other).

Following the inclusion criteria of the clinical trials of interferon (alone or in combination), and current practice in the UK, the model does not consider treatment in patients with persistent chaotic intravenous drug use, excessive alcohol consumption, psychiatric disorders including depression, ischaemic heart disease, severe respiratory disease, or diabetic retinopathy.

Natural history

The model has been described in more detail previously.¹³ For progression of non-compensated disease, we used pooled estimates from three retrospective observational studies of non-A non-B hepatitis in which subsequent serology showed HCV as the causative agent,²³⁻²⁵ and a published cohort study of compensated cirrhosis.¹⁴ Prognosis following decompensation varies according to the predominant clinical feature at presentation—that is, ascites (diuretic sensitive or refractory), variceal haemorrhage, and hepatic encephalopathy.²⁶⁻²⁸ We assumed that recovery from decompensated to compensated states would only occur in the event of transplantation. Risk of development of hepatocellular carcinoma was estimated as 1–3% per year in patients with cirrhosis.^{14, 29, 30} Probability of death from other causes was calculated from UK age specific tables.

Transplantation

It is difficult to estimate the transplantation rate in the UK population. In England and Wales in 1998, there were 632 liver transplantations (UKTSSA, personal communication, September 1999). This gives an overall population rate for transplantation of 12 per million, which is 80% of that in the USA where the annual probability for transplantation in the eligible HCV infected population is 3.1%. We therefore estimated the annual UK transplantation probability as 2.5% (80% of 3.1%).

Antiviral treatment

Response rates were based on the results of combined US and international trials of interferon and ribavirin combination therapy.^{10, 11} Individual patient data were combined to examine response rates in several subgroups.

- Genotype 1 versus genotype 2 or 3; 50% of UK HCV sufferers have genotype 1.
- Viral load, defined as (a) >2 million copies/ml or (b) ≤2 million copies/ml.
- Sex.
- Histological grade: mild or moderate hepatitis.
- Age: 40 years and under; 41–50 years; and over 50 years of age.

As a bias against therapy, we assumed that a few treatment responders could experience ongoing progression after sustained viral clearance,³¹ despite the observation of regression of fibrosis following response to interferon monotherapy.³²

Treatment duration was 24 weeks for genotype 2 or 3, and 48 weeks otherwise. If the patient remained viral positive, we assumed monotherapy would be stopped at 12 weeks and combination therapy would be stopped at 24 weeks. Where response was shown at these points, it was assumed treatment would continue for 12 months except in the subgroup of genotype 2 or 3 where treatment would be limited to 24 weeks. We calculated average costs of treatment for the treated cohorts based on these stopping rules.

Drug costs were calculated on a per diem basis with prices taken from the *British National Formulary*.³³ Drug dosage is related to weight. Based on the experience of the randomised controlled trials of combination therapy, dosage was as received in the combined trials. In a European population, this likely overestimates the dose because US patients were heavier.

Resource use and valuation

Resource use is based on typical UK management of HCV disease in each of the health states concerned (see table 1). Management patterns were determined using a questionnaire survey of nine UK liver units, including five transplant centres. Net ingredient costs for drug treatments are from the *British National Formulary*, March 1999.³³ Cost of transplantation was estimated from the average contract price of liver transplantation in the UK for 1997/8.³⁴ This includes costs for transplantation and follow up. Costs have been estimated for 1998/9 using, where appropriate, the Hospital and Community Health Services Index to adjust values.³⁵

Cost estimates for procedures and diagnostic tests (at 1998 prices) were provided by the costings units at Ninewells Hospital, Dundee (Dr D Carson, personal communication, September 1999), from a small purposive sample of NHS trust financial managers surveyed in September 1999 (listed at the end of the paper) and by reference to published tariffs from hospitals in the South and West regions of the UK.³⁶ Unit costs of items associated with drug treatment and outpatient management of HCV disease are shown in table 2. Costs of inpatient admissions for complications of chronic HCV infection were taken from NHS Healthcare Resource Group (HRG) reference costs. HRGs used in relation to health states involved are shown in table 3. HRGs include all hotel and treatment costs associated with admission, including drugs and investigations. However, as combination therapy was not a standard part of management at the time HRG costs were estimated by trusts, we have assumed that HRGs exclude this element.

Utility of health states

We used the utility values obtained by Wong *et al* from American hepatologists using the standard gamble and time trade off techniques in their study of pretreatment evaluation strategies in HCV disease³¹ to weight the time spent in each health state for quality of life (see table 4). These values were checked with UK hepatologists.

Table 1 Assumptions regarding resource use in health states considered in the model and management on combination therapy

Health state	Assumptions
Mild hepatitis	Annual outpatient review with LFT, FBC, U&E, clotting studies, urinalysis. Liver biopsy at initial staging only.
Moderate hepatitis	Six monthly or annual review with LFT, FBC, U&E, clotting studies, urinalysis. Liver biopsy at initial staging only.
Compensated cirrhosis	Three monthly outpatient review with LFT, FBC, U&E, clotting studies, urinalysis. Liver biopsy at 5 year intervals if not on treatment. Six monthly screening for hepatocellular carcinoma using AFP and ultrasound.
Decompensated cirrhosis	Six monthly screening for hepatocellular carcinoma using AFP and ultrasound. For specific health state we assumed the following, based on US information, verified as being appropriate by UK hepatologists: <ul style="list-style-type: none"> • Ascites sensitive to diuretics: 2.3 admissions per year • Variceal haemorrhage: 2.3 admissions in the first year and 0.033 thereafter • Hepatic encephalopathy: 2.3 admissions in the first year and 0.033 thereafter
Hepatocellular cancer	We assumed there would be two admissions for palliative care in the year after diagnosis, based on the local experience of one of us (WR).
Post liver transplantation	We assumed there would be 2.4 admissions in the first year after transplantation and thereafter 0.7 admissions per year and an ongoing 5% annual probability of further transplantation, based on US practice and supported by UK hepatological opinion
Management on combination therapy	We based management practice on reports from our survey of nine specialist hepatology centres and local data from one of us (WR). Baseline tests: FBC, U&E, clotting studies, LFT, HCG (females), urinalysis, AIS, USS, TFT. Psychiatric assessment in 2% of cases, fundal photography in 3.5%, ultrasound scan in 7.5%, pulmonary function tests in 2%. Thyroid function tests at initiation of therapy and then three monthly during treatment. Liver biopsy following treatment in 68%

AFP, α fetoprotein; LFT, liver function tests; FBC, full blood count; U&E, urea and electrolytes; HCG, human chorionic gonadotrophin; AIS, autoimmune screen; USS, ultrasound scan; TFT, thyroid function tests.

Table 2 Unit costs of items associated with drug treatment of HCV or outpatient management of hepatic complications

Variable	Cost (£)	Source and notes
Liver transplant	46 289	National Specialist Commissioning Advisory Group
Routine pathology testing (LFT, FBC, U&E, clotting, urinalysis)	25.09	Ninewells Hospital costings unit
Thyroid function test	8.00	Ninewells Hospital costings unit
Serum HCG	9.80	Ninewells Hospital costings unit
Liver ultrasound	29.72	Average of estimates from survey of small sample of NHS trusts undertaken for this study
Chest x ray	13.86	Average of estimates from survey of small sample of NHS trusts undertaken for this study
Liver biopsy	449.00	ECR cost for investigation of HCV disease (Southampton University Hospitals Trust)
Outpatient attendance	81.00	ECR cost of outpatient attendance for HCV disease (Southampton University Hospitals Trust)
Psychiatric assessment	97.57	From 1998 national pay scales (assuming 50% client contact time and one hour for assessment).
Treatment costs		
IFN- α per mU	5.40	Schering Plough
Ribavirin, per pill	3.53	
Fundal photography	20.00	University of Bristol Hospitals Trust (the only trust in the survey able to make an estimate)
Inpatient palliative care	2544	ECR price for admission to palliative care (medium complexity case) at Southampton University Hospitals Trust

HCV, hepatitis C virus; IFN- α , interferon α ; LFT, liver function tests; FBC, full blood count; U&E, urea and electrolytes; HCG, human chorionic gonadotrophin; ECR, extracontractual referral.

Sensitivity analysis

We carried out one way sensitivity analyses to investigate the effect on the model of varying key cost and disease progression parameters by 50% upwards and downwards. Costs and benefits were discounted at 6%.

RESULTS

Main analysis

The results of the main analysis are shown in table 5. Average cost of drug treatment per patient was £2738 for interferon monotherapy and £7014 for combination therapy.

Subgroup analyses

The results of the subgroup analyses are shown in table 6. We present only the results with benefits and costs discounted at 6%. These therefore represent the highest estimates of cost effectiveness to current commissioners.

Sensitivity analyses

The results of sensitivity analyses are shown in table 7. The conclusions of the main analysis are not markedly sensitive to variation in key parameters, although drug cost appears to be

Table 3 Healthcare resource groups (HRGs) used to estimate inpatient resource use and costs

Health state	HRG	Cost (£)	Notes
Chronic hepatitis	G07	1406.00	Non-elective cost (accounting for 89% of activity)
Hepatocellular carcinoma	G07	1406.00	
Compensated cirrhosis	G07	1406.00	
Ascites	G07	1406.00	
Refractory ascites	G07	1406.00	
Variceal bleeding	F64	800.41	Average of elective and non-elective costs
Hepatic encephalopathy	G07	1406.00	

Table 4 Quality of life weights applied to health states

Health state	Quality of life weight (on scale 0–1)
Seropositive for HCV	0.95
Mild chronic hepatitis	0.98
Moderate chronic hepatitis	0.92
Compensated cirrhosis	0.82
Diuretic sensitive ascites	0.75
Diuretic resistant ascites	0.52
Hepatic encephalopathy	0.53
Variceal haemorrhage	0.55
Hepatocellular carcinoma	0.55

HCV, hepatitis C virus.

monotherapy, our results suggest that changing to combination therapy is cost effective in most groups, with cost per QALY below £5000. The results do not appear to be sensitive to major changes in assumptions regarding key parameters although drug costs emerge as the most important source of variation in the sensitivity analyses.

A number of limitations in our study should be acknowledged. Cost estimates are inevitably imprecise, being based on reports from a small number of trusts or on reported costs for HRGs. In the absence of sound bottom up costings of the consequences of HCV disease, this is difficult to remedy although the sensitivity analysis demonstrates that the findings of our analysis are insensitive to 50% upward and downward variation in cost assumptions. HRGs were used to estimate inpatient costs and there are likely to be variations in what has

Table 5 Results: main analyses

Strategy	QALY	Lifetime cost (£)	Marginal cost (£)	Marginal effectiveness (QALY)	Marginal cost effectiveness (£/QALY)	Discounted marginal cost effectiveness @ 6% (£/QALY)
Combination therapy v no treatment						
No treatment	22.8	13 729				
Combination therapy	27.6	14 456	523.47	4.82	151	3791
Combination therapy v monotherapy						
Monotherapy	24.7	14 363				
Combination therapy	27.6	14 456	93.93	2.95	32	3485

QALY, quality adjusted life year.

a more important determinant of cost effectiveness than assumptions about costs of treatment or disease progression.

DISCUSSION

Our results suggest that interferon and ribavirin are quite cost effective. Without considering the timing of costs and benefits, the additional cost of combination therapy is almost completely offset by future savings. Because the benefits are delayed, discounting is important. Although the appropriate rate is contentious, using a discount rate of 6% for both costs and benefits, we showed that combination therapy was likely to produce an additional QALY for less than £3000. This is considered by some as below a decision threshold for obtaining strong support from NHS commissioners.³⁷ In some groups of patients combination therapy appears to be more cost effective, with discounted cost effectiveness below £1000 per QALY. Our results show that even in groups least likely to respond, the cost effectiveness of combination over monotherapy falls below £10 000. Compared with accepted

been included in these costs. For example, inclusion of terlipressin or octreotide in the management of varices in HRG costs (which we believe is unlikely) would bias our results against therapy for HCV as these elements are costed separately. Our survey of hepatologists revealed a move towards nurse led clinics for the management of patients on combination therapy. This will reduce the outpatient management costs of treatment although such changes are very unlikely to be captured in standard NHS accounting practices, further emphasising the importance of better costing studies.

We have assumed that viral clearance is lifelong for almost all patients and that life expectancy is nearly normal. However, with reduction in HCV spread through blood transfusions, the proportion of the seroprevalent population made up of intravenous drug users is likely to increase. Reinfection of those treated because of recurrent injection drug use may be a significant problem, and resumed drug use would also reduce their life expectancy. These factors suggest that our

Table 6 Results: subgroup analyses

Subgroup	Combination therapy v no treatment			Combination therapy v monotherapy		
	Marginal cost (£)	Marginal effectiveness (QALY)	Marginal cost effectiveness (£/QALY)	Marginal cost (£)	Marginal effectiveness (QALY)	Marginal cost effectiveness (£/QALY)
Men	4701	1.11	4247	2603	0.76	3429
Women	4289	1.47	2913	2556	0.73	3514
Genotype 1	6330	0.69	9170	4327	0.50	8626
Genotype 2 or 3	2848	1.73	1646	861	0.99	872
Age 40 y or less	4398	1.50	2942	2511	0.79	3197
Age 41–50 y	4868	1.00	4855	2722	0.73	3705
Age over 50 y	4873	0.76	6402	2901	0.58	5016
Viral load >2 million counts	4796	1.12	4299	2772	0.75	3676
Viral load ≤2 million counts	4620	1.27	3627	2688	0.56	4792
Mild hepatitis	5507	0.80	6925	3083	0.52	5900
Moderate hepatitis	4161	1.44	2897	2356	0.86	2735

QALY, quality adjusted life year.

Table 7 Results: sensitivity analyses

Sensitivity analysis	Combination therapy v no treatment			Combination therapy v monotherapy		
	Marginal cost (£)	Marginal effectiveness (QALY)	Marginal cost effectiveness (£/QALY)	Marginal cost (£)	Marginal effectiveness (QALY)	Marginal cost effectiveness (£/QALY)
Reduce cost of combination therapy by 50%	1313	1.21	1084	-683	0.74	Dominated
Increase cost of combination therapy by 50%	7866	1.21	6497	5871	0.74	7887
Reduce cost of treating consequences of HCV infection by 50%	5571	1.21	4602	3286	0.74	4415
Increase cost of treating consequences of HCV infection by 50%	3607	1.21	2980	1902	0.74	2555
Reduce annual likelihood of progressive liver disease by 50%	5385	0.71	7617	3072	0.44	7039
Increase annual likelihood of progressive liver disease by 50%	3847	1.68	2286	2151	1.03	2081

QALY, quality adjusted life year.

results may be optimistic for this population although it is impossible to predict to what extent.

The transplantation rates we have imputed are lower than those calculated for the USA and possibly lower than current UK practice. It is likely that improvements in transplant technology and organ availability with consequent reduction in the clinical threshold for transplantation could increase the value of avoiding this costly procedure through early treatment.

Our results are necessarily based on the results of clinical trials carried out to date. But exclusion criteria imply that these included only a small proportion of those who might now be considered for combination therapy in the UK. Our survey of hepatologists revealed considerable variation in the application of criteria for combination treatment, reflecting the genuine uncertainties of clinicians. A better understanding of this variation will be important to inform further pragmatic research into the value of combination therapy and to ensure equity of access to this potentially valuable treatment. While such variation and uncertainty exists, we consider it important that treatment should be confined to specialist centres, as recommended by the British Society of Gastroenterology and the European Society for the Study of the Liver.

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Contributions: Ken Stein helped to design the study. He was involved in ensuring the design of the decision analysis model reflected UK practice and collected UK based information to inform the analysis. He drafted the manuscript and is the corresponding author. William Rosenberg helped to design the study. He was involved in the design of the decision analysis model to reflect UK practice. He contributed to the drafting of the manuscript. John Wong helped to design the study. He designed the basic decision analysis model and amended this to reflect UK practice. He contributed to the drafting of the manuscript.

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