A health economic model to assess the long term effects and cost-effectiveness of PEG IFN α-2a in hepatitis C virus infected patients

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Abstract

Objectives : **Chronic Hepatitis C (CHC) is associated with long-term complications. Treating CHC with Pegylated interferon α-2a (PEG IFN α-2a) improves response rates and may contribute to less morbidity and mortality compared to standard interferon therapy. The objectives of this study were to estimate the long-term clinical consequences of such treatment as well as the resulting cost-effectiveness.**

Research design and methods : **A Markov model was developed in order to predict the clinical and economic outcomes over a 25 year period. Three analyses were conducted : 1. for all Hepatitis C Virus (HCV) genotypes where PEG IFN α-2a was compared to interferon α-2a (IFN α-2a) in monotherapy for 48 weeks ; 2. for the HCV genotypes 1-4-5-6 comparing PEG IFN α-2a with interferon α-2b (IFN α-2b) both combined with ribavirin 1000/1200mg for 48 weeks ; and 3. where PEG IFN α-2a with 800 mg ribavirin was compared to IFN α-2b with ribavirin 1000/1200 mg for 24 weeks in genotypes 2 and 3.**

Results : **In analysis one the cost-effectiveness of PEG IFN α-2a is 4,569 /quality adjusted life year (QALY) gained. In the second analysis, the result was € 14,763 / QALY, while for the 24 weeks therapy (analysis 3) the result was 903 per QALY gained. In an extensive sensitivity analysis cost-effectiveness was confirmed within reasonable assumptions.**

Conclusions : **These results suggest that PEG IFN α-2a is cost-effective in the management of all CHC patients. Real life evidence about longer term benefits of PEG IFN α-2a will be of importance for future decision making.** (Acta gastroenterol. belg., **2004**, 67, **1-8**).

Key words : interferons, cost effectiveness, hepatitis C virus.

Introduction

A clinical Hepatitis C virus (HCV) infection is estimated to affect 3/100,000 people per year in Belgium (1). Its prevalence is estimated at 0.87% (2).

Few patients with chronic hepatitis C are treated, which is explained by different factors : no adherence to evaluations procedures, medical or psychiatric contraindications, not diagnosed, etc… According to Shepherd *et al.* (3) only 50% of the patients diagnosed with chronic hepatitis C are under specialist care. Of those, only 50% receive a liver biopsy and only 26% is treated. For Belgium, this would mean about 725 treated patients each year. Note that Delwaide (4) reports 700 treated patients per year in Belgium. It is stated by the same author that the prevalence of chronic hepatitis C will not increase in the future but that the number of complications related to chronic hepatitis C will rise.

Twenty per cent of cirrhosis cases and 47% of hepatocellular carcinoma (HCC) in the French Community are related to Hepatitis C and more than 29% of the current indications for liver transplantation are related to Hepatitis C in Belgium (5). Hence, there is clearly still room for improving the outcomes of managing hepatitis C.

Chronic HCV infection is currently mostly managed with interferon alpha, in combination with ribavirin. Treatment with interferon alpha in monotherapy is only indicated in exceptional cases of intolerance or contra-indication to ribavirin. The NHS in the UK showed that in interferon alpha naïve patients, the cost-effectiveness of combination therapy is equal to $ 7,578 /QALY gained, which is considered as a good result (3), and confirms the current use of this combination therapy as standard therapy.

It is recommended, however, to assess after a number of weeks of treatment the prediction of a sustained viral response by using a qualitative PCR (polymerase chain reaction) test, assessing the presence or absence of HCV-RNA. This predictive management of patients is different depending on the treatment strategy and the genotype :

– in patients receiving monotherapy, it is recommended to conduct an early predictive qualitative test after 12 weeks. Total treatment takes usually at least 48 weeks in these patients.
– in genotype 1 patients receiving combination therapy, a predictive test is recommended after 24 weeks. Again, total treatment takes usually 48 weeks in these patients.
– patients with genotype 4-5-6 should be treated and followed-up in a similar way as genotype 1 patients. The number of these patients, however, is very small compared to the other genotypes.
– in genotypes 2-3 patients, a predictive test is not recommended, because of shown poor predictability. Total treatment takes usually only 24 weeks in these patients.

The advantages of using PEG IFN α-2a versus standard interferon α (IFN) include a higher sustained viral

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response (SVR), less side effects such as depression and flu-like symptoms, an earlier prediction of success of therapy (12 weeks vs 24 weeks), and a better quality of life (6,7,8,9). Different studies showed indeed that PEG IFN α-2a 180 µg once a week was more effective than interferon α-2a 3MIU 3 tiw (10,11,12,13) in terms of SVR, whereby SVR is defined as a PCR negative test (absence of HCV RNA), 24 weeks post treatment cessation.

Moreover, in trials involving PEG IFN α-2a, testing for early viral response (EVR) was performed by applying a *quantitative* test measuring the reduction of HCV RNA (a reduction by more than 2 log10 or unquantifiable HCV RNA being considered as EVR), and leading to better predictability as well in monotherapy (11) as in combination therapy (13,14).

In current health care environments, safety and efficacy are insufficient for decision making on new drugs. The "value for money" (the cost-effectiveness) is becoming a key criterion in decision making especially from a societal viewpoint.

The objective of this study was therefore to compare the costs and effects of applying PEG IFN α-2a in combination with quantitative testing versus IFN alpha in combination with qualitative testing in chronic HCV patients. Both were analysed in monotherapy and combination therapy with ribavirin, and the Belgian health care setting was used as a case.

Research design and methods

Epidemiological model

Cost-effectiveness was analysed using a Markov state transition model (15). This model was developed using MS Excel 2000. The design of this model was based in part on an earlier decision-analytic model of the outcomes, clinical management, and costs of hepatitis C that was developed by Younossi *et al.* (16).

The Markov-process technique is used to model the evolution of a cohort of patients over time, when therapy is initiated with a specific treatment option. Markov processes occur within discrete time frames. Time progresses in units of fixed length, called stages. In our analysis, this time frame is set at 1 year. At each stage, a patient is in a given health/treatment state. Each new stage, the patient can move from one state to another. In total, 25 stages (= 25 years) were considered. This 25 years horizon was applied since complications related to hepatitis C virus infection only become apparent after many years and since clinical guidelines in hepatology systematically refer to 25 years as a relevant period for assessing a risk of complications.

The model is programmed in order to assess 2 possible treatment scenarios in 3 considered patient populations : PEG IFN α-2a versus IFN α-2a in monotherapy for 48 weeks (analysis 1) ; PEG IFN α-2a versus IFN α-2b both in combination with ribavirin 1000-1200 mg / day in genotype 1-4-5-6 for 48 weeks (analysis 2), and PEG IFN α-2a with ribavirin 800 mg / day for 24 weeks versus IFN α-2b with ribavirin 1000-1200 mg / day for 24 weeks in patients with genotype 2 or 3 (analysis 3). In the latter population lower doses of ribavirin are used in the PEG IFN α-2a arm because these genotypes (2 and 3) are much more sensible to PEG IFN α-2a and therefore need less ribavirin(14). All patients enter the Markov model in a health state defined as "HCV infected, free of complications".

Stages of HCV after treatment depend on the results of the treatment. Patients with sustained virological response do not progress, while non responding patients may progress to compensated cirrhosis. Compensated cirrhosis can evolve to hepatocellular carcinoma or decompensated cirrhosis. From decompensated cirrhosis a patient can evolve to hepatocellular carcinoma, may need to undergo a liver transplant or may die. From hepatocellular carcinoma and liver transplant a patient can only evolve to death. The model is shown in figure 1.

It was assumed that patients cannot evolve directly from compensated cirrhosis to the death state. Furthermore, we assume that within the same year, only one transition is possible. For instance, a patient can not have a compensated cirrhosis and a hepatocellular carcinoma in the same year, which is a conservative assumption.

Clinical data applied in the model

Sustained Viral Response rates

In analysis 1 (monotherapy) PEG IFN α-2a is compared to IFN α-2a in monotherapy in all patients, without distinction between genotypes. Note that currently in Belgium, the use of this monotherapy is quite rare.

Clinical data in this analysis are based on Zeuzem *et al.* (9). This was a randomised clinical trial (RCT) (n = 267) with PEG IFN α-2a 180 µg once weekly for 48 weeks (267 patients) versus IFN α-2a 6 MIU tiw for 12 weeks, followed by IFN α-2a 3 MIU tiw for 36 weeks (264 patients). The PEG IFN α-2a arm showed a SVR at week 72 of **38.1%** vs. **15.7%** for IFN α-2a. Analysis of the early viral responses (EVR) showed that at week 12, **78.9%** (HCV RNA negative *or* decreased HCV RNA by 2 log 10) of PEG IFN α-2a patients had an early response compared to **33.7%** (qualitative test) of patients on Interferon at week 12 (table 1). As explained before, in the case of PEG IFN α-2a a quantitative method is used for assessing the EVR, while in the IFN arm a qualitative test is used. Note also that in reality, in case of no EVR, treatment is normally stopped. In the clinical trials, however, the treatment was continued in patients without an EVR. Therefore, in our model we adjusted this anomaly by only taking into account SVR rates for patients with EVR and omitting the patients without EVR (see Table 1).

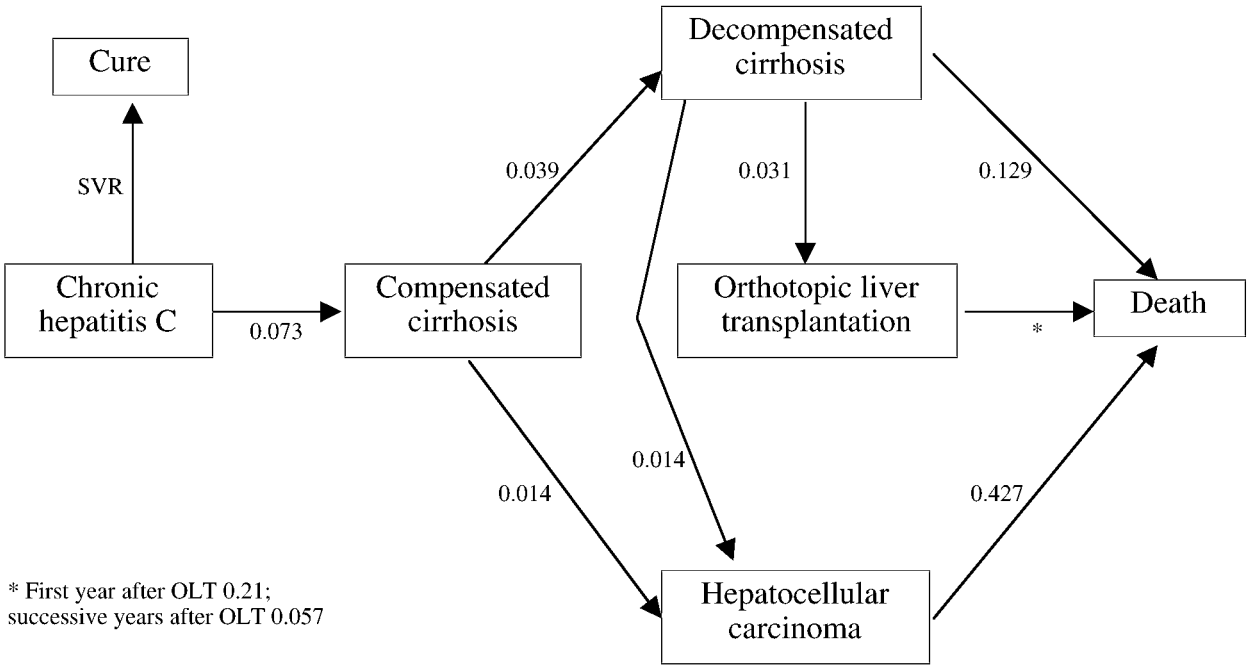

Figure 1. — Simplified structure of the model

Table 1. — **EVR's rates and corresponding SVR's rates for all genotypes in monotherapy**

PEG IFN α-2a	SVR	no SVR	TOT	EVR%
EVR 12 weeks no EVR 12 weeks	101 1	108 55	209 56	**78.9%**
TOT	102	163	265	
SVR (if EVR)	**38.1%***			
	NPV PPV	0.982 0.483		
IFN	SVR	no SVR	TOT	
EVR 24 weeks no EVR 24 weeks	47 1	128 85	175 86	**33.7%**
TOT	48	213	261	
SVR (if EVR)	**15.7***			
	NPV PPV	0.988 0.257		

* note that the patients without EVR at 12 weeks and who still showed a SVR later on, are not calculated in the final SVR rate, since in real life treatment will be stopped, whereas in the trial treatment was continued. EVR = early viral response ; SVR = sustained viral response ; NPV = negative predictive value ; PPV = Positive predictive value.

In analysis 2 (combination therapy, genotype 1-4-5-6) PEG IFN α-2a is compared to IFN α-2b, both in combination with ribavirin 1000-1200 mg/day in genotype 1-4-5-6 (GT 1-4-5-6) patients.

Results are based on a study by Fried *et al.* (13). This was a RCT including, among others, 725 GT1-4-5-6 patients comparing PEG IFN α-2a 180 µg once a week plus ribavirin 1000-1200 mg / day for 48 weeks with interferon alfa-2b 3 MIU tiw plus ribavirin 1000-1200 mg/d. From this trial, we obtained the detailed data related to early response and sustained response for the different genotypes separately and for both arms. Patients with HCV genotype 1-4-5-6 receiving PEG IFN α-2a 180 µg once a week with Ribavirin 1000-1200 mg / day for 48 weeks showed a **44.4%** SVR rate (Table 2) and a **81.4**% EVR rate (HCV RNA unquantifiable or decreased HCV RNA by 2 log 10) at 12 weeks. Patients with HCV genotype 1-4-5-6 receiving IFN alfa-2b with Ribavirin 1000-1200 mg / day for 48 weeks showed a **33.6%** SVR rate (see Table 2) and a **51.3**% EVR rate at 24 weeks (qualitative).

In analysis 3 (combination, genotype 2,3) we compared genotype 2 or 3 patients receiving PEG IFN α-2a 180 µg once a week and ribavirin 800 mg / day for 24 weeks with interferon alfa-2b and ribavirin 1000-1200 mg / day for 24 weeks.

In these patients no testing is recommended at week 12 given the poor predictive value of early response rates in these patients. Unfortunately, we were not able to use the Fried *et al.* (13) trial for PEG IFN α-2a, since in this trial 1000-1200 mg of ribavirin / day during 48 weeks was used in all treatment arms. Therefore, we used data from Hadziyannis *et al.* (14), a study comparing a combination of PEG IFN α-2a with 800 mg/day ribavirin during 24 weeks and during 48 weeks with a combination with 1000-1200 mg/day ribavirin during 24 and 48 weeks. Detailed data per genotype were available on file. Genotype 2,3 patients receiving PEG IFN α-2a 180 µg once a week and ribavirin 800 mg/day for 24 weeks showed a SVR rate of 82.3%. Note that in that trial the results after 48 weeks of treatment were slightly worse than after 24 weeks.

Table 2. — **EVR's rates and corresponding SVR's rates for genotype 1,4,5,6**

PEG IFN α-2a	SVR	no SVR	TOT	EVR%
EVR 12 weeks no EVR 12 weeks	138 1	115 57	253 58	**81.4%**
TOT	139	172	311	
SVR (if EVR)	**44.4%***			
	NPV PPV	0.983 0.549		
IFN	SVR	no SVR	TOT	
EVR 24 weeks no EVR 24 weeks	100 5	53 140	153 145	**51.3%**
TOT	105	193	298	
SVR (if EVR)	**33.6%***			
	NPV PPV	0.966 0.654		

* note that the patients without EVR at 12 weeks and who still showed a SVR later on, are not calculated in the final SVR rate, since in real life treatment will be stopped, whereas in the trial treatment was continued. EVR = early viral response ; SVR = sustained viral response ; NPV = negative predictive value ; PPV = Positive predictive value.

In Fried *et al.* (13), however, genotype 2,3 patients receiving INF α -2b and ribavirin 1000-1200 mg/day for 48 weeks had a SVR of 60.5%. Given the observation from Hadziyannis *et al.* (14) above, we assume these INF α -2b patients would obtain the same results after 24 weeks of treatment. Since in both Hadziyannis *et al.* (14) and in Fried *et al.* (13) one arm with PEG IFN α-2a plus ribavirin 1000-1200 mg/day for 48 weeks was included, there is a common arm in both trials which allows to compare and adjust outcomes from both trials. Concretely, for this common arm, the SVR after 48 weeks treatment is 73.8% in Hadziyannis *et al.* (14) and 71.4% in Fried *et al.* This means that the above mentioned 82.3% for PEG IFN α-2a 180 µg / week and ribavirin 800 mg/day for 24 weeks (from Hadziyannis *et al.* (14)) should be adjusted in order to be comparable with the IFN alfa-2b result from Fried (13). Simple adjustment using hazard rates results in a SVR rate for PEG IFN α-2a 180 µg/week and ribavirin 800 mg / day for 24 weeks of 80.1%.

In summary, the applied SVR rates are **80.1%** for PEG IFN α-2a 180 µg and ribavirin 800 mg/day and **60.5%** for IFN alfa-2b and ribavirin 1000-1200 mg/day, both for 24 weeks.

Probability estimates of progression in non responders

Since the model was based on Younossi *et al.* (16), we considered the probabilities published by these authors. Table 3 shows the annual transition probabilities as described by Younossi *et al.* (16). The advantage of the Younossi *et al.* (16) data is that ranges for the different transition probabilities are provided, which allows the use of worst case and best case scenarios in sensitivity analyses. A study by Wong *et al.* (17) shows similar probabilities partly based on the same studies as Younossi *et al.* (16), however, without showing ranges.

Table 3. — **Probabilities based on Younossi *et al.* (16)**

From	**To**	**Annual probability in% (range)**
Chronic hepatitis	Cirrhosis	7.3 (1.0-23.2)
Cirrhosis	Hepatocellular carcinoma	1.4 (1.0-4.4)
	Decompensated cirrhosis	3.9 (2.0-8.3)
Decompensated cirrhosis	HCC	1.4 (1.0-4.4)
	Liver transplantation	3.1 (1.0-6.2)
	Death	12.9 (6.5-19.3)
Hepatocellular carcinoma	Death	42.7 (33-86)
Liver transplantation	Death (first year)	21 (6-42)
	Death (subsequent years)	5.7 (2.4-11)

Table 4. — **Utilities estimates**

Utilities estimates	Younossi 1999	Sagmeister 2001	Sennfält 2001
viral negative	**1**		**1**
Chronic Hepatitis C	**0.82 (0.6-0.9)**	0.9	
Mild			0.82
Moderate			0.78
Compensated Cirrhosis	**0.78 (0.5-0.9)**	0.75	0.7
Decompensated Cirrhosis	**0.65 (0.3-0.88)**		
Hepatocellular Carcinoma	**0.25 (0.1-0.5)**	0.2	0.1
Liver transplantation, 1st year	**0.5 (0.11-0.7)**	0.7	0.5
Liver transplantation, subsequent years	**0.7 (0.24-0.87)**	0.8	0.7
IFN		0.8	0.93
IFN-Ribavirin		0.7	0.86

Sagmeister *et al.* (18) used the time trade-off technique to estimate the quality of life of the health states in a panel of Swiss physicians (3 hepatologists and 2 gastroenterologists). Sennfällt *et al.* (19) based utility data on the study of Wong (20). Younossi *et al.* (16) based utilities estimates on the studies of Bennett *et al.* (21), and Kim *et al.* (1997). Note that the Sagmeister *et al.* (18) and Sennfält *et al.* (19) data are always within the range of Younnosi *et al.* (16).

Utilities estimates

The model aims at estimating the total amount of QALYs for the different treatment strategies. In the literature we found different estimates of utilities. The bold figures in Table 4 show the current estimates used in the model. The utilities reported by Younossi *et al.* (16) are used in the model and show similarity with the other utilities found in different studies.

Note, however, that some authors (see last rows of the table) apply utilities for IFN treatment as such (decreased utility due to adverse events). This approach may be beneficial for PEG IFN α-2a, but utility data associated with the latter are not available.

Cost

Complications from hepatitis C

In the literature we found different values for cost of the different states of hepatitis. In the model, we applied costs obtained from a Belgian setting (23). Table 5 shows that the Belgian cost estimates are in general lower than the cost estimates in the other, foreign publi-

Table 5. — **Medical care costs**

Studies (see footnotes)	**1**	**2**	**3**	**4**	**5**	**6**
Cost for health state per year	$	$	€	$	£	€
Chronic hepatitis C				319	95	**125**
Compensated cirrhosis	110	163	276	425	237	**250**
Decompensated cirrhosis		6,885		22,100		**8,060**
Hepatocellular carcinoma						
no operation, 1st year			12,251		13,320	**10,000**
no operation, subsequent years			2,925			
Liver transplantation 1st year	108,659	97,281	125,515	269,072		**50,000**
subsequent years	18,976	16,093	11,598	25,910		**8,700**

1) Wong *et al.* (17) ; 2) Sennfält *et al.* (19) ; 3) Sagmeister *et al.* (18) ; 4) Younossi *et al.* (16) ; 5) Shepherd *et al.* (3) ; 6) Wong *et al.* (23).

cations. As a result, the cost-effectiveness estimates for PEG IFN α-2a versus IFN α will be conservative.

Drug cost

The cost of treatment was calculated for the three models from the health care payer perspective. For the drug treatments, the current public price was taken into account. Thereby, the dosages from the trials, as well as drug cessation rates in case of negative early predictive tests were taken into consideration.

The cost for the treatment in analysis 1 with PEG IFN α-2a and IFN α was respectively € 11,529 and € 4,051. For analysis 2 this was € 17,192 for PEG IFN α-2a combined with ribavirin and € 8,893 for IFN α in combination with ribavirin, after correction for the use of early predictive testing. In analysis 3 the cost for PEG IFN α-2a is € 9,144 versus € 5,878 for IFN α-2b both combined with ribavirin but at different doses (see above).

Results

Base case

The results for the different subgroups are shown in table 6.

In all HCV patients treated with monotherapy PEG IFN α-2a vs. standard IFN, 0.97 quality adjusted life years (QALY) can be gained over the study period. The incremental cost-effectiveness was € 4,569 per QALY gained, which is generally considered as a cost-effective result. In HCV patients with genotype 1-4-5-6 treated with PEG IFN α-2a, both combined with ribavirin 1000/1200 mg 0.47 QALY are gained over the study period. The incremental cost-effectiveness was € 14,763 /QALY gained, which can be considered as acceptable, within the current societal value judgement. Indeed, for instance, in the Netherlands, a cost-effectiveness ratio below € 20,000 /QALY is in general considered cost-effective (24).

In HCV patients with genotype 2-3 treated with PEG IFN α-2a and ribavirin 800 mg vs. IFN α-2a combined with ribavirin 1000/1200 mg 0.83 QALY are gained over the study period. The incremental cost-effectiveness was € 903 per QALY gained, which is very cost-effective.

Sensitivity analysis

Different sensitivity analyses were applied in the different subgroups. Table 7 shows the costs for the different health states. If the costs of the health states are increased by 20%, then treatment becomes less expensive per QALY because more expensive complications are avoided and vice versa. The conclusions are not affected.

When performing the same analysis for the transition probabilities, whereby the range of possible values is assessed, monotherapy stays cost-effective (table 8). The combination therapy in genotype 1-4-5-6 shows a result above the threshold of € 20,000, i.e. € 24,855 for the lower values of transition probabilities and € 7,206 for the highest value. In analysis 3, PEG IFN α-2a remains cost effective.

Finally, in a similar sensitivity analysis, now for utilities, monotherapy stays cost-effective for the entire range of possible utility values. Combination therapy in genotype 1-4-5-6 shows a result slightly above the threshold of € 20,000 (€ 22,468) when applying the high utility values for the disease states and € 8,176 for the low utility values. In analysis 3, PEG IFN α-2a remains very cost effective.

Discussion

The objective of this study was to predict the long term health and economic outcomes of PEG IFN α-2a in chronic hepatitis C patients in combination with quantitative testing. We evaluated the treatment with PEG IFN α-2a in different genotypes and its impact on morbidity and mortality outcomes based on results of long-term trials in chronic HCV patients.

We found that PEG IFN α-2a was cost-effective in all genotypes, both in monotherapy, as in combination therapy with ribavirin.

Table 6. — **Basecase results**

	Costs (in Euro)			Effectiveness	
Treatment cost	Drug cost	Complication	**Total cost**	Total effect Dis QALY	**Result (ICER)**
Monotherapy in all genotypes					
PEG IFN α-2a	9,704	7,884	17,589	13.56	
IFN α-2a	2,407	10,737	13,144	12.59	
Difference	7,297	-2,853	**4,444**	0.97	**4,569/QALY***
Combination therapy GT 1-4-5-6					
PEG IFN α-2a + ribavirin	17,192	7,082	24,274	13.84	
IFN α-2a + ribavirin	8,893	8,459	17,351	13.37	
Difference	8,299	-1,376	**6,923**	0.47	**14,763/QALY**
Combination therapy GT 2-3					
PEG IFN α-2a + ribavirin	9,144	2,535	11,679	15.37	
IFN α-2a + ribavirin	5,878	5,031	10,909	14.54	
Difference	3,266	-2,496	**770**	0.83	**903/QALY**

* note that reported ICER figures in the above and following tables differ slightly from expected figures (4569 ≠ 4444/0.97) due to rounding. The true gain in QALY is indeed 0.9724, which has been rounded to 2 decimals.

Table 7. — **Sensitivity analyses on cost of complications (costs in Euro)**

	cost + 20%	cost	cost - 20%
HCV	150	125	100
comp cirr	300	250	200
decomp cirr	9,672	8,060	6,448
HCC	12,000	10,000	8,000
Ltx 1st y	60,000	50,000	40,000
Ltx subs y	10,440	8,700	6,960
monotherapy all patients			
Cost of drug PEG IFN α-2a	9,704	9,704	9,704
Complication cost PEG IFN α-2a	9,461	7,884	6,307
Total cost PEG IFN α-2a	19,465	17,589	16,012
Cost of drug interferon	2,407	2,407	2,407
Complication cost interferon	12,885	10,737	8,590
Total cost interferon	15,292	13,144	10,997
Cost/QALY	**3,983**	**4,569**	**5,156**
Genotype 1-4-5-6			
Cost of drug PEG IFN α-2a	17,192	17,192	17,192
Complication cost PEG IFN α-2a	8,498	7,082	5,665
Total cost PEG IFN α-2a	25,690	24,274	22,857
Cost of drug interferon	8,893	8,893	8,893
Complication cost interferon	10,149	8,457	6,766
Total cost interferon	19,042	17,351	15,659
Cost/QALY	**14,176**	**14,763**	**15,350**
Genotype 2-3			
Cost of drug PEG IFN α-2a	9,144	9,144	9,144
Complication cost PEG IFN α-2a	3,042	2,535	2,028
Total cost PEG IFN α-2a	12,186	11,679	11,172
Cost of drug interferon	5,878	5,878	5,878
Complication cost interferon	6,037	5,031	4,025
Total cost interferon	11,915	10,909	9,903
Cost/QALY	**318**	**903**	**1,419**

In the sensitivity analysis of combination therapy in HCV genotype 1-4-5-6 with PEG IFN α-2a and ribavirin v.s. IFN α-2b and ribavirin we found that the cost passed a frequently cited societal acceptance limit of € 20,000 only in extreme circumstances.

It should be noted that in the data of combination therapy in genotype 2-3 we assumed that a 24 week result for IFN would be comparable to a 48 weeks result. This was based on the observation that with PEG IFN α-2a the SVR at 48 weeks is comparable to the results at

Table 8. — **Sensitivity analyses on transition probabilities and utility values (costs in Euro)**

Transition probabilities			
	Minimal value probabilities	**Basecase**	**Maximal value probabilities**
Monotherapy			
Total cost PEG IFN α-2a	11,784	17,589	19,209
Total cost IFN α-2a	5,239	13,144	15,341
Difference Dis QALY	0.66	0.97	1.91
Incremental cost/QALY	**9,883**	**4,569**	**2,019**
Combination therapy GT 1-4-5-6			
Total cost PEG IFN α-2a + ribavirin	19,060	24,274	25,723
Total cost IFN α-2a + ribavirin	11,124	17,351	19,081
Difference Dis QALY	0.32	0.47	0.93
Incremental cost/QALY	**24,855**	**14,763**	**7,206**
Combination therapy GT 2-3			
Total cost PEG IFN α-2a + ribavirin	9,813	11,679	12,197
Total cost IFN α-2a + ribavirin	7,205	10,909	11,939
Difference Dis QALY	0.58	0.85	1.67
Incremental cost/QALY	**4,500**	**903**	**81**
Utility values			
	Minimal value utilities	**Basecase**	**Maximal value utilities**
Monotherapy			
Difference QALY	1.76	0.97	0.64
Incremental cost/QALY	**2,531**	**4,569**	**6,954**
Combination therapy GT 1-4-5-6			
Difference QALY	0.84	0.47	0.3
Incremental cost/QALY	**8,176**	**14,763**	**22,468**
Combination therapy GT 2-3			
Difference QALY	1.54	0.85	0.56
Incremental cost/QALY	**501**	**903**	**1,376**

24 weeks. Therefore, we believe this assumption is justified.

As it is common practice in Belgium for the treatment of chronic hepatitis C, we applied in the models EVR rates for IFN a based on qualitative HCV RNA tests, which is current practice. For the PEG IFN α-2a treatment groups we applied the quantitative PCR test detecting -2 log 10 in HCV RNA. This assumption could be criticised since not only two different drugs but also different testing methods are compared. However, we felt that is was more relevant to reflect real practice here, rather than have an artificial comparison.

Another remark is that extra-hepatic consequences of HCV have not been taken into account, leading to a conservative estimate of potential savings and thus an underestimation of the cost-effectiveness of PEG IFN α-2a .

With regard to costs, we observed a discrepancy between the cost data for liver transplant obtained for Belgium and those in other countries. This is likely due to the active liver transplant policy in Belgium resulting in less expensive liver transplants than in the surrounding countries. At the same time, this suggests that the transition probability to liver transplants is likely underestimated, which means that the model results in conservative estimates of cost-effectiveness. In the US, in 2000, almost 16.4 persons per million had a liver transplant (based on Organ Procurement and Transplantation Network/Scientific Registry of Transplant Patients data of August 1, 2001). In Belgium, in 2001 this figure was 22.4 (23). If we adjust our transition probability to transplantation from 0.031 to 0.042 (i.e. applying a factor = 22.4/16.4) in our models then the cost/QALY becomes € 4,490 in monotherapy, € 14,695 in combination therapy for genotype 1-4-5-6 , and € 821 in combination for genotype 2-3 respectively.

Regardless of the above issue, it seems that the costs for hepatitis C complications provided by Wong *et al.* (23) seem to be an underestimation when compared to the UK and Switzerland. Hence we believe that the true costs will be closer to the upper limit of our sensitivity analysis on cost. When the costs per complication increase, then the more effective treatment will become more cost-effective as well.

Finally, the utility loss associated with IFN was not taken into account since no utility data are available for PEG IFN α-2a. Since PEG IFN α-2a is better tolerated than IFN, this again means that our analysis is conservative and underestimates the true value of PEG IFN α-2a.

In conclusion, our results suggest that PEG IFN α-2a is cost-effective in the management of chronic HCV patients. As with all new drugs, exercises like this one are important for timely assessment of the potential cost-effectiveness of new technologies. Observational evidence on longer term benefits of PEG IFN α-2a would be of importance for future decision making and validation of our results.

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