TITLE:

Cost-effectiveness analysis of therapeutic strategies for patients with chronic hepatitis C previously non-responders to interferon.

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SHORT TITTLE: Pharmacoeconomic analysis in NR.

ABSTRACT:

Background: The efficacy of combination therapy in previous non responders to interferon (IFN) monotherapy with chronic hepatitis C is lower than in naïve patients, and there has been no economic evaluation in this population.

Aim: To develop a cost-effectiveness analysis of therapeutic regimens with IFN alpha and ribavirin in previous interferon non-responders.

Methods: A Markov simulation model was used to project the clinical and economic outcomes of five different therapeutic strategies including a "no treatment" alternative using the health care system perspective. The effectiveness data for the different doses and durations was obtained from a previously performed meta-analysis. A sensitivity analysis was performed to test robustness of the model, analysing changes in different variables.

Results: Applying a 3% discount rate, the standard patient on combination therapy for 12 months showed an increase of 0.80 years and 1.55 quality adjusted life years (QALYs), when comparing combination therapy for 12 months vs. "no treatment" strategy. This option led to an incremental cost-effectiveness ratio of 11,767 euros per year of life gained and 6,073 euros per QALY.

Conclusions: Combination therapy with interferon plus ribavirin in previous interferon non-responders shows an incremental cost-effectiveness ratio within the range of some well accepted medical interventions in our health care system.

Key words: Hepatitis C; Interferon; Markov model; Non-responders; ribavirin.

INTRODUCTION

Chronic hepatitis C is the leading cause of chronic liver disease and liver transplantation in Western Europe and the United States. Over 4 million individuals are infected with hepatitis C virus (HCV) in the USA, and more than 5 million are estimated in Western Europe, of whom 800,000 are in Spain[1-3].

Chronic hepatitis C represents an important public health problem. Firstly, because of the large number of patients infected, and secondly because it is a progressive disease that may lead to cirrhosis, liver failure and hepatocellular carcinoma, resulting in a loss of life expectancy and a decline in the quality of life. The complications of chronic hepatitis C are associated with high health care costs, particularly for advanced liver disease, which often requires liver transplantation.

Monotherapy with alpha interferon (IFN) was the first effective treatment for chronic hepatitis C[4]. Later, ribavirin was combined with interferon for 6 or 12 months depending on HCV genotype. The combination of interferon plus ribavirin increased end of treatment response and sustained response by reducing the relapse rate. The sustained virologic response, i.e. viral clearance 6 months after the end of therapy, is higher in naïve patients than in previous interferon non-responders. Currently, combination therapy is the standard of care for patients with chronic hepatitis C. Its role in interferon non-responders is still controversial but some meta-analyses suggest an acceptable rate of sustained virologic response in this population[5].

Several cost-effectiveness studies on interferon monotherapy and combination therapy in naïve and relapser patients have been published [6-14], but none on combination therapy for previous interferon non-responders. Since the efficacy of combination therapy in this population is lower than in naïve patients, cost-effectiveness analysis could be useful in building guidelines for collective decision making in health care systems.

The aim of this study is to estimate the cost-effectiveness of different therapeutic regimens with IFN alpha and ribavirin for patients with chronic hepatitis C previously non-responders to interferon monotherapy.

MATERIALS AND METHODS

Patient characteristics and virological treatment response rates were taken from a hypothetical cohort of previous non-responder patients reported in a recent meta-analysis carried out by our group[5]. The details of this study have been published previously. The standard patient was a 42 year-old man from a cohort of patients with histological lesions of chronic hepatitis C in 88% of cases (21% mild and 66% moderate), and compensated cirrhosis in 13%. The distribution of histological lesions was obtained from the studies included in the meta-analysis[5].

Decision-Analytic Model

A Markov decision analysis model, based on previous validated examples from the literature[5,7,10], was used to describe disease progression and determine the long-term morbidity, life expectancy and lifetime costs of different treatment strategies based on the time spent in each clinical state for the hypothetical cohort. This model simulates the course of the disease from its initial stages of mild disease until death due to liver-related or other causes, and the effects of IFN monotherapy and combination therapy on the outcome of the disease (Figure 1). The model uses probabilities of progression from chronic hepatitis to cirrhosis, decompensated liver disease and finally death, obtained from the results of several published studies validated in previous analyses[6,8,11] (Table 1).

During the follow-up, represented by annual cycles, the patient may remain in the same clinical state, progress to another state, die from liver disease, die from other causes, or go up to a healthy state if a sustained virological response is achieved. The resources used and the costs for the different strategies have been estimated based on data published in previous studies[9,11].

Calculations were done with DATA 3.5 (Tree-Age Software, Inc Boston Massachusetts). Outcome calculations were performed in years of life gained, and also in quality adjusted life years (QALYs), including utility assignments associated with each health state.

Therapeutic options

Five different strategies were examined. Strategy 1: No treatment; Strategy 2: IFN monotherapy for 6 months; Strategy 3: Combination therapy for 6 months with standard doses of IFN; Strategy 4: Combination therapy for 6 months with high doses of IFN; Strategy 5: Combination therapy for 12 months with standard doses of IFN.

All patients were treated for the total period of time. The characteristics of these therapeutic alternatives, their effectiveness and costs are shown in Table 2.

Health-Related Quality of Life

The quality of life analysis was performed with assigned estimates of utility for each health state determined by a panel of hepatologists. These utility assignments are based on those published by Bennett[6] and Wong[8] and ranged from "1" (viral negativity) to "0" (death). To calculate quality-adjusted life years (QALYs), the time spent in each health state according to the projected model was multiplied by each utility value. Those figures were adjusted to the healthy population quality of life value for Spain[15], 0.89 on a 0-1 scale, obtained from the visual analogue scale of the EQ-5D questionnaire (Table 3).

Cost data, discount rate and perspective

In the analysis, all direct health care costs, i.e., of screening patients for therapy, diagnostic and laboratory tests, drugs, monitoring during therapy and follow-up, and

hospital stays (for each specific health care state that might require hospitalisation) were included. The annual costs of disease states considered in the model were based on previous reports obtained from the Spanish health care system's cost database SOIKOS[9,11]. All costs were converted to year 2001 euros using the Consumer Price Index (Table 4). No indirect costs, such as lost workdays, loss of productivity, nor intangible costs related to patient suffering were included in this model.

The perspective adopted in the analysis was that of the Spanish national health care system, which is the final payer of direct treatment costs over the patients' lifetimes.

Discounting was used to consider time preference, converting both future costs and health benefits into present values. A discount rate of 3% was applied to costs and health benefits, based on international recommendations[16].

Drug costs were obtained from current pharmaceutical prices charged to the Spanish health care system, that is 6.01 euros for 1 MU of IFN alpha and 22.60 euros for 1 g of Ribavirin.

Health care costs for treatment monitoring were based on general clinical practice[9,11] and included: first specialist visit (144.3 euros), follow-up visits (72.4 euros), laboratory testing (22.14 euros), HCV-RNA determination (68.3 euros), and TSH determination (9.77 euros).

Total cost calculation for each option, as shown in Table 4, included total drug costs, health care resources costs based on previously cited unit prices, the cost of ribavirin induced haemolytic anaemia, and the cost of monitoring patients who responded to treatment (even those who relapsed), consisting of one follow-up visit, one laboratory test and one hepatitis C virus RNA determination. The cost of haemolytic anaemia was estimated at around 1% of 12 months' combination therapy cost[17]. This side effect represents the main differential adverse effect between combination therapy

and monotherapy with IFN and not considering it would have biased the results against the IFN monotherapy option.

No therapy costs were considered in strategy 1 since the health resources in strategies 2 to 5 were drug monitoring costs (drugs, lab tests, visits …), not including routine visits or other possible health resources.

Assumptions

The natural history model assumes a constant rate of disease progression over time as in other published cost-effectiveness studies[6,8-13]. The model assumes that a sustained response (normal serum alanine aminotransferase levels and hepatitis C virus RNA negativity) at 6 months of follow-up is equivalent to a prolonged response and, therefore a "cure". Furthermore, a cure is considered to restore population-specific life expectancy. Similarly, non-responders or relapsers are considered to gain no benefit from therapy.

An inherent restriction of Markov models is their reliance on the "Markovian assumption". This states that the behaviour of the process subsequent to any cycle depends only on its description in that cycle. That is, the process has no memory for earlier cycles.

The model assumes that disease progression and treatment efficacy are equal for all age groups, due to the lack of evidence on age dependent differences.

The incremental cost-effectiveness ratio was calculated as the additional cost divided by the number of years of increased life expectancy or the increase in QALYs for the options compared. Most well accepted medical interventions in our health care system environment have incremental cost-effectiveness ratios falling below 30,000 euros per QALY[18-20].

Sensitivity analysis

A one-way sensitivity analysis for some of the uncertain variables used in the model was performed, in order to identify how changes would affect costs and therapeutic outcomes. The following variables were modified: the discount rate from 0% to 5%, the patients ages at the start of therapy from 30 to 60 years, some probabilities of progression between the different states of chronic hepatitis C disease including liver transplantation were doubled and halved and effectiveness data along the confidence interval for each strategy, keeping the base case figures for the other strategies.

A therapeutic option using 5 MU of IFN daily in combination therapy studied by Puoti *et al*, was also evaluated[21]. This option was included in the sensitivity analysis because, despite the small number of patients treated (21 patients), it showed a sustained virological response of 40%, making it an interesting option to study in depth, both from a clinical and pharmacoeconomic point of view.

Model validation

The validity of the model was tested by predicting the life expectancy for a healthy 42-year-old man, 34.72 years, which is very similar to the Spanish average life expectancy of 34.09 years. For a cohort of patients with compensated cirrhosis, we predicted a 5-year survival rate of 48%, similar to the 50% described by Fattovich et al and to the 55% predicted by Bennett's model[6,22].

The life expectancy for a 42-year-old patient with different states of chronic hepatitis C disease was also calculated: 26.48 years with chronic hepatitis, 18.17 years with cirrhosis and 6.12 years with decompensated cirrhosis. These results reflect the natural history of hepatitis C.

Support source

This pharmacoeconomic study was performed exclusively as an academic work, and has not been supported by any pharmaceutical company, government agency or grant.

RESULTS

Base-Case Analysis.

Five strategies were applied to a base-case patient cohort of previous non-responders to IFN. The highest sustained virological response, 20.5%, was achieved with strategy 5, that is treating non responders with combination therapy for 12 months. The pharmacoeconomic results for each strategy are shown in tables 5 and 6. The highest increase in life expectancy, applying a 3% discount rate, was observed with strategy 5, with an increase of 0.8 years of life and 1.55 QALYs. The incremental cost-effectiveness ratio (ICER) between the four therapeutic strategies (strategies 2-5) vs. "no treatment" (strategy 1) was calculated as well as for each strategy and the next most effective one (Figure 2).

Figure 2 shows the "efficiency frontier" that is given by the lines joining strategies 1 (the origin), 4 and 5. There is no simple dominance in this analysis, which means that an alternative has higher costs and lower effectiveness than some other option. Nevertheless, strategies 2 and 3 can be ruled out through the principle of extended dominance[16]. Under this concept, a strategy is not surpassed by any other alternative (as in simple dominance) but by a mixed strategy of two other programs. In this case, a combination of strategies 1 and 4 can produce more QALYs and be less costly than strategies 2 and 3.

All the figures obtained from the analysis fall below the benchmark cost per QALY of many well-accepted medical interventions in Spain and other countries[18-20].

Sensitivity Analysis.

Table 7 shows results of sensitivity analysis. The *age at the start of treatment* is a variable that significantly affects the results. Increasing this variable reduces the

benefits while raising costs. Ages less than 60 years show a cost-effectiveness ratio lower than the benchmark of well-accepted medical interventions.

Discount rates were modified showing a decrease in the ICER for 12 months of combination therapy vs. "no treatment" of 2,450 euros per year of life gained without discounting, while it rose to 9,329 euros with an annual discount rate of 5%.

Annual progression rates from mild to moderate chronic hepatitis C and from moderate chronic hepatitis C to cirrhosis were also modified from half to twice their original value. A very small change in the ICER was observed when the annual progression rate between mild to moderate disease was modified but a more significant impact was observed when the progression rate from moderate disease to cirrhosis was changed.

Effectiveness data were analysed throughout the confidence interval values. Using the lower end of the confidence interval for strategy 5 (IC95%: 15.5%-26.0%), cost-effectiveness ratio of strategy 5 vs. 4 reached the figure of 62,900 € per QALY.

Cost-effectiveness ratio of strategy 4 vs. 3 was evaluated throughout the 95% confidence interval (95%CI: 10.2%-19.9%) of strategy 4. Using the upper limit for strategy 4 led strategy 3 to become a dominated option (strategy 4 was more effective and less costly due to future costs saved as a consequence of the increase in effectiveness). The lower bound of the confidence interval did not need a cost-effectiveness ratio calculation since strategy 4 is less effective and more costly.

Applying the same procedure to the upper end of strategy 5, and extreme values of 95% confidence interval of strategies 2 and 3, general conclusions kept unchanged.

The *high daily dose schedule* of interferon in combination therapy studied by Puoti et al (5 MU of IFN daily plus ribavirin for 6 months) was also considered in the sensitivity analysis. The cost of this option during the treatment period was 9,595 euros,

exceeded only by 12 months combination therapy. However, the total cost (including future costs derived from disease progression) was 17,390 euros, lower than the cost of the three strategies using combination therapy (strategies 3-5, Table 5 and 6). With a sustained virologic response of 40%, the high daily doses of interferon plus ribavirin increased life years gained by 1.56 and QALYs by 3.03 years vs. “no treatment”, with an incremental cost of 4,373 euros. The ICER for this strategy vs. the “no treatment” option was 2,803 euros per year of life gained and 1,443 euros per QALY, giving it the most favourable incremental cost-effectiveness ratio. However, the small number of patients treated with this schedule does not allow robust conclusions to be made.

DISCUSSION

This is the first study evaluating the cost-effectiveness of combination therapy in previous IFN non responders using a decision analysis model. The study shows how the best option with combination therapy eradicated HCV infection in 2 out of 10 treated patients which prevented further disease complications making this therapy the most efficient from the health care system perspective. An incremental cost per QALY between 6,000 and 10,000 euros and from 9,000 to 20,000 euros per year of life gained depending on the strategy is well within the range of many well-accepted medical interventions and far below the benchmark of 30,000 euros per QALY. The recommended alternative within the undominated options (strategies 1, 4 and 5) would be alternative 5 (combination therapy for 12 months) because it is more effective than strategies 1 and 4, and its incremental cost-effectiveness ratio is still under the indicated benchmark.

However, one of the drawbacks of applying decision models to long-term chronic diseases, like hepatitis C, is that the progression rates between disease states may not accurately reflect real rates. The use of high progression rates may bias the results in favour of better cost-effectiveness ratios[23]. However, the characteristics of non-responder patients who usually have bad prognostic factor such as higher age, more advanced liver disease and high levels of viremia, making the scenario more realistic may balance this bias.

Many cost-effectiveness studies on hepatitis C have focused on untreated patients and relapser patients. In these studies, treatment efficacy rates were obtained from multicenter studies of interferon plus ribavirin including large numbers of patients with chronic hepatitis C[24-26]. IFN non responder patients, in spite of the high proportion they represent, have been involved in fewer clinical trials with fewer patients than other population groups, and only two of the trials included more that 100 patients for each of

the therapeutic options compared[5,27,28]. Unlike other pharmacoeconomic studies, in which treatment efficacy rates were obtained from a pool of clinical trials without specifying the method of estimating global efficacy, our data on sustained virological response was obtained from a previously performed meta-analysis that considered therapeutic strategies in depth using different dosages and durations[5].

Sensitivity analysis for effectiveness data showed some important changes as compared with the base case scenario. However extreme values of the 95% confidence intervals seem highly improbable. But, if it were the case, since the 62,900 € / QALY of incremental cost-effectiveness ratio of strategy 5 vs. 4 can be outside the boundaries of accepted medical interventions, then strategy 4 could be the strategy adopted.

Some studies in untreated patients have suggested a 0.2% probability of spontaneous resolution of hepatitis C while others do not mention about it at all. In our model for non-responder patients spontaneous resolution was not considered because of its rarity in this population.

On efficiency grounds, the decision to treat naïve patients with chronic hepatitis C is sometimes difficult, particularly in patients with mild disease, low degree of fibrosis, normal ALT levels or older age. In previous non-responders, the decision to treat is still more difficult because the treatment response with interferon and ribavirin is lower than in naïve patients and the probabilities of achieving a sustained virological response are also lower. On the other hand, these patients have more aggressive disease with a higher frequency of cirrhosis than untreated patients. Appropriate candidate selection, good patient care and motivation, and correct management of side effects could increase therapy compliance and therefore improve sustained virological response rates as well as cost-effectiveness ratios. Age at the start of treatment is an important

factor in candidate selection, because the benefits of treating patients over 65 are small, and the decision to treat should be individualized for each patient.

Most published studies in non-responders have focused on different therapeutic strategies. However, data on patients baseline characteristics such as HCV genotype, viral load, ALT levels, degree of fibrosis, etc … are too scarce to apply to cost-effectiveness analyses. Analysing these factors, as well as new therapeutic strategies, could improve cost-effectiveness ratios in non-responders but more studies in this setting are necessary to obtain robust results.

In the coming years, the non-responder population will grow to become one of the main challenges in Hepatitis C virus therapy due to their higher probabilities of developing complications. This population, together with genotype 1 patients, will be an important focus of future studies. Until new effective therapies appear, combination therapy with interferon plus ribavirin for 12 months should be considered the most efficient option for these patients.

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TABLE 1. Annual transition probabilities of progression between health states[6,11].

INITIAL STATE	TO	% PROGRESSION
Mild chronic hepatitis C	Moderate chronic hepatitis C	4.1
Moderate chronic hepatitis C	Cirrhosis	7.3
Cirrhosis	Hepatocellular carcinoma	1.5
	Hepatic encephalopathy	0.4
	Variceal bleeding	1.1
	Ascites	2.5
Hepatocellular carcinoma	Death	86.0
Hepatic encephalopathy	Death 1st year	68.0
	Death subsequent yrs.	40.0
	Liver transplantation	3.1
Variceal bleeding	Death 1st year	40.0
	Death subsequent yrs.	13.0
	Liver transplantation	3.1
Ascites	Death	11.0
	Refractory ascites	6.7
	Liver transplantation	3.1
Refractory ascites	Death	33.0
Liver transplantation	Death 1st year	21.0
	Death subsequent yrs.	5.7

TABLE 2. Effectiveness, health resources use and total cost for the therapeutic strategies considered[5,9,11].

	THERAPEUTIC STRATEGIES				
	1	**2**	**3**	**4**	**5**
Duration (months)	-	6	6	6	12
IFN dose	-	3 MU t.t.w.	3 MU t.t.w.	5 MU t.t.w.	3 MU t.t.w.
Rivabirin dose	-	-	1 g / day	1 g / day	1 g / day
End of treatment response	0.0%	7.5%	26.0%	29.0%	27.0%
Sustained response	0.0%	2.0%	12.5%	14.5%	20.5%
First visit	-	1	1	1	1
Follow-up visits	-	2	3	3	5
Lab test	-	3	4	4	6
HCV-RNA test	-	1	2	2	3
TSH lab test	-	2	2	2	3
Drug cost (€)	-	1,407	5,531	6,469	11,063
Monitoring Cost (€)	-	455	603	608	917
Total cost (€)	-	1,862	6,244	7,187	12,090

LEGENDS:

€: euros; t.t.w.: three times a week.

TABLE 3. Utility values for health states[6,11].

HEALTH STATES	ASSOCIATED UTILITY
Viral negative	0.89
Mild chronic hepatitis C	0.73
Moderate chronic hepatitis C	0.69
Cirrhosis	0.62
Liver transplantation (subsequent yrs.)	0.62
Liver transplantation (1st year)	0.45
Ascites	0.31
Hepatic encephalopathy	0.27
Variceal bleeding	0.25
Hepatocellular carcinoma	0.09
Death	0.00

TABLE 4. Annual cost of clinical states involved in chronic hepatitis C progression[11].

CLINICAL STATE	Euros 2001
Mild chronic hepatitis C	189
Moderate chronic hepatitis C	189
Cirrhosis	339
Ascites	1,106
Refractory ascites	8,428
Variceal bleeding (1st year)	3,857
Variceal bleeding (subsequent yrs.)	1,174
Hep. encephalopathy (1st year)	4,686
Hep. encephalopathy (subsequent yrs.)	1,196
Hepatocellular carcinoma	5,294
Liver transplantation (1st year)	108,349
Liver transplantation (subsequent yrs.)	11,965
Death	5,529

TABLE 5. "Base case" results and incremental cost-effectiveness ratios using QALYs as measure of outcomes.

Base case analysis results			Incremental cost-effectiveness ratio comparing each option vs. "no treatment" option.			Incremental cost-effectiveness ratio comparing each option vs. the next most efficacious one.		
Strategy	**Total Cost (€)**	**Effectiveness (QALYs)**	**Incremental Cost (€)**	**Incremental Effectiveness (QALYs)**	**Cost / Effectiveness (€/QALY)**	**Incremental Cost (€)**	**Incremental Effectiveness (QALYs)**	**Cost / Effectiveness (€/QALY)**
Strategy 1	13,159	10.89	-	-	-			
Strategy 2	14,760	11.04	1,601	0.15	10,673 (Ext Dom)	1,601	0.15	10,673 (Ext Dom)
Strategy 3	17,771	11.83	4,612	0.94	4,907 (Ext Dom)	3,011	0.79	3,812 (Ext Dom)
Strategy 4	18,453	11.99	5,294	1.1	4,813	682	0.16	4,262
Strategy 5	22,573	12.44	9,414	1.55	6,073	4,120	0.45	9,155

LEGENDS:

€: euros; Ext Dom: extended dominance.

TABLE 6. "Base case" results and incremental cost-effectiveness ratios using years of life gained as measure of outcomes.

Base case analysis results			Incremental cost-effectiveness ratio comparing each option vs. "no treatment" option.			Incremental cost-effectiveness ratio comparing each option vs. the next most efficacious one.		
Strategy	**Total Cost (€)**	**Effectiveness (years of life)**	**Incremental Cost (€)**	**Incremental Effectiveness (years of life)**	**Cost / Effectiveness (€/year of life)**	**Incremental Cost (€)**	**Incremental Effectiveness (years of life)**	**Cost / Effectiveness (€/year of life)**
Strategy 1	13,159	16.97	-	-	-	-	-	-
Strategy 2	14,760	17.05	1,601	0.08	20,011 (Ext Dom)	1,601	0.08	20,011 (Ext Dom)
Strategy 3	17,771	17.46	4,612	0.49	9,413 (Ext Dom)	3,011	0.41	7,345 (Ext Dom)
Strategy 4	18,453	17.54	5,294	0.57	9,288	682	0.08	8,524
Strategy 5	22,573	17.77	9,414	0.8	11,767	4,120	0.23	17,912

LEGENDS:

€: euros; Ext Dom: extended dominance.

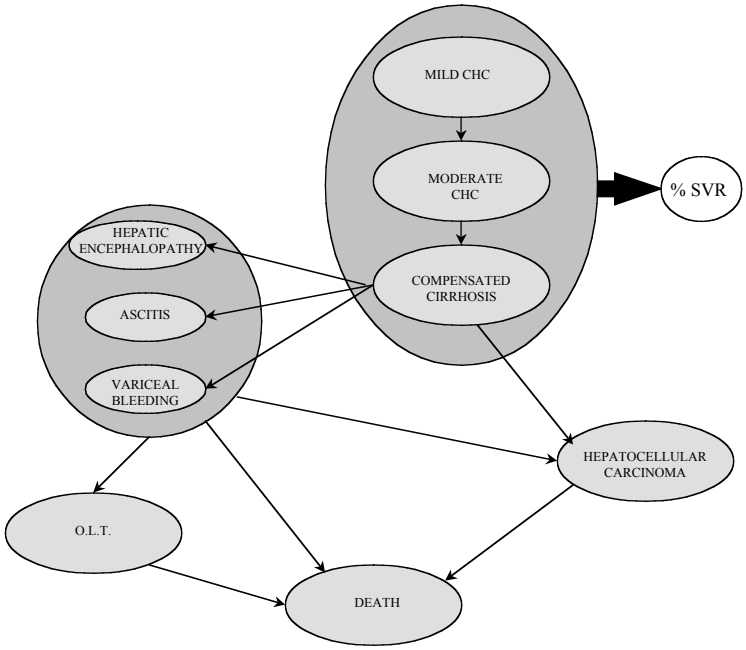
TABLE 7. Sensitivity analysis for Incremental cost-effectiveness ratio of different options vs. "no treatment" in the base case patient.

Variable	Rank (lower-higher)	STRATEGY 2 vs. 1 (€ / QALY)	STRATEGY 3 vs. 1 (€ / QALY)	STRATEGY 4 vs. 1 (€ / QALY)	STRATEGY 5 vs. 1 (€ / QALY)
Age (years)	**30 - 60**	8,176 - 18,946	3,596 - 9,932	3,561 - 9,758	4,532 - 12,049
Discount rate (%)	**0% - 5%**	4,793 - 16,745	1,820 - 7,685	1,793 - 7,569	2,450 - 9,329
Annual transition probabitily from mild to moderate CHC	**2.05% - 8.2%**	10,713 - 9,959	5,000 - 4,707	4,943 - 4,637	6,193 - 5,872
Annual transition probabitily from moderate CHC to cirrhosis	**3.65% - 14.6%**	12,676 - 9,165	5,910 - 4,060	5,869 - 4,019	7,276 - 5,129
Annual rate of liver transplantation	**1.55% - 6.2%**	10,305 - 10,140	5,116 - 4,376	5,082 - 4,326	6,309 - 5,582

LEGENDS:

€: euros.

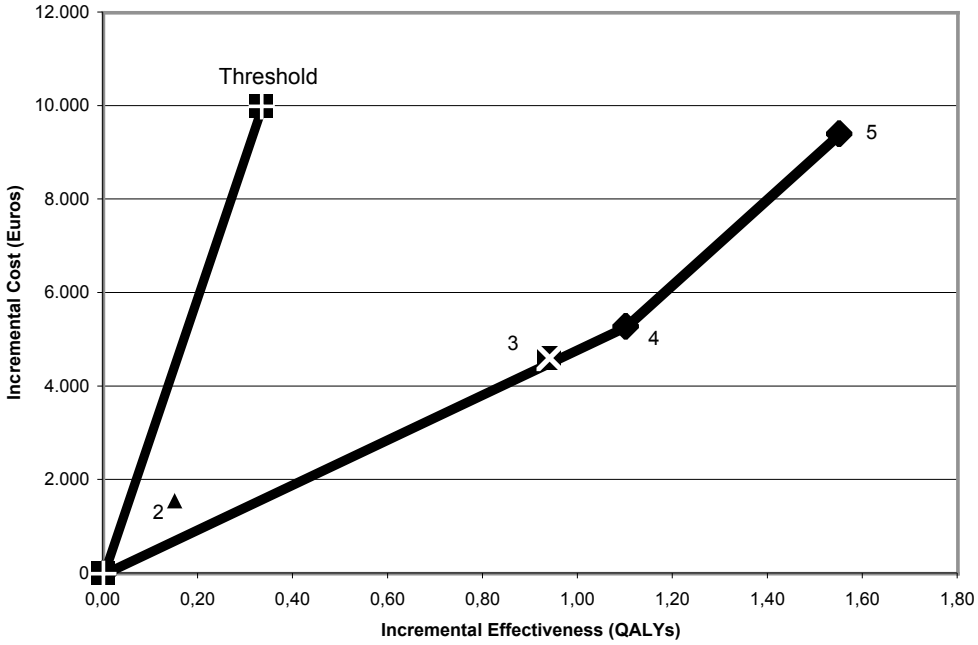
FIGURE 1. Hepatitis C progression health states and transitions.



LEGENDS:

CHC: chronic hepatitis C; O.L.T.: ortho liver transplant; SVR: sustained virological response.

FIGURE 2. Incremental cost-effectiveness ratio for each therapeutic strategy vs. "no treatment" and threshold of 30,000 €/QALY.



LEGENDS:

2: 1,601 € / 0.15 QALYs; **3**: 1,612 € / 0.94 QALYs; **4**: 5,294 € / 1.1 QALYs; **5**: 9,414 € / 1.55 QALYs.

€: euros; Threshold: 30,000 € / QALY.