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ORIGINAL RESEARCH ARTICLE

Early Treatment in HCV: Is it a Cost-Utility Option from the Italian Perspective?

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Abstract

Background and Objective In Italy, the Italian Pharmaceutical Agency (AIFA) criteria used F3–F4 fibrosis stages as the threshold to prioritise the treatment with interferon (IFN)-free regimens, while in genotype 1 chronic hepatitis C (G1 CHC) patients with fibrosis of liver stage 2, an approach with pegylated interferon (PEG-IFN)-based triple therapy with simeprevir was suggested. The key clinical question is whether, in an era of financial constraints, the application of a universal IFN-free strategy in naïve G1 CHC patients is feasible within a short time horizon. The aim of this study is to perform an economic analysis to estimate the cost-utility of the early innovative therapy in Italy for managing hepatitis C virus (HCV)-infected patients.

Methods The incremental cost-utility analysis was carried out to quantify the benefits of the early treatment approach in HCV subjects. A Markov simulation model including direct and indirect costs and health outcomes was developed from an Italian National Healthcare Service and societal perspective. A total of 5000 Monte Carlo simulations were performed on two distinct scenarios: standard of care (SoC) which includes 14,000 genotype 1 patients in Italy treated with innovative interferon-free regimens in the fibrosis of liver stages 3 and 4 (F3–F4) versus early-treatment scenario (ETS) where 2000 patients were additionally treated with simeprevir plus PEG-IFN and ribavirin in the fibrosis stage 2 (F2) (based on Italian Medicines Agency AIFA reimbursement criteria). A systematic literature review was carried out to identify epidemiological and economic data, which were subsequently used to inform the model. Furthermore, a one-way probabilistic sensitivity was performed to measure the relationship between the main parameters of the model and the cost-utility results.

Results The model shows that, in terms of incremental cost-effectiveness ratio (ICER) per quality adjusted life year (QALY) gained, ETS appeared to be the most cost-

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utility option compared with both perspective societal (ICER = EUR11,396) and NHS (ICER = EUR14,733) over a time period of 10 years. The cost-utility of ETS is more sustainable as it extends the time period analysis [ICER = EUR 6778 per QALY to 20 years and EUR4474 per QALY to 30 years]. From the societal perspective, the ETS represents the dominant option at a time horizon of 30 years. If we consider the sub-group population of treated patients [16,000 patients of which 2000 not treated in the SoC, the ETS scenario was dominant after only 5 years and the cost-utility at 2 years of simulation. The one-way sensitivity analysis on the main variables confirmed the robustness of the model for the early-treatment approach.
Conclusion Our model represents a tool for policy makers and health-care professionals, and provided information on the cost-utility of the early-treatment approach in HCV-infected patients in Italy. Starting innovative treatment regimens earlier keeps HCV-infected patients in better health and reduces the incidence of HCV-related events; generating a gain both in terms of health of the patients and correct resource allocation.

Key Points

This cost-utility analysis shows that in G1 CHC patients the early-treatment strategy improves survival compared with the restrictive-treatment strategy. The robustness of these results was confirmed in the deterministic and probabilistic sensitivity analyses.

These data require a reflection on a debated question: should all G1 CHC patients be treated with IFN-free regimens, especially considering their high costs, in an era in which resource scarcity is a prominent issue? Our study provides evidence that an early treatment strategy, fulfilling the moral framework of distributive justice could be a tenable solution for this allocation dilemma and increase cost-utility.

We found that early treatment strategy with PEG-IFN, ribavirin and simeprevir should be the first-line treatment in naïve and relapsed G1 CHC HCV-infected patients with F2 fibrosis stage. Restrictive-treatment strategy was not cost-utility compared to early treatment strategy. These results were robust over a wide range of model assumptions. Following the above evidence, every effort must be made to increase the proportion of patients who achieve viral eradication using the early treatment strategy.

1 Introduction

The estimated global prevalence of hepatitis C virus (HCV) infection is 2.2 %, corresponding to about 130 million HCV-positive people worldwide, most of whom are chronically infected [1]. HCV is one of the main causes of cirrhosis, hepatocellular carcinoma (HCC) and liver transplant in Western countries. HCV-related burden of disease data referred to the USA and Europe and indicate that hepatitis C is a major health problem whose mortality rate exceeds that of human immunodeficiency virus infection, highlighting the importance of timely antiviral treatment [2].

Sustained virological response (SVR) is a clinically relevant surrogate outcome in the management of HCV-infected patients because early viral eradication in patients with chronic hepatitis C (CHC) prevents the development of cirrhosis [3] and the occurrence of its complications, such as oesophageal varices [4], and liver-related death [5], also reducing HCC occurrence [6, 7].

In the last few years, the treatment of genotype 1 (G1) CHC patients, the most common genotype in the USA and Europe, has been rapidly changing from dual therapy (DT) with peginterferon alfa (PEG-IFN) and ribavirin to PEG-IFN-based triple therapies (TT) with first- and second-generation direct antiviral agents (DAAs), namely simeprevir or sofosbuvir. These agents achieve high SVR rates in naïve and relapsed patients [8, 9], but do not encourage results in non-responder patients (data for simeprevir only) [10]. Recent clinical trials also showed that all oral IFN-free regimens combining different DAAs are able to achieve SVR rates ranging from 90 to 100 %, independently of the severity of liver damage, the pattern of previous response to DT or first-generation protease inhibitors, and, of note, without significant side effects [11–19].

In Italy, the Italian Pharmaceutical Agency (AIFA) criteria used F3–F4 fibrosis of liver stages as the threshold to prioritise the treatment with IFN-free regimens, while in G1 CHC patients with F2 fibrosis stage an approach with PEG-IFN-based TT with simeprevir was suggested. However, the key clinical question is whether, in an era of financial constraints, the application of a universal IFN-free strategy in naïve G1 CHC patients is feasible within a short time horizon.

The aim of this analysis was to determine the cost-utility of the following competing strategies in treatment-naïve G1 patients: (1) restrictive-treatment strategy where only patients with fibrosis stages 3 or 4 (F3–F4) were treated with the interferon-free regimen; (2) early-treatment strategy where patients with fibrosis stage 2 (F2) were additionally treated with PEG-IFN-based TT using second-generation protease inhibitors (PI), namely simeprevir.

2 Method

The cost-utility analysis was conducted from both the NHS and societal perspectives (including indirect costs) in a 10-, 20- and 30-year time horizon. Two therapeutic strategies were compared:

- The first scenario includes the treatment of patients following common clinical practice. According to this approach, it is assumed that only the patients in F3 and F4 fibrosis stages are treated. Therefore, the new direct interferon-free antiviral drugs are indicated (base-case scenario);
- In the second scenario, a share of patients in F2 fibrosis stage may access the new innovative treatments, benefitting from an early treatment with high levels of SVR (early treatment scenario).

The costs are reported in Euro 2015 values. A yearly 3 % discount rate is applied to both cost results and effectiveness outcomes. The comparison between the two treatment scenarios in terms of cost-utility was expressed as the incremental cost-effectiveness ratio (ICER), corresponding to the ratio between incremental costs and incremental effectiveness in the early treatment scenario and the base-case scenario, where the effectiveness is expressed in terms of quality adjusted life years (QALYs). In Italy there is no ICER value currently acceptable internationally. As of today, range values of acceptability have been proposed with a value ranging from EUR20,000 to EUR40,000 [20, 21]. For this reason, in this study an ICER value below EUR30,000 per gained QALY was considered cost-utility.

2.1 Model Overview

In order to evaluate the cost-utility of an early treatment for HCV-affected patients nationally, a discrete state Markov model [22] was developed in Microsoft Excel 2013, reproducing the natural history of HCV infection. Starting from the mortality-morbidity multistate model recently developed by Mennini et al. [23], a new Markovian process was developed including 13 disease states [fibrosis stages from F0 to F4, decompensated cirrhosis, hepatocellular carcinoma (HCC), first-year transplant and following year transplant, SVR, SVR from F4, HCV-related death, death from other causes] and 40 transition probabilities (Fig. 1). Each cycle includes a yearly time lag. The transition probabilities of the health states reflect the main steps to define the clinical course of a patient contracting HCV.

2.2 Reference Population and Treated Patients

The model was aimed at projecting two cohorts of individuals representing the Italian epidemiological reality. In particular, the initial population simulated within the model was estimated starting from patients in genotype identified in the model of Mennini et al. [23]. These patients were broken down in different fibrosis stages according to a study promoted by the National Health Institute in more than 100 clinical centres with a target of 10,000 enrolled patients, accurately reflecting the types of HCV patients followed nationally [24]. The population includes 100,130 individuals to be treated in Italy, distributed in fibrosis stages from F0 to F4 (Table 1).

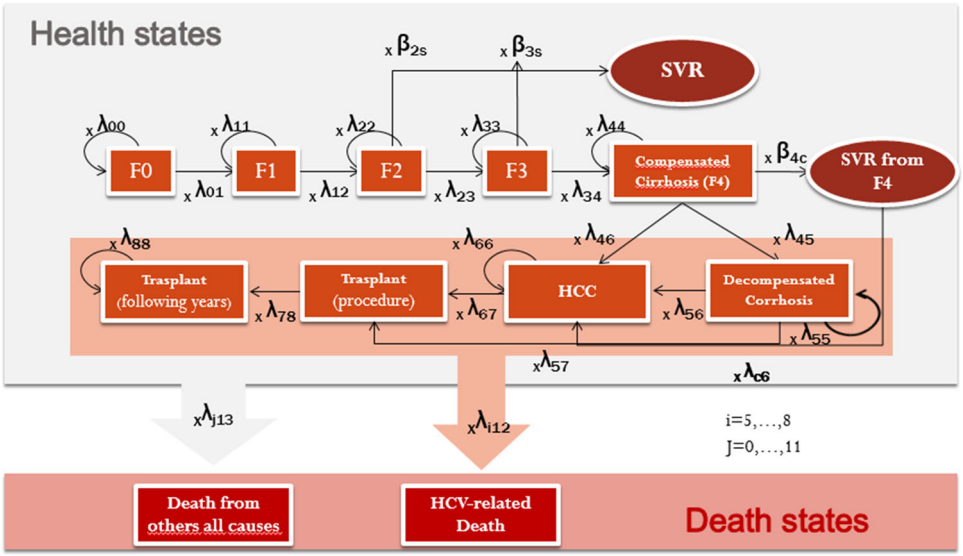

Fig. 1 Markov state-transition diagram for chronic hepatitis C and liver disease. *F* fibrosis of liver, *HCC* hepatocellular carcinoma, *SVR* sustained virological response, *Peg-INF* peginterferon alfa, *Rib* ribavirin, *HCV* hepatitis C virus infection

Table 1 Reference population and treated patients by scenario of analysis

	Simulation of treatable patients			Simulation of treated patients	
	Treatable patients	Treated patients Base-case	Early treatment patients	Base-case	Early treatment
Total	100,130	14,000	16,000	16,000	16,000
Breakdown by fibrosis stage					
F0	20,026	0	0	0	0
F1	21,027	0	0	0	0
F2	15,020	0	2000	2000 (untreated)	2000 (treated)
F3	12,016	8960	8960	8960	8960
F4	32,042	5040	5040	5040	5040

The model projection includes the comparison between two different therapeutic strategies, according to the population treated:

- The first scenario, the base-case, projects the cohort of patients being studied, assuming that 14,000 patients in F3–F4 have received new-generation treatments (14 % of the patients eligible for treatment), of which 8960 patients were in the fibrosis stage F3 group and 5040 in the F4 group [23].
- The early treatment scenario projects the same patients treated in F3–F4, already included in the base-case scenario group, with an additional 2000 patients treated in F2 fibrosis stage (13 % of the patients treatable in F2). The total number of subjects treated in the early treatment scenario was about 16,000 patients (14 % of total treatable patients), compared with 14,000 patients treated in the base-case scenario (16 % of total treatable patients).

The simulations and the resulting cost-utility have been reported considering both the whole treatable population (cohort of 100,130 patients treatable in F0–F4) and specifically only the patients treated in F2–F4 (Table 1).

2.3 Transition Probability and Efficacy of Treatments

The model was populated by the transition probabilities already used in previous Markovian processes specifically developed for the national context [23, 25], with the probability of hepatocellular carcinoma progression in subjects with compensated cirrhosis (F4), even if they had reached an SVR (Table 2).

For the patients with an F3 fibrosis stage and compensated cirrhosis (F4) costs and efficacy of treatment with innovative interferon-free therapies were assumed, while for early treated patients (fibrosis stage F2) the treatment with TT was considered (simeprevir + Peg-IFN) + ribavirin (Rib) [26]. The efficacy estimate was expressed in terms of probability to reach SVR per treated patient. SVR levels were estimated through efficacy data coming from pivotal clinical trials of treatments at present indicated for G1 in the national health context [27], equal to 95.5 % for F3 and F4 patients and 90.5 % for F2 patients [23, 28, 29] (Table 2).

The model considered only adverse events of treatments decisively impacting costs and the patients' quality of life. In particular, data coming from pivotal clinical trials indicate the probability of anaemias deriving from the treatment of patients with F2 fibrosis stage treatable with TT of Peg-INF + Rib [28] (Table 2).

2.4 Costs

To estimate costs, direct health costs were considered together with indirect ones. These indicate a loss of productivity due to absence from work caused by the disease. The yearly direct health costs considered in the model refer to aggregate costs to manage HCV-related diseases (specialist visits, analyses and check-ups), support pharmacological therapies and hospital admissions already published in previous studies specifically conducted in the national context [10] (Table 3).

The average cost of treatments available in Italy for the considered indications was added to the average cost of the patient's management. For patients with chronic infection (F3) and compensated cirrhosis (F4), the mean of interferon-free treatments calculated through the average dose reported in the technical sheet and the sale price to the NHS net of discounts, as provided for by the law [30–33], were considered. For patients with an F2 fibrosis stage the cost of TT was taken into account, adding up the cost of simeprevir to that of Peg-IFN + Rib through the average dose reported in the technical sheet and the sale price to NHS [34].

For the treatment of anaemias and their related cost, an average expense was assumed deriving from the rate of

Table 2 Transition probability and epidemiological parameters

	Base-case	Sources	Range[a]	
Annual probability of disease progression				
F0 to F1	0.025	[23]		
F1 to F2	0.018	[23]		
F2 to F3	0.026	[23]	0.019	0.033
F3 to F4	0.025	[23]	0.018	0.031
F4 to decompensated cirrhosis	0.008	[23]		
F4 to HCC	0.003	[23]		
Decompensated cirrhosis to HCC	0.014	[23]		
Decompensated cirrhosis to transplant	0.005	[23]		
HCC to transplant	0.008	[23]		
SVR from F4 to HCC	0.0007	[39]		
Annual probability of progressing to death				
Decompensated cirrhosis to death (liver-related)	0.030	[23]		
HCC to death (liver-related)	0.111	[23]		
Transplant (procedure) to death (liver-related)	0.036	[23]		
Transplant (following years) to death (liver-related)	0.008	[23]		
Death from all other causes	0.010	[40]		
Efficacy of treatments				
F2 to SVR	0.905	[23, 28, 29]	0.462	1.000
F3 to SVR	0.950	[23, 28, 29]	0.764	1.000
F4 to SVR	0.950	[23, 28, 29]	0.764	1.000
Utilities estimates				
F0	0.82	[36, 37]	0.4	1.0
F1	0.82	[36, 37]	0.4	1.0
F2	0.82	[36, 37]	0.4	1.0
F3	0.82	[36, 37]	0.4	1.0
F4	0.78	[36, 37]	0.4	1.0
Decompensated cirrhosis	0.65	[36, 37]	0.3	1.0
HCC	0.25	[36, 37]	0.1	0.4
Transplant (procedure)	0.5	[36, 37]	0.3	0.7
Transplant (following years)	0.7	[36, 37]	0.4	1.0
SVR	1	[36, 37]	0.5	1.0
SVR from F4	0.91	[37]	0.5	1.0
Disutility for Peg-INF + Rib	0.029	[37]		

F fibrosis of liver, *HCC* hepatocellular carcinoma, *SVR* sustained virological response, *Peg-INF* peginterferon alfa, *Rib* ribavirin

[a] The range was calculated on the basis of a deterministic variation of ± 25 %

anaemias recorded in the pivotal trials of simeprevir in the treatment of TT [28], multiplied by the average weekly cost found in the literature [35], assuming a two-week treatment with epoietin.

2.5 Utility

In order to estimate the QALYs lived by the populations in the two scenarios being analysed, a utility value was associated with each state of the model, in order to quantify the loss of life quality caused by the pathological state. In particular, the utilities estimated in the work of Petta et al. [36] for the base case, and the utilities found in the literature for the deterministic sensitivity analyses [37], were considered (Table 2).

For F2 patients treated with Peg-INF + Rib, in addition to the cost of the adverse event, a disutility of the health state equal to 0.029 associated with the patients actually treated in the early treatment scenario [37] was assumed.

Table 3 Cost parameters

	Base-case (EUR)	Sources	Range[a] (EUR)
Cost of treatment			
Treatment for F2	31,057	[34]	15,839–46,275
of which due to anaemia	57	[35]	
Treatment for F3	47,500	[30–33]	24,225–70,775
Treatment for F4	47,500	[30–33]	24,225–70,775
Direct medical costs			
F0	292	[35]	435–149
F1	292	[35]	435–149
F2	292	[35]	149–435
F3	292	[35]	149–435
F4	397	[35]	203–592
Decompensated cirrhosis	4385	[35]	2236–6533
HCC	5792	[35]	2954–8631
Transplant (procedure)	84,900	[35]	43,299–126,501
SVR	0	[35]	0
SVR from F4	397	Assumption from [39]	203–592
Death (liver-related)	0	[35]	0
Death from all other causes	0	[35]	0
Indirect costs			
F0–F4 (treated patient)	6063	[35]	3092–9034
F0–F4 (untreated patient)	2183	[35]	1113–3252
Cirrhosis (treated patient)	8488	[35]	4329–12,648
Cirrhosis (untreated patient)	2547	[35]	1299–3794
HCC	10,914	[35]	5566–16,261
Transplant (procedure)	21,827	[35]	11,132–32,523
Death	26,678	[35]	13,606–39,750

F fibrosis of liver, *HCC* hepatocellular carcinoma, *SVR* sustained virological response, *Peg-INF* peginterferon alfa, *Rib* ribavirin

[a] The range was calculated on the basis of a standard deviation equal to 25 % of the mean value

2.6 Statistical Analyses

In order to consider the intrinsic variability of the data used to inform the model, both a probabilistic sensitivity analysis (PSA) and a deterministic sensitivity analysis (DSA) were developed.

For PSA the choice of the probabilistic distribution was attributed applying what is generally reported for the development of economic evaluation models, distinguishing between costs (gamma distribution) and epidemiological parameters (beta distribution) [38]. Furthermore, 5000 Monte Carlo simulations were performed in order to represent the cost-effectiveness acceptability curve (CEAC) for different scenarios of analysis.

DSA was conducted through a one-way analysis in which the main parameters of the model were changed according to the ranges estimated through the literature. The following parameters were considered in the deterministic analysis: transition probability from F2 to F3 and from F3 to F4 (±25 % at the same time), change in the discount rate (0 % cost, 5 % efficacy; 5 % cost, 0 % efficacy), efficacy parameters (±25 %), treatment costs (−40 and −60 %), utility (±5 %) and costs of health states (from the study of Cortesi et al. [37]).

3 Results

Figure 2 shows the expense differences between SoC and early treatment scenario broken down by costs of treatments, direct and indirect health costs over a 10-, 20- and 30-year time horizon. The projections show that after 30 years the investment for treatments is absorbed by the reduction of direct and indirect costs generated by the efficacy guaranteed by the early approach to the treatment. The projection of cost-utility results in the societal perspective shows that the early treatment is already cost-utility after 5 years, while in a time horizon of 30 years of early treatment scenario becomes prevailing (less expensive and more effective) (Fig. 2d).

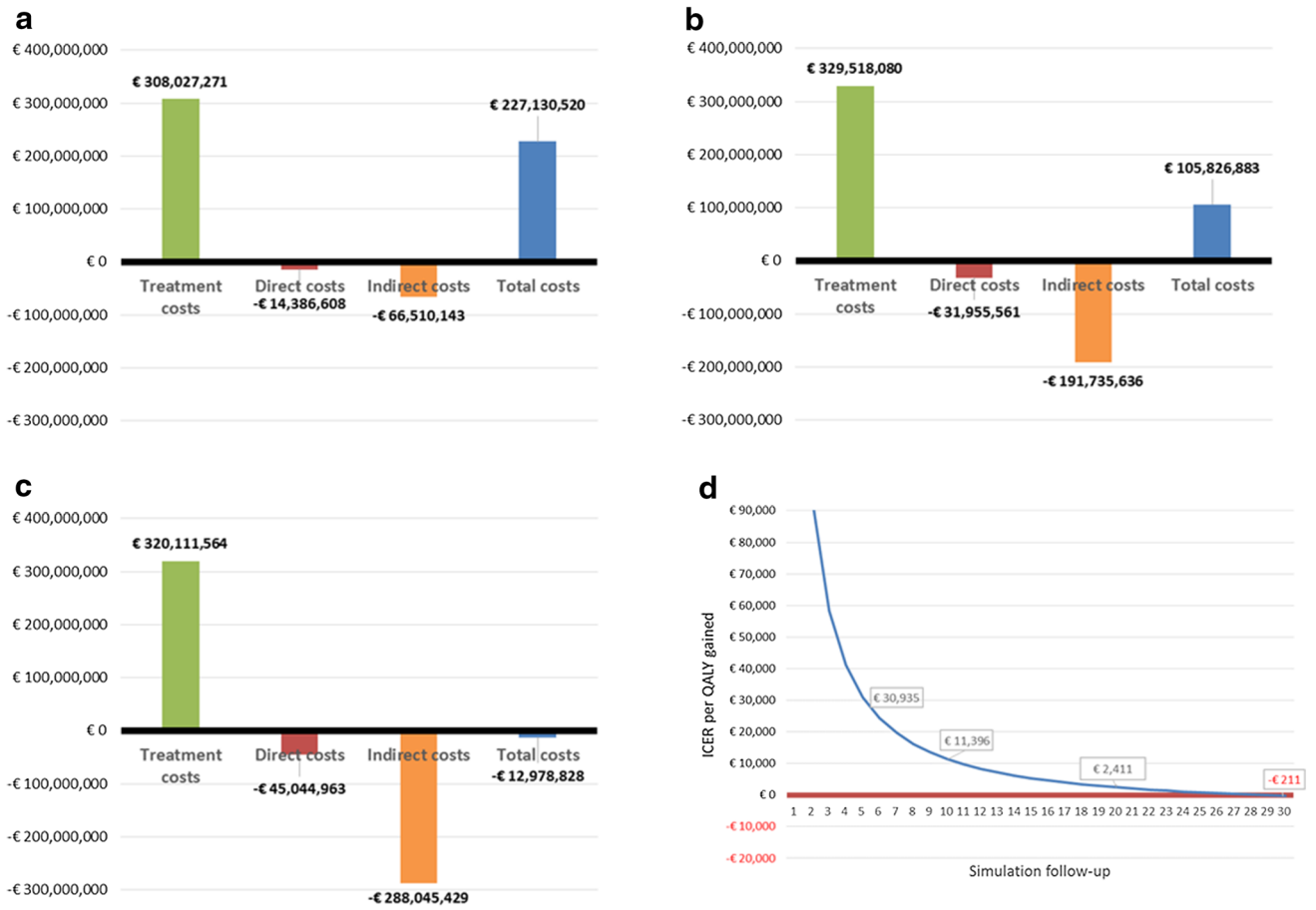

Fig. 2 Expense impact in 10, 20 and 30 years of analysis and ICER per QALY gained. **a** Expense impact in 10-year analysis. **b** Expense impact in 20-year analysis. **c** Expense impact in 30-year analysis. **d** ICER per gained QALY early treatment versus standard of care. *ICER* incremental cost-effectiveness ratio, *QALY* quality adjusted life years

Table 4 Cost-utility results after 10-, 20-, 30-year follow-up from the National Health Service perspective

	Cost	QALY	Incremental cost	Incremental QALY	ICER × QALY
10 years					
Base-case	EUR 2,324,706,986	766,730			
Early treatment	EUR 2,618,347,649	786,661	EUR 293,640,663	19,931	EUR 14,733
20 years					
Base-case	EUR 2,796,125,722	1,236,916			
Early treatment	EUR 3,093,688,241	1,280,818	EUR 297,562,519	43,902	EUR 6778
30 years					
Base-case	EUR 3,011,275,422	1,554,998			
Early treatment	EUR 3,286,342,023	1,616,477	EUR 275,066,601	61,479	EUR 4474

ICER incremental cost-effectiveness ratio, *QALY* quality adjusted life years

Observing only the National Health Service (NHS) perspective (Table 4), it may be noted that the early treatment remains below EUR15,000 per QALY already after 10 years.

The deterministic sensitivity analysis (Fig. 3) shows that the most sensitive parameters of the model are represented by the variation of the utilities associated with the disease states (a +5 % variation causes an ICER increase three

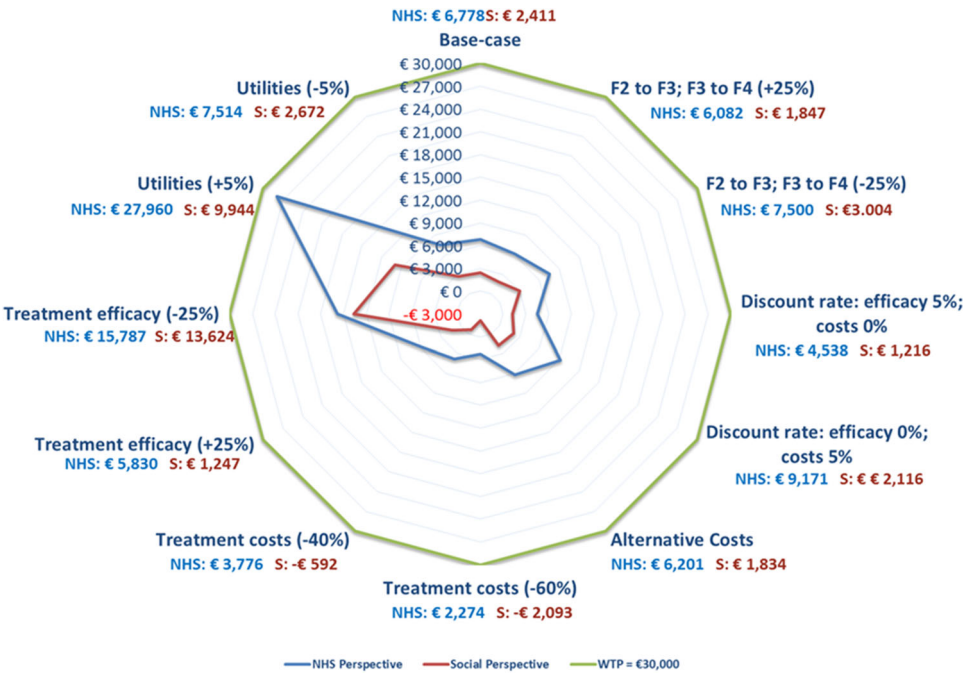

Fig. 3 One-way sensitivity analysis: radar diagram (20 years' follow-up). *F* fibrosis of liver, *NHS* National Health Service perspective, *S* social perspective, *WTP* willingness-to-pay

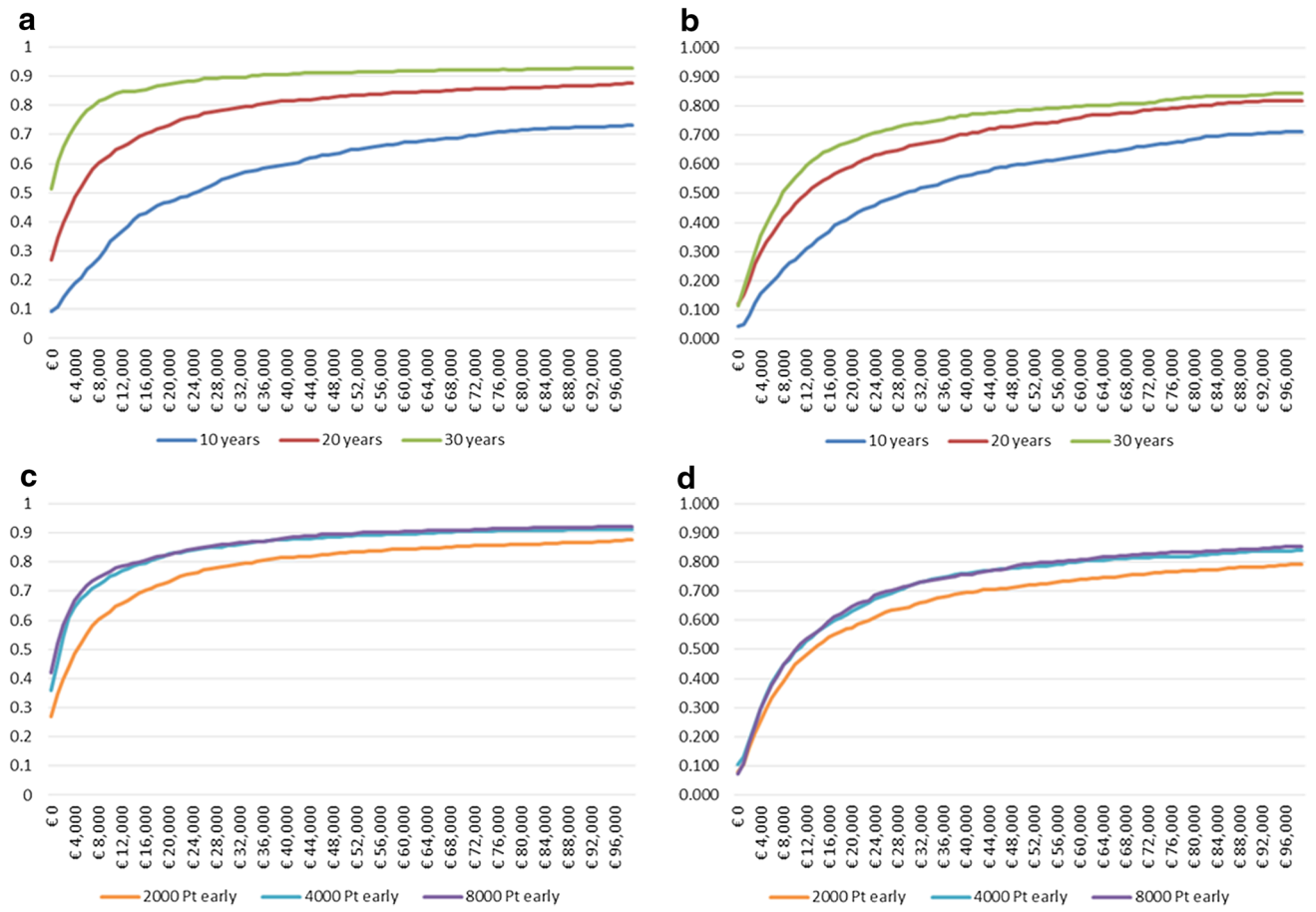

Fig. 4 Cost-effectiveness acceptability curve (CEAC): early treatment versus standard of care. **a** Social perspective. **b** NHS perspective. **c** Social perspective: 20 follow-up. **d** NHS perspective: 20 follow-up. *NHS* National Health Service, *Pt* patients

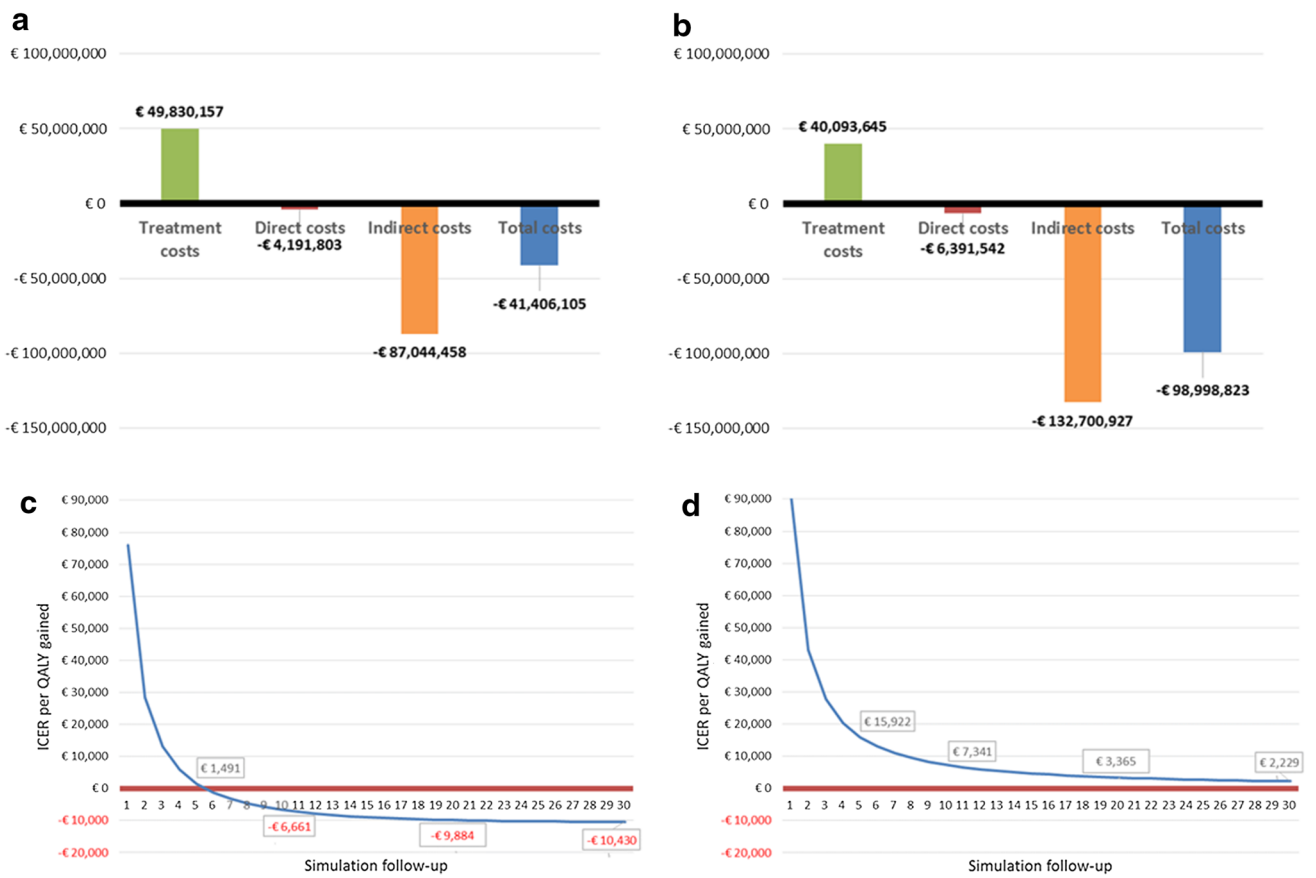

Fig. 5 Sub-analysis of cohort of treated patients. **a** Expense impacts at 10-year analysis. **b** Expense impacts at 20-year analysis. **c** ICER per QALY gained early treatment versus standard of care: Societal perspective. **d** ICER per QALY gained early treatment versus standard of care: NHS perspective. *ICER* incremental cost-effectiveness ratio, *QALY* quality adjusted life years, *NHS* National Health Service

times higher than the base-case), a 25 % efficacy reduction of the treatments (involving a more than double ICER increase with reference to the base-case) and a variation of treatment costs (involving about 40 or 60 % reduction of the cost-effectiveness ratio).

Including indirect costs in the analysis, the sensitivity parameters are basically unchanged. In this case, the reduction of treatment efficacy is the parameter with higher weight. Furthermore, with a 40 or 60 % cost reduction the early treatment prevails. In any case, no parameters exceed the acceptability threshold considered in the study (green line of the chart).

The probabilistic sensitivity analysis shows that paying EUR30,000 per gained QALY, the early treatment is cost-utility and its probability changes according to the considered time horizon, ranging from 55 to 90 % in the societal perspective and from 50 to 75 % in the NHS perspective (Fig. 4a, b). The higher the number of analysis years, the lower the uncertainty associated with the actual cost-utility in the early treatment scenario (the curves grow with higher inclination in longer time horizons). Figure 4c, d show that by increasing the number of patients to be treated, the probability that the early treatment is cost-utility increases.

Finally, the treated population was specifically focused. In this analysis, the expense impact at 10 years shows that the reduction of direct and indirect health costs is higher than the initial investment in treating 2000 F2 additional patients (Fig. 5a, b). Observing the cost-effectiveness ratio of early treatment compared with SoC in the societal perspective (Fig. 5c), ICER per gained QALY is below the threshold of EUR30,000 starting from the second year, and the early therapy is prevailing just after 5 years. Considering only the NHS perspective, ICER is below EUR30,000 per gained QALY after the third year, and it has very low values over the years (Fig. 5d).

4 Discussion

In 2014 several randomised controlled trials were published showing that different IFN-free regimens allow to reach >90 % SVR rates in HCV G1-infected patients with

short-term therapy (12 weeks) and without significant side effects [11–19]. These strategies represent a new challenge for CHC treatment, even if, due to the very high cost, their universal use in all HCV G1 patients, casts doubt on the ability of health-care systems to effectively deliver these innovations. In line with these considerations, in Italy AIFA criteria used F3–F4 fibrosis stage as the threshold to prioritise the treatment with IFN-free regimens.

To our knowledge, this is the first cost-utility analysis comparing a restrictive-treatment strategy—where only patients with F3–F4 fibrosis stage were treated with IFN-free regimen—with an early-treatment strategy—where patients with F2 fibrosis stage were additionally treated with PEG-IFN-based TT with simeprevir. We demonstrated that in G1 patients the early-treatment strategy improves survival compared with the restrictive-treatment strategy. Our base-case analysis estimated that early-treatment strategy compared with restrictive-treatment strategy became cost-utility already after 5 years. This was the most cost-utility option from both societal and NHS perspectives, over a time horizon of 10 years, and the dominant option from the societal perspective over a time horizon of 30 years.

The robustness of these results was confirmed in the deterministic and probabilistic sensitivity analyses.

It is worth underlining that using an early treatment strategy we are able show reduction in costs and improvement in benefits in comparison with a restrictive-treatment strategy.

These data require a reflection on a debated question: should all G1 patients be treated with IFN-free regimens, especially considering their high costs, in an era in which resource scarcity is a prominent issue? Our study provides evidence that an early treatment strategy, fulfilling the moral framework of distributive justice [41] could be a tenable solution for this allocation dilemma and increase cost-utility. However, the objective of treating all G1 infected patients with IFN-free regimens, could be achieved only after negotiating a significantly lower price for the new IFN-free regimens.

Although the proposed early treatment strategy may be a useful tool for decision making and better allocation of the new direct antiviral agents, any treatment strategy must be carefully agreed upon with the individual patient, taking into account the different factors that can interfere with treatment response. In particular, the choice of treatment should be targeted to select the best possible option in each patient, without any economic analysis constraining the clinical value and ethical impact of this decision. We should also take into account that chronic HCV infection is associated with metabolic, cardiovascular, neurological and immune-mediated conditions and HCV increases the risk of death from both hepatic and non-hepatic disease [42]. Thus, theoretically, all efforts should be made to maximize access to treatment, also by identifying strong SVR predictors to triple treatment, and optimise and personalise the therapy in patients with a higher likelihood of responding to triple treatment. IFN-free regimens should be appropriately reserved only for intolerant patients or those with a lower likelihood of response to TT. By applying this principle, stratification of patients according to predictors of SVR could affect the cost-utility of early treatment strategy.

Some caveats apply to our results. (1) The efficacy data are derived from registered trials of HCV DAA. In fact, data from RCTs are not directly transferable to clinical practice, since trial patients are healthier, more closely monitored and ensure greater adherence to treatment protocol. (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 patient data or combining the different variables affecting the achievement of SVR using multivariate risk modelling. (3) Another important limitation regards the transition probabilities from CHC to cirrhosis that were assumed to remain constant over time and may slightly differ from those reported in other models. 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 with other models. (4) Finally, the decrease of the disease burden due to the reductions in the pool of infected subjects was not an input of our model.

5 Conclusion

In conclusion, we found that early treatment strategy with Peg-IFN, ribavirin and simeprevir should be the first-line treatment in naive and relapsed G1-infected patients with F2 fibrosis stage. Restrictive-treatment strategy was not cost-utility compared to ETS. These results were robust over a wide range of model assumptions. Following the above evidence, every effort must be made to increase the proportion of patients who achieve viral eradication using the early-treatment strategy.

Compliances with Ethical Standards

Declaration of Funding This analysis was funded by Janssen-Cilag SpA. The authors confirm that the paper is an accurate representation of the study results. FD is an employee of the sponsor and was involved in the study design, data collection and analysis, interpretation of data.

Conflict of interest FD is employee of Janssen-Cilag SpA. GT, CC has received consulting fees from Janssen-Cilag SpA, MSD.

AM, RV and FSM declare that there is no conflict of interest regarding the publication of this paper.

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