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Cost-Effectiveness of Sofosbuvir-Based Triple Therapy for Untreated Patients With Genotype 1 Chronic Hepatitis C

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We assessed the cost-effectiveness of sofosbuvir (SOF)-based triple therapy (TT) compared with boceprevir (BOC)- and telaprevir (TVR)-based TT in untreated genotype 1 (G1) chronic hepatitis C (CHC) patients discriminated according to IL28B genotype, severity of liver fibrosis, and G1 subtype. The available published literature provided the data source. The target population was made up of untreated Caucasian patients, aged 50 years, with G1CHC and these were evaluated over a lifetime horizon by Markov model. The study was carried out from the perspective of the Italian National Health Service. Outcomes included discounted costs (in euros at 2013 value), life-years gained (LYG), quality-adjusted life year (QALY), and incremental cost-effectiveness ratio (ICER). Cost of SOF was assumed to be €3,500 per week, i.e., the price generating a willingness-to-pay threshold of €25,000 per LYG compared with TVR in the entire population of untreated G1 patients. The robustness of the results was evaluated by one-way deterministic and multivariate probabilistic sensitivity analyses. SOF was cost-effective compared with BOC in all strategies with the exception of cirrhosis and IL28B CC patients. In comparison with TVR-based strategies, SOF was cost-effective in IL28B CT/TT (ICER per LYG €22,229) and G1a (€19,359) patients, not cost-effective in IL28B CC (€45,330), fibrosis F0-F3 (€26,444), and in cirrhosis (€34,906) patients, and dominated in G1b patients. The models were sensitive to SOF prices and to likelihood of sustained virological response. *Conclusion:* In untreated G1 CHC patients, SOF-based TT may be a cost-effective alternative to first-generation protease inhibitors depending on pricing. The cost-effectiveness of SOF improved in IL28B CT/TT and G1a patients. SOF was dominated by TVR in G1b patients even if, in clinical practice, this issue could be counterbalanced by the good tolerability profile of SOF and by the shorter treatment duration. (HEPATOLOGY 2014;59:1692-1705)

The estimated global prevalence of hepatitis C virus (HCV) infection is 2.2%, corresponding to about 130 million HCV-positive persons worldwide, most of whom are chronically infected.[1] In Europe, a recent revision[2] reported that the estimated prevalence of HCV infection ranges from 0.6% to 5.6%. This is of growing interest because HCV is one of the main causes of both cirrhosis and hepatocellular carcinoma (HCC) in Western countries.

Considering the burden of HCV-related cirrhosis and its complications, the achievement of a sustained virological response (SVR) is a very important surrogate outcome in the management of chronic hepatitis C (CHC) patients. In fact, viral eradication prevents

Abbreviations: BOC, boceprevir; CHC, chronic hepatitis C; DT, dual therapy; G1, genotype 1; ICER, incremental cost-effectiveness ratio; PEG-IFN, pegylated interferon; RBV, ribavirin; PI, protease inhibitors; SOF, sofosbuvir; TVR, telaprevir.

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not only the development of cirrhosis in CHC[3] but also, in subjects with cirrhosis, the occurrence of its complications, such as esophageal varices,[4] and liver-related death,[5] also reducing HCC occurrence.[6,7]

In the last few years the standard of care for untreated genotype 1 (G1) CHC patients changed from dual therapy (DT) with peginterferon α (PEG-IFN) and weight-based ribavirin (RBV), to triple therapy (TT) with PEG-IFN, RBV, and first-generation NS3-NS4 HCV protease inhibitors (PI) boceprevir (BOC) or telaprevir (TVR).[8] Registered randomized controlled trials (RCTs), namely SPRINT2 and ADVANCE,[9,10] showed that a course of 12 to 44 weeks of a first-generation PI combined with 24 to 48 weeks of PEG-IFN plus RBV, with the duration of therapy guided by the on-treatment response and the presence of cirrhosis, provided a gain in SVR rate of about 25% compared with DT. Although we demonstrated that TT with first-generation PI is a highly cost-effective treatment in untreated G1 CHC patients,[11] particularly when allocation systems based on rapid virological response or IL28B genotype-guided strategies are applied, the use of these new drugs in clinical practice needs to be carefully evaluated because of such factors as the low genetic barrier to the development of resistance, the poor tolerability profile especially in cirrhosis patients,[12] the issue of drug interactions, and the long-term complicated regimens with high pill burdens.

A nucleotide analog HCV NS5B polymerase inhibitor, sofosbuvir (SOF), has recently been developed and is waiting for approval by regulatory authorities. The NEUTRINO RCT showed that SOF, in combination with DT for 12 weeks, achieves SVR in 89% of untreated G1 CHC patients with a very good tolerability profile.[13] This RCT identified IL28B CC and the absence of cirrhosis as the only independent predictors of SVR, also showing a higher SVR rate in G1a compared with G1b-infected patients.

The aim of this analysis was to determine the cost-effectiveness of SOF-based TT compared with TVR- and BOC-based TT in different subsets of untreated G1 CHC patients differentiated according to IL28B genotype, severity of liver fibrosis, and G1 subtype.

Materials and Methods

Study Population. Our base case was a hypothetical cohort of Caucasian male patients, 50 years old, with a weight of 70 kg. We also discriminated the patients according to the presence/absence of cirrhosis, the presence/absence of IL28B CC genotype, and G1a/G1b subtype. The base case represents the prototype of patients enrolled in NEUTRINO,[13] ADVANCE,[10] and SPRINT2 RCTs[8] in which data for cost-effectiveness analyses were recorded.

Structure of the Model. We assumed that SVR eliminates the risk of developing progressive liver disease[14-17] in CHC patients. Instead, in patients with cirrhosis, we considered a residual risk for HCC.[7,18] We used a semi-Markov model to simulate the natural history of CHC in the nontreated patients and in the nonresponder group of each treatment strategy over a lifetime horizon. Annual cycles were considered with a half-cycle correction.[19] Independent of the treatment option chosen, patients could follow one of three different paths in each 1-year cycle, based on their transition probabilities: 1) continue in the same health state without suffering from any event; 2) have a liver-related event (i.e., variceal bleeding, HCC, ascites, encephalopathy, jaundice); or 3) die of a liver-related cause.

Since the study was conducted over a lifetime horizon, deaths from other causes are implicitly taken into account by using age-related mortality rates from the National Institute of Statistics (ISTAT)[20] in CHC and compensated patients. All patients suffering from an acute event could die during that year (liver-related death) or survive (at least for that year). The health states were mutually exclusive, i.e., a patient could only experience one health state at any given time. Transition probabilities were taken from previously published studies[21-25] that used survival curves, cumulative risk functions, or aggregate data published in the literature (the average annual probability of transition is given in Table 1). Such survival curves were reproduced using a Weibull distribution for each transition. The transition probability from CHC to compensated cirrhosis was assumed to depend linearly on time,[26]

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Table 1. Base Case Values and Ranges From the Literature

Initial state	State after transition	Annual probability			
		Base case	Lower limit	Upper limit	Ref.
(a) Probability of progression of liver disease					
Chronic hepatitis C	→ Compensated cirrhosis	0.014	0.012	0.016	[25]
	→ Liver-related death	-	-	-	-
	→ Age specific-related mortality	0.003	0.0026	0.034	[19]
Compensated cirrhosis	→ Decompensated cirrhosis	0.07	0.052	0.088	[24]
	→ Hepatocellular carcinoma	0.022	0	0.072	[23]
	→ Liver (esophageal bleeding) and not liver-related death	0.017	0.008	0.026	[24]
Decompensated cirrhosis	→ Hepatocellular carcinoma	0.022	0	0.072	[23]
	→ Liver transplantation	0.0003	0.00025	0.00035	[21]
	→ Liver-related death	0.075	0.072	0.078	[24]
Hepatocellular carcinoma	→ Liver transplantation	0.0003	0.00025	0.00035	[21]
	→ Liver-related death for BCLC A	0.21	0.15	0.27	[20]
	→ Liver-related death for BCLC B	0.27	0.17	0.38	[20]
	→ Liver-related death for BCLC C	0.32	0.21	0.42	[20]
	→ Liver-related death for BCLC D	0.33	0.22	0.43	[20]
Liver transplantation	→ Liver-related death	0.043	0.033	0.053	[22]
(b) Therapeutic strategies			SVR % (95% C.I.)		
	Overall				
Boceprevir - response-guided- therapy			66.8 (61.4-71.4) [8,35,36]		
Telaprevir - response-guided-therapy			74.6 (69.9-78.8) [9,37,38]		
Sofosbuvir - therapy			89.0 (84.8-92.1) [12]		
	IL28B Genotype				
Boceprevir - response-guided-IL28BCC therapy			81.8 (71.7-88.8) [8,35,36]		
Telaprevir - response-guided-IL28BCC therapy			90.0 (78.6-95.6) [9,37,38]		
Sofosbuvir - IL28BCC therapy			97.9 (92.6-99.9) [12]		
Boceprevir - response-guided-IL28BCT/TT therapy			63.4 (53.9-69.5) [8,35,36]		
Telaprevir - response-guided-IL28BCT/TT therapy			71.1 (61.0-79.4) [9,37,38]		
Sofosbuvir - IL28BCT/TT therapy			87.1 (82.1-91.1) [12]		
	Stage of Fibrosis				
Boceprevir - response-guided-F0/F3 therapy			65.8 (60.6-70.7) [8,35,36]		
Telaprevir - response-guided-F0/F3 therapy			78.9 (74.3-82.9) [9,37,38]		
Sofosbuvir - F0/F3 therapy			92.3 (88.5-95.2) [12]		
Boceprevir - F4 therapy			41.6 (24.4-61.1) [8,35,36]		
Telaprevir - F4 therapy			71.4 (50.0-86.1) [9,37,38]		
Sofosbuvir - F4 therapy			79.6 (66.5-89.4) [12]		
	Genotype 1 Subtype				
Boceprevir - G1a therapy			59.2 (51.9-66.1) [8,35,36]		
Telaprevir - G1a therapy			73.7 (67.4-79.1) [9,37,38]		
Sofosbuvir - G1a therapy			91.6 (87.1-94.8) [12]		
Boceprevir - G1b therapy			66.4 (58.0-73.8) [8,35,36]		
Telaprevir - G1b therapy			85.2 (78.6-90.0) [9,37,38]		
Sofosbuvir - G1b therapy			81.8 (70.4-90.2) [12]		
(c) Weekly cost of drugs (euros at 2013 value)					
Peginterferon α+ribavirin+telaprevir		**2,354.72**	**1,648.3**	**3,061.14**	-
- peginterferon α		165.57	115.90	215.23	-
- ribavirin		106.15	74.31	138.00	-
- telaprevir		2,083	1,458	2,708	-
Peginterferon α+ribavirin+boceprevir		**984.47**	**689.13**	**1,279.81**	-
- peginterferon α		165.57	115.90	215.23	-
- Ribavirin		106.15	74.31	138.00	-
- Boceprevir		712.75	498.93	926.58	-
Peginterferon α+ribavirin+sofosbuvir		**3,771.72**	**2,640.21**	**4,903.23**	-
- peginterferon α		165.57	115.90	215.23	-
- ribavirin		106.15	74.31	138.00	-
- sofosbuvir		3,500	2,450	4,550	-
Epoetin		156	109.2	202.8	-
(d) Annual costs for disease progression (euros at 2013 value)					
Chronic hepatitis C		220.37	176.29	264.44	[32,33]
Compensated cirrhosis		479.07	383.24	574.89	[32,33]
Decompensated cirrhosis		4,994.28	3,995.76	5,993.64	[32,33]

TABLE 1. *Continued*

Initial state	State after transition	Annual probability			
		Base case	Lower limit	Upper limit	Ref.
Hepatocellular carcinoma		6,438.79	5,150.56	7,725.86	[32,33]
Liver transplantation		90,733.6	72,586.88	108,880.3	[32,33]
Liver transplantation after 1st year		5,923.46	4,738.76	7,108.15	[32,33]
(e) Cost discounting rate, %		3	0	5	-
(f) Base case value of Quality of Life			Utilities (Q values)		
Well			1 [29]		
Chronic hepatitis C			0.820 [29]		
Compensated cirrhosis			0.780 [29]		
Decompensated cirrhosis			0.650 [29]		
Hepatocellular carcinoma			0.250 [29]		
Liver transplantation			0.500 [29]		
Liver transplantation after 1st year			0.700 [29]		

i.e., each patient experiences a constant annual progression rate of fibrosis, without any difference in the annual fibrosis progression rate. Cross-model validation was performed by comparing differences in outcomes generated by our model with those of other models. The 30-year cumulative probability of developing compensated cirrhosis for the base-case patients of our model (male, 50 years old, fibrosis F2) was 42%. This number is consistent with results from other studies[27-29] reporting mean rates from 25% to 32% in men 40 years old with F0 fibrosis. In addition, our model produced a rate of death for compensated cirrhosis of 10.5%, and for decompensated cirrhosis and HCC of 34.7% (30.2% for decompensated cirrhosis and 4.5% for HCC), being similar to the 32.5% of the model used by Rein et al.[30] Specifically, the rate of death for compensated cirrhosis included death for esophageal bleeding and not hepatic-related death. Model creation and analyses were performed using R (R Foundation for Statistical Computing, Vienna, Austria)[31] and Microsoft Excel 2007 software (Microsoft, Redmond, WA). Figure 1 shows the basic format of the model.

Treatment Strategies, Effectiveness, and Quality of Life Data. Overall, and in each of the six groups (IL28B CC, IL28B CT/TT, cirrhosis, F0-F3 fibrosis,

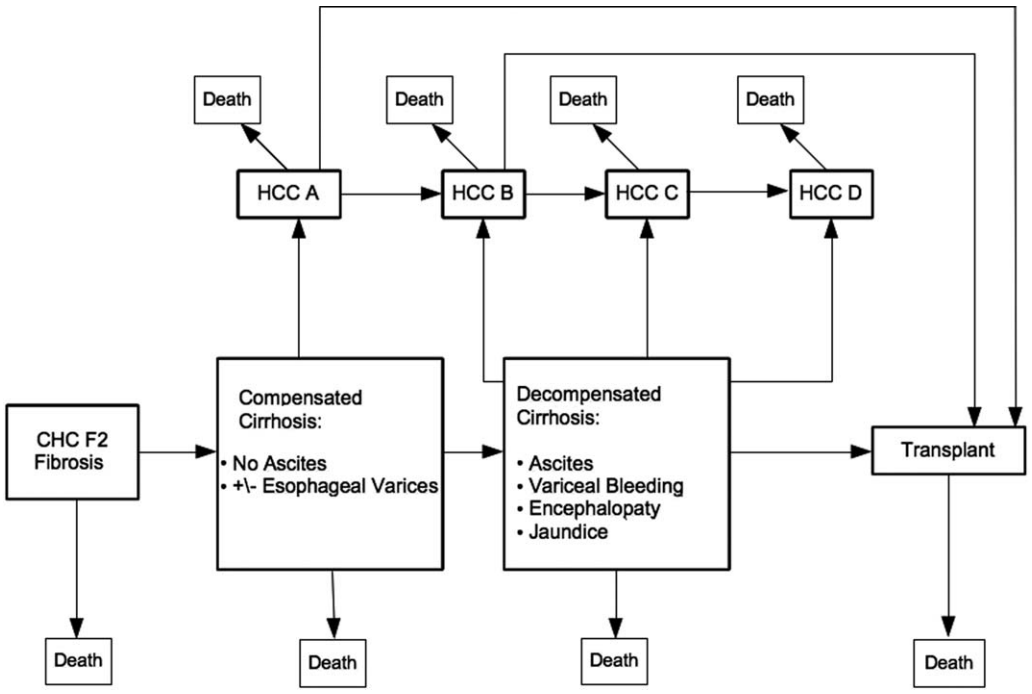

Fig. 1. Schematic of the Markov Model. Every year patients could move between heath states in the model according to a defined transition rate.

G1a, G1b), patients in arm 1 of the model received SOF-based TT, while patients in arm 2 TVR- and BOC-based TT. We weighted the transition probabilities of the Markov model for the SVR resulting from the RCT effectiveness data so that, according to the treatment administered, every patient who completed each cycle in any state other than death received 1 life year gained (LYG). We used LYG as the main measure of effectiveness. Owing to relevant differences in the Quality of Life estimates (utility) reported worldwide[32] in patients with CHC, we assessed quality-adjusted life year (QALY) as a secondary outcome.[27,33] Quality of Life is a specific utility value calculated using the Health Utility Index (HUI-Mark III),[34] and it was associated with each health state considered in the model (Table 1). A summary of the main parameters used to model the treatment effectiveness of TT, based on the RCTs actually available, is shown in Table 1. Further details are available in Supporting Materials 1.

Finally, analyses were also repeated taking into account the cost of epoetin (EPO) therapy (40,000 IU/week) for the management of anemia (Hb <10g/dL). In this line, we assumed an use of EPO for 20 weeks in patients on BOC, i.e., the mean duration reported in the trial of Poordad et al,[35] and no EPO use for SOF as reported by Lawitz et al.[13] Considering TVR, no data exist on the mean duration of EPO use. Therefore, due to the lower prevalence of anemia and to the lower course of TVR respect to BOC, we assumed a mean EPO duration of 12 weeks in patients on TVR treatment.

Use of Resources and Costs. Costs of treatment cycles were expressed in euros at the 2013 value (€)[36] and only direct costs were considered, according to the perspective of the Italian National Health Service.

In particular, the drug costs (PEG-IFN, RBV, SOF, BOC, TVR, EPO) and the costs associated with disease progression (e.g., diagnostic tests, visits, hospitalization) were considered. Costs of PEG-IFNα-2a, PEG-IFNα-2b, RBV, BOC, TVR, and EPO were valued using the ex-factory price. Although PEG-IFNα2a and PEG-IFNα2b have slightly different costs, in order to obtain only one cost for DT we considered the mean cost of the two PEG-IFNs.

SOF is in the pipeline and its cost has not been established worldwide yet. Accordingly, we assumed that the cost of SOF is €3,500 per week. This price represents the rounding of €3,508.9 per week, i.e., the price of SOF generated in our model a willingness-to-pay threshold of €25,000 per LYG compared with TVR in the entire population of untreated G1 patients. Cost drivers were priced in euros by using tariffs included in a previous study[37] in which the medical resource use associated with each disease state was estimated according to the DRG tariffs and national ambulatory fees.[38,39] The costs associated with disease progression are reported in Table 1. Future costs and life-years were discounted at 3% per year.

Effectiveness of Therapeutic Strategies in Different Groups of Untreated Patients. Data on therapeutic strategies are reported in Table 1 and Supporting Figure 1.

Cost-Effectiveness Analysis. We calculated the incremental cost-effectiveness ratio (ICER) of SOF-based therapy compared with both BOC- and TVR-based therapies, overall and among IL28B CC, IL28B CT/TT, cirrhosis, F0-F3, G1a, and G1b patients in a lifetime horizon. When a strategy was not dominant, ICERs of the most effective strategy versus the next nondominated strategy were also calculated.

Specifically, the ICERs among the different options were calculated using difference in drug and disease costs in euros at 2013 value (€) divided by the difference in LYG or QALY effectiveness.

To ascertain the cost-effectiveness, we used a cutoff of €25,000 per LYG, which is actually the willingness-to-pay threshold used by the main regulatory and decision-making agencies in the European Union (i.e., the NICE Treaty and the Italian Medicines Agency, AIFA).[40]

Sensitivity Analyses. We performed a one-way deterministic analysis (DSA) and a multivariate probabilistic sensitivity analysis (PSA) to explore the impact of the uncertainty on the results for the six subgroups evaluated. Tornado diagrams were used to represent results of univariate DSA. Since no confidence intervals were available for the variables used in the model, a range of variation was assumed for each variable: transition probabilities range ±25%, discount rate range intervals of 0-5%, costs of disease range ±20%. Ranges for SVRs were derived from confidence intervals reported in the NEUTRINO, SPRINT-2, and ADVANCE RCTs for each evaluated group.

Finally, a Monte Carlo simulation with 1,000 interactions was conducted to map the uncertainty across the cost and effectiveness parameters included in the DSA (multivariate PSA) in a simulated cost-effectiveness plane. Each point was randomly drawn by using a beta distribution for SVR rates of SOF, BOC, and TVR, annual discount rate, and transition probability from CHC to cirrhosis and from compensated to decompensated cirrhosis, and a normal distribution for costs of SOF and of disease, with parameters given by the same ranges used in the

univariate DSA. Finally, results of the Monte Carlo simulation were ordered by using Cost-Effectiveness Acceptability Curves (CEACs) to test for the probability of the estimated ICERs being under an assumed value of €25,000 per LYG.

Results

Base-Case Analysis. Total costs, undiscounted and discounted LY and QALY, and ICERs of SOF-based TT were calculated versus BOC- and TVR-based TT overall and in the different subgroups (Table 2).

SOF was cost-effective compared with BOC in all strategies with the exception of cirrhosis and IL28B CC patients (Table 2). In comparison with TVR-based strategies, SOF was cost-effective in IL28B CT/TT (ICER per LYG €22,229) and G1a (ICER per LYG €19,359) patients, not cost-effective in IL28B CC (ICER per LYG €45,330), fibrosis F0-F3 (ICER per LYG €26,444), and in cirrhosis (ICER per LYG €34,906) patients. In G1b patients, SOF-G1b strategy was dominated by the TVR-RGT-G1b strategy, this latter being less expensive and more effective than the SOF-G1b strategy.

When including in the models EPO cost for the management of anemia, overall similar results were observed. Specifically, SOF was cost-effective compared with BOC in all strategies (ICER per LYG of €23,459 in G1b, €21,027 in IL28B CC, €23,459 in G1b, €14,321 in IL28B CT/TT, €12,357 in F0-F3, €9,725 in G1a, and €2,635 in F4 patients). Instead, compared to TVR, SOF was cost-effective in fibrosis F0-F3 (ICER per LYG €21,776), IL28B CT/TT (ICER per LYG €18,375), and G1a (ICER per LYG €15,887) patients, and not cost-effective in IL28B CC (ICER per LYG €37,267), and in cirrhosis (ICER per LYG €25,409) patients.

One-Way Sensitivity Analyses. One-way sensitivity analyses were carried out in all subsets of untreated patients for the SOF-based TT. Sensitivity analyses of SOF-G1b strategy compared with TVR-RGT-G1b were not performed, since SOF was dominated by TVR in this setting of patients. Figure 2 summarizes the results of one-way sensitivity analyses using tornado diagrams.

The cost of SOF had a strong effect on its cost-effectiveness. In fact, sensitivity analysis with a hypothesized variation of SOF cost of ±30% showed a significant variation in ICER per LYG for all evaluated strategies. Accordingly, SOF is cost-effective compared with TVR also in IL28B CC, F0-F3, and in cirrhosis patients at SOF price of €3,106, €3,489, and €3,445 per week, respectively.

The model was highly sensitive to variations in SVR rates according to data from NEUTRINO RCT, as well as to variations of SVR rates of both BOC and TVR within 95% confidence intervals.

Cost-effectiveness of SOF was sensitive to a variation in the annual discount rate ranging from 0% to 5%, while it was insensitive to a variation of 20% in the disease costs.

Finally, the model was sensitive to change in transition probabilities from CHC to compensated cirrhosis, while it was insensitive to change in transition probabilities from compensated to decompensated cirrhosis. With a faster progression of the disease, the ICER per LYG marginally improved in all strategies.

Probabilistic Sensitivity Analysis. In IL28B CC patients, varying all variables simultaneously in the Monte Carlo simulation, and using a willingness-to-pay threshold of €25,000 per LYG, SOF-IL28BCC, compared with BOC-RGT-IL28BCC and TVR-RGT-IL28BCC strategies, was cost-effective in 41.2% and 18.2% of the simulations, respectively (Fig. 3A). In 1,000 interactions, the SOF-IL28BCC strategy resulted in a 1,000-fold gain in LYG compared with BOC-RGT-IL28BCC, and in a 999-fold gain in LYG compared with TVR-RGT-IL28BCC.

In IL28B CT/TT patients, SOF-IL28BCT/TT, compared with BOC-RGT-IL28BCT/TT and TVR-RGT-IL28BCT/TT strategies, was cost-effective in 81.1% and 62.4% of the simulations, respectively (Fig. 3B). In 1,000 interactions, the SOF-IL28BCT/TT strategy resulted in a 1,000-fold gain in LYG compared with both BOC-RGT-IL28BCT/TT and TVR-RGT-IL28BCT/TT.

In F0-F3 patients, SOF-F0/F3, compared with BOC-RGT-F0/F3 and TVR-RGT-F0/F3 strategies, was cost-effective in 90.1% and 46.4% of the simulations, respectively (Fig. 3C). In 1,000 interactions, the SOF-F0/F3 strategy resulted in a 1,000-fold gain in LYG compared with both BOC-RGT-F0/F3 and TVR-RGT-F0/F3.

In cirrhosis patients, SOF-F4, compared with BOC-F4 and TVR-F4 strategies, was cost-effective in 99.9% and 48.3% of the simulations, respectively (Fig. 3D). In 1,000 interactions, the SOF-F4 strategy resulted in a 1,000-fold gain in LYG compared with BOC-F4, and in a 981-fold gain in LYG compared with TVR-F4.

In G1a patients, SOF-G1a, compared with BOC-RGT-G1a and TVR-RGT-G1a strategies, was cost-effective in 98.8% and 73.8% of the simulations, respectively (Fig. 3E). In 1,000 interactions, the SOF-G1a strategy resulted in a 1,000-fold gain in LYG compared with both BOC-RGT-G1a and TVR-RGT-G1a.

Table 2. Base Case Results: Undiscounted Absolute Life-Years (LY), Quality-Adjusted Life Years (QALY), and Discounted Lifetime Costs, LY, QALY, and Incremental Cost-Effectiveness Ratios (ICER)

Strategy	Undiscounted Absolute LY	Undiscounted Absolute QALY	Discounted Costs (euros at 2013 value)	Discounted LY	Discounted QALY	ICER vs. TVR (Euro/ LYG)	ICER vs. BOC (Euro/ LYG)	ICUR vs. TVR (Euro/ QALY)	ICUR vs. BOC (Euro/ QALY)
Overall									
Boceprevir -response-guided-therapy	28.57	27.04	32,965	19.01	18.34	-	-	-	-
Telaprevir -response-guided-therapy	29.13	27.95	35,675	19.24	18.74	-	-	-	-
Sofosbuvir - therapy	30.19	29.68	46,431	19.67	19.47	24,754	20,166	16,914	14,048
IL28B CC									
Boceprevir -response-guided-IL28BCC therapy	29.66	28.82	32,325	19.46	19.11	-	-	-	-
Telaprevir -response-guided-IL28BCC therapy	30.26	29.80	34,960	19.71	19.52	-	-	-	-
Sofosbuvir -IL28BCC therapy	30.85	30.75	45,484	19.94	19.90	45,330	27,563	29,770	18,838
IL28B CT/TT									
Boceprevir -response-guided-IL28BCT/TT therapy	29.31	26.61	33,123	18.90	18.15	-	-	-	-
Telaprevir -response-guided-IL28BCT/TT therapy	28.87	27.53	35,837	19.14	18.56	-	-	-	-
Sofosbuvir -IL28BCT/TT therapy	30.05	29.45	46,633	19.62	19.38	22,229	18,622	15,335	13,097
F0-F3 Fibrosis									
Boceprevir -response-guided-F0/F3 therapy	28.48	26.90	29,378	18.97	18.28	-	-	-	-
Telaprevir -response-guided-F0/F3 therapy	29.45	28.47	33,230	19.37	18.96	-	-	-	-
Sofosbuvir -F0/F3 therapy	30.43	30.08	46,079	19.77	19.63	26,444	16,235	18,036	11,760
Cirrhosis									
Boceprevir -F4 therapy	26.70	23.99	40,891	18.19	16.93	-	-	-	-
Telaprevir -F4 therapy	28.90	27.57	38,675	19.14	18.58	-	-	-	-
Sofosbuvir -F4 therapy	29.50	28.55	47,431	19.39	19.00	34,906	5,445	22,761	5,117
Genotype 1a									
Boceprevir -G1a therapy	27.98	26.08	33,330	18.76	17.91	-	-	-	-
Telaprevir -G1a therapy	29.06	27.84	35,716	19.22	18.70	-	-	-	-
Sofosbuvir -G1a therapy	30.38	29.99	46,154	19.75	19.60	19,359	12,851	13,707	9,676
Genotype 1b									
Boceprevir -G1b therapy	28.53	26.97	32,991	18.99	18.31	-	-	-	-
Telaprevir -G1b therapy	29.91	29.22	35,183	19.56	19.28	-	-	-	-
Sofosbuvir -G1b therapy	29.66	28.82	47,197	19.46	19.11	dominated	30,062	dominated	19,842

ICER and ICUR are incremental to the next nondominated strategy. Index year 2013.

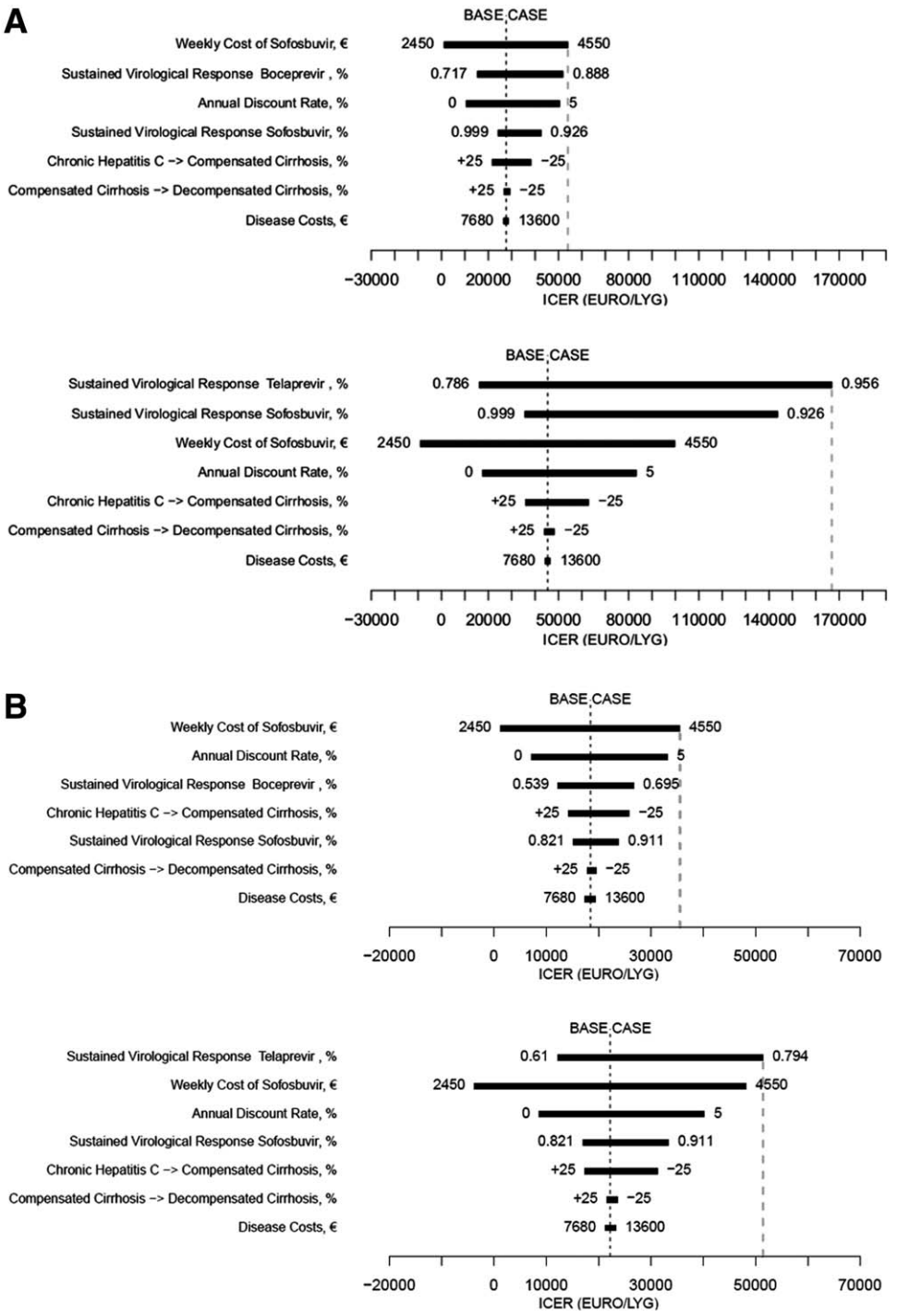

Fig. 2. Tornado diagrams of one-way sensitivity analyses on the influence of model parameter uncertainty on ICER (in euro/LYG). Tornado diagrams for the one-way sensitivity analyses of variables that influenced the ICER per additional life year gained (LYG) of SOF-IL28BCC (A), SOF-IL28BCT/TT (B), SOF-F0F3 (C), SOF-F4 (D), SOF-G1A (E), and SOF-G1B (F) therapies compared with BOC (top) and TVR (bottom)-based therapies. The horizontal axis represents the incremental cost-effectiveness ratio for LYG. The width of the bars illustrates the range of cost per additional LYG of evaluated strategies compared with DT. Upper and lower limits of values evaluated in sensitivity analysis are indicated next to the bars. The bars are ordered from greatest width at the top to least width at the bottom. The vertical dashed line represents the base case.

In G1b patients, SOF-G1b, compared with BOC-RGT-G1b strategy, was cost-effective in 31% (Fig. 3F). In 1,000 interactions, the SOF-G1b strategy resulted in a 1,000-fold gain in LYG compared with BOC-RGT-G1b.

Discussion

We demonstrated that SOF-based TT improves survival compared with first-generation PI-based TT in untreated G1 CHC patients, and that it is cost-effective by assuming a drug price of €3,500 per week. SOF was always, but not in patients with cirrhosis and in IL28B CC patients, cost-effective compared with BOC. SOF was cost-effective compared with TVR in IL28B CT/TT and G1a patients, not cost-effective in IL28B CC, fibrosis F0-F3, and in cirrhosis patients, and dominated in G1b patients. The robustness of these results was confirmed in the probabilistic sensitivity analyses. The cost-effectiveness of SOF was sensitive to SOF price, SVR rate variations

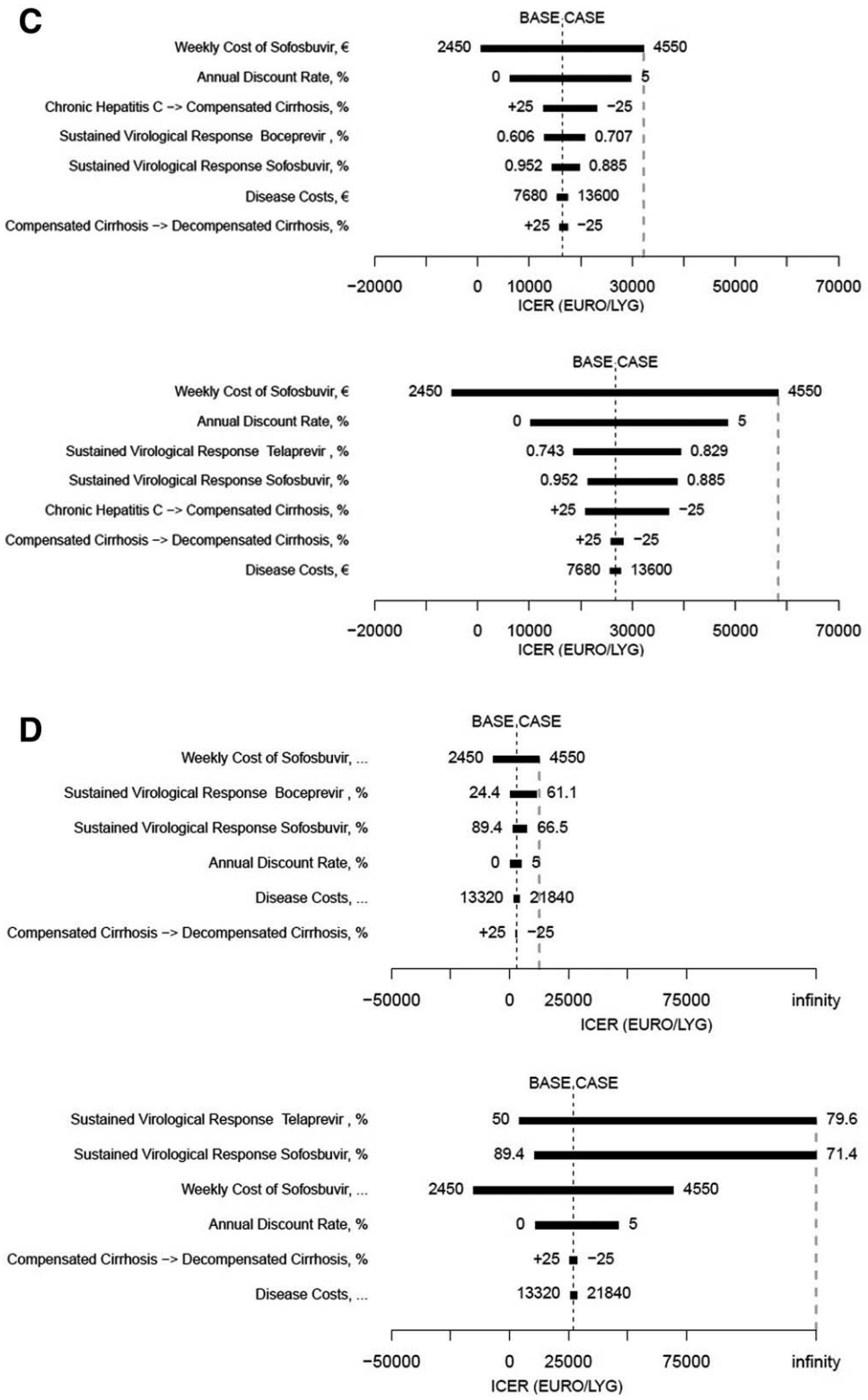

Fig. 2. Continued.

of both SOF and first-generation PI, and annual discount rate.

To our knowledge, this is the first cost-effectiveness analysis evaluating SOF-based TT in untreated G1 CHC patients. SOF is waiting for FDA and EMA authorization, and therefore our results were obtained by assuming that the SOF price is €3,500 per week, i.e., the price generating a willingness-to-pay threshold

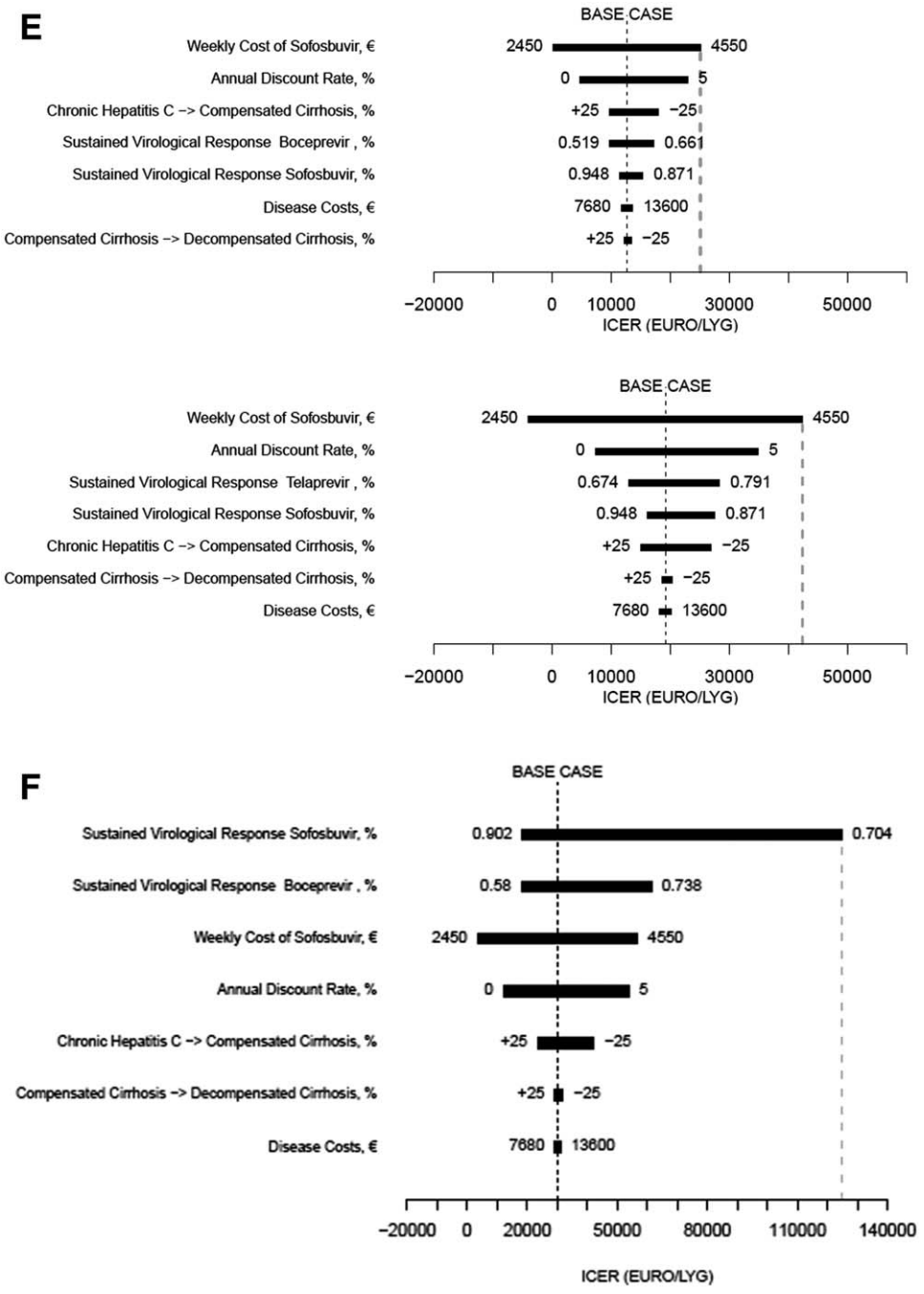

Fig. 2. Continued.

of €25,000 per LYG compared with TVR in the entire population of untreated G1 patients. According to this assumption and considering different subsets of patients, we found that, on the one hand, SOF-based therapy was almost always cost-effective compared with BOC while, on the other hand, it was cost-effective compared with TVR in some clinical subgroups only, i.e., IL28B CT/TT and G1a, lacking its cost-effectiveness in easy to treat (IL28B CC), F0-F3, and in difficult to treat (cirrhosis) patients. Following from this, sensitivity analyses showed that the cost-effectiveness of SOF was sensitive to SOF price variation, lacking its cost-effectiveness in some assumptions, and that, by considering the value of €25,000 per LYG as the threshold for willingness-to-pay, the cost-effectiveness of SOF compared with TVR was maintained at the minimum cost of €3,106 per week in IL28B CC, and at the maximum cost of €3,763 per week in G1a patients.

We observed that in the subset of the G1b population, SOF was slightly less effective and more

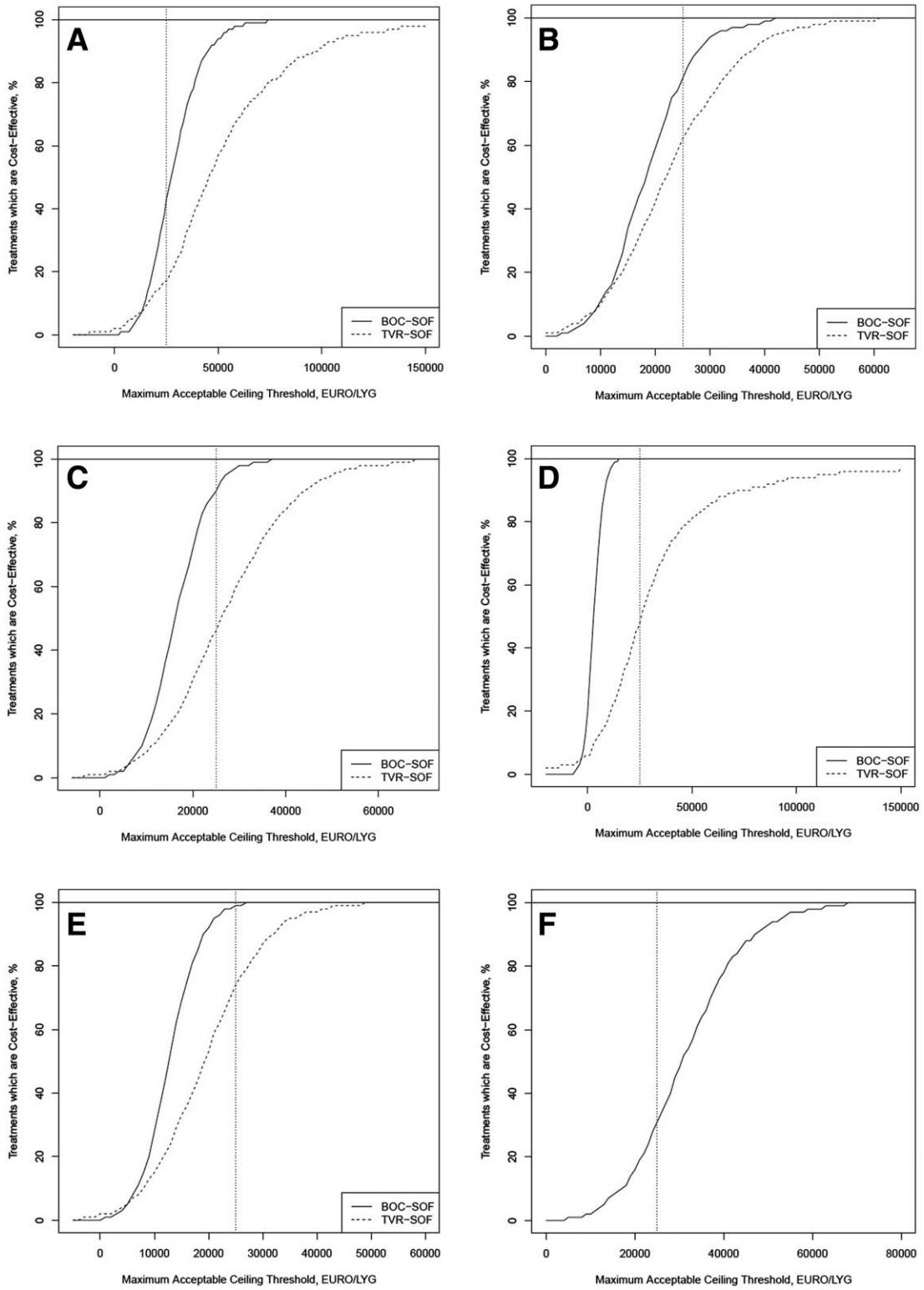

Fig. 3. Probabilistic sensitivity analysis. CEAC of evaluated strategies for IL28B CC (A), IL28B CT/TT (B), F0-F3 (C), cirrhosis (D), G1A (E), and G1B (F) patients.

expensive than TVR and, consequently, it was dominated. This issue is of particular interest, since G1b is the most prevalent G1 subtype in Europe.

From a clinical point of view, considering that SOF approval is expected in the first quarter of 2014 and that relevant efforts should be performed to give SOF

cost-effectiveness in all clinical scenarios, all the above-quoted data suggest that a deferral strategy for IL28B CT/TT, F0-F3, and G1a patients should be adopted, where SOF is clearly more effective than first-generation PI.

In G1b patients, if the lower SVR rates of SOF compared with TVR will be further confirmed in future studies, its slightly lower efficacy could be counterbalanced by the good tolerability profile of SOF. In fact, the major advantages of SOF-based therapies compared with first-generation PI strategies are the short treatment duration, i.e., 12 weeks, the good tolerability profile, and the simplicity of the therapeutic schedule, one pill per day.

Finally, in patients with cirrhosis, even if SOF is more effective than both TVR and BOC, deferral should be carefully evaluated due to the risk of liver disease decompensation potentially associated with a delay of treatment. However, deferring treatment may be counterbalanced by the good tolerability of SOF in patients with cirrhosis and by the risk of life-threatening adverse events during TVR and BOC treatment, as observed in the CUPIC cohort.[12]

All these issues, together with the high likelihood of SVR achievement, give SOF highly promising and preferable perspectives compared with BOC and TVR, if sold at an acceptable cost. In any case, especially in patients with mild liver damage, and/or with a contraindication to PEG-IFN and/or RBV, the indication to SOF-based TT should be carefully evaluated considering the promising results arising from IFN-free protocols including SOF or not.

Congruent with the above data, although the proposed algorithms are useful tools for decision-making, the treatment strategy must be carefully agreed upon with the individual patient. In particular, according to the editorial of Aronsohn and Jensen[45] reporting that deferring treatment is justifiable and appropriate for many patients, an informed deferral is needed considering risks related to inaccurate staging of liver disease, inability to predict progression of fibrosis, and comorbidity changes over time. Obviously, the clinical value and ethical impact of treatment or deferral should not be compromised by any economic analysis.[46]

This study has several limitations. 1) The efficacy data are derived from registered trials of HCV PI. In fact, data from RCTs are not directly transferable to clinical practice, since trial patients are healthier, show greater adherence to trial protocol, and are more closely monitored. 2) The current model uses aggregate rather than individual patient data. Consequently, our results reflect group averages rather than individual data. More detailed treatment comparisons could be achieved by an analysis of individual patient data, or by combining the different variables affecting the achievement of SVR using multivariate risk modeling. In addition, the hypo-representation of G1b patients in the NEUTRINO RCT[13] further limits our analyses in this setting of patients, where the real effectiveness and cost-effectiveness of SOF-based TT needs to be further evaluated in larger studies. 3) The lack of data on the economic impact of drug-drug interaction and on management of all side effects, of the induction of viral mutations, and especially of the tolerability profile of TT in real life and in patients with cirrhosis[12] could also have affected our analyses. 4) We used the utilities considered acceptable for an Italian population. However, it is well known that utilities may vary widely across different patient subgroups and that they critically depend on Quality of Life assumptions.[32] Accordingly, we assessed LYG, but not QALY, as the primary measure of effectiveness. 5) Another important limitation regards the transition probabilities from CHC to cirrhosis that were assumed to stay constant over time, sometimes slightly differing from those reported in other models.[27-30,46,47] However, our results were robust under a broad range of parameters used in the model as assessed by both deterministic and probabilistic sensitivity analyses, and produced similar outcomes compared to other models. In addition, the possible variation of BOC and TVR prices after SOF registration could also affect our results. 6) This was not a societal study. Therefore, our analysis was limited to direct medical costs; indirect costs, such as lost productivity and salaries of caregivers, were not included.

In conclusion, we found that treatment with SOF-based TT could be a cost-effective alternative to first-generation PI in untreated G1 CHC patients aged 50 years. These results were robust over a wide range of model assumptions but were sensitive to SOF costs. For IL28B CT/TT and G1a patients, the ICER of SOF compared with first-generation PI improved. SOF was dominated by TVR in G1b patients. However, this last issue could be counterbalanced by the good tolerability profile of SOF and by the shorter treatment duration.

Author Contributions: S. Petta, M. Enea, F.S. Macaluso, G. Cabibbo, R. Bruno, A. Gasbarrini, A. Plaia, A. Craxì, C. Cammà take full responsibility for the study design, data analysis and interpretation, and preparation of the article. All authors were involved in planning the analysis and drafting the article. All authors approved the final draft of the article.

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