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ORIGINAL ARTICLE

Cost-effectiveness analysis of antiviral treatment in liver transplant recipients with HCV infection

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Summary

Within 5–10 years, 20–40% of hepatitis C virus (HCV)-infected liver transplant recipients can be expected to develop cirrhosis. Here, cost-effectiveness of antiviral therapy was assessed. A Markov model was developed to simulate disease progression and calculate outcome and costs of treatment. In the baseline analysis, Peg-IFN/RBV treatment prevented organ loss/death, gained quality-adjusted life-years (QALYs) and undercut the limit of cost-effectiveness of €50 000/QALY with an incremental cost-effectiveness ratio of approximately €40 400/QALY and €21 000/QALY for HCV genotype 1 and 2/3 patients, respectively. Furthermore, sensitivity analysis testing modified model parameters according to extreme data described in the literature confirmed cost-effectiveness for a lower or higher rate of fibrosis progression, increased non-HCV-related mortality, lower limits of utilities, a time horizon of 30 years, and additional costs in the year of death. On the other hand, cost-effectiveness was lost for patients with genotype 1 in case of doubled antiviral or life-time costs or an increased discount rate of 7%. New treatment strategies for HCV genotype 1 infected patients remained on the same level cost-effective, if additional costs did not exceed €10 774 per 10% sustained virologic response gain. We conclude that Peg-IFN/RBV treatment is cost-effective post transplant. This may support treatment decision in individual cases.

Hepatitis C virus (HCV)-associated liver cirrhosis is the most common indication of liver transplantation (OLT) in Western Europe and the United States [1]. However, because of recurrence of disease, outcome is worse than in non-HCV-infected patients [2]. Recurrent viremia develops universally and reinfection of the graft has been shown to cause graft cirrhosis in 20–40% of untreated patients within 5–10 years [2–5].

In nontransplant patients with chronic hepatitis C, combination therapy with pegylated interferon α and ribavirin (Peg-IFN/RBV) is an established therapy achieving sustained virologic response (SVR) rates between 40% and 60% in genotype 1 [6] and 70–90% in genotype 2/3 patients [7–9]. Several analyses verified efficacy and cost-effectiveness of this antiviral treatment based on high costs for sequelae treatment as well as productivity loss of untreated patients and on the other hand, long-term resource savings after successful treatment and virus eradication [10].

Compared with chronic HCV patients, treatment with Peg-IFN/RBV has far more side effects and, in addition, is much less effective in transplant recipients [6,11–13]. On average, only SVR rates between 20% and 35% in patients with genotype 1 and 40% and 70% in patients with genotype 2/3 have been achieved [11]. To optimize treatment response, hematopoietic growth factors are often given.

However, this is very expensive and erythropoietin and granulocyte colony-stimulating factors are not licensed for this indication. So far, in the transplant setting, cost-utility of Peg-IFN/RBV treatment with respect to long-term outcome of treated versus untreated patients has not been well established. Furthermore, neither in the nontransplant nor in the transplant setting, cost-effectiveness of new treatment strategies, which increase response rate using expensive hematopoietic growth factors or new direct-acting antiviral drugs, has been considered.

In general, a cost-effectiveness analysis (CEA) measures outcome of competitive interventions – here treatment versus no treatment – by comparing their economic costs and clinical effectiveness, using the ICER (incremental cost-effectiveness ratio), i.e., the ratio of differences of costs to effectiveness. To standardize measurement of clinical effectiveness, quality-adjusted life-years (QALYs) are used, which combine quantity (longevity) and quality (morbidity) of life. A treatment strategy is regarded as cost-effective if the ICER undercuts the societally accepted limit, which is in Germany and many other European countries €50 000 per QALY saved.

Here, we developed a mathematical decision model, i.e., a Markov model [14,15] to simulate in transplant patients disease progression of HCV reinfection with the aim to assess cost-effectiveness of treatment with Peg-IFN/RBV and of future, more expensive, but also more effective treatment modalities.

Methods

Decision model

Using a Markov model, we simulated the evolution of a cohort of HCV-positive liver transplant recipients over a period of 20 years. The clinical and economic outcomes of different treatment strategies with Peg-IFN/RBV were assessed. In a Markov model, patients progress in periodical cycles from one health-state to the next. This happens with a certain probability once in the cycle. Here, a cycle length of 1 year was used. Health-states in our model are fibrosis stage 0 to stage 3 according to Desmet Score (F0: no fibrosis, F1: minimal fibrosis, F2: portal and parenchymal fibrosis with no septa, F3: bridging fibrosis) and compensated cirrhosis (F4/CC), decompensated cirrhosis (DC), and organ loss (=death) (OL/D) (Fig. 1).

Evaluation of the model was conducted by computer-based simulation of a hypothetical patient cohort of 50 000 treated and untreated patients, respectively. Following international [16–18] and German recommendations [19], we used an annual discount rate of 3% for both, costs and benefits. In all analyses, we adopted a health system perspective. A half cycle correction was performed.

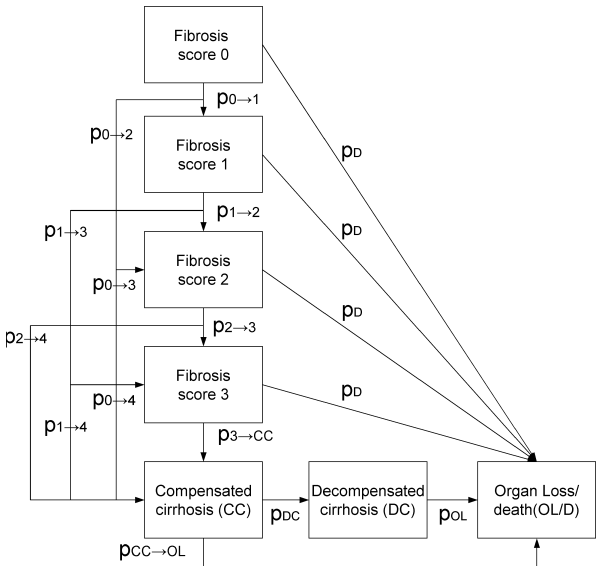

Figure 1 Markov model of HCV recurrence.

Reference patients with recurrent HCV viremia after liver transplantation had a weight of 75 kg and started treatment with Peg-IFN alpha 2b and RBV 1 year post liver transplantation.

Cost-effectiveness of each strategy was assessed by determining the ICER, defined as the incremental discounted lifetime costs divided by the incremental discounted quality-adjusted life expectancy. To avoid double counting, indirect costs such as productivity loss were not included in the numerator of the ICER (costs), but as effects on the working ability incorporated in the denominator of the ICER (QALYs).

Baseline analysis and deterministic sensitivity analysis were performed using the open source statistic software R, respectively, with Microsoft® Excel 2003 (Microsoft Corporation, Redmond, Washington, USA). Monte Carlo simulation and bootstrapping are performed exclusively with R.

Efficacy rates of treatment strategies

Standard treatment with Peg-IFN/RBV over 48 or 24 weeks in patients with HCV genotype 1 and HCV genotype 2/3, respectively, was performed using EVR (early virologic response) as stopping rule. Response rates for patients not receiving any hematopoietic growth factors were based on our own experience and pooled literature data considering only post-transplant patients (SVR HCV genotype 1: 95% CI: 8.7–29.0%, pooled mean: 20.4% [6,20–22]; SVR HCV genotype 2/3: 95% CI: 36.5–85.2%, pooled mean 69.1% [20–22]). EVR was estimated to be 40% and 90%, SVR 21% and 66% for HCV genotype 1 and genotype 2/3 patients, respectively.

Natural history data

To simulate disease progression cohort, patients run through Markov model health-states in periodic intervals based on predefined probabilities. Here, the annual transition probabilities were derived from published data of M. Berenguer [23]. From the excepted median duration (mT_F) of developing fibrosis scores 1–4 ($p_{Fq \to Fq+n}$), annual transition probabilities were calculated using the formula given below:

$$p_{Fq \to Fq+n} = \left(0.5/\left(mT_{F \geq q+n} - mT_{F \geq q}\right)\right) - \left(0.5/\left(mT_{F \geq q+n+1} - mT_{F \geq q}\right)\right).$$

Similarly, probabilities for development and death from DC were derived from published literature data [24]. Baseline as well as lower and upper limits of annual transition probabilities are shown in Table 1. The non-HCV-related mortality rate was derived from a study of Rabkin *et al.* on late mortality after OLT [25].

Table 1. Annual transition probabilities of Markov model health-states.

Annual transition probabilities				
	Baseline	Lower limit	Upper limit	Reference
p F0 → F1	0.124	0.111	0.139	[23]
p F0 → F2	0.025	0.023	0.026	
p F0 → F3	0.037	0.032	0.040	
p F0 → F4/CC	0.047	0.043	0.053	
p F1 → F2	0.073	0.072	0.073	
p F1 → F3	0.072	0.062	0.081	
p F1 → F4/CC	0.06	0.054	0.067	
p F2 → F3	0.286	0.257	0.312	
P F2 → F4/CC	0.084	0.072	0.312	
p F3 → F4/CC	0.109	0.089	0.139	
p CC → DC	0.42	0.2	0.6	[24]
p CC → OL/D	0.19	–	–	
p DC → OL/D	0.68	–	–	
p F0. F1. F2. F3 → D	0.0084	–	–	[25]

Costs

Estimates of annual direct costs for each model health-state, including costs for inpatient and outpatient visits, diagnostic and laboratory testing, immunosuppressive and other necessary drugs, and procedures were based on published data of the German Hepatitis C Model (GEHMO) Group [26] estimating costs in chronic HCV before and after OLT. Because data were published in 2003, we adjusted costs by annual inflation rates reported by the federal statistical office of Germany based on the consumer price index up to 2012. Baseline values of annual costs of all health-states are shown in Table 2. Costs for medication with Peg-IFN/RBV were based on the German drug panel considering full dose standard treatment over the complete treatment duration.

Table 2. Baseline assumptions for annual health-state costs and utilities

Model health-states	Annual costs (in €)	Utilities
Achieved SVR	19 586 [26]	0.79 [27]
Fibrosis stage 0–3	19 586 [26]	0.71 [28]
Compensated cirrhosis	20 363 [26]	0.71 [28]
Decompensated cirrhosis (1st year)	59 415 [26]	0.63 [28]
Decompensated cirrhosis (subsequent years)	43 398 [26]	0.63 [28]

SVR, sustained virologic response.

Quality of life

To estimate quality of life of model health-states, one-dimensional utilities were assigned to each health-state, scaled from 1 equal to full health to 0 equal to death. To assess QALYs, life-years spent in each health-state and associated utilities of these health-states were multiplied. The health-state utilities used in our analysis were based on recently published systematic reviews on utilities in different stages of liver disease [27,28]. For patients with compensated and DC, utilities are only available pre transplant, but not post transplant. Therefore, we calculated the ratio of utilities pre to post transplant for patients with hepatitis and then reduced the described utilities of pretransplant patients with cirrhosis by the same factor. Furthermore, based on our own experience and with respect to the large number of described side effects of peg-IFN/RBV [6,12,13], it was assumed that quality of life was reduced by factor 0.3 during the treatment year.

Model assumptions

In our model, we made several assumptions: (i) antiviral treatment has no impact of graft rejection; (ii) there is no spontaneous HCV clearance; (iii) fibrosis progression is an irreversible process; (iv) no development of hepatocellular carcinoma; (v) graft loss always results in death of the patient (re-OLT is not considered); (vi) SVR leads to definite cure with no further fibrosis progression [29–32]; (vii) relapser and nonresponder have identical disease progression; and (viii) all patients qualify for treatment with Peg-IFN/RBV. Furthermore, the model does not consider effects of cofactors for disease progression such as age, co-infection with HBV and HIV or alcohol.

Model analysis

Baseline analysis

In the baseline analysis, efficacy of treatment as compared with no treatment was assessed by comparison of mean life expectancy, QALYs gained, cases of graft loss and cirrhosis prevented, total costs per case, as well as costs per QALY.

Sensitivity analysis

To investigate the robustness of the base-case results, we performed univariate and multivariate sensitivity analyses by variation of several model parameters, i.e., fibrosis progression, costs, discount rate, time horizon, non-HCV-related mortality, and utilities according to ranges published in the literature (Table 1) [23,24]. Furthermore, a two-way sensitivity analysis was performed to assess drug costs in relation to virologic response.

To assess the uncertainty of the CEA, a Monte Carlo simulation-based bootstrap technique [33] was performed using 50 000 treated and 50 000 untreated patients. Each patient's follow-up was simulated using the corresponding prespecified transition matrix. We then drew repeatedly a large number ($k = 1000$) of random samples (bootstraps) from this cohort, each of a size of 1000 patients. The significance of the cost-effectiveness, mean, and 95% confidence interval of ICER were calculated from the resulting bootstrap samples.

Results

Baseline analysis

To validate our model assumptions, survival rate of patients in our model was compared with clinical observations. The 10-year survival rate for HCV genotype 1 infected patients with SVR and nonresponse (NR) was, in our model, 92.7% and 62.7%, respectively. This compares very well with recently published data revealing in reality a 10-year survival of 93% and 67%, respectively, in this group of patients [29].

Further results of our baseline analysis and costs are given in Table 3. In the model 1 year post OLT, HCV-positive patients have a life expectancy of 12.00 years and cause lifetime costs of €207 259. Treatment prevents organ loss/death, gains life-years, and QALYs in patients with genotypes 1 and 2/3. Patients infected with genotype 1 gain on average only 1.44 life-years and 0.71 QALYs, while HCV genotype 2/3 infected patients gain 4.53 life-years and 2.66 QALYs. In all patients, treatment increases lifetime costs, but the additional costs spent per QALY gain, represented by the ICER, do not exceed the in Germany societally accepted limit of cost-effectiveness of €50 000/QALY with an ICER of approximately €40 400/QALY and €21 000/QALY for HCV genotype 1 and 2/3 patients, respectively (Table 3).

Cost-effectiveness of more effective treatment strategies

In a two-way sensitivity analysis, costs of more effective antiviral treatment strategies with additional drugs added to Peg-IFN/RBV and improving SVR were calculated. For patients with genotype 1, costs per QALY will remain stable as long as additional drug costs do not exceed €10 774 per 10% SVR improvement. Based on the upper limit of the societally accepted cost-effectiveness of €50 000/QALY, costs for additional drugs could go up to €21 732 per 10% SVR gain.

In patients with genotype 2/3, the ICER remains stable as long as additional drug costs do not exceed €1513 per 10% SVR gain. With regard to an ICER of €50 000/QALY, drug costs could be as high as €87 065 per 10% SVR improvement.

Sensitivity analysis

For assessment of the robustness of the base-case analysis, several model parameters were modified (Fig. 2). In patients with genotype 2/3, cost-effectiveness of treatment was preserved under all conditions (Fig. 2). In no situation, antiviral treatment resulted in transgression of the limit of

Table 3. Outcome, benefit, costs, and ICER of treatment strategies in HCV recipients within a time horizon of 20 years after treatment initiation.

	Organ loss/death prevented (%)	Life expectancy (years)	Discounted QALYs	Δ discounted QALYs	Drug cost (€)	Discounted total costs (€)	Δ Discounted total costs (€)	Discounted ICER (€/QALY)
Patients not treated	–	12.00	6.75	–	–	207 259	–	–
Genotype 1 patients treated	13.6	13.44	7.46	0.71	14 070	235 752	28 493	40 398
Genotype 2/3 patients treated	42.6	16.53	9.42	2.66	10 667	263 047	55 788	20 973

ICER, incremental cost-effectiveness ratio; HCV, hepatitis C virus; Tx, treatment; Δ, difference between treatment and no treatment; QALYs quality-adjusted life-years.

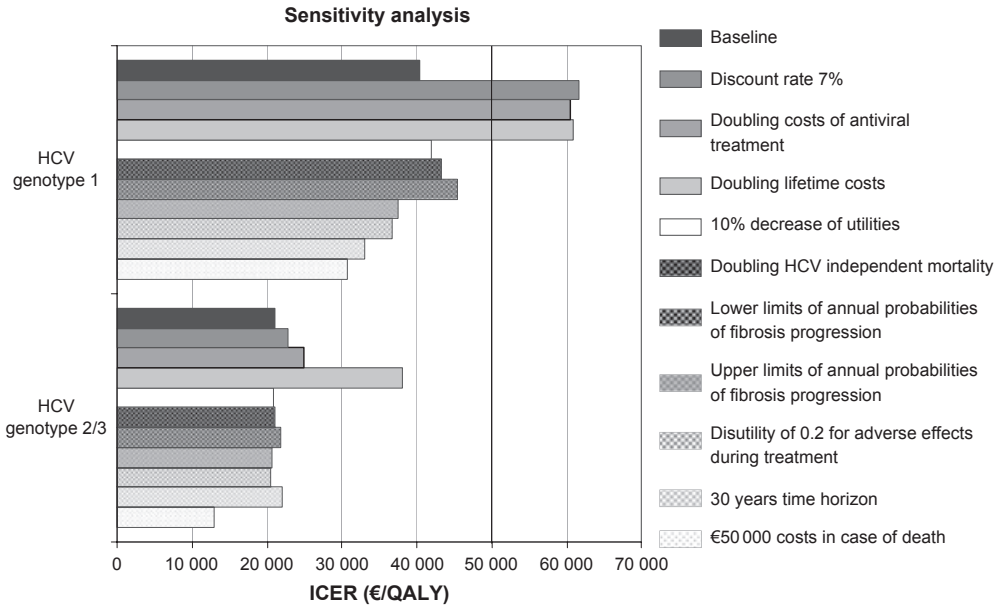

Figure 2 Sensitivity analysis of treatment strategies. Model parameters were modified according to extreme conditions described in the literature. ICERs of the treatment strategies are calculated in comparison with the no treatment strategy.

cost-effectiveness of €50000/QALY. In patients with genotype 1, an increase in the discount rate to 7% and doubling of life-time or antiviral costs resulted in transgression of the limit of cost-effectiveness of €50000/QALY. In contrast, a disutility of 0.2 for the side effects during the treatment, an increase in fibrosis progression, extension of the time horizon to 30 years, as well as including additional costs for the last year survived before death of €50000 decreased baseline ICERs in genotype 1 patients.

Using the Monte Carlo simulation-based bootstrap technique, the calculated 95% confidence interval of the ICER was €35391/QALY to €52176/QALY in genotype 1 patients and €20695/QALY to €22884/QALY in genotype 2/3 patients, respectively. The mean ICER was €41929/QALY and €21916/QALY in patients with genotype 1 and 2/3, respectively. None of the 1000 bootstraps exceeded the limit of cost-effectiveness of €50000/QALY in the genotype 2/3 cohorts and only 37 per 1000 bootstraps in the genotype 1 cohorts. Overall, the hypothesis of cost-ineffectiveness could be rejected with $P = 0.0185$.

Discussion

Here, a mathematical model was applied to assess cost-effectiveness of antiviral treatment in HCV-infected liver transplant recipients. Our analysis revealed that peg-IFN/RBV treatment prevents organ loss, gains life-years and QALYs in patients infected with HCV genotype 1 and 2/3. Because of the markedly better SVR in patients infected with HCV genotype 2/3, life expectancy and therefore also lifetime costs are higher than in patients with genotype 1. However, the gain in QALYs exceeds the cost increase resulting in a remarkably lower ICER, i.e., higher cost-effectiveness in patients with genotype 2/3 as compared with patients with genotype 1.

In patients infected with all HCV genotypes treatment increased overall costs, but without surpassing the in Germany societally accepted limit of cost-effectiveness of €50 000/QALY in the baseline analysis. Cost-effectiveness was also confirmed for all HCV genotypes when a lower or higher rate of fibrosis progression, increased non-HCV-related mortality, lower limits of utilities, or a time horizon of 30 years were considered in the model. On the other hand, in patients treated with HCV genotype 1, extreme economical conditions like doubling the discount rate, lifetime costs or costs of antiviral treatment resulted in loss of cost-effectiveness. In patients with genotype 2/3 infection, antiviral treatment remained always cost-effective.

Furthermore, we calculated in a two-way sensitivity analysis the cost-effectiveness of more effective treatment strategies with addition of further drugs, such as hematopoietic growth factors or direct-acting antivirals, to the Peg-IFN/RBV regimen [34–37]. In patients infected with HCV genotype 1, additional €10 774 can be spent per 10% SVR gain without changing cost-effectiveness. Even additional €21 732 could be spent for each 10% SVR gain without exceeding the upper limit of cost-effectiveness of €50 000/QALY.

Previously, several CEAs [26,38–41] in the nontransplant population showed that antiviral treatment in patients with chronic HCV infection is, in general, cost-effective, but – as shown here – always additional costs are generated. The calculated ICERs vary enormously between $200 and 36 000 per QALY gained, depending on various factors, such as the drug scheme used, the reference treatment strategy, the duration of therapy, the HCV genotype, the time horizon of the study, and others. In comparison, here treatment of transplant recipients with Peg-IFN/RBV is also cost-effective, but with higher incremental costs per QALY of about €40 400 and €21 000 in HCV genotype 1 and HCV genotype 2/3 infected patients, respectively.

Prior to our analysis, cost-effectiveness of HCV treatment post OLT has only been studied by Saab *et al.* in a North American cohort of patients [42,43]. In his first study [42], antiviral treatment with an estimated SVR of 20% resulted in a gain of 0.41 life-years compared with no treatment. Quality of life was not considered. Although not directly comparable, here gain was higher with 0.71 and 2.66 QALYs in HCV genotype 1 and genotype 2/3 infected patients, respectively. As in our calculation, treatment created costs, but based on the American upper limit of cost-effectiveness of 50 000/QALY, treatment was also cost–effective with a calculated ICER of 29 100 per life-year saved.

Aim of another CEA of Saab *et al.* [43] was to determine the best time point for Peg-IFN/RBV treatment in cirrhotic patients. Clinical and economic outcome of antiviral treatment of patients with compensated cirrhosis versus DC versus post OLT was assessed. Compared with no treatment, all treatment strategies did not only gain QALYs but also saved costs. However, because of the different approach, this CEA cannot really be compared with the data presented here.

In principle, CEAs are based on models, which have to simplify reality. Because of model assumptions, results of CEAs may be imprecise and have to be interpreted within their limitations. For validation of our Markov model, we calculated the 10-year survival rates of patient with SVR and NR and compared those with the recently published clinical observation of Berenguer *et al.* [29]. The 10-year survival rates in the model for patients with SVR and NR of 92.7% and 62.7%, respectively, are very close to those observed in reality with 93% and 67%, respectively, confirming the proximity of our model to reality.

To study the effect of varying model assumptions, we here performed a large sensitivity analysis with modification of several model parameters. The weakest part of our model is an inaccurate assumption of fibrosis progression, in particular since nowadays, it is assumed that fibrosis progression is not always linear and varies considerably between individuals as a result of several influencing factors, such as quality of the graft, age of the donor and recipient, coinfections, diabetes mellitus, type of immunosuppressive medications, rejection episodes, and others [2]. In our model, annual transition probabilities between fibrosis stages were extrapolated from the data of Berenguer *et al.* [23], which are based on over 700 liver biopsies taken prior to antiviral treatment and mostly per protocol. There fibrosis progression was found to be linear over time, with 10% of the US recipients studied and 31% of the Spanish recipients developing cirrhosis 5 years post OLT. In our baseline calculation, the risk of cirrhosis development was similar to Berenguer's US population with a 15% and 42% cirrhosis incidence after 5 and 10 years, respectively. This assumption is also consistent with several other previous investigations in which fibrosis progression was linear and revealed a cirrhosis rate of 10–30% after 5 years and 40% after 10 years [3,4,44,45].

To consider a slower or quicker fibrosis progression of the transplant, population limits of annual transition probabilities were varied over a wide range (Fig. 2). Reducing fibrosis progression resulted in a slight decrease in cost-effectiveness, but the ICER stays still below the societally accepted limit of cost-effectiveness of €50 000/QALY in patients infected with all genotypes. Furthermore, increase in fibrosis progression – a development we see nowadays with the rising number of patients receiving grafts with extended donor criteria – improves cost-effectiveness of antiviral treatment, in particular, in patients infected with genotype 1.

Furthermore, cost-effectiveness increases with improvement of treatment outcome. Our CEA is based on a very low SVR of only 21% in genotype 1 infected patients, thereby rather underestimating cost-effectiveness. However, a low treatment efficacy was chosen as data have to be regarded on an intention to treat basis: in reality, not all transplant recipients would qualify for antiviral treatment and several patients would not complete the treatment course. Furthermore, treatment costs in our study are based on full dose treatment over the complete anticipated time period, although in clinical routine, dose reductions of both medications or even treatment interruptions are common because of adverse events. Moreover, in reality, also patients with relapse after treatment have a slower disease progression as compared with nonresponders, which is not considered in the mathematical model. By both factors, cost-effectiveness is also underestimated.

Furthermore, here non-HCV-related mortality rate was based on a study of Rabkin *et al.* on late mortality of OLT recipients with various etiologies [25]. However, it is well known that the prevalence of diabetes mellitus [46] and of a metabolic syndrome [47] – both risk factors for non-HCV mortality – is higher in HCV-positive than in HCV-negative transplant recipients. Therefore, we doubled non-HCV-related mortality rate within the sensitivity

analysis. This resulted in a decrease of cost-effectiveness, but not exceeding the societally excepted limit of €50000/QUALY, in patients infected with HCV genotype 1, while there was no relevant impact in patients with HCV genotype 2/3.

Finally, it has to be taken into consideration that in our model, all patients undergo antiviral treatment 1 year after transplantation. This pre-emptive therapy approach implies that a proportion of approximately 20–25% of patients receives treatment, although significant fibrosis progression may not occur within a 10-year follow-up. On the other hand, eradication of HCV infection has, apart from cirrhosis prevention, also other medical, psychological, and social advantages justifying treatment. In the recent American PHOENIX study, no benefit for fibrosis progression of pre-emptive therapy over treatment of patients with histological evidence of hepatitis recurrence plus stage 2 fibrosis was evident [48]. However, the study results are weakened, in particular, by a lack of follow-up liver biopsies of approximately half of the patients [48]. Despite this and confirmation of prevention of fibrosis progression by pre-emptive therapy in other studies [49], currently the American guidelines, but not the EASL guidelines [50], recommend antiviral treatment only after development of fibrosis stage 2. In our and other German transplant centers, pre-emptive antiviral treatment within the first year post OLT is often favoured, if possible, also with regard to social and psychological reintegration of the OLT recipients.

In conclusion, this model demonstrates cost-effectiveness of pre-emptive Peg-IFN/RBV treatment in post-transplant patients in a wide variety of different settings. This may support treatment decision in individual cases.

Authorship

CL: performed study, wrote the paper. EV: performed statistics and Markov model. LF: contribution with writing the maunuscript. BN: contribution in writing the manuscript. MS: designed study, wrote the paper.

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