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ORIGINAL ARTICLE

Cost-effectiveness of pretransplant sofosbuvir for preventing recurrent hepatitis C virus infection after liver transplantation

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cost-effectiveness analysis, hepatitis C virus infection, liver transplantation, recurrent HCV, sofosbuvir.

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Summary

There are reports of pretransplant sofosbuvir (SOF) plus ribavirin being effective in preventing recurrent hepatitis C virus (HCV) infection after liver transplantation (LT). The aim of this study was to assess the cost-effectiveness of this strategy in the area served by the North Italy Transplant program. We retrospectively assessed the impact of HCV infection on post-LT survival in 2376 consecutive adult patients (MELD $\leq$ 25, unknown genotype, period 2004–2009) and the prevalence costs of conventional standard of care (SOC) antiviral therapy (pegylated interferon plus ribavirin) after LT. A Markov model was developed to compare two strategies: 12–24 weeks of SOF+ ribavirin for pre-LT anti-HCV treatment versus on-demand post-LT SOC antiviral therapy. Among the 1794 patients undergoing LT, 860 (48%) were HCV+ and 50% of them were given SOC therapy after LT (mean cost of drugs and adverse effect management = 14 421€ per patient). HCV etiology had a strong impact on post-LT survival (hazard ratio = 1.59, 95% CI = 1.22–2.09, P = 0.0007). After Monte Carlo simulation, pre-LT SOF therapy showed a median survival benefit of 1.5 quality-adjusted life years and an Incremental cost-effectiveness ratio (ICER) of 30 663€/QALY, proving cost-effective in our particular Italian scenario. The costs of SOF therapy, sustained viral response rate 12 weeks after LT, and recipient's age were the main ICER predictors at multivariate analysis. This study proposes a dynamic model based on real-life data from northern Italy for adjusting the costs of pre-LT direct-acting antiviral therapies to the actual sustained virological response reached after LT.

Introduction

Hepatitis C virus (HCV) infection is the most common indication for liver transplantation (LT) worldwide. About 50% of LTs performed in Europe and the United States are necessitated by HCV-related cirrhosis. HCV infection always recurs after LT and follows an accelerated course. Around 30% of patients eventually develop aggressive recurrent HCV, with rapid fibrosis progression (RFP) culminating in liver failure or death [1].

Until 2011, a combination of pegylated interferon (peg-IFN) and ribavirin (RBV) was the standard of care (SOC) and the only therapy available for treating HCV recurrences in the graft. Regimens based on peg-IFN and RBV are burdened, however, not only by several side effects resulting in poor tolerability and contraindications (i.e., decompensated liver diseases and immune-mediated disorders), but also by suboptimal sustained virological response (SVR) rates, particularly in patients who are difficult to treat (i.e., HCV genotypes 1–4 and patients with advanced liver fibrosis) [2]. Direct-acting antivirals (DAAs) promise to drive a therapeutic revolution in HCV-infected patients, improving SVR rates while minimizing the side effects of SOC. Sofosbuvir (SOF) was the first compound to enter the market as part of an IFN-free combination, approved by the Food and Drug Administration (FDA) in December 2013. It belongs to the nucleotide inhibitors of viral polymerase NS5B and acts as a chain terminator during the HCV replication process, exhibiting pan-genotypic antiviral activity with a high barrier to resistance. Clinical trials have demonstrated its optimal efficacy in patients with HCV-2 infection, where the combination SOF/RBV for 12 weeks has achieved over 90% SVR rates [3,4]. SOF has been shown to improve the efficacy of previous regimens when used in difficult-to-treat genotypes, such as HCV-1, 4, 5, and 6 [3]. Its tolerability and safety profile have led to the introduction of SOF-based regimens for pre- or post-LT treatment in several clinical trials. Curry *et al.* [5] recently published the results of a multicenter study on LT candidates with hepatocellular carcinoma (HCC) and HCV-related end-stage liver disease. The SOF plus RBV regimen administered before LT prevented graft reinfection (measured as the SVR at 12 weeks after LT) in 75% of 32 patients given SOF $\geq$ 12 weeks, whereas the SVR dropped significantly to only 45% of 11 transplanted patients who had SOF therapy <12 weeks before LT.

In the Italian economic scenario, as recently reported by Messori *et al.* [6], the most adequate treatment for comparing with SOF is dual therapy with peg-IFN plus RBV, commonly used to treat HCV recurrences after LT.

The strategy that involves treating all HCV-infected patients awaiting LT is preferable to treating patients with recurrent HCV after LT because of the potentially synergic effects of antiviral therapy and LT in eradicating HCV infection, and more importantly, there is also a chance of the virus being eradicated and the complications of liver cirrhosis being brought under control, thus enabling the LT to be postponed or even avoided. The optimal duration of pre-LT SOF plus RBV treatment has yet to be established, however. In addition to standard clinical outcomes, it is important to consider the impact on healthcare costs when considering the benefits of treatment regimens.

To the best of our knowledge, no studies published to date have compared the cost-effectiveness of post-transplantation SOC therapy versus pretransplantation SOF plus RBV in HCV-positive patients undergoing cadaveric LT. The aim of this study was therefore to construct a decision-analytic model to estimate the cost-effectiveness of post-LT SOC therapy on demand as opposed to SOF plus RBV before LT in all HCV-positive patients.

Patients and methods

The overall design of this study involved a survival analysis on a real cohort of patients on the waiting list (WL) for LT and then followed up afterward, and a Markov model was used to calculate the survival benefit and cost-effectiveness of two different therapeutic strategies for HCV-positive patients undergoing LT, based on published studies [5,7–11].

Study population

The study population comprised all adult patients with chronic end-stage liver disease listed for LT from January 2004 to December 2009 in the area served by the North Italy Transplant program (NITp), which includes nine LT centers. The NITp central office prospectively recorded data from each center in a shared database at different time points (when a patient was added to the WL, during pre-LT monitoring, at the time of LT, and during post-LT follow-up). The NITp allocation policy was described in a previous study [12] and has been added in Data S1.

As the aim of this study was to assess the potential cost-effectiveness of pre-LT SOF, as in a recent prospective study [5], the following exclusion criteria were applied in selecting the study population from the whole cohort of 2628 patients: recipients with previous transplantations, MELD > 25, patients with HCC beyond the Milan criteria, and patients receiving partial grafts from *in situ* splitting or living donors. We adopted a MELD threshold of 25 because there are no robust data available on the safety of SOF in patients with higher MELD scores [5].

In the Italian HCV population, genotype 1 is the most common (62%), followed by genotype 2 (27%), genotype 3 (6%), and genotype 4 (5%) [13,14]. Due to the retrospective

nature of this study, HCV genotype could not be ascertained from the NITp database. Patients co-infected with HIV were not included in this study.

All patients gave their written informed consent to LT and to the use of their personal data for retrospective studies based on the NITp database.

In all, 2376 patients met our inclusion criteria (Table 1). Details of the descriptive and survival statistics applied to the study population are summarized in Data S2.

Table 1. Characteristics of the study group.

Variables	Patients (n = 2376) N (%) or median (IQR)
Age	55 (49–61)
Female sex	576 (24%)
HCV positive	1127 (47%)
HBV positive	486 (20%)
Alcohol abuse	677 (28%)
HCC at listing	900 (38%)
MELD score at listing	13 (10–17)
Transplanted	1794 (76%)
Dropout/deaths	383 (16%)
Still waiting	199 (8%)
Median WL time, months	5.3 (2.2–14.0)
MELD score at transplant	14 (10–18)
Donor age	56 (42–68)

HCV, hepatitis C virus; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; MELD, model for end-stage liver disease; WL, waiting list.

Definitions and end points for the Markov model

This study focused on HCV-positive patients with MELD scores ≤25 who were potential candidates for LT. The median values of covariates and their interquartile ranges derived from our study population were considered as reference case characteristics (Table 1). The decision tree and states of health used in the model are shown in Fig. 1.

The aim of this study was to compare two strategies: post-LT SOC therapy on-demand with peg-IFN plus RBV (Strategy A) versus 12–24 weeks of SOF plus RBV administered to all patients before LT (Strategy B).

As no more than 2% of the HCV-positive patients were listed for retransplantation due to HCV recurrence after a first LT during the study period, the economic impact of retransplantation in the model was considered negligible. We considered the following end points in our model:

1. Survival benefit: The effectiveness of each strategy was measured in terms of quality-adjusted intention-to-treat survival, and this was expressed in quality-adjusted life years (QALYs). The survival benefit of SOF was defined as Strategy B survival—Strategy A survival;
2. Incremental costs, defined as Strategy B cost—Strategy A cost;
3. Incremental cost-effectiveness ratio (ICER), defined as Incremental costs/survival benefit;
4. Willingness to pay (WTP), a fundamental cost-effectiveness end point representing the limit for the additional cost per unit of effectiveness gained that a rational decision-maker will accept to allocate resources efficiently

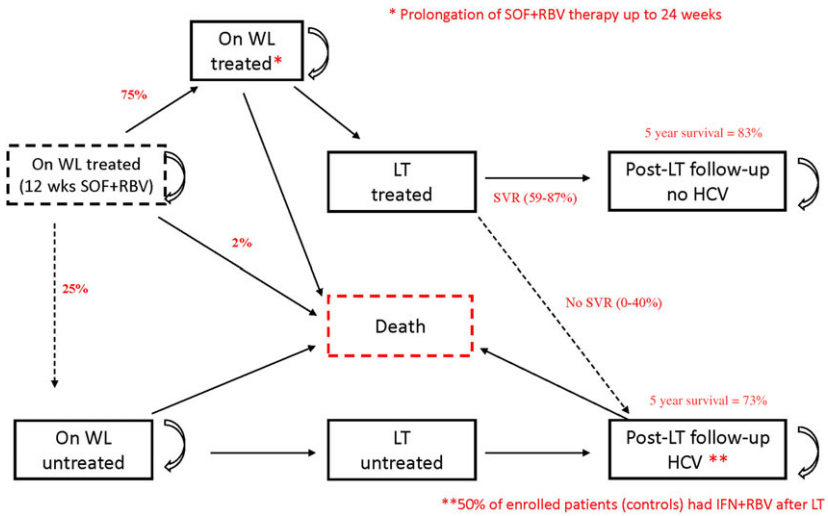

Figure 1 The Markov model. The event pathway: decision tree and states of health. Patients treated on the waiting list had to complete at least 12 weeks of SOF + RBV therapy before they were eligible for LT. During this period, they were considered at risk of dropping off the WL and losing the chance of being transplanted. After this 12-week period, patients continued SOF + RBV therapy for up to 24 weeks. HCV, hepatitis C virus; WL, waiting list; LT, liver transplantation; SVR, sustained virological response; SOF, sofosbuvir; RBV, ribavirin; IFN, interferon; wks, weeks; yr, year.

Table 2. Base-case value and sensitivity range extracted from literature for transition probabilities.

Variables	Base-case analysis	Range tested	Source
Pretransplant variables			
Background (all-cause) mortality	Age-based	18–70	
Median time to transplant (months)	5.3	2.2–14.0	SG
Transplant probability per month	7%	4–10%	SG
Dropout/death probability per month	0.7%	0–1.3%	SG
HCC median survival after dropout (months)	20	19–21	[8,10]
Proportion of patients discontinuing Sofosbuvir	25%	15–35%	[5]
Median duration of therapy with Sofosbuvir (weeks)	12–24	12–24	[5]
Pretransplant quality-of-life utility	0.67	0.60–0.80	[7,11]
Incurable HCC quality-of-life utility	0.40	0.32–0.48	[7]
Post-transplant variables			
5-year survival in HCV negative	83%	75–90%	SG
HCV-related hazard ratio	1.59	1.22–2.09	SG
Proportion of patients with SVR after Sofosbuvir	75%	59–87%	[5]
Proportion of patients treated with standard of care therapy	50%	30–70%	SG
Post-transplant quality-of-life utility	0.71	0.60–0.80	[7,11]
Post-SVR quality-of-life utility	0.83	0.81–0.85	[9]
Variables for cost analysis			
Follow-up while awaiting LT (€/month)	3605	3000–4000	N/A
Sofosbuvir while waiting (€/12 weeks)	37 000	15 000–60 000	[18]
Interferon + Ribavirin therapy after LT (€/patient)	14 421	10 000–20 000	SG
Ribavirin therapy before LT (€/month)	423	300–600	N/A
Follow-up after dropout (€/month)	4326	3500–5000	N/A
Transplantation (€)	80 000	60 000–100 000	N/A
Follow-up therapy after transplantation (€/month)	1803	1000–3000	N/A
HCC after dropout (€/month)	5408	5000–6000	N/A
Time horizon (years)	Life time	N/A	N/A

SG, study group; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; SVR, sustained virological response.

among competing priorities. In this study, we adopted the Italian Gross Domestic Product (GDP) per capita (31 514€) as a reference value, assuming an ICER of 1xGDP to consider an intervention cost-effective [15,16].

Model assumptions and variables

In our study, it was assumed that each patient treated with SOF plus RBV pre-LT and obtaining a SVR at 12 weeks after LT had the same 5-year survival as HCV-negative patients, which was estimated to be 83% from previously performed survival analyses (Fig. 2, Table 2, and Table S1). All patients carried a risk of dropping off the WL due to tumor progression and mortality (estimated to be 0.7% per month) (Table 2 and Table S1), and median survival of patients with HCC after dropping out due to tumor progression was estimated to be 20 months (Table 2). Median probability of undergoing LT was based on the survival analysis on patients on the WL and calculated at 7% per month (Table 2 and Table S1). The HCV-related hazard ratio was 1.59 in the survival analysis on patients after LT (Table S1). Based on recent data showing a 75% SVR 12 weeks after LT when SOF therapy had been administered for at least 12 weeks [5], we assumed that all enrolled

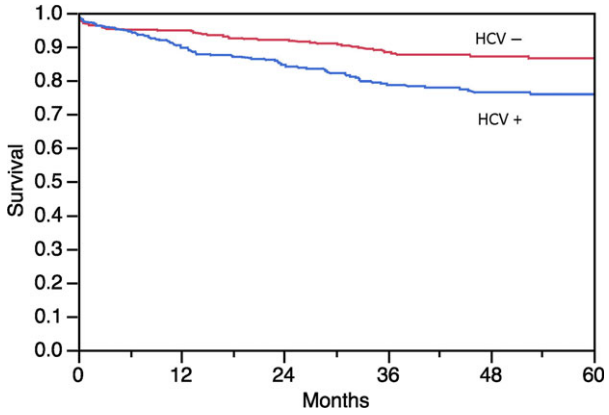

Figure 2 Impact of hepatitis C virus (HCV) recurrence on post-transplant survival in the historical study group (n = 1794). Kaplan–Meier survival curves after liver transplantation of HCV-positive (n = 861) versus HCV-negative patients (n = 933). Log rank test, P = 0.0002. In the historical study, group HCV-positive patients received post- liver transplantation standard of care therapy on demand with pegylated interferon (peg-IFN) plus RBV (Strategy A).

patients had to complete at least a 12-week period of SOF + RBV therapy before they were suitable for LT. Patients were considered at risk of dropping off the WL

and losing the chance of receiving a transplant during this period (Fig. 1). After the 12 weeks, patients continued SOF + RBV therapy for up to 24 weeks in all. The proportion of patients discontinuing SOF was estimated to be 25% [5]. Annual survival, decompensation, and progression rates were converted into monthly probabilities, applying the declining exponential approximation of life expectancy (DEALE) approach: $\mu = -1/t \times \ln(S)$ [17]. Transitional probabilities were varied within their relative 95% confidence intervals assuming a triangular distribution.

Base-case estimates for all utilities extracted from the literature are detailed in Table 2. Ranges were assumed to be within 20% of the base-case values.

The costs were obtained from the current payments made by the Italian public health system. Table 2 summarizes our hospital's median variable costs for each clinical situation. Indirect costs such as lost earnings due to poor health were not estimated. In Italy, the final cost of SOF therapy was recently established at 37 000€ for 12 weeks of therapy (12 333€ per box) with no additional costs for treatments lasting more than 12 weeks [18]. This means that SOF therapy in Italy for 12, 24, or 48 weeks costs the same amount, so we defined this situation as the 12-week cost scenario. To make our results generalizable to other international settings, we also considered a scenario in which the total costs are directly proportional to the number of weeks of treatment, and we defined this second situation as the 12- to 24-week cost scenario. The cost of SOC therapy after LT was established by means of a detailed analysis on the study group (Table 2). The costs of drugs and adverse effect management (i.e., blood transfusions or use of erythropoietin) were also calculated in the study group (14 211€ per patient). The costs and utilities were discounted at an annual rate of 3% [19]. The cost-effectiveness analysis was performed based on the EVEREST guidelines [20].

Probabilistic sensitivity analysis

The correct calibration of the Markov model for predicting survival was confirmed for all patients with a MELD score ≤25, to ascertain the impact of variable uncertainties on the modeled results and to estimate the confidence that can be placed in the analysis of the results. One-way sensitivity analysis was performed for all transition probabilities, costs, and utilities. The outcomes measured were QALYs, incremental QALY, lifetime costs, incremental costs, and ICER.

A probabilistic sensitivity analysis (the Monte Carlo simulation) was performed. A total of 1000 outcomes were compared for each therapeutic strategy (A versus B). The outcomes measured were QALYs, incremental costs, and ICER. Transitional probabilities were varied within their relative 95% confidence intervals, while costs and utilities were varied within their plausible ranges, assuming a uniform or triangular distribution. Information on the uncertainty in cost-effectiveness was reported as a cost-effectiveness acceptability curve (CEAC) [21].

We could not estimate the impact of HCV genotype or Child-Pugh class on the cost-effectiveness of SOF + RBV vis-à-vis SOC therapy for two reasons: (i) we had no data on these two variables for our study population due to the retrospective nature of this study; (ii) in Curry's study [5], the impact of genotype and Child-Pugh class on post-LT SVR was either not significant or not reported. The effects of HCV genotype, Child-Pugh class, or other potential confounding covariates not considered in the present analysis were globally included in the SVR covariate range (between 50% and 100%).

The impact of the variables on the NHB distribution of the 1000 outcomes obtained from the Monte Carlo simulation was measured using the multivariate standard least square regression method. Statistical significance was set at $P < 0.05$.

The calculations were performed with the JMP package version 9.0 (2010 SAS Institute Inc., Cary, NC, USA) and TREEAGE PRO version 2013 (1988-2013 TreeAge Software, Williamstown, MA, USA).

Results

Study population and survival analysis

We identified 2376 patients with chronic end-stage liver disease and a MELD score ≤ 25, listed for primary full-size cadaveric liver transplantation from January 2004 to December 2009 in the NITp area (Table 1). The patients were a median 55 years of age (IQR: 49, 61). The majority were male (n = 1800, 76%). Nearly half of the cohort was HCV positive (n = 1127, 47%), while 27% had both HCC- and HCV-related cirrhosis. The median time on the WL was 5.3 months (2.2–14.0), and the dropout rate was 16% (n = 383). As reported previously in another Italian cohort, the median age of donors was quite high, at an estimated 56 years (IQR: 42, 68) [22].

Among 1794 patients who underwent LT during the study period, 861 (48%) were HCV positive; 50% of the latter received SOC therapy after LT. The median estimated costs of their drugs and adverse event management (i.e., transfusions, erythropoietin, etc.) were 14 211€ per patient.

We performed a multivariate competing risk analysis to find predictors of dropout or death and transplant probability: the only independent predictors of dropout or death among patients on the WL were recipient's age and MELD score, whereas HCV-positive cirrhosis was not. Recipient's age and HCC were the only independent factors influencing transplant probability. HCV-positive cirrhosis, MELD

score, and donor's age were the only independent prognostic factors after LT (Table S1).

Probabilistic sensitivity analysis

Some particular Italian base-case scenarios are described in the Supplementary material (Data S3, Table S2).

Hazard ratios (see Table S1) were used together with the ranges of variables (Table 2) to perform the Monte Carlo simulation.

The cost-effectiveness acceptability curves demonstrated that Strategy B generally had a higher probability of being more cost-effective than Strategy A when the WTP was higher than €45 200/QALY or €30 100/QALY for the 12- to 24-week cost scenarios (Fig. 3a) or 12-week cost scenarios (Fig. 3b), respectively.

To obtain a more complete assessment of the relative benefits of Strategy B versus Strategy A, a multivariate regression method was used to determine the impact of different model covariates on the ICER distribution of the 1000 outcomes obtained from the Monte Carlo simulation. Specifically, the impact of a number of different factors—such as recipient's age, donor's age, recipient's MELD score at LT, presence of HCC, HCV hazard ratio, cost of 12 weeks of SOF therapy, post-LT SVR rate after pre-LT SOF therapy—on the ICER of Strategy A versus Strategy B was assessed (Fig. 4a,b). The main variables influencing the cost-effectiveness of SOF were the cost of 12 weeks of therapy, recipient's age, and the SVR rate 12 weeks after LT. Recipients' and donors' other clinical variables (MELD score, presence of HCC, donor's age, HCV hazard ratio) had a lower impact on cost-effectiveness. As it is ethically unacceptable to adjust costs to patient's age or deny a patient SOF therapy based on his/her age (age discrimination), we focused on the two most relevant remaining variables, treatment costs, and SVR.

An isometric profiler graph was used to compare Strategy A and Strategy B for different treatment costs and SVR (measured 12 weeks after LT) (Fig. 5a,b). The maximum acceptable costs of 12 weeks pre-LT SOF therapy to maintain an ICER ≤Italian GDP in the 12- to 24-week cost scenario (Fig. 5a) ranged between €15 000 and €33 000 when the SVR varied between 66% and 100%. Thus, in this setting, the €37 000 base-case price for 12 weeks of SOF therapy seems too high.

On the other hand, the maximum acceptable costs of 12 weeks pre-LT SOF therapy to maintain an ICER ≤ Italian GDP in the 12-week cost scenario (Fig. 5b) ranged between €22 000 and €48 000 when the SVR varied between 50% and 100%. In this second scenario, the €37 000 base-case price for 12 weeks of SOF therapy should be considered appropriate if a post-LT SVR of about 77% is assured.

Figure 5b may also be a useful model for assessing the cost-effectiveness of potential new combinations of DAAs to use before LT. For instance, if we considered a new DAA combination that reached a post-LT SVR nearing 100%, the maximum price that would be acceptable in our particular north Italian situation should not exceed €50 000.

Discussion

Recurrent HCV is the most common cause of death and graft loss among patients who undergo LT for HCV-related cirrhosis, as has been amply reported in the literature [1,13–15] and confirmed in the survival analysis in the present study. Liver decompensation occurs more rapidly and in a higher proportion of transplanted than nontransplanted HCV-positive patients [23–25]. Retransplantation

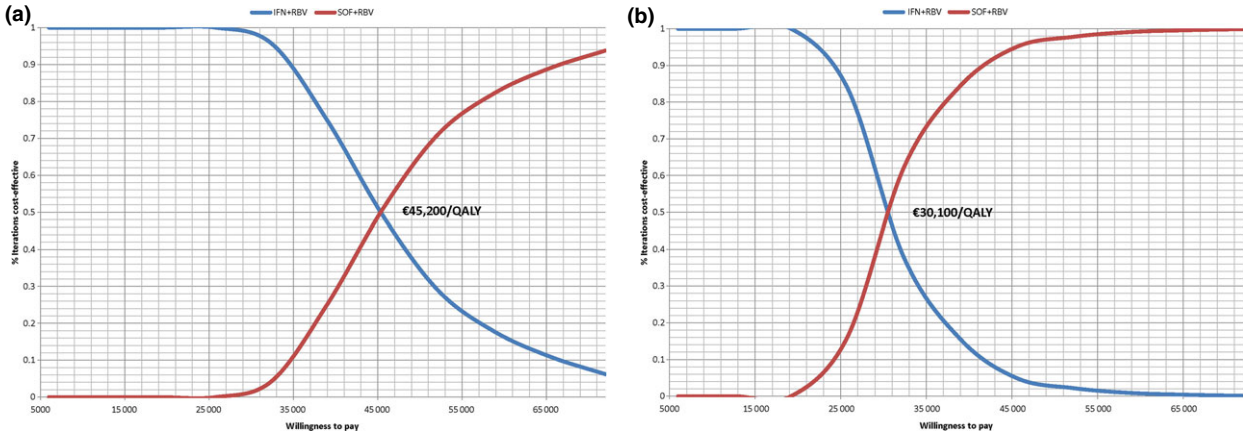

Figure 3 Cost-effectiveness acceptability curves. Cost-effectiveness acceptability curve (CEAC) of SOF + RBV pre-liver transplantation (LT) therapy (Strategy B) versus post-LT standard of care therapy on demand (Strategy A) in the 12- to 24-week cost scenario (a) and in the 12-week cost scenario (b). The CEAC represents the uncertainty in the cost-effectiveness analysis and enables the willingness-to-pay threshold to be identified [21].

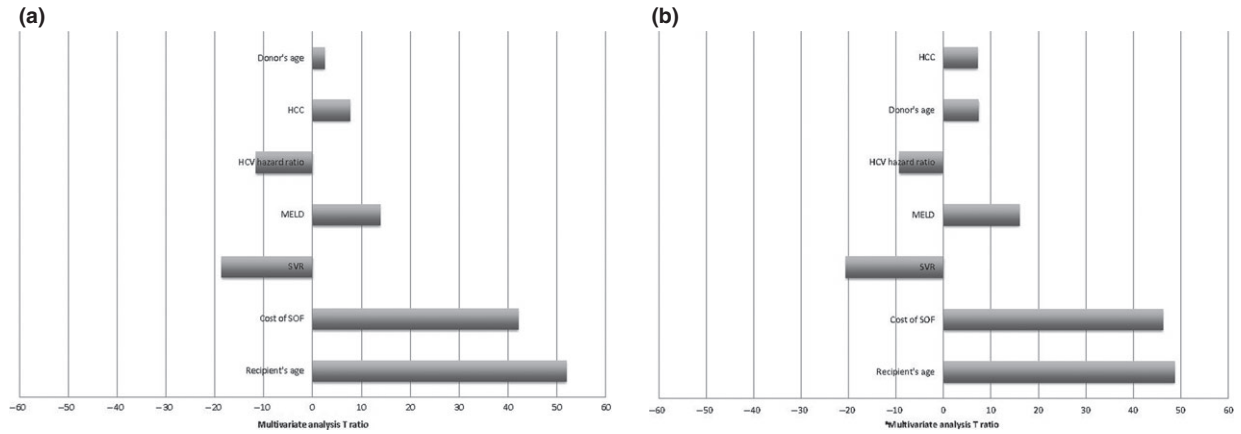

Figure 4 Multivariate analysis on Monte Carlo simulation outcomes. Multivariate analysis on Monte Carlo simulation outcomes showing the contribution of each covariate to the incremental cost-effectiveness ratio of Strategy B versus Strategy A in the 12- to 24-week costs scenario (a) and in the 12-week costs scenario (b). The T ratio describes the overall contribution of each covariate to the multivariate standard least square regression model. HCV, hepatitis C virus; MELD, model for end-stage liver disease; SVR, sustained virological response; SOF, sofosbuvir.

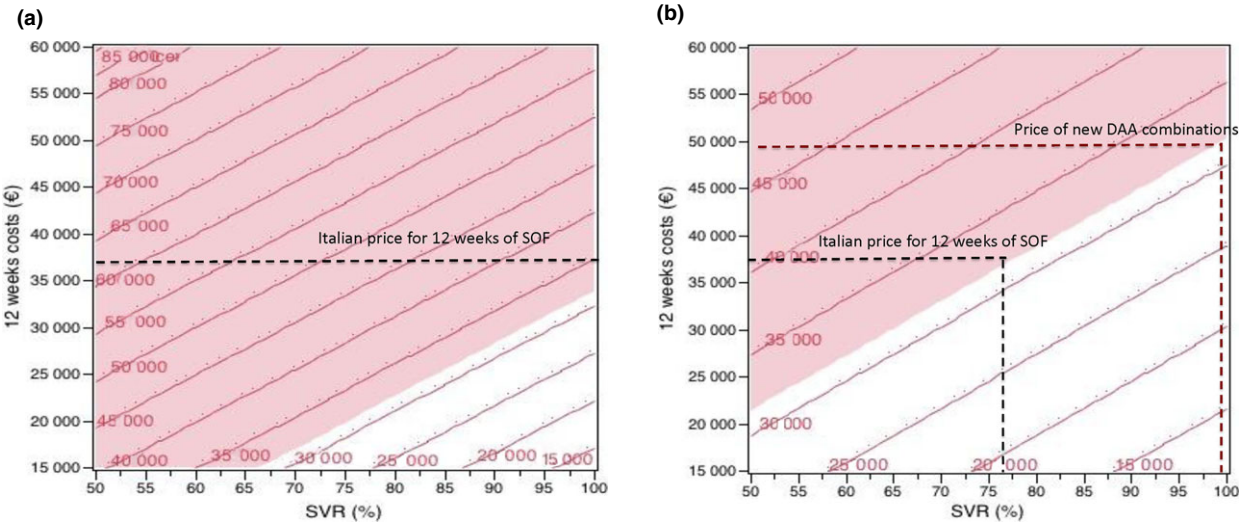

Figure 5 Impact of sofosbuvir costs and sustained virological response (SVR) on incremental cost-effectiveness ratio (ICER). Variation in ICER (isometric profiler graphs) by cost of therapy versus SVR using Strategy B versus Strategy A in the 12- to 24-week costs scenario (a) and in the 12-week cost scenario (b). Other variables included in the multivariate analysis were set at their base-case values. The red area in the graphs represents the area above the Italian Gross Domestic Product (GDP) (€31 514); the white area, the area below Italian GDP. The effect of hepatitis C virus genotype, Child-Pugh class, and other potential confounding covariates not considered in the present analysis was globally included in the SVR covariate range (between 50% and 100%).

is the only curative treatment for patients who experience recurrent HCV-related cirrhosis. Retransplantation enables a long-term survival to be achieved in patients with decompensated cirrhosis after LT, but there is evidence to suggest that patients whose HCV recurs after LT have a 3-year survival rate of only 50% after retransplantation [26]. Among patients who experience HCV recurrence after LT, the overall survival rate of those presenting with cholestatic hepatitis or rapid fibrosis progression is even lower.

In this scenario, there is a need to improve the strategy for treating HCV-positive cirrhotic patients in order to prevent HCV from recurring or treat recurrences effectively, and thereby improve patient and graft survival. The development of DAAs has seen the start of a new era for the treatment of patients with HCV infection. The recent introduction of SOF on the market has already made it anachronistic to use triple therapies with boceprevir or telaprevir to treat HCV recurrence after LT [6] (the first generation of such triple therapy

regimens was rarely used in Italy anyway, due essentially to regulatory delays).

We aimed to assess the potential cost-effectiveness of SOF-based regimens before transplantation in HCV-positive patients by comparison with SOC therapy based on peg-IFN plus RBV for the treatment of established HCV recurrences after LT.

Price *et al.* suggested that [27] "to optimize post-LT viral response rates, pre-LT treatment should be best reserved for those with predictable waiting-list times, allowing sufficient time to achieve and maintain undetectable HCV RNA levels for at least 4 weeks pre-LT." Our analysis thus focused on HCV-positive patients with a MELD score ≤25 who were candidates for LT. These selection criteria limited our analysis to patients who joined the WL with relatively low MELD scores, such as individuals with HCC. This specific population might not be representative of all the HCV-positive patients on the WL, but the only available promising results on the effect of the SOF-based regimen concern a cohort of patients with Child-Pugh scores ≤7 [5]. More trials are expected to confirm their promising results in a larger population, but in the meantime, the present analysis seems to support the effectiveness of the SOF plus ribavirin treatment, also considering its economic impact. In patients with higher MELD scores, other strategies such as bridging sofosbuvir/ribavirin treatment from the WL to the post-transplant phase should be considered—also in terms of their cost-effectiveness [28].

As the revolutionary introduction of DAAs, to the best of our knowledge, this is the first study to analyze the cost-effectiveness of SOF plus RBV administered pre-LT. Due to the potentially positive impact of such treatment on the lives of thousands of people undergoing LT for HCV-related cirrhosis, this study is important because rather than just confirming the effect of this regimen, it shows that the costs should be modeled on the basis of the SVR.

In the present study, we assumed that all enrolled HCV-infected patients used SOF + RBV for 12–24 weeks pre-transplant. This strategy proved to be a more cost-effective treatment strategy than post-LT SOC when appropriate combinations of the costs and post-LT SVR were maintained (Fig. 5).

We considered two possible cost scenarios: (i) the international scenario where total costs are directly proportional to the number of weeks of treatment (our 12- to 24-week cost scenario); and (ii) the actual Italian scenario, where the final cost of SOF therapy has recently been established at 37 000€ for 12 weeks of therapy (our 12-week cost scenario) with no additional cost for any further treatment beyond 12 weeks [18].

The maximum acceptable cost of 12 weeks SOF therapy pre-LT to maintain an ICER ≤ Italian GDP in the 12- to 24-week cost scenario (Fig. 5a) ranged between €15 000 and €33 000 when the SVR varied between 66% and 100%. In this scenario, the €37 000 base-case price for 12 weeks of SOF therapy therefore seems too high. The cost scenario in Spain, where the price of SOF is about €25 000 for 12 weeks of therapy, could be considered appropriate if a post-LT SVR of about 85% were achieved (Fig. 5a).

Conversely, the maximum acceptable costs of 12 weeks pre-LT SOF therapy to maintain an ICER ≤ Italian GDP in the 12-week cost scenario (Fig. 5b) ranged between €22 000 and €48 000, when the SVR varied between 50% and 100%. In this scenario, the €37 000 base-case price for 12 weeks of SOF therapy should be considered appropriate if a post-LT SVR of about 77% is assured.

This study has some limitations. First, base-case values and sensitivity ranges drawn from the literature concerning pretransplant SOF + RBV therapy were based on a relatively small group of patients enrolled in the only study published on this topic to date [5]. For this reason, some variables introduced in the model may not be accurate enough and a systematic bias in the outcome estimates cannot be ruled out.

Second, data on HCV genotype and Child-Pugh class were not available in the present study, but it is well known that SOF is less effective in patients with some HCV genotypes or Child-Pugh classes [29]. We believe that these limitations have not strongly influenced the findings of this study, however, because (i) genotype 1 is the most common in the Italian HCV population (62% of cases), followed by genotype 2 (27%), genotype 3 (6%), and genotype 4 (5%) [13,14]; (ii) using a Monte Carlo simulation, we explored the impact of a wide range of possible SVR values (between 50% and 100%) on the cost-effectiveness of the SOF + RBV strategy by comparison with the SOC strategy (Figs 3 and 4); and in this setting, the SVR variable may be considered a sort of surrogate marker of viral or liver function variables. A last important consideration lies in that this study concerns the effect not of SOF + RBV, but of SOF + RBV + LT in cirrhotic patients. It may be that synergies between antiviral therapy and LT reduce the negative impact of genotype on SVR, and this is probably why genotype had no influence on SVR 12 weeks post-transplant in Curry's study [5].

Another potential limitation of our study lies in that our results may appear to relate only to the north Italian context and be scarcely generalizable to other liver transplant settings. Observational data are prone to confound by indication, unlike randomized clinical trials. For example, only about 50% of our enrolled patients received SOC therapy, but this was not a random sample. The median survival benefit of 1.5 QALYs achieved by SOF + RBV vis-à-vis SOC therapy may therefore be too optimistic. We tried to mitigate such potential biases by performing a multivariate analysis

on the Monte Carlo simulation data (Fig. 4), which showed that factors concerning both recipient (MELD score, presence of HCC, HCV hazard ratio) and donor (donor's age) that are the main determinants of drop-out, transplant, and post-LT survival probabilities had a low impact on ICER. The main factors influencing the cost-effectiveness of the pre-LT SOF + RBV strategy were SOF-related SVR and costs, and recipient's age, which are variables unrelated to the characteristics of the local WL or donor resources.

Apart from pre-LT therapy for all HCV-positive patients on the WL, other therapeutic strategies may be used to reduce the prognostic impact of HCV recurrence after LT, involving the treatment of established HCV recurrences, the early treatment of acute phases of recurrent HCV, or preemptive HCV therapy.

The efficacy and safety of IFN-free SOF-based regimens in LT recipients with recurrent HCV were demonstrated in a case report of the successful rescue of a LT recipient with cholestatic HCV following 24 weeks of treatment with SOF plus daclatasvir, an NS5A inhibitor [30]. In the first open-label Phase II study, 40 LT recipients with compensated recurrent hepatitis C virus (all HCV genotypes) were treated with SOF/RBV for 24 weeks. All patients achieved HCV RNA undetectable at 4 weeks and 77% of them achieved post-treatment SVR [5,31]. As many as 13 of the 40 patients in this study were classified as lost at follow-up, however, and this may have influenced the final ITT results. Adding a second DAA could be expected to improve the efficacy of this approach and enable the duration of the therapy to be reduced to 12 weeks or less [32,33].

The peculiar Italian cost scenario makes SOF therapy comparable with other new potential 12-week drug combinations in terms of cost-effectiveness because the cost of SOF + RBV therapy per patient in Italy is uninfluenced by any prolongation of SOF therapy beyond 12 weeks (to 24 or 48 weeks). Figure 5b may therefore be seen as a useful model for assessing the cost-effectiveness of other new DAA combinations for use before LT. For example, if we were to consider a new DAA combination capable of reaching a post-LT SVR nearing 100%, the maximum acceptable price in our particular north Italian situation should not exceed €50 000.

In conclusion, SOF plus RBV as pre-LT therapy in HCV-infected patients with relatively low MELD scores may be more cost-effective than post-LT SOC therapy based on the assumptions currently applicable in northern Italy. As expected, however, the costs of this new therapy need to be contained for such a treatment strategy to be cost-effective. The main value of the present study thus lies in providing a dynamic model based on real-life data for adjusting the costs of pre-LT DAA therapies to the actual SVR achieved after LT.

Authorship

AV, TMDF, PB, LB, FD, GSB, TM, AP, PT, SB, NP, MGL, UC and SF: collected the data. AV, PB, UC and SF: designed the study. AV, GS, FR, UC and SF: analyzed the data. AV, GS, PB and SF: wrote the paper. I, AV, certify that I have had full access to all the data in this study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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Disclosures

S. Fagiuoli has acted as either Advisory Board Member or Speaker's Bureau for BMS, MSD, Gilead Sciences, Abvie, Roche, Janssen, Novartis, Grifols, Biotest, Kedrion, and Bayer.

Supporting Information

Additional Supporting Information may be found in the online version of this article:

Data S1. NITp allocation policy.

Data S2. Descriptive statistics.

Data S3. Base case analyses.

Table S1. Multivariate analyses to detect covariates with a significant impact on pre- and post-LT survival.

Table S2. Base-case scenario analysis.

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Appendix

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