A health economic model to assess the cost-effectiveness of pegylated interferon α-2a and ribavirin in patients with moderate chronic hepatitis C and persistently normal alanine aminotransferase levels

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Abstract

Background and study aims : **The treatment of patients with moderate chronic hepatitis C and persistently normal alanine aminotransferase levels is still under discussion and the cost-effectiveness of such strategy is unknown. The objective of this study was to estimate the cost-effectiveness of their treatment in comparison with no treatment.**

Patients and methods : **The assessed treatment is composed of pegylated interferon α-2a and ribavirin, which is the current standard treatment. Two groups were studied : patients with genotype 1 and patients with genotypes 2-3. At the beginning of the study, patients were aged of 45.**

Long-term economic and clinical outcomes over a 30 year period were predicted using a Markov simulation model. A health care payer perspective was chosen. Data were obtained from published literature. Variations of uncertainty parameters were assessed through a sensitivity analysis.

Results : **The incremental cost-effectiveness ratios (ICERs) were € 5,338/QALY for genotype 1 and € 1,080/QALY for genotypes 2-3. In the sensitivity analysis, ratios remained lower than € 20,000. A Monte Carlo simulation with 1,000 iterations gives a 95% confidence interval for the ICER of € 3,199 to € 8,972 for genotype 1 and € 56 to € 1,981 for genotypes 2-3.**

Conclusion : **Even though the treatment of these patients generates a cost, it has the advantage that in comparison with no treatment, a great number of people are cured, complications are less frequent and patients gain more quality-adjusted life-year (QALY), which involves an ICER considered as acceptable for the European society (< € 20,000).** (Acta gastroenterol. belg., **2007**, 70, **177-187**).

Key words : economic, cost-effectiveness, moderate chronic hepatitis C, persistently normal alanine aminotransferase, pegylated interferon, Markov model.

Introduction

Hepatitis C virus (HCV) is a major public health problem. Worldwide, it is estimated that 170 million persons are infected, i.e. 3% of the world population (1). In Belgium, the prevalence is estimated at nearly 1% (2). People infected by HCV can remain asymptomatic during more than 20 years and 35 to 80% of infected people are unaware of their seropositivity. Moreover, when the infection is diagnosed, few patients are treated (3). However, 80% of the infected persons will develop chronic hepatitis C, which will evolve for 20% of them to cirrhosis 20 to 30 years later. Afterwards, 3.9% of patients per year will develop a decompensated cirrhosis and 1.4% per year a hepatocellular carcinoma (4). In Belgium, more than 29% of the liver transplantations are related to hepatitis C (5).

Chronic hepatitis C can be classified into three different categories, according to the type and the amount of fibrosis. Mild chronic hepatitis C is characterized by no or few fibrosis, located in the portal area and without septa (METAVIR fibrosis scores of F0-F1). Moderate chronic hepatitis C shows portal or periportal fibrosis with some septa (METAVIR fibrosis score of F2) and severe chronic hepatitis C is determined by the presence of septal fibrosis without cirrhosis (METAVIR fibrosis score of F3) (6-8). Among patients with chronic hepatitis C, approximately 25% have persistently normal aminotransferase (PNALT) levels (9). PNALT levels is defined as normal serum alanine transaminase (ALT) over a 6-18 months period on three separate occasions with a minimum of 4 weeks apart (10).

At this time, no vaccine is available but curing the disease remains possible. The current standard therapy for patients with moderate to severe hepatitis C (METAVIR fibrosis scores of F2 and F3) and elevated ALT is the combination of pegylated interferon with ribavirin (1,11). The treatment of patients with persistently normal alanine aminotransferase is still under discussion (12). Indeed, these patients will not always develop a complication and treating them is stated to be expensive (1). However, it would be interesting to see whether, taking into account the long term complications, it would not be more effective and possibly less expensive to treat them.

The goal of this study was to compare two kinds of strategies :

- To treat patients with moderate chronic hepatitis C (METAVIR fibrosis scores of F2) and PNALT
- Not to treat and to only monitor patients with moderate chronic hepatitis C (METAVIR fibrosis scores of F2) and PNALT

With the growing cost of health care, efficacy and safety become insufficient for a good decision making.

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In the current environment, the priority becomes to reduce the costs without deteriorating the quality of care, or to improve quality of care at a reasonable cost (13). Consequently, the effectiveness but also the costs of these two strategies were investigated in this study.

Methods and design

The Markov model

The cost-effectiveness was conducted using a Markov simulation model representing the natural history of chronic hepatitis C. This technique allows to model the evolution of a cohort of patients over time and assumes that individuals are always in one of a finite number of states of health, called "Markov state". They progress in a fixed unit of time, referred to as "Markov cycle". For each Markov state, a fixed annual transition probability towards the following state, a cost and a utility are referred (14,15). Annemans *et al.* recently developed a model for patients with chronic hepatitis C based on the literature (16). Within the framework of this study, this model was used and adapted in order to distinguish the various states of chronic hepatitis C, i.e. the scores of fibrosis.

The cycles considered in this study were annual, so each year, a patient evolved or not to the following state. At the beginning of the study, all patients had moderate chronic hepatitis C (METAVIR fibrosis score of F2) with PNALT and were 45 years old. Because in Belgium there was no statistical significant difference in HCV seroprevalence for gender (2), 50% of the studied population were men at the beginning of the study. Modifications of the age and of the proportion of men at the beginning of the study were tested in the sensitivity analysis.

This model assessed two strategies : to treat these patients or to not treat and to only monitor them. The programming was done in Microsoft excel.

For genotype 1, the treatment assessed was PEG IFN α-2a 180 mg once a week in combination with ribavirin 1000-1200 mg/day for 48 weeks, as recommended in the guidelines for patients with elevated ALT. For these genotypes, an early predictive test is performed after 12 weeks of treatment and if the viral load is not reduced by more than 2log10, the treatment is stopped (11). This early virological response (EVR) is determined by a quantitative test (Cobas Amplicor HCV Monitor test) which measures the reduction of HCV RNA and is positive when the test shows a reduction of more than 2 log10 or unquantifiable HCV RNA.

In the analysis, the duration of treatment considered if no EVR was detected was 16 weeks and not 12, in order to take into account the time to obtain the results and to stop the therapy.

For genotypes 2 and 3, the treatment considered was PEG IFN α-2a 180 mg once a week in combination with ribavirin 800 mg/day for 24 weeks. For these genotypes, no early predictive test is performed (11).

For each genotype, the sustained viral response rate (SVR) was calculated 24 weeks post treatment cessation and was defined as a polymerase chain reaction (PCR) negative test (absence of HCV RNA ; Cobas Amplicor HCV test). Patients with SVR were cured while the other patients could evolve to compensated cirrhosis. Afterwards, they could progress towards decompensated cirrhosis or hepatocellular carcinoma. Patients with decompensated cirrhosis could die, have a hepatocellular carcinoma or undergo a liver transplantation. Finally, patients with hepatocellular carcinoma or liver transplantation could also die (Fig. 1). As in the model developed by Annemans *et al.* (16), it was assumed that patients with compensated cirrhosis could not directly progress towards the death state and that a patient could not be found in two different states within the same year.

The viral response rates (SVR and EVR)

For genotype 1, the sustained viral response rate of the model came from the study completed by Fried *et al.* (17). This randomized clinical trial compared two types of treatments : PEG IFN α-2a 180 mg once a week in combination with ribavirin 1000-1200 mg/day for 48 weeks and Interferon α-2b 3 MIU three times per week in combination with ribavirin 1000-1200 mg/day for 48 weeks. Among the 298 patients with genotype 1 receiving PEG IFN α-2a and ribavirin, 138 had a SVR 24 weeks after the end of the treatment, which gives a SVR rate of 46.3%. In this study, patients had elevated ALT. Zeuzem *et al.* (10) assessed the SVR rate for patients with genotype 1 and PNALT. However, the treatment studied was PEG IFN α-2a 180 mg once a week in combination with ribavirin 800 mg/day and not 1000-1200 mg/day for 48 weeks. They found a SVR rate of 40.4% and concluded that this rate was similar to the rate for patients with elevated ALT. Hadziyannis *et al.* (18) tested different levels of ribavirin and concluded that ribavirin 1000-1200 mg/day for 48 weeks resulted in a significantly higher SVR rate than for ribavirin 800 mg for 48 weeks. Thus, the use of the SVR rate determined by Fried *et al.* (17) was the most suitable rate for this study because 1000-1200 mg/day of ribavirin was assessed. A variation of this rate was done in the sensitivity analysis. An EVR rate of 80.9% was determined for genotype 1 patients with PNALT and treated with peginterferon and ribavirin during 48 weeks (19).

For genotypes 2-3, SVR came from the study of Zeuzem *et al.* (10). This randomized clinical trial compared three groups of patients with PNALT : patients treated with PEG IFN α-2a 180 mg once a week in combination with ribavirin 800 mg/day for 48 weeks, patients treated with PEG IFN α-2a 180 mg once a week in combination with ribavirin 800 mg/day for 24 weeks and patients not treated. Patients were monitored for 72 weeks. Among the 58 patients with genotypes 2-3

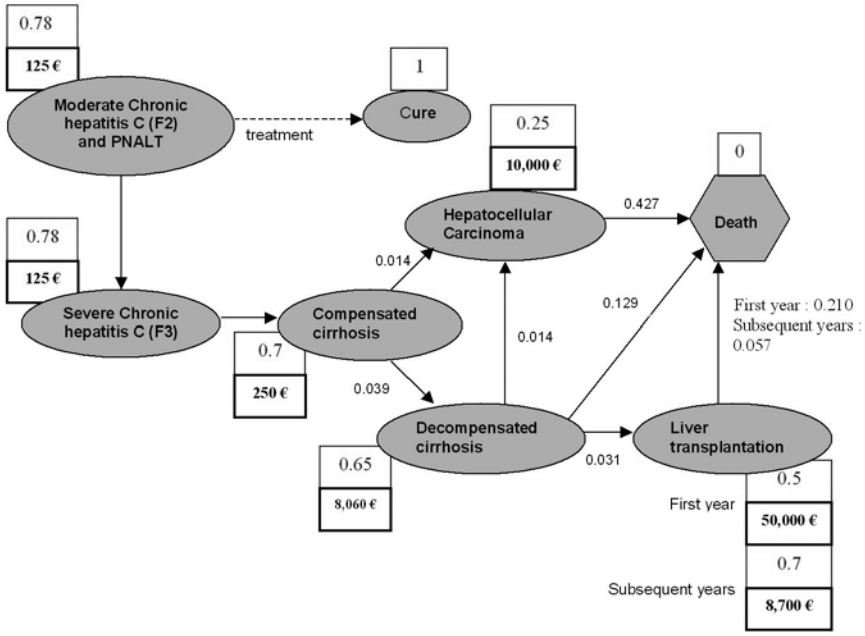

Fig. 1. — Markov model of HCV disease progression.
For each Markov state, a fixed annual transition probability towards the following state (xx), a cost (**xx**) and a utility (xx) are specified. Annual transition probabilities between the states of moderate chronic hepatitis C, severe chronic hepatitis C and compensated cirrhosis differ according to the patients age and gender (detailed in Table 1).

Table 1. — **Annual transition probabilities**

Markov States (references)	%
Fibrosis progression in men per age (20-25)	
40-49	0,0302 (0,0151-0,0532)
50-59	0,0700 (0,0409-0,0902)
60-69	0,1238 (0,0700-0,1954)
>= 70	0,1686 (0,0851-0,2677)
Fibrosis progression in women per age (20-25)	
40-49	0,0157 (0,0073-0,0325)
50-59	0,0364 (0,0157-0,0650)
60-69	0,0638 (0,0235-0,1322)
70-79	0,0862 (0,0454-0,1557)
>=80	0,1176 (0,0476-0,1988)
Compensated Cirrhosis to Decompensated Cirrhosis (4,27)	3.9 (2.0-8.3)
Compensated Cirrhosis to Hepatocellular carcinoma (4,28-29)	1.4 (1.0-4.4)
Decompensated Cirrhosis to Hepatocellular carcinoma (4,28-29)	1.4 (1.0-4.4)
Decompensated Cirrhosis to Liver transplantation (30)	3.1 (1.0-6.2)
Decompensated Cirrhosis to Death (4,30-31)	12.9 (6.5-19.3)
Hepatocellular Carcinoma to Death (4)	42.7 (33-86)
Liver transplantation to Death (First Year) (32-34)	21.0 (6-42)
Liver transplantation to Death (Subsequent Years) (32-34)	5.7 (2.4-11)

and treated with PEG IFN α-2a 180 mg once a week in combination with ribavirin 800 mg/day for 24 weeks, 42 patients had a SVR 24 weeks after the end of the treatment, which gives a SVR rate of 72.4%. In the untreated group, no patient cleared HCV RNA.

Annual transition probabilities

From previous studies (20-23), Salomon *et al.* (24) estimated annual transition probabilities between Metavir fibrosis score F2 to F4 for patients with elevated ALT. Results were stratified by age and gender. A longitudinal study performed by Hui *et al.* (25) compared the FPR for patients with PNALT and for patient with elevated ALT. The relative rate of fibrosis progression (FPR PNALT/FPR elevated ALT) was estimated from the figure representing the cumulative probability of fibrosis progression for patients with PNALT and with elevated ALT. This figure was analysed using a graphical analysis software called "Grab-It", which permitted to extract data from the figure. The median time (50th percentile) to progression for elevated ALT

occurred at year 7 and corresponded to the 28th percentile for PNALT. Consequently, at year 7 the relative rate of progression was 0.56 (0.28/0.50). By applying this rate to results of Salomon *et al.* (24), annual transition probabilities between Metavir fibrosis score F2 to F4 for patients with PNALT were obtained.

The other probabilities came from the model developed by Annemans *et al.* (16), themselves coming from the model of Younossi *et al.* (26) and based on previous studies (4,27-34) (Table 1). The mortality due to natural causes was also included in the model using age-specific mortality rates by gender (35).

Utilities

Utilities represent the preferences of individuals for a specific health state. They vary from 0, which represents death, to 1, which represents the perfect health state. These utilities are used to estimate the health-related quality of life and then the cost-effectiveness ratio in terms of cost per quality-adjusted life-year (QALY). For each strategy investigated, a QALY is calculated by multiplying the time spent in each health state by the utility of the state and then by summing the whole over the life expectancy (14). In other published models (26,30,36-37), several estimates of utilities can be found. In this study, the utilities relating to the states of moderate chronic hepatitis C, severe chronic hepatitis C and compensated cirrhosis came from the study of Bennett *et al.* (30) because fibrosis scores were distinguished. They used linear scaling and time trade-off methods. For the other states, the utilities of the model used by Annemans *et al.* (16) were preserved. Some of these utilities came from the study of Bennett *et al.* (30) and others came from the study of Kim *et al.* (31). Kim *et al.* (31) estimated utilities from a panel of hepatologists and a nurse specialist (Table 2). Deterioration of the quality of life due to the treatment was included in the model using the utility multiplier for peg-interferon and ribavirin assessed by Siebert *et al.* (38).

In order to take into account the differences between the studies, a sensitivity analysis, which assessed the range of values coming from the literature (16,26,30-31,36-37), was performed.

Complications costs

The Belgian health care payer perspective was adopted in this study. Various estimates of the costs are present in other published models (1,26,37,39-41).

For this study, the costs came from the model of Annemans *et al.* (16) because they were derived from a Belgian study performed by Wong in 2002 (41) (Table 3). The medical care costs of moderate and severe chronic hepatitis were supposed to be the same, these patients requiring no different caring.

Drug costs

The current public prices published by the "Institut national d'assurance maladie invalidité" (INAMI) in January 2006, VAT included and patient contribution deduced, were used. For genotype 1, the treatment cost € 18,187/patient. By taking into account the EVR rate, and thus the proportion of patient for which the treatment was stopped after 16 weeks, the mean treatment cost was reduced to € 15,865/patient. For genotypes 2-3, the treatment cost € 8,427/patient.

Table 2. — **Utilities estimates**

Utilities					
Markov State	Younossi 1999 (26)	Bennett 1997 (30)	Sagmeister 2001 (36)	Sennfält 2001 (37)	Model
utility multiplier for peg-interferon and ribavirin					0.90
SVR	1	1		1	1
Chronic hepatitis C	0.82 (0.6-0.9)		0.90		
Mild		0.82 (0.63-0.98)		0.82	0.82 (0.63-0.98)
Moderate to severe		0.78 (0.6-0.9)		0.78	0.78 (0.6-0.9)
Compensated cirrhosis	0.78 (0.5-0.9)	0.7 (0.5-0.9)	0.75	0.70	0.70 (0.5-0.9)
Decompensated cirrhosis	0.65 (0.3-0.88)				0.65 (0.3-0.88)
Hepatocellular carcinoma	0.25 (0.1-0.5)	0.1 (0.02-0.5)	0.20	0.10	0.25 (0.1-0.5)
Liver transplantation, first year	0.5 (0.11-0.70)	0.5 (0.11-0.70)	0.70	0.50	0.5 (0.11-0.70)
Liver transplantation, subsequent years	0.7 (0.24-0.87)	0.7 (0.24-0.87)	0.80	0.70	0.7 (0.24-0.87)

The utility multiplier used in the model came from the study of Siebert *et al.* (38). Other utilities came from the studies of Younossi *et al.* (26) and Bennett *et al.* (30). Younossi *et al.* (26) themselves based their estimates on the study of Bennett *et al.* (30) and Kim *et al.* (31). Bennett *et al.* (30) used linear scaling and time trade-off techniques to estimate utilities from a panel of hepatologists. In the study of Kim *et al.* (31), utilities were based on expert opinion (a panel of hepatologists and a nurse specialist).

Table 3. — **Costs estimates**

Costs per year						
Markov states	Wong 2000 (39)	Sennfält 2001 (37)	Jusot 2001 (40)	Younossi 1999 (26)	Shephred 2000 (1)	Wong 2002 (41)
Devise	$	$	€	$	£	€
Chronic hepatitis C			579	319	95	125
Compensated cirrhosis	110	163	1,400	425	237	250
Decompensated cirrhosis		6,885	11,500	22,100		8,060
Hepatocellular carcinoma			10,400		13,320	10,000
Liver transplantation						
First year	108,659	97,281	92,700	269,072		50,000
Subsequent years	18,976	16,093	7,900	25,910		8,700

Temporal characteristics of the study

Because the evolution of the disease is slow the period taken into account in this study was 30 years. Future costs were discounted at a rate of 3% and future utilities were discounted at a rate of 1.5%, as recommended by Belgian guidelines for cost-effectiveness analysis (42).

Sensitivity analysis

Considering the variations of input estimates from different sources, a sensitivity analysis was necessary. Firstly, an univariate sensitivity analysis assessing the impact of changes in key parameters on results was performed. Then, elasticity of each decision parameter was calculated to identify variables having an important impact on results. Finally, a probabilistic sensitivity analysis on all uncertain parameters using a Monte Carlo simulation with 1,000 iterations was done in order to determinate the 95% confidence interval of the ICERs.

Results

For genotype 1

The Markov technique had permitted to model the evolution of a cohort of patients with moderate chronic hepatitis C over a 30 year period. At each state of the model, a cost and a utility were associated and thus, the total cost and the quality-adjusted life-year (QALY) of the strategies could be calculated.

Treatment costs € 15,865 per patient. On the other hand, the studied model showed that the costs for medical care other than treatment cost were reduced by € 2,667 because 46.3% patients were cured after the treatment. In terms of health related life expectancy, people gained 2,47 QALY with a treatment.

Thus, even if the therapy was expensive, the other medical care costs were reduced and the average life expectancy in good health was higher, which resulted in an incremental cost-effectiveness ratio (ICER) of € 5,338/QALY (Table 4).

For genotypes 2-3

These patients were treated less longer and therefore the impact of the treatment cost (€ 8,427 per patient) was less important than with genotype 1. The costs for other medical care than therapy cost were 3.6 times lower thanks to the treatment (€ 1,589 versus € 5,760) and patients gained 3,94QALY. Consequently, the ICER was better than for genotype 1 and was € 1,080/QALY (Table 4).

Sensitivity analysis

The key parameters of the model were the annual transition probabilities, the utilities, the costs, the SVR rates, the duration of the study, the age at the beginning of the study, the discount rate, the proportion of men at the beginning of the study and the age-specific mortality rates by gender.

Univariate sensitivity analysis on the probabilities of evolution

The range of possible values of annual transition probabilities, estimated from the literature (see table 1), was assessed. With a faster progression of the disease, the ICER rate improved. In all situations considered, the medical care costs other than the therapy cost were lower with a treatment and the health-related life expectancy was better. The ICERs ranged between € 3,550 to € 6,411 for genotype 1 and between € 254 to € 1,693 for genotypes 2-3 (Table 5).

Univariate sensitivity analysis on the utilities

The range of possible utilities used by Younossi *et al.* (26) and Bennett *et al.* (30) was assessed for this sensitivity analysis (see table 2). The more the patients would consider their state as “unpleasant”, the more the cost-effectiveness ratio improved. Conversely, if patients regarded their state as few disturbing, a treatment became less cost-effective. However, whatever the value

Table 4. — **Basecase results**

Genotype 1	Treatment	No treatment	Difference
Cost			
Drug cost	€ 15,865.03	€ 0.00	€ 15,865.03
Medical care cost	€ 3,092.64	€ 5,760.04	€ -2,667.40
Total cost	€ 18,957.67	€ 5,760.04	€ 13,197.63
Effectiveness			
Life expectancy (Years)	27.05	26.78	0.27
QALY	19.11	16.63	2.47
% cured people after 30 years	46.31%	0.00%	46.31%
Cost-effectiveness rate			
Cost/Life Year	€ 700.76	€ 215.10	€ 485.66
Cost/QALY	€ 992.20	€ 346.28	€ 645.93
ICER			€ 5,337.97/QALY
Genotypes 2-3	Treatment	No treatment	Difference
Cost			
Drug cost	€ 8,427.08	€ 0.00	€ 8,427.08
Medical care cost	€ 1,588.98	€ 5,760.04	€ -4,171.06
Total cost	€ 10,016.06	€ 5,760.04	€ 4,256.02
Effectiveness			
Life expectancy (Years)	27.21	26.78	0.43
QALY	20.57	16.63	3.94
% cured people after 30 years	72.41%	0.00%	72.41%
Cost-effectiveness rate			
Cost/Life Year	€ 368.14	€ 215.10	€ 153.04
Cost/QALY	€ 486.81	€ 346.28	€ 140.53
ICER			€ 1,080.06/QALY

of utility assessed, the health-related life expectancy remained higher with a treatment. The ICERs ranged between € 3,030 to € 11,689 for genotype 1 and between € 619 to € 2,305 for genotypes 2-3 (Table 5).

Univariate sensitivity analysis on the costs

For the sensitivity analysis on the costs, a variation of 20% was assessed (as in many studies) (16, 31, 37). With an increase in the complications costs, treatment of patients became more cost-effective because more expensive complications were avoided. As in the two preceding sensitivity analyses, the medical care costs other than the therapy cost were always lower with the treatment strategy. The ICERs ranged between € 5,122 to € 5,554 for genotype 1 and between € 868 to € 1,292 for genotypes 2-3 (Table 5).

Univariate sensitivity analysis on the rates of SVR and EVR

Because no confidence interval was given in the study of Fried *et al.* (17), a variation of 20% of the SVR and EVR rates was done. The same conclusion could be drawn. Whatever the levels of SVR and EVR within the limits of the sensitivity analysis assessed, the costs of the medical care other than the therapy cost were lower with a treatment and the health-related life expectancy was better. The ICERs ranged between € 4,908 to € 5,990 for genotype 1 and between € 723 to € 1,618 for genotypes 2-3 (Table 5). Variations beyond 20% were also assessed and ICERs became > € 20,000 from SVR rates below 14.9% for genotype 1 and below 7.9% for genotypes 2-3.

Univariate sensitivity analysis on the duration of the study

For this analysis, a variation of 10 years was assessed and the result showed that the benefits of a treatment increased with time. The ICERs ranged between € 3,866 to € 8,692 for genotype 1 and between € 502 to € 2,362 for genotypes 2-3 (Table 5).

Univariate sensitivity analysis on the age at the beginning of the study

Different values were tested in this sensitivity analysis. As results, the ICERs became > € 20,000 from 78 years old for genotype 1 and from 88 years old for genotypes 2-3.

Table 5. — **Univariate sensitivity analysis**

ICER for genotype 1			
Variables	Minimal values	Base case	Maximal values
Annual transition probabilities (Ranges of table 1)	€ 6,411.35	€ 5,337.97	€ 3,550.11
Utilities (Ranges of table 2)	€ 3,029.76	€ 5,337.97	€ 11,689.41
Costs (+/- 20%)	€ 5,553.75	€ 5,337.97	€ 5,122.20
SVR and EVR rates (+/- 20%)	€ 5,989.63	€ 5,337.97	€ 4,908.19
Time frame (20-40 years)	€ 8,692.08	€ 5,337.97	€ 3,865.69
Discount rate (0-5%)	€ 3,536.49	€ 5,337.97	€ 9,127.76
% men (0-100%)	€ 5,702.62	€ 5,337.97	€ 4,965.61
Age-specific mortality rates by gender (+/- 20%)	€ 5,189.74	€ 5,337.97	€ 5,488.06
ICER for genotypes 2-3			
Variables	Minimal values	Base case	Maximal values
Annual transition probabilities (Ranges of table 1)	€ 1,693.00	€ 1,080.06	€ 253.98
Utilities (Ranges of table 2)	€ 619.00	€ 1,080.06	€ 2,304.58
Costs (+/- 20%)	€ 1,291.76	€ 1,080.06	€ 868.36
SVR rate (+/- 20%)	€ 1,617.98	€ 1,080.06	€ 722.66
Time frame (20-40 years)	€ 2,362.40	€ 1,080.06	€ 502.26
Discount rate (0-5%)	€ 188.68	€ 1,080.06	€ 2,222.87
% men (0-100%)	€ 1,341.97	€ 1,080.06	€ 825.54
Age-specific mortality rates by gender (+/- 20%)	€ 1,028.45	€ 1,080.06	€ 1,132.11

Table 6. — **Elasticity**

Parameters	Elasticity	
	Genotype 1	Genotypes 2-3
Utility related to moderate hepatitis C (METAVIR fibrosis score F2)	3.140	3.015
Utility related to severe hepatitis C (METAVIR fibrosis score F3)	0.917	0.897
SVR rate	-1.019	-1.655
EVR rate	0.743	/

Univariate sensitivity analysis on the discount rate

Belgian guidelines recommend to test different scenarios concerning the discount rate in the sensitivity analysis : 0% for benefits and 3% for costs, 0% for benefits and 5% for costs and finally 0%, 3% or 5% for both benefits and costs (42). As results, ICERs ranged between € 3,536 to € 9,128 for genotype 1 and between € 189 to € 2,223 for genotypes 2-3 (Table 5).

Univariate sensitivity analysis on the proportion of men

In the basecase, 50% of the studied population were men. In this sensitivity analysis, extreme values were tested, i.e. 0 and 100%. As results, ICERs ranged between € 4,966 to € 5,703 for genotype 1 and between € 826 to € 1,342 for genotypes 2-3 (Table 5).

Univariate sensitivity analysis on the age-specific mortality rates by gender

For this analysis, a variation of 20% was assessed. As results, ICERs ranged between € 5,190 to € 5,488 for genotype 1 and between € 1,028 to € 1,132 for genotypes 2-3 (Table 5).

Elasticity of the parameters

In order to assess which variables had an important impact on results, elasticity of each decision parameter was calculated. Elasticity can be obtained by divided the percentage change of the results by the percentage change of the parameter. The more the absolute value of the elasticity was elevated, the higher the impact of the parameter was on the ICER. In this study, elasticity was

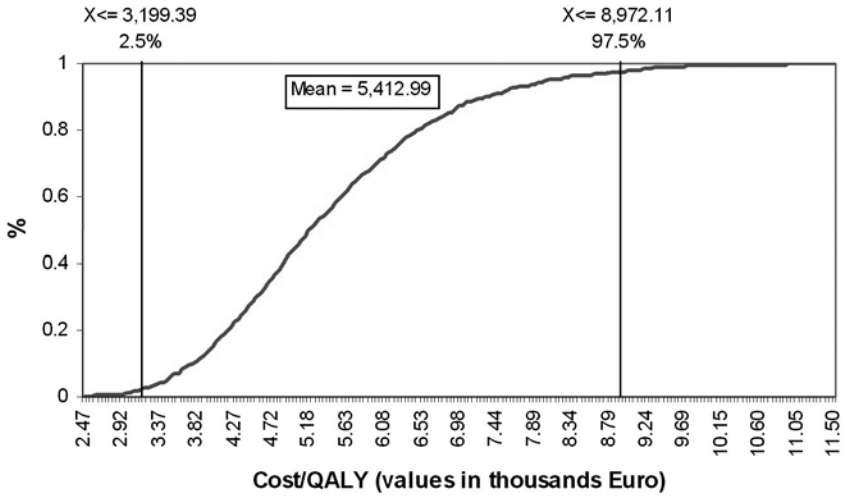

Fig. 2. — Cumulative distribution of the incremental cost-effectiveness ratio (ICER) for patients with genotype 1. These data are provided by a Monte Carlo simulation with 1,000 iterations and permit to determine the 95% confidence interval of the ICER.

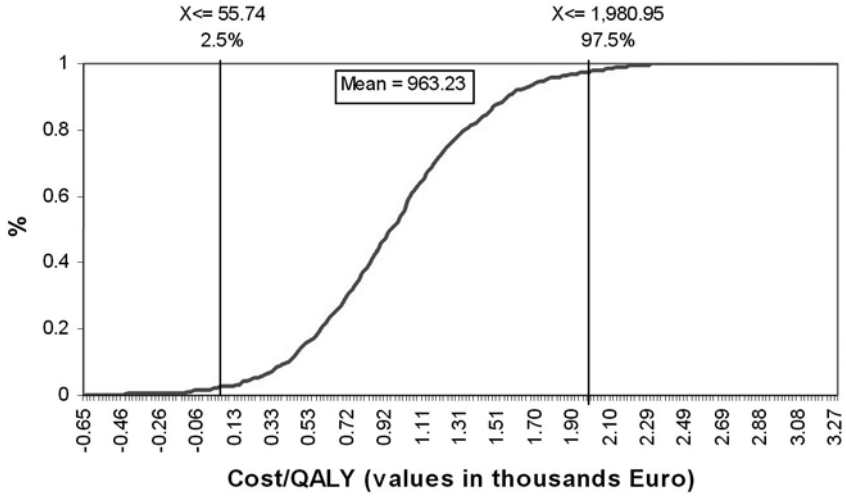

Fig. 3. — Cumulative distribution of the incremental cost-effectiveness ratio (ICER) for patients with genotypes 2 and 3. These data are provided by a Monte Carlo simulation with 1,000 iterations and permit to determine the 95% confidence interval of the ICER.

considered as elevated beyond a ratio of 0.5. As results, the utilities associated with the states of moderate and severe hepatitis C and the SVR and EVR rates had elevated elasticity (> 0.5) (Table 6).

Probabilistic sensitivity analysis

A risk analysis on the uncertain parameters of the model with a Monte Carlo simulation was done using the software @risk (Palisade Inc). Triangular distributions were introduced for each utility using the ranges tested above (see table 2). For the discount rate, a range of 0% to 5% was tested as advised in guidelines (42-43). For SVR and EVR rates, beta distributions instead of normal distributions were used because standard errors were not available. Costs were modelled as a lognormal distribution due to the positive nature and positive skew of costs. After 1,000 iterations, the 95% confidence interval for the ICER was € 3,199 to € 8,972 for genotype 1 and € 56 to € 1,981 for genotypes 2-3 (Figs. 2-3). By assuming a societal willingness-to-pay equal to € 20,000 per QALY, 100% of the ICERs fall bellow the limit for genotype 1 and for genotypes 2-3.

Discussion

In the literature, the decision to treat or not patients with PNALT is still under discussion (12,44,45). The aim of this study was to assess, in terms of cost and health, the impact of such decision, i.e. to determine the ICER of the treatment of patients with PNALT compared to no treatment. The therapy studied was the combination of pegylated interferon and ribavirin, i.e. the standard treatment for patients with elevated ALT (1,11).

Compared to no treatment, results showed that the treatment was a cost-effective strategy for all genotypes and mainly for genotypes 2 and 3 (€ 5,338/QALY for genotype 1 and € 1,080/QALY for genotypes 2-3). Indeed, in the Netherlands, a ratio below € 20,000/QALY is considered as cost-effective whereas, in US, the limit is $ 50,000/QALY (46-47). Our results were thus far from those exceeding the limit acceptable for the society. The sensitivity analysis confirmed these results and showed that utility associated to the state of moderate chronic hepatitis had the biggest impact on results. A Monte Carlo simulation showed that the 95% confidence interval was € 3,199 to € 8,972 for genotype 1 and € 56 to € 1,981 for genotypes 2-3.

As in other studies (16,24,26,30-31,36-41), the SVR rates selected came from randomized clinical trials. Thus, these rates measured the efficacy and not the effectiveness of the therapy, i.e. the theoretical effect of the treatment and not its effect in practice. In the "real world", the SVR rate is maybe lower than the rate assessed in the model. In practice, a treatment would not be any more cost-effective if the SVR rate went down below 14.9% for genotype 1 and below 7.9% for genotypes 2 and 3.

In this study, patients were aged of 45. However, by selecting older patients and thus patients with a lower life expectancy, the difference of quality-adjusted life-year between the two strategies was more limited and the cost-effectiveness ratio increased. Consequently, a treatment was not any more cost-effective (> € 20,000/QALY) from 78 years old for genotype 1 and from 88 years old for genotypes 2-3.

In other models of HCV disease progression, similar annual transition probabilities between later disease states, such as decompensated cirrhosis and liver transplantation, were generally found (16,26,30,38-39). However, there was less agreement about rates between Metavir fibrosis scores F2 to F4. In this model, these rates came from the study of Salomon *et al.* (24) because they were stratified by age and gender and large ranges were tested in the sensitivity analysis.

Annual transition probabilities between Metavir fibrosis scores F2 to F4 were adapted to patients with PNALT from only one study (25). Few studies have compared the progression rates of fibrosis between patients with PNALT and patients with elevated ALT and their methodology appears to be limited (25, 48-51). In the study of Hui *et al.* (25), ALT determination was only performed yearly. Moreover, the number of patients with F2 fibrosis score in this study was very small (9 in the group with PNALT and 11 in the group with elevated ALT). More data on the progression rates of fibrosis for patients with PNALT are thus needed. The impact of such limitation was reduced by performing a sensitivity analysis on these progression rates.

It would be interesting to develop a specific model on populations at risk like alcoholic patients or patients co-infected by HIV or HBV. For these patients, annual transition probabilities are higher (52). Moreover, for these patients, health care costs can be expected higher and utilities lower than for patients with hepatitis C alone. As shown in the sensitivity analysis, higher annual transition probabilities, higher health care costs and lower utilities were in favour of the treatment strategy. Not include these patients in this analysis was thus a conservative assumption.

In the model, patients with hepatocellular carcinoma and compensated cirrhosis were supposed not to evolve towards liver transplantation, which was a conservative assumption. In practice, patients with hepatocellular carcinoma or even compensated cirrhosis are transplanted even if their number remains limited.

It should also be noted that extra-hepatic consequences of the disease, as cryoglobulinemia and glomerulonephritis (53-55), were not taken into account in this study. However, taking into account these extra-hepatic consequences would increase health care costs for patients who are not cured and as shown in the sensitivity analysis, higher health care costs improved the ICERs. The approach adopted was thus conservative.

Moreover, the costs considered originated from an analysis based on the actual Belgian prices. Those being lower than the prices imposed abroad, the ICERs tends to be improved in other countries with similar mortality rates, annual transition probabilities and utilities. It was also assumed that the costs between the various degrees of severity of chronic hepatitis C were the same, their caring being not different.

In conclusion, even if the treatment of people with moderate chronic hepatitis C and PNALT generates a cost compared to no treatment, a great number of people are cured, complications are less frequent and patients gain more QALYs, which involves an ICER acceptable for the European society (< € 20,000).

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