

Budget impact analysis of sofosbuvir-based regimens for the treatment of HIV/HCV-coinfected patients in northern Italy: a multicenter regional simulation

Giovanni Cenderello¹Stefania Artioli²Claudio Viscoli³Ambra Pasa⁴Mauro Giacomini⁵Barbara Giannini⁵Chiara Dentone⁶Laura Ambra Nicolini³Giovanni Cassola¹Antonio Di Biagio³

¹Infectious Diseases Unit EO, Ospedali Galliera, Genoa, ²Infectious Diseases Unit, ASL-5 Spezzina, La Spezia, ³Infectious Diseases Unit, AOU San Martino, IST, Genoa University, Genoa, ⁴IT Unit, Ospedali Galliera, Genoa, ⁵Department of Informatics, Bioengineering, Robotics and System Engineering (DIBRIS), University of Genoa, Genova, ⁶Infectious Diseases Unit, ASL-I Imperiese, Sanremo, Imperia, Italy

Objectives: Chronic hepatitis C virus (HCV) is a leading cause of hospitalization and death in populations coinfecting with human immunodeficiency virus (HIV). Sofosbuvir (SOF) is a pan-genotypic drug that should be combined with other agents as an oral treatment for HCV. We performed a 5-year horizon budget impact analysis of SOF-based regimens for the management of HIV/HCV-coinfecting patients.

Methods: A multicenter, prospective evaluation was conducted, involving four Italian Infectious Diseases Departments (Galliera, San Martino, Sanremo, and La Spezia). All 1,005 genotype-coinfecting patients (30% cirrhotics) under observation were considered (patients in all disease-stages were considered: chronic hepatitis C, cirrhosis, transplant, hepatocellular carcinoma). Disease stage costs per patient were collected; the expected disease progression in the absence of treatment and sustained virological response (SVR) success rate for SOF-based regimens were calculated based on the literature and expert opinion. Drug prices were based on what the National Health Service paid for them. The comparison of “no treatment” disease progression costs versus the economic impact of SOF-based regimens was investigated.

Results: Over the following 5 years, the disease progression scenario resulted in direct costs of approximately €54 million. Assuming an SVR success rate of 90%, average SOF-based regimens cost up to €50,000 per person, resulting in a final cost of more than €56 million, so this option is not economically viable. At the average price of €12,000, SOF-based regimens, expense was €17 million, saving 68%. At this price level, the economic resources invested in treating mild to moderate fibrosis stage patients would be equal to the amount of direct costs of disease management in this stage, resulting in a valid return of investment in the short-term.

Conclusion: Given the high rates of SVR, in the Italian Healthcare System, SOF-based regimens, price is a determinant and a predictor of the overall cost for the Hepatitis C patient's management. At the average price per therapy of €12,000 over the next 5 years, SOF-based regimens are becoming highly sustainable.

Keywords: HCV treatment, sofosbuvir, HIV, budget impact, HIV/HCV coinfection, cirrhosis

Introduction

Human immunodeficiency virus (HIV) and hepatitis C virus share the same mode of transmission (through direct blood to blood contact), and therefore, the incidence of coinfection in Italy is extremely high, reaching a peak of 45% as reported by Italian Cohort Naive Antiretrovirals foundation in 2002.¹ This issue is largely due to the high percentage of former drug users among Italian people living with HIV.¹

Correspondence: Giovanni Cenderello
Infectious Diseases Unit EO, Ospedali
Galliera, Mura delle Cappuccine 14,
16128 Genoa, Italy
Tel +39 010 5634 478
Fax +39 010 5744 480
Email giovanni.cenderello@galliera.it

The most recent guidelines from the European Liver Association do not make any distinction between mono or coinfecting patients² for the treatment with anti-HCV directly active antivirals. On the other hand, it is generally accepted that in HIV/HCV patients there is faster progression toward cirrhosis and hepatocellular carcinoma (HCC) than in mono-infected.^{3–11}

Several study cohorts have shown the natural history of end-stage liver disease in HIV/HCV-coinfecting patients.^{12–14} In addition, the natural history of compensated cirrhosis in coinfecting patients has been described in smaller cohorts of less than 200 patients.^{15,16} Moreover in HIV/HCV coinfection, SVR may also decrease the progression of HIV infection and mortality not related to liver disease.^{17,18}

The clinical benefits associated with the eradication of HCV have been well characterized in patients with advanced fibrosis or cirrhosis but not in patients with less advanced stages of liver fibrosis. Also, a comprehensive costs–opportunity evaluation in patients with a less severe disease is missing. This is a relevant question, particularly in HIV/HCV-coinfecting patients, for whom the delivery of effective HCV treatment could be a priority even in mild to moderate stages of liver fibrosis, in order to prevent a more rapid disease progression. Based on hospital databases, in Liguria region one out of three HIV patients is coinfecting with HCV; in addition, Liguria has the highest prevalence of AIDS among other regions in Italy.¹⁹ Chronic HCV in Italy is also a leading cause of infectious admissions in hospital for HIV patients.²⁰ Therefore, earlier treatment in this population is crucial in terms of clinical benefits, prevention of disease progression and HCV-related health care direct costs limitation.²¹ Sofosbuvir (SOF) is a pan-genotypic drug which can be combined with other agents like ribavirin, simeprevir, daclatasvir or, in single-tablet regimen, together with ledipasvir as all oral treatment for HCV, with different entry price levels paid and reimbursed by the National Health Service.

Also, SOF and sofosbuvir/ledipasvir are linked to a price/volume payback scheme covered by a secrecy agreement²² that, in practice, affects regimen's cost variations. Due to budget constraints, as of year 2015, the national registration in terms of reimbursement of such regimens has been restricted to patients with more severe stages of disease, according to ethical and clinical considerations.^{23–26} But, we may expect in the near future costs declining, according to new price negotiations that try to include patients with less severe conditions to be eligible to reimbursement by National Health Authorities.

Therefore, we tried to assess a 5-year horizon budget impact (ie, the Regional Health System Management's

term) and cost saving analysis related to the effects of SVR after treatment with SOF regimens on mortality and liver related complications in HIV/HCV-coinfecting patients in any disease stage.

Patients and methods

Model structure

A Markov model has been applied to conduct a multicenter, 5-year horizon prospective costs evaluation, involving four Italian Infectious Diseases Departments (Galliera, San Martino, Sanremo, and La Spezia) in Liguria region, Italy. In all, 1,005 all genotypes adult HIV/HCV patients, under observation by clinicians as of May 2015, were included in the analysis. The patients' characteristics in the group of pooled data were classified according to their current disease stage: non cirrhotics, cirrhotics, HCC, and transplants (Table 1).

On completion of treatment (at 12 or 24 weeks), patients who achieve SVR are considered to be permanently cured of the infection (SVR at 12 weeks has been set as an appropriate endpoint for regulatory approval and is accepted by most clinical and regulatory authorities).²⁷ Patients who do not achieve SVR progress to more advanced stages of the disease. In this case, transition probabilities and disease progression rates are based both on literature and clinical experts' opinion. All cause mortality rates were applied to all health states in the model.

The cycle length was 3 months to account for the 12-week treatment duration for some SOF-based regimens, costs and outcomes were discounted at 3% as recommended by the Italian Association of Health Economics.²⁸ All data were anonymously processed and analyzed. The comparison of 1) “no treatment” disease progression costs vs 2) the economic impact of SOF-based regimens was investigated.

This study was developed with the data available inside the IANUA study (Indagine sull'appropriatezza prescrittiva degli antiretrovirali antiretrovirali) which was approved by Comitato Etico Regione Liguria, with provision number PR 032 REG2014, obtained on 08 April, 2014.

Table 1 HIV/HCV-coinfecting patients* under observation in four Ligurian hospitals (Galliera, San Martino, Sanremo, and La Spezia, as of May 2015)

	Fibrosis stage	N
Chronic hepatitis C (CHC)	F0–F2	528
	F3	174
Liver cirrhosis	F4	288
HCC		15
Total		1,005

Note: *Nine patients underwent liver transplantation.

Abbreviations: HCC, hepatocellular carcinoma; HCV, hepatitis C virus; HIV, human immunodeficiency virus.

Efficacy: SVR rates

The SVR rates of SOF-based regimens for each patient disease stage were derived from trials and literature^{29–33} and validated by expert opinion. The average SVR success rate for SOF-based regimens included in the model was 90%.

Transition probabilities

Transition probabilities in the analysis related to HCV progression from one disease stage to another were taken from the literature^{17,34–37} (Table 2); where this was not possible, we obtained them from expert opinion. These estimates were converted to annual probabilities for the analysis.

Resource consumption and costs

In this study, cost data were analyzed from the Regional Health Service point of view. Costs associated with each health state were obtained from the White Paper by the Italian Association of the Study of the Liver³⁸ and the COME Study,²¹ which are aligned with the costs for each health state resulting from the Ospedale Galliera budgeting system (which is a component of Italian Network for Standard Costs in Healthcare). As part of the reimbursement agreement with the Italian reimbursement agency, we assumed that 24 weeks of treatment with SOF had the same price as 12 weeks of treatment. Drug prices (VAT included) for all the regimens used in the analysis are those applied to the Italian NHS hospital pharmacies (Table 3).

Sensitivity analysis

The sensitivity analysis verified the impact of a series of variations of the base case with a large influence on the obtained results. A series of univariate analyses was carried out on some parameters of the simulation model, such as SVR rates, anti-HCV cost regime, and mortality rate. Each parameter was varied with $\pm 10\%$ with respect to the base-case scenario on the basis of Italian guidelines on economic evaluation.²⁴

Results

Table 4 shows the main results. In the “disease progression” scenario, over the next 5 years, the disease progression without treatments resulted in €54 million ca costs and 89 deaths. On the other hand, treatment containing SOF would save 68 people from HCV-related deaths. Overall, the SOF-based regimens with an average price $>€50,000$ do not offer a favorable cost saving profile, as this cost generates more than €56 million expense. Moreover, when the average price of an SOF regimen varies from €45,000 to €15,000 the budget impact ranges from €50 to €20 million ca, ie, saving from 6% to 53% of liver-related disease management costs, respectively (min: 3.5€M–max: 34.1€M ca). At the average price of €12,000, SOF-based regimens’ expense was €17 million ca, saving 68% (€37 million ca) of costs compared with the disease progression scenario.

This result indicates that at this price level, the economic resources invested to treat from mild to moderate fibrosis

Table 2 Transition probabilities: expected progression rates in 5 years (without treatment intervention)

Year 0	Year 5	Probabilities	Source
Non-cirrhotic, HIV-coinfected		Base case: 0	Benhamou et al ⁷
	Compensated cirrhosis	5 years: 0.05	
	Decompensated cirrhosis	5 years: 0.06	
	HCC	5 years: 0.06	
	Liver transplant	5 years: 0.04	
	Death	5 years: 0.06	
Compensated cirrhosis		Base case: 0	Fattovich et al ⁸
	Decompensated cirrhosis	5 years: 0.15	
	HCC	5 years: 0.12	
	Liver transplant	5 years: 0.12	
	Death	5 years: 0.10	
Decompensated cirrhosis		Base case: 0	Pineda et al ¹²
	HCC	5 years: 0.12	
	Liver transplant	5 years: 0.12	
	Death	5 years: 0.10	
HCC		Base case: 0	Expert opinion
	Death	5 years: 0.4	
	Liver transplant	5 years: 0.5	
Pre-OLT/Post-OLT		Base case: 0	Clinical observation
	Death, Year 3	5 years: 0.5	

Note: The probabilities show the probability for each single patient to progress from the conditions shown in Year 0 to each single condition by 5 year.

Abbreviations: OLT, liver transplant; HCC, hepatocellular carcinoma; HIV, human immunodeficiency virus.

Table 3 SOF-based regimens' treatment prices (VAT included)

Treatment regimen	Treatment prices (€) (≥ 12 weeks)
SOF + LDV (8 weeks)	29,810
SOF + LDV	44,770
SOF + SMV	57,200
SOF + DCV (60 mg/die)	59,400
SOF + DCV (90 mg/die)	78,100

Abbreviations: SOF, sofosbuvir; DCV, daclatasvir; LDV, ledipasvir; SMV, simeprevir; mg/die, mg a day.

stage patients are equal to the amount of direct costs of disease management in this stage, resulting in a convenient return of investment in the short term. The sensitivity analysis carried out on the main variables does not highlight significant variations with respect to the base case (Table 5).

Discussion

The use of SOF regimens substantially reduces the clinical burden of HCV disease. We decided to focus on SOF-based regimens because, today, it is the only pan-genotypic drug (backbone) available. Although several studies reported that SOF therapies are cost-effective,^{39–44} the resources needed to treat a large number of patients with HCV/HIV infection could be challenging for the Regional Healthcare System. On the other hand, an average SOF-based regimen price that starts descending progressively from the level of €45,000 would save direct costs optimizing economic resources and bringing a return on investments in the mid-term, at the same time. SOF and sofosbuvir/ledipasvir joint reimbursed agreement is affected by a price/volume scheme leading to incremental economic payback when patient thresholds are achieved.⁴⁵ In fact as stated in the National

Drug Agency (AIFA) resolution published,⁴⁶ Liguria region received its first amount of payback related to the usage of SOF-based regimens of €0.7 million starting to show benefit from the cost reduction. Therefore, it is reasonable to assume that in the near future the real average cost of SOF-based regimens will be lower than the initial entry prices. Finally, the agreement signed between the company and the AIFA lasts 18 months^{47,48} as a consequence it will expire by mid-2016 leading to a new price negotiation. To our knowledge, this is the first study that evaluates the budget impact of SOF-based regimens for HIV/HCV-coinfected patients in Italy.

Our study presents some limitations. First, clinical disease progression and SVR rates included in our analysis by clinicians may differ in clinical practice; therefore, our study used only the best available evidence on treatment efficacy for this population. Moreover, this analysis assumed that the achievement of SVR was equivalent to a permanent cure of patients, which could overestimate the benefits of therapies. In addition, additional potential costs of failures related to adverse events and interactions were not calculated. We also did not include the future possibility of re-treatment with next generation of antiviral agents because of a lack of data at the time of this evaluation. A much more comprehensive evaluation may consider budget impact including new unknown mono-infected patients that may emerge through awareness campaigns aiming to eradicate the disease. This data showing the reduction of coinfection of HIV/HCV is a clear sign that in a five year period the target population could not increase.⁴⁹ Finally, this analysis was focused just on the HCV issues of such patients; additional HIV drugs expense and related direct

Table 4 Results: disease stage costs (€) of disease progression scenario vs costs of SOF-based regimen scenarios (5-year horizon) for HIV/HCV-coinfected patients

Scenario	Average cost (€)	CHC	Cirrhosis	HCC	Transplant	Total	Diff vs Dis Progr	N of deaths
Disease progression		9,347,851	8,433,814	3,364,394	33,260,750	54,406,809		89
SOF-based regimen no 1	12,000	9,358,785	3,877,691	516,439	3,506,075	17,258,990	–37,147,819	
SOF-based regimen no 2	15,000	11,464,785	4,741,691	561,439	3,551,075	20,318,990	–34,087,819	
SOF-based regimen no 3	20,000	14,974,785	6,181,691	636,439	3,626,075	25,418,990	–28,987,819	
SOF-based regimen no 4	25,000	18,484,785	7,621,691	711,439	3,701,075	30,518,990	–23,887,819	
SOF-based regimen no 5	30,000	21,994,785	9,061,691	786,439	3,776,075	35,618,990	–18,787,819	
SOF-based regimen no 6	35,000	25,504,785	10,501,691	861,439	3,851,075	40,718,990	–13,687,819	
SOF-based regimen no 7	40,000	29,014,785	11,941,691	936,439	3,926,075	45,818,990	–8,587,819	
SOF-based regimen no 8	45,000	32,524,785	13,381,691	1,011,439	4,001,075	50,918,990	–3,487,819	
SOF-based regimen no 9	50,000	36,034,785	14,821,691	1,086,439	4,076,075	56,018,990	1,612,181	
SOF-based regimen no 10	55,000	39,544,785	16,261,691	1,161,439	4,151,075	61,118,990	6,712,181	

Abbreviations: CHC, chronic hepatitis C; HCC, hepatocellular carcinoma; Diff, difference in cost; Dis Progr, disease progression; HCV, hepatitis C virus; HIV, human immunodeficiency virus; SOF, sofosbuvir.

Table 5 Results of one-way sensitivity analyses

Scenario	Average cost (€)	Base case	Therapy cost -10%	Therapy cost +10%	SVR rates -10%	SVR rates +10%	No of F0-F2 patients -10%	No of F0-F2 patients (CHC) +10%
Treatment								
SOF-based regimen no 1	12,000	17,258,990	15,533,091	18,984,889	22,277,980	12,240,000	16,200,306	18,347,473
SOF-based regimen no 2	15,000	20,318,990	18,287,091	22,350,889	25,337,980	15,300,000	19,056,306	21,617,473
SOF-based regimen no 3	20,000	25,418,990	22,877,091	27,960,889	30,437,980	20,400,000	23,816,306	27,067,473
SOF-based regimen no 4	25,000	30,518,990	27,467,091	33,570,889	35,537,980	25,500,000	28,576,306	32,517,473
SOF-based regimen no 5	30,000	35,618,990	32,057,091	39,180,889	40,637,980	30,600,000	33,336,306	37,967,473
SOF-based regimen no 6	35,000	40,718,990	36,647,091	44,790,889	45,737,980	35,700,000	38,096,306	43,417,473
SOF-based regimen no 7	40,000	45,818,990	41,237,091	50,400,889	50,837,980	40,800,000	42,856,306	48,867,473
SOF-based regimen no 8	45,000	50,918,990	45,827,091	56,010,889	55,937,980	45,900,000	47,616,306	54,317,473
SOF-based regimen no 9	50,000	56,018,990	50,417,091	61,620,889	61,037,980	51,000,000	52,376,306	59,767,473
SOF-based regimen no 10	55,000	61,118,990	55,007,091	67,230,889	66,137,980	56,100,000	57,136,306	65,217,473

Notes: All costs are shown in Euros. F0-F2 is relating to hepatic fibrosis (stage of liver disease) (mild to moderate).

Abbreviations: CHC, chronic hepatitis C; SOF, sofosbuvir; SVR, sustained virological response.

costs management were not considered but should be included by the Regional Healthcare System at the time of a comprehensive economic budget planning.

Conclusion

Given the high rates of SVR these results suggested that, in the Italian Healthcare System, SOF-based regimens' price is a determinant and a predictor of the overall cost for the HCV management. At the average price per therapy of €12,000 over the next 5 years, SOF-based regimens are highly sustainable for the Healthcare System saving several million Euro of economic resource money needed to manage HCV in the HIV-coinfected population.

Disclosure

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