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Cost per care of the first year of direct antiviral agents in the Liguria Region: a multicenter analysis

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Aims: Despite the remarkable efficacy shown in clinical practice, concerns have been raised about the costs associated with direct antiviral agent (DAA) therapy. This article presents the real-life costs for DAA treatment sustained by the Italian National Health Service in the Liguria Region (Northern Italy).

Methods: A retrospective analysis of the cost per care sustained for DAA treatment, relating to the period from January 1 to December 31, 2015 in five centers in Liguria was performed. All patients undergoing DAA-based treatments for hepatitis C virus (HCV) infection were enrolled. On-treatment costs included: HCV treatment, laboratory test, outpatient services, attended visits, drugs used for the management of adverse events (erythropoietin, albumin or red blood cell packs) and inpatient service admissions.

Results: In total, 327 patients were enrolled. No difference in terms of sustained virologic response (SVR) rate among different treatments was reported. The majority (85.0%) of patients did not report any side effects and only 15 (4.6%) required hospital admission. Forty-two patients (12.8%) required high-cost drugs for the management of adverse events. The overall cost sustained was €14,744,433. DAA±ribavirin (RBV) accounted for the wide majority of this cost (98.9%; €14,585,123). Genotype (GT) 1, the most commonly treated GT, was associated with an average cost of €43,445 per patient. Detailed analysis of the costs for GT 1 showed the treatment based on ritonavir boosted paritaprevir/ombitasvir + dasabuvir±RBV with an average cost of €24,978 (RBV+) and €25,448 (RBV−) per patient was the most cost-effective. The average cost per SVR was €48,184. Once again, the ritonavir boosted paritaprevir/ombitasvir + dasabuvir regimen was associated with the lowest cost/SVR (€25,448/SVR [GT 1b] and similar results for other GTs).

Conclusion: Antiviral regimen is the major contributor to costs in the treatment of HCV infection. Appropriate regimen selection could result in a major cost saving, which can be reinvested to allow more patients to be treated.

Keywords: HCV treatment, HCV costs, cost efficacy

Introduction

Infection by hepatitis C virus (HCV) represents a major health issue. HCV is estimated to infect 180 million people worldwide and it is the seventh cause of death globally.[1] More than 2 million Italian individuals have contracted the HCV virus; of note, 20%–50% of infections are reported in intravenous drug abusers.[2–4] The predominant genotype (GT) of HCV is 1b, with a higher prevalence in women and elderly, followed by GT 2.[5]

The main target of antiviral treatment is to reduce the onset of disease complications, including liver cirrhosis and hepatocellular carcinoma. To this end, antiviral

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therapy is aimed at achieving eradication of HCV infection, that is, a sustained virologic response (SVR).

Interferon-based antiviral therapy resulted in long-term success and a reduced mortality.[6,7] However, the recent introduction of interferon-free regimens based on second-generation direct antiviral agents (DAAs) led to a dramatic improvement in clinical outcomes, with SVR rates >90%. In 2015, the interferon-free regimens available were: 1) sofosbuvir + ledipasvir (SOF+LDP),[8,9] 2) daclatasvir + sofosbuvir (SOF+DCV),[10–12] 3) ombitasvir + paritaprevir/ritonavir (PTVr/OBV) + dasabuvir (DSV),[13–17] and 4) SOF+simeprevir (SOF+SIM).[18] All these regimens can be associated, or not, with ribavirin (RBV). The treatment schedules defined by the Italian Society for Liver Diseases according to the European Association for Liver Diseases are included in Table S1. Despite their high efficacy, concerns have been raised about the costs associated with DAA therapy. With respect to the Italian scenario, different budget impact analyses have been published, however, considering only the drug cost[19] or the complete treatment path.[20] To date, no studies have investigated the actual cost sustained by the Italian National Health Service (NHS) during the first year of clinical use of second-generation DAAs. This manuscript aims to present the real-life costs for DAA treatment sustained by the NHS in the Liguria Region.

Methods

Study design

In order to achieve the primary objective, a retrospective analysis of the cost per care sustained for DAA treatment, in the period from January 1 to December 31, 2015 (Northern Italy), was conducted in the Liguria Region. Six centers, linked in a network, were involved: Infectious Disease Unit, San Remo; ASL 2 Infectious Disease Unit, San Paolo Hospital, Savona; Infectio us Disease Unit, Galliera Hospital, Genoa; Infectious Disease Clinic, San Martino Hospital, Genoa; Liver Unit, San Martino Hospital, Genoa and Infectious Disease Unit, ASL 5, La Spezia. The study was approved by the Regione Liguria ethical committee (approval ID 268REG2016). An informed consent form was signed by each patient.

All patients undergoing DAA-based regimens for HCV infection and reaching the 12-week posttreatment evaluation by March 31, 2016 (end of treatment by December 31, 2015) were enrolled. Patients belonging to special categories (e.g., those in hemodialysis, organ transplant recipients or thalassemia major carriers) were excluded due to the high costs involved in their underlying disease.

Health care providers generated a list of the subjects with HCV who started treatment in the study period, with all relevant demographic and treatment details. An automated system collected all data from laboratory and administrative services on an online platform, in order to obtain data on hospitalizations, medical visits and laboratory tests for each patient.[21,22] The clinicians involved in the study provided the final data about the treatment outcome at 12 weeks after treatment.

Additional data were recorded on the use of special drugs characterized by high cost, such as erythropoietin, albumin or red blood cell packs.

Use of resources and costs

On-treatment costs included HCV treatment, laboratory tests, outpatient services, attended visits, drugs used for the management of adverse events (erythropoietin, albumin or red blood cell packs) and inpatient service admissions. Hospitalizations were classified by ICD -9 codes, and the financial costs considered were those established by the Italian NHS.

The drug-related costs of SOF and SOF/LDV are linked to a price/volume payback scheme covered by confidential agreement.[23] However, the Emilia-Romagna Region periodically reports an update of the average costs of each drug on its institutional website.[24] Therefore, this source at the moment represents the most reliable one for the economic analysis, and hence was used in this study.[25–27] The cost of the treatment was defined on the basis of the month of the first prescription. Given the contract existing between the Italian NHS and pharmaceutical companies, 24 weeks of treatment have the same cost as 12 weeks (Table S2).[28]

For patients who discontinued treatment for any reason before the scheduled end, the following costs were attributed: 1) within 4 weeks, one-third of 12-week treatment; 2) within 8 weeks, two-thirds of 12-week treatment and 3) >8 weeks, the same as 12-week treatment.

The costs attributed to each additional procedure, including treatment with RBV and erythropoietin, were those defined by the Liguria Region for the year 2015 (Table S3).[29–31] However, albumin and red cell blood pack-related costs were not included because they were administered during hospital admission and hence were already considered in diagnosis related group reimbursement for the hospital stay from patients' perspective (Tables S4 and S5).[32]

The cost per SVR was defined as the total cost for each regimen divided by the number of SVR observed for that specific regimen.

According to the Italian Drug Agency (AIFA), DAAs are fully reimbursable only for subjects affected by METAVIR fibrosis at F3 or F4 stage or those with lower fibrosis but presenting an extrahepatic disease (malignant lymphoma, HCV-related vasculitis and symptomatic cryoglobulinemia).[28,33] These rules have been summarized in the six criteria defined by AIFA as follows: 1) patients with liver cirrhosis Child Pugh A or B and/or HCC with complete treatment; 2) patients with recurrence of HCV infection after liver transplantation with a METAVIR score >2; 3) patients with chronic hepatitis and serious extrahepatic liver diseases (malignant lymphoma, HCV-related vasculitis and symptomatic cryoglobulinemia); 4) patients with chronic hepatitis C and METAVIR F3; 5) patients on the waiting list for liver transplantation and 6) patients with chronic hepatitis C and solid organ transplantation (different from liver) or bone with fibrosis METAVIR >2.

Statistical analysis

Data were analyzed by descriptive statistics. Demographic and clinical characteristics were also reported according to the HCV treatment. Differences in categorical variables were compared with the chi-squared test or Fisher's exact test, whereas continuous variables were compared with analysis of variance or Kruskal–Wallis test, as appropriate. Normality of continuous variables was tested using Kolmogorov–Smirnov test.

To account for the different prices of HCV treatments during the year (depending on treatment initiation) and to control simultaneously for the possible confounding effect of different variables, a multivariate linear regression analysis was performed. Only the variables with a univariate $p<0.05$ were introduced in the model.

A univariate sensitivity analysis was conducted to determine the impact of the SVR rate, HCV treatment prices, and direct cost on the cost-per SVR. The rate of SVR varied over a range of 2%–5%, the anti-HCV treatment prices varied over a range of 10%–50%, and direct costs varied over a range of 10%–30%.

A p-value <0.05 was considered significant. Analyses were performed by R software.

Results

Population

In total, 327 patients were enrolled, covering 49% of all DAA-based regimens started in 2015 in the involved center (cut-off: December 31, 2015). The remaining 51% were those not meeting the inclusion criteria, mainly the patients who were still undergoing treatment or did not reach the 12-week posttreatment evaluation point by March 31, 2016. The demographic and clinical details are presented in Table 1. The majority of patients were males (71%) living in Liguria (97%) and had been already treated for HCV (53%; Table 1). The rate of SVR at 12 weeks posttreatment was 93.5% (n=306). Among the 21 patients who did not reach this goal, a relapse was observed in 11 (52%), a vital breakthrough in 2 (9%), treatment interruption in 5 (24%), death (between the end of treatment and the 12 weeks time point) in 2 (9%) and failure in 1 (5%) patient. Reasons for treatment interruption were: two deceased, toxicity in two patients and personal decision in the last one. The main clinical features according to the treatment prescribed are shown in Table S6.

SVR rates

No differences in terms of SVR rate among different treatments were reported (Table 2). A detailed analysis of the SVR according to HCV GT showed a significant difference

Table 1 Clinical and demographic features at baseline

Features	All patients, absolute value (%) (N=327)
Demographics	
Prescribing center	
San Martino – UOS epatologia	114 (34.86)
San Martino – Clinica Malattie Infettive	61 (18.65)
La Spezia – SC Malattie Infettive	57 (17.43)
Genova – Galliera SC Malattie Infettive	47 (14.37)
Sanremo – SC Malattie Infettive	36 (11.01)
Savona – SC Malattie Infettive	12 (3.67)
Resident in Regione Liguria	318 (97.25)
Gender	
Male	233 (71.25)
Female	94 (28.75)
Age, years	57.11±9.72
HCV treatment details	
Previous treatment	174 (53.21)
Criteria for prescription according to Italian Drugs Agency	
1	251 (76.76)
2	1 (0.31)
3	14 (4.28)
4	60 (18.35)
6	1 (0.31)
Genotype	
1a	80 (24.46)
1b	94 (28.75)
2	31 (9.48)
3	78 (23.85)
4	44 (13.46)
Fibrosis stage	
F1	4 (1.22)
F2	6 (1.83)
F3	64 (19.57)
F4	253 (77.37)

(*Continued*)

Table 1 (*Continued*)

Features	All patients, absolute value (%) (N=327)
Child Pugh (only for fibrosis stage 4)*	
Child A	228 (90.12)
Child B	24 (9.49)
Child C	1 (0.40)
Treatment regimen	
SOF+RBV	76 (23.24)
SOF+LDP+RBV	52 (15.90)
SOF+SIM+RBV	51 (15.60)
PTVr/OBV+DSV+RBV	44 (13.46)
SOF+DCV+RBV	36 (11.01)
SOF+SIM	26 (7.95)
SOF+LDP	16 (4.89)
PTVr/OBV+RBV	10 (3.06)
PTVr/OBV+DSV	9 (2.75)
SOF+DCV	7 (2.14)
Length of treatment (weeks)	15.87±5.75
Comorbidities	
Patients presenting with at least one comorbidity	168 (51.38)
Number	
No comorbidity	159 (48.62)
1 comorbidity	85 (25.99)
2 comorbidities	59 (18.04)
≥3 Comorbidities	24 (7.34)
Comorbidities	
Drug abuse	104 (31.80)
HIV infection	74 (22.63)
Heart disease	52 (15.90)
Metabolic syndrome	34 (10.40)
Renal disease	10 (3.06)
HBV infection	3 (0.92)

Notes: *% Calculated in patients with fibrosis stage F4. Data are presented as: continuous variables: mean±SD; categorical variables: n (%).

Abbreviations: DCV, daclatasvir; DSV, dasabuvir; HCV, hepatitis C virus; HIV, human immunodeficiency virus; LDP, ledipasvir; OBV, ombitasvir; PTVr, ritonavir boosted paritaprevir; RBV, ribavirin; SD, standard deviation; SIM, simeprevir; SOF, sofosbuvir; UOS, Unità Operativa Semplice; SC, Struttura Complessa; HBV, hepatitis B chronic infection.

between GT 3 (SVR 85.9%) and other GTs. GT 1 is the most susceptible to treatment with DAA, with an overall SVR rate of 95.9%, while GT 2 and GT 4 were associated with an overall SVR rate of 96.7% and 95.4%, respectively. A combined analysis of treatment and regimen confirms these findings. In GT 1b-infected patients, the SVR rate ranged from 90.9% to 100%, according to the regimen prescribed. Very similar rates were observed in GT 1a (from 93.7% to 100%), GT 2 (96.7%) and GT 4 (from 92.3% to 100%; Table 2). On the other hand, GT 3 was associated with an SVR rate ranging from 82.2% to 100%, according to therapy. DCV was available in Italy later than in other European countries, and therefore, our study (aimed at the description of the first year of treatment in Liguria) included only a small quote of patients affected by GT 3 treated with this molecule; the only combination available was SOF and RBV.

Adverse events

The majority (85.0%) of patients did not present any side effects, and only 15 (4.6%) patients required hospital admission; the median length of hospital stay was 11 days (interquartile range: 3–18 days). Forty-two (12.8%) patients required high-cost drugs for the management of adverse events: erythropoietin was necessary in 39 (11.9%) patients, albumin in 5 (1.5%) patients and red blood cell packs in 3 (1%) patients; and 3 patients required 2 of these treatments and 1 patient required all of them.

Pharmacoeconomic analysis

The overall cost sustained for the treatment of 327 patients was €14,744,433. DAA±RBV accounted for the highest proportion of cost (98.9%; €14,585,123), followed by the

Table 2 SVR rate according to genotype and regimen prescribed

Regimen anti-HCV prescribed	Genotype 1	Genotype 1a	Genotype 1b	Genotype 2	Genotype 3	Genotype 4	Total
	n/N (%)	n/N (%)	n/N (%)	n/N (%)	n/N (%)	n/N (%)	n/N (%)
SOF+RBV				30/31 (96.77)	37/45 (82.22)		67/76 (88.16)
SOF+LDP+RBV	43/45 (95.56)	*30/32 (93.75)*	*13/13 (100.00)*			7/7 (100.00)	50/52 (96.15)
SOF+SIM+RBV	35/38 (92.11)	*15/16 (93.75)*	*20/22 (90.91)*			12/13 (92.31)	47/51 (92.16)
PTVr/OBV+DSV+RBV	42/44 (95.45)	*13/14 (92.86)*	*29/30 (96.67)*				42/44 (95.45)
SOF+DCV+RBV	3/3 (100.00)	*2/2 (100.00)*	*1/1 (100.00)*		26/29 (89.66)	4/4 (100.00)	33/36 (91.67)
SOF+SIM	21/21 (100.00)	*9/9 (100.00)*	*12/12 (100.00)*			5/5 (100.00)	26/26 (100.00)
SOF+LDP	12/12 (100.00)	*6/6 (100.00)*	*6/6 (100.00)*			4/4 (100.00)	16/16 (100.00)
PTVr/OBV+RBV						9/10 (90.00)	9/10 (90.00)
PTVr/OBV+DSV	9/9 (100.00)		*9/9 (100.00)*				9/9 (100.00)
SOF+DCV	2/2 (100.00)	*1/1 (100.00)*	*1/1 (100.00)*		4/4 (100.00)	1/1 (100.00)	7/7 (100.00)
Total	167/174 (95.98)	*76/80 (95.00)*	*91/94 (96.81)*	30/31 (96.77)	67/78 (85.90)	42/44 (95.45)	306/327 (93.58)
p-value	0.90	*1.00*	*0.81*	-	0.74	1.00	0.56

Note: Italics indicate data on GT 1a/b.

Abbreviations: DCV, daclatasvir; DSV, dasabuvir; GT, genotype; HCV, hepatitis C virus; LDP, ledipasvir; OBV, ombitasvir; PTVr, ritonavir boosted paritaprevir; RBV, ribavirin; SIM, simeprevir; SOF, sofosbuvir; SVR, sustained virologic response.

management of adverse events (hospital admissions and high-cost drugs for treatment support; €89,078; 0.6%). A marginal impact was attributed to laboratory analysis and outpatient service visits (€38,180, 0.26% and €32,053, 0.22%, respectively).

When the average costs per care were evaluated according to the GT, GT 2 was the one absorbing the lowest resources, while GT 3 and GT 4 were those with higher costs per patient (Table 3). GT 1, the most commonly treated GT (174 patients), was associated with an average cost of €43,445 per patient. A detailed analysis of the costs of GT 1 showed the treatment based on PTVr/OBV+DSV±RBV with an average cost of €24,978 (with RBV) and €25,448 (without RBV) per patient was the most economical; on the other hand, SOF+SIM+RBV regimen was the most expensive, with an average cost of €61,027. Between GT 1a and GT 1b, an important difference in costs was reported (Table 4). In GT 1a treatment, the PTVr/OBV+DSV±RBV regimen was associated with the lowest cost, although it was prescribed only in 17.5% of cases. On the other hand, the PTVr/OBV+DSV±RBV regimen was the most frequently prescribed for GT 1b (31.9%/9.6%), and it was associated with the lowest cost (Table 5).

Multivariate linear regression model confirmed a significant difference in costs of care according to HCV treatment, even after adjusting for the clinical characteristics at treatment initiation (Table S7).

The average cost per SVR was €48,184, with negligible differences between pretreated patients and naïve subjects. Also, the PTVr/OBV+DSV regimen was associated with lowest cost per SVR (€25,448 per SVR [GT 1b] and similar results for other GTs; Table 6).

Sensitivity analysis (Table 7) confirms the antiviral drug cost as the major contributor to the total cost. A second contributor was the achievement of SVR: an increase in SVR rate led to a major reduction in cost per SVR.

Table 3 Total cost and average cost (in €) per patient according to genotype

Genotype	Patients	Total	Percentage	Mean	SD
1	174	7,559,389	51.27	43,445	15,430
1a	80	3,616,227	24.53	45,203	14,034
1b	94	3,943,162	26.74	41,949	16,451
2	31	1,269,035	8.61	40,937	2,620
3	78	3,810,101	25.84	48,847	9,405
4	44	2,105,908	14.28	47,862	15,001
Total	327	14,744,433	100.00	45,090	13,603
p-value	0.004				

Abbreviation: SD, standard deviation.

Discussion

We have reported a detailed analysis of all costs related to the first year of use of all oral DAAs for the treatment of HCV infection. Our study allowed us to identify the less-costly options, with possible indications on how to optimize the treatment schedule and, hence, treat more patients at the same global cost. In our opinion, in a condition of limited resources available, this is the only strategy that could increase the number of treated patients. It is worth nothing that our analysis was conducted in a "field-practice" cohort of consecutive unselected patients, regardless of comorbidities, coinfections, age, gender or prior therapies.

Our results highlight some critical issues: safety, efficacy and costs. Overall, SVR was reached in 93.8% of the patients treated, a rate that is well-aligned with the current clinical experience. The majority of our population was composed of patients with more severe fibrosis, as regulated by AIFA that allows the prescription of DAAs only to METAVIR F3 or F4 fibrosis stage.[28] Nevertheless, DAA-based regimens were safe and effective, with SVR rates in line or even better compared with those reported in other real-life studies.[34,35] In our study, hospital admissions were limited to a small proportion of patients (12.4%). This finding is in contrast with those existing for the first-generation DAAS – as recorded, for instance, in the CUPIC study, where 40% of patients reported a serious adverse event requiring hospital admission.[36]

Anemia requiring support with high-cost drugs was observed in 42 patients (12.4%). The PAN study, a large German study based on first-generation DAAs, reported the same side effect only in 2.4%,[37] but in that study, only 17.3% of the cohort presented an advanced fibrosis or liver cirrhosis (determined by AST to platelet ratio index). In our cohort, 77.3% of patients had a METAVIR score F4 defined by fibroscan or liver biopsy.[37] Therefore, the more advanced the liver fibrosis, the higher the risk of anemia, as already shown by other studies.[38] However, given the current trend in reducing the use of RBV,[39] the impact of this element will be further reduced.

When the evaluation of costs was correlated with SVR rate, the two GTs with the lowest SVR rates, namely, GT 3 and GT 4, were those associated with the highest costs. On the other hand, GT 1b was the most frequently reported in our cohort – and all over Italy – and therefore, a treatment associated with a low total cost, such as PTVr/OBV+DSV±RBV (€24,978/25,448), could represent an interesting option for the reduction of total expense. Moreover, the notable difference in average cost reported between GT 1a and GT 1b could be attributed to the different pattern of treatment.

Table 4 Total and mean costs for different DAA treatments in patients according to HCV genotype

Anti-HCV regimen	Genotype 1					Genotype 2				
	n	Total	Percentage	Mean	SD	n	Total	Percentage	Mean	SD
SOF+RBV						31	1,269,035		40,937	2,620
SOF+LDP+RBV	45	1,886,982	24.96	41,933	7,217					
SOF+SIM+RBV	38	2,319,038	30.68	61,027	875					
PTVr/OBV+DSV+RBV	44	1,099,015	4.54	24,978	3,644					
SOF+DCV+RBV	3	184,185	2.44	61,395	2,645					
SOF+SIM	21	1,254,155	16.59	59,722	3,564					
SOF+LDP	12	467,681	6.19	38,973	9,350					
PTVr/OBV+RBV										
PTVr/OBV+DSV	9	229,036	3.03	25,448	0					
SOF+DCV	2	119,299	1.58	59,649	0					
Total	174	7,559,389	100.00	43,445	15,430	31	1,269,035	100.00	40,937	2,620
p-value	<0.0001					–				

Abbreviations: DAA, direct antiviral agent; DCV, daclatasvir; DSV, dasabuvir; HCV, hepatitis C virus; LDP, ledipasvir; OBV, ombitasvir; PTVr, ritonavir boosted paritaprevir; RBV, ribavirin; SD, standard deviation; SIM, simeprevir; SOF, sofosbuvir.

Table 5 Total cost and average cost (in €) per patient according to genotype and regimen prescribed; focus on genotype 1

Regimen anti-HCV	Genotype 1a					Genotype 1b				
	n	Total	Percentage	Mean	SD	n	Total	Percentage	Mean	SD
SOF+RBV										
SOF+LDP+RBV	32	1,343,382	37.15	41,981	7,687	13	543,600	13.79	41,815	6,189
SOF+SIM+RBV	16	9,72,878	26.90	60,805	227	22	1,346,160	34.14	61,189	1,116
PTVr/OBV+DSV+RBV	14	3,46,455	9.58	24,747	3,588	30	752,560	19.09	25,085	3,726
SOF+DCV+RBV	2	1,24,269	3.44	62,134	3,272	1	59,916	1.52	59,916	.
SOF+SIM	9	5,42,536	15.00	60,282	1,100	12	711,619	18.05	59,302	4,666
SOF+LDP	6	2,27,058	6.28	37,843	7,748	6	240,622	6.10	40,104	11,369
PTVr/OBV+RBV										
PTVr/OBV+DSV						9	229,036	5.81	25,448	0
SOF+DCV	1	59,649	1.65	59,649		1	596,49	1.51	59,649	
Total	80	3,616,227	100.00	45,203	14,034	94	3,943,162	100.00	41,949	16,451
p-value	<0.0001					<0.0001				

Abbreviations: DCV, daclatasvir; DSV, dasabuvir; HCV, hepatitis C virus; LDP, ledipasvir; OBV, ombitasvir; PTVr, ritonavir boosted paritaprevir; RBV, ribavirin; SD, standard deviation; SIM, simeprevir; SOF, sofosbuvir.

Table 6 Cost per SVR-12 (in €) according to genotype and treatment regimen

Anti-HCV regimen	Genotype						Total
	1	1a	1b	2	3	4	
SOF+RBV				42,301	50,148		46,634
SOF+LDP+RBV	43,883	44,779	41,815			42,985	43,757
SOF+SIM+RBV	66,258	64,859	67,308			65,634	66,099
PTVr/OBV+DSV+RBV	26,167	26,650	25,950				26,167
SOF+DCV+RBV	61,395	62,135	59,916		66,507	59,803	65,230
SOF+SIM	59,722	60,282	59,302			59,988	59,773
SOF+LDP	38,973	37,843	40,104			44,874	40,448
PTVr/OBV+RBV						26,579	26,579
PTVr/OBV+DSV	25,448		25,448				25,448
SOF+DCV	59,649	59,649	59,649		56,359	59,548	57,754
Total	45,266	47,582	43,331	42,301	56,867	50,141	48,184

Abbreviations: DCV, daclatasvir; DSV, dasabuvir; HCV, hepatitis C virus; LDP, ledipasvir; OBV, ombitasvir; PTVr, ritonavir boosted paritaprevir; RBV, ribavirin; SIM, simeprevir; SOF, sofosbuvir; SVR, sustained virologic response.

Table 4 (*Continued*)

Genotype 3					Genotype 4				
n	Total	Percentage	Mean	SD	n	Total	Percentage	Mean	SD
45	1,855,475	48.70	41,233	630					
					7	300,893	14.29	42,985	5,345
					13	787,608	37.40	60,585	992
29	1,729,192	45.38	59,627	4,071	4	239,213	11.36	59,803	12
					5	299,942	14.24	59,988	1,476
					4	179,495	8.52	44,874	50
					10	239,209	11.36	23,921	662
4	225,434	5.92	56,358	6,448	1	59,548	2.83	59,548	.
78	3,810,101	100.00	48,847	9,405	44	2,105,908	100.00	47,862	15,001
<0.0001					<0.0001				

Table 7 Cost per SVR (in €) and sensitivity analysis

Variable	Cost per SVR
Baseline	48,184
SVR (%)	
−2	49,237
−5	50,904
+2	47,176
+5	45,740
Anti-HCV treatment (DAA and/or ribavirin) (%)	
−10	43,418
−20	38,652
−30	33,885
−50	24,353
+10	52,951
+20	57,717
+30	62,484
+50	72,016
Direct costs (visits, diagnostic tests, hospitalizations, supportive care)* (%)	
−10	48,132
−20	48,080
−30	48,028
+10	48,236
+20	48,289
+30	48,341

Note: *All costs issues varied at the same time and in the same percentage.
Abbreviations: DAA, direct antiviral agent; HCV, hepatitis C virus; SVR, sustained virologic response.

In fact, the most frequently prescribed drug for GT 1b was PTVr/OBV/DSV±RBV, that is, the less-expensive option. Of note, in GT 1, the regimen based on PTVr+OBV+DSV±RBV demonstrated the lowest cost per SVR, granting a considerable saving of about 37%–38% with the major comparator LDP+SOF±RBV. In a scenario of limited health care resources, this option would allow treatment for more patients while maintaining the same SVR rate.

The average cost per SVR is distinctly less than those observed in previous studies on first-generation DAAs, which ranged from €70,163 to €110,156 in the PAN study.[39] Noteworthy, first-generation DAAs were associated with a higher incidence of costs due to the management of adverse events (up to 8%),[40] compared with the costs reported in our analysis (0.6%). These findings may lend support to the more favorable safety profile of second-generation DAAs, compared with previous regimens.[41]

All treatment regimens with RBV are far more expensive than the same regimen without this drug. In addition, multivariate analysis showed a significant difference in costs of care according to the HCV treatment, even after adjusting for the clinical characteristics at treatment initiation.

Our analysis confirms indirectly that the direct cost of the drug and – above all – RBV-associated toxicities with necessary laboratory analysis increase the total expenditure. The only exception was GT 1b; however, three patients infected by this GT started treatment and stopped it after 2 weeks (two for toxicity) and 8 weeks (personal decision in one patient), therefore reducing the total cost.

Given the observed differences in SVR rates among different GTs, the correct determination of GT is of paramount importance in order to avoid errors in treatment selection[42] and failure derived from inadequate therapy (about 15%–40% of the estimated reduction in SVR attainment). In agreement with this, a recent Italian study has shown the cost-effectiveness of retesting HCV GT.[43]

The sensitivity analysis conducted on the cost per SVR clearly shows that the more pronounced the reduction in the cost of HCV treatment, the higher the savings for the NHS. On the other hand, the same decrease in costs for

laboratory and visits would only have a minimal influence. The foreseeable reduction in RBV use will likely minimize the impact of laboratory-driven and erythropoietin-associated costs.[36] Furthermore, the potential increase in SVR rate (2%–5%) with next-generation drugs might further decrease the cost for treatment by diminishing the failures, provided that the cost per SVR remains stable. On the other hand, sensitivity analysis suggests that, should the drug cost be cut by 50%, the cost per SVR would be €24,353. This cost corresponds to 5 years of management for one HCV-infected patient according to a recent study by Perrone et al.[44]

Moreover, in the context of price reduction, the drug-related cost (SOF+LDP €6,715±RBV; PTVr/OBV+DSV±RBV €12,833 PTVr/OBV+RBV €11,807±RBV) observed at the time of the drafting of this article (November 2016)[45] was aligned with the sensitivity analysis of 50% of reduction. Therefore, considering these drug-related costs, the total cost is very similar to that of interferon-based therapy, but the latter is associated with a much lower SVR rate (ranging from 46% to 80%).[46–51]

By taking into consideration all the above, this dramatic cost reduction and its impact on the NHS budget could probably allow to expand the treatment criteria.

Our study is not without its limitations. For instance, treatment costs for other antiviral agents in coinfected patients were not considered. Similarly, costs for radiology/ultrasound examination or fibroscan examinations before treatment were not taken into account, as well as those costs necessary during follow-up after SVR achievement. Even more importantly, our estimations were based according to the only available data, that is, those published by the Emilia-Romagna on its institutional website. However, Liguria benefits from a higher discount from total costs than Emilia-Romagna (more HCV patients have been treated in Liguria than in Emilia-Romagna), and therefore, the costs might result in an overestimation of those actually sustained in Liguria.

Despite these limitations, our analysis shows that the leading contributor to costs in the treatment of HCV infection is the antiviral regimen; an appropriate regimen selection could result in a great cost saving which can be reinvested to allow more patients to be treated.

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Disclosure

The authors report no conflicts of interest in this work.

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Supplementary materials

Table S1 Italian guidelines for the treatment of HCV at the time of study (Documento Società Italiana Studio Fegato-AISF December 17, 2014)[1]

Regimen prescribed	Genotype 1a	Genotype 1b	Genotype 2	Genotype 3	Genotype 4
PTVr/OBV+DSV±RBV	PTVr/OBV+DSV+RBV for 24 weeks	12 weeks with RBV	No	No	No
SOF+LDP±RBV	12 weeks with RBV 24 weeks without RBV	12 weeks with RBV 24 weeks without RBV	No	No	12 weeks with RBV 24 weeks without RBV
PTVr/OBV+RBV	No	No	No	No	24 weeks with RBV
SOF+DCV	12 weeks with RBV 24 weeks without RBV	12 weeks with RBV 24 weeks without RBV	12 weeks without RBV	24 weeks with RBV preferred regimen	12 weeks with RBV 24 weeks without RBV
SOF+RBV	No	No	16–20 weeks	24 weeks suboptimal	No
SOF+SIM	12 weeks with RBV 24 weeks without RBV	12 weeks with RBV 24 weeks without RBV	No	No	12 weeks with RBV 24 weeks without RBV

Abbreviations: DCV, daclatasvir; DSV, dasabuvir; HCV, hepatitis C virus; LDP, ledipasvir; OBV, ombitasvir; PTVr, ritonavir boosted paritaprevir; RBV, ribavirin; SIM, simeprevir; SOF, sofosbuvir.

Table S2 Drug-related costs (according to Regione Emilia-Romagna)

Treatment regimen	From January 1 to May 31, 2015	From June 1 to August 31, 2015	From September 1 to October 31, 2015
SOF+RBV	40,700+RBV	40,700+RBV	27,839+RBV
SOF+LDP+RBV	44,770+RBV	44,770+RBV	30,622+RBV
SOF+SIM+RBV	60,500+RBV	57,200+RBV	44,338+RBV
PTVr/OBV+DSV+RBV	25,300+RBV	25,300+RBV	25,300+RBV
SOF+DCV+RBV	59,400+RBV	59,400+RBV	46,539+RBV
SOF+SIM	60,500	57,200	44,338
SOF+LDP	44,700	44,700	30,622
PTVr/OBV+RBV	23,276+RBV	23,276+RBV	23,276+RBV
PTVr/OBV+DSV	25,300	25,300	25,300
SOF+DCV	59,400	59,400	46,539

Note: All costs are indicated in Euros.
Abbreviations: DCV, daclatasvir; DSV, dasabuvir; LDP, ledipasvir; OBV, ombitasvir; PTVr, ritonavir boosted paritaprevir; RBV, ribavirin; SIM, simeprevir; SOF, sofosbuvir.

Table S3 Laboratory code

Code (according to the Regione Liguria classification)	Description	Cost/procedure
Laboratory costs		
90.62.2	Complete blood cell count	3.35
91.19.4	HCV RNA quantification	9.03
90.09.2	AST	0.77
90.04.5	ALT	0.77
90.10.4	Bilirubin total	0.87
90.10.5	Bilirubin direct/indirect	0.90
90.25.5	GGT	0.83
90.16.3	Creatinine	0.77
90.23.5	Alkaline phosphatase	0.66
90.75.4	INR	1.75
90.38.4		4.95
Outpatient service visits		
	Initial visit	20.66
	Subsequent visit	12.90

Note: All costs are indicated in Euros.
Abbreviations: HCV, hepatitis C virus; INR, international normalized ratio; GGT, gamma glutamil transferase; AST, aspartate transaminase; ALT, alanine transaminase.

Table S4 Other costs (indicated in Euros)

DRG code	Clinical category	Threshold	Financial cost
203	Liver tumor (HCC)	35 days	€4,085+175 a day each day >threshold
205	Liver cirrhosis complicated	27 days	€3,760+157 a day per day >threshold

Abbreviation: DRG, diagnosis related group.

Table S5 Cost of drugs

Drug	Cost
Albumin	€43.49 per unit (VAT included)
Red blood cells	€153 per unit (VAT included)
Erythropoietin (beta epoetin) 30,000 IU/mL	€90.75 per unit (VAT included)
Ribavirin 200 mg	€23.80 per unit (VAT included) 168 tablets

Table S6 Patients' features according to HCV treatment

Patients' main features	SOF+ RBV	SOF+ LDP+ RBV	SOF+ SIM+RBV	PTVr/ OBV+ DSV+RBV	SOF+ DCV+ RBV	SOF+ SIM	SOF+ LDP	PTVr/ OBV+ RBV	PTVr/ OBV+ DSV	SOF+ DCV	*p*-value
	n=76	n=52	n=51	n=44	n=36	n=26	n=16	n=10	n=9	n=7	
Age, years	55 (51–71)	55 (52–59)	55 (52–61)	55 (51–63)	55 (52–55)	57 (51–62)	56 (51–64)	54 (51–59)	56 (51–60)	57 (54–62)	0.43
Gender (male)	55 (72.73)	41 (78.85)	38 (774.51)	32 (72.73)	31 (86.11)	8 (30.77)	13 (81.25)	7 (70.00)	4 (44.44)	4 (57.14)	<0.0001
Fibrosis stage											<0.0001
1	1 (1.32)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	1 (3.85)	1 (6.25)	0 (0.00)	1 (11.11)	0 (0.00)	
2	1 (1.32)	0 (0.00)	1 (1.96)	0 (0.00)	0 (0.00)	1 (3.85)	2 (12.50)	0 (0.00)	0 (0.00)	1 (14.29)	
3	19 (25.00)	2 (3.85)	8 (15.69)	6 (13.64)	1 (2.87)	9 (34.62)	7 (43.75)	4 (40.00)	6 (66.67)	2 (28.57)	
4	55 (72.37)	50 (96.15)	42 (82.35)	38 (86.36)	35 (97.22)	15 (57.69)	6 (37.50)	6 (60.00)	2 (22.22)	4 (57.14)	
Genotype											<0.0001
1	0 (0.00)	45 (86.54)	38 (74.51)	44 (100.00)	3 (8.33)	21 (80.77)	12 (75.00)	0 (0.00)	9 (100.00)	2 (28.57)	
2	31 (40.79)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	
3	45 (59.21)	0 (0.00)	0 (0.00)	0 (0.00)	29 (80.56)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	4 (57.14)	
4	0 (0.00)	7 (13.46)	13 (25.49)	0 (0.00)	4 (11.11)	5 (19.23)	4 (25.00)	10 (100.00)	0 (0.00)	1 (14.29)	
Comorbidities	37 (48.68)	39 (75.00)	27 (52.94)	22 (50.00)	24 (66.67)	4 (15.38)	7 (43.75)	2 (20.00)	2 (22.22)	4 (57.14)	<0.0001
Previous treatment HCV	35 (46.05)	29 (55.77)	37 (72.55)	27 (61.36)	18 (50.00)	7 (26.92)	5 (31.25)	4 (40.00)	8 (88.89)	4 (57.14)	0.002

Note: Data are presented as median (interquartile range) for continuous variables and as frequency (%) for categorical variables.
Abbreviations: DCV, daclatasvir; DSV, dasabuvir; HCV, hepatitis C virus; LDP, ledipasvir; OBV, ombitasvir; PTVr, ritonavir boosted paritaprevir; RBV, ribavirin; SIM, simeprevir; SOF, sofosbuvir.

Table S7 Correlates of the total cost: results of multivariate analyses

Variables	β	95% CI	*p*-value
HCV treatment			
PTVr/OBV+DSV+RBV	–	–	–
PTVr/OBV+DSV	1,863	−752; 4,477	0.16
PTVr/OBV+RBV	−2,222	−4,980; 536	0.11
SOF+DCV	29,988	26,724; 33,253	<0.0001
SOF+DCV+RBV	31,922	29,161; 34,683	<0.0001
SOF+LDP	16,392	14,277; 18,506	<0.0001
SOF+LDP+RBV	16,954	15,537; 18,372	<0.0001
SOF+RBV	10,091	6,754; 13,429	<0.0001
SOF+SIM	30,481	28,415; 32,546	<0.0001
SOF+SIM+RBV	30,173	28,365; 31,981	<0.0001
Gender (female vs male)	−510	−1,405; 386	0.26
Fibrosis grade			
1	–	–	–
2	2,422	−2,067; 6,912	0.29
3	2,152	−1,435; 5,738	0.24
4	1,825	−1,772; 5,422	0.32
Genotype			
1	–	–	–
2	2,563	−583; 5,708	0.11
3	749	−1,891; 3,389	0.58
4	573	−787; 1,932	0.41
Comorbidites (yes vs no)	623	−201; 1,446	0.14
Prior anti-HCV treatment (yes vs no)	712	−100; 1,525	0.09
Time start treatment	−4,726	−5,682; −3,769	<0.0001

Abbreviations: CI, confidence interval; DCV, daclatasvir; DSV, dasabuvir; HCV, hepatitis C virus; LDP, ledipasvir; OBV, ombitasvir; PTVr, ritonavir boosted paritaprevir; RBV, ribavirin; SIM, simeprevir; SOF, sofosbuvir.

Reference

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