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ORIGINAL RESEARCH

Budget impact analysis of the use of daclatasvir in Italy for the treatment of Hepatitis C Virus (HCV) genotype 3 patients

Umberto Restelli [1,2], Alfredo Alberti [3], Adriano Lazzarin [4,5], Marzia Bonfanti [1], Carmela Nappi [6], Davide Croce [1,2]

[1] Centre for Research on Health Economics, Social and Health Care Management (CREMS) – LIUC – Carlo Cattaneo University, Castellanza (VA), Italy
[2] School of Public Health, Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, South Africa
[3] Department of Molecular Medicine, University of Padua, Padua, Italy
[4] Department of Infectious Diseases, IRCCS Ospedale San Raffaele, Milan, Italy
[5] Università Vita-Salute San Raffaele, Milan, Italy
[6] Health Economic&Outocome Research Bristol Myers Squibb S.r.l., Rome, Italy

ABSTRACT

BACKGROUND: Hepatitis C Virus (HCV) infection represents a global health problem, leading to chronic cirrhosis, hepatocellular carcinoma (HCC), hepatic decompensation and liver transplant. The aim of the study was the evaluation of the impact on the budget of the Italian National Health Service (INHS) of the use of Daclatasvir (DCV) for the treatment of HCV genotype 3 in patients with advanced fibrosis.

METHODS: An analytical decision model with a five year time horizon was implemented. Two scenarios were considered: a. 100% of market share for Interferon (INF-α)+Ribavirin (RBV)+Sofosbuvir (SOF) for 12 weeks; b. SOF+DCV+RBV for 24 weeks with annual market shares of 50% in 2015 and 2016, 55% in 2017 and 2018, 60% in 2019, and INF-α+RBV+SOF for 12 weeks with the remaining market shares. Every annual cycle a percentage of patients equal to the effectiveness of the antiviral treatment reach a sustained virologic response and during the first year of treatment patients may experience treatment related adverse events. The costs considered (2015) are those of the antiviral therapy, and direct medical costs for health state and adverse events management. Univariate and multivariate sensitivity analyses were performed.

RESULTS: DCV would lead to an increase of the costs for the INHS (year 1 +21.31 millions, year 2 +21.35 millions, year 3 + 23.37 millions, year 4 + 23.26 millions and year 5 +16.37 millions). The sensitivity analysis confirmed the robustness of the results.

CONCLUSIONS: The use of DCV is likely to have a short term impact on the INHS budget increasing resources use compared to the sole use of INF-α+RBV+SOF. However, a trend of reduction of the costs increase is observed due to the management of health states and adverse events which may lead to the possibility to reduce costs in the long term.

Keywords

Hepatitis C Virus; Daclatasvir; Budget Impact Analysis; Genotype 3

BACKGROUND

Infections due to Hepatitis C Virus (HCV) represent a global health problem, affecting patients worldwide [1] with different prevalence and incidence among countries [2-4]. They may progress to chronic cirrhosis, hepatocellular carcinoma (HCC), hepatic decompensation and may lead to liver transplant [5].

The economic and social impact of the disease was investigated in different contexts, showing the cost increase for health services to manage HCV positive patients, leading to the conclusion that a lack of treatment of the pathology would lead to an increase of the disease burden due to HCV induced pathologies and the related worsening of the health condition of HCV positive patients [6-9].

Among HCV genotypes, genotype 3 is associated with higher HCC incidence and with accelerated fibrosis progression [10,11], and only two treatments are recommended by

Corresponding author
Umberto Restelli
urestelli@gmail.com

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	Pts (n.)	% of the previous category	Source
Italian population (1st January 2014)	60,782,668		[14]
HCV prevalence	2,725,359	4.5	[15]
HCV positive patients	300,000	11.0	[16]
HCV positive patients eligible to treatment (F3 – F4)	24,600	8.2	[16]
HCV genotipe 3 infected patients	2,706	11.0	[17]

Table I. *Epidemiological data and number of HCV genotype 3 infected patients eligible to treatment*

Health states transition	Rate	Source
F3 → F4	0.112	[18]
F4 → Decompensated cirrhosis	0.039	
F4 → HCC	0.014	
Decompensated cirrhosis → HCC	0.014	
Decompensated cirrhosis → Transplant	0.030	
Decompensated cirrhosis → Death	0.130	[19]
HCC → Transplant	0.030	
HCC → Death	0.430	
Transplant (Year 1) → Death	0.210	
Transplant (Year 2+) → Death	0.057	

Table II. *Model's health states transition rates*

Antiviral treatment	SVR at 12 weeks (%)	Anemia (%)	Rash (%)
SOF + DCV + RBV – 24 weeks	100 [20]	10.3 [21]	6.9 [21]
INF-α + RBV + SOF – 12 weeks	92.1 [22-24]	12.0 [22]	12.0 [22]

Table III. *Effectiveness and adverse events rates of the two treatments*

the Guidelines of the European Association for the Study of Liver for the treatment of HCV genotype 3 infected patients with compensated cirrhosis [12]: sofosbuvir (SOF) + daclatasvir (DCV) + ribavirine (RBV) for 24 weeks and peg interferon α (INF-α) + RBV + SOF for 12 weeks.

Due to the high cost of new HCV antiviral treatments and in absence of scientific evidence about their economic impact on the Italian National Health Service (NHS), the study presented aimed at evaluating the impact on the budget of the Italian NHS of the use of daclatasvir for the treatment of HCV genotype 3 infected patients compared with the sole use of INF-α + RBV + SOF.

MATERIALS AND METHODS

An analytical decision model was implemented to forecast the impact on the budget of the Italian NHS of the use of DCV in a five year time horizon for the treatment of HCV positive patients [13].

The patients eligible to antiviral treatment were those with a fibrosis rate of 3 and 4 (F3 and F4), as recommended by the Italian NHS. The number of eligible patients was estimated using published prevalence and incidence data, as reported in Table I.

Two scenarios were structured based on the recommendations of the guidelines of the European Association for the Study of Liver [12]. In details the only two treatments recommended for cirrhotic genotype 3 HCV infected patients were considered in two scenarios, one not considering the use of DCV, therefore having a 100% market share of INF-α + RBV + SOF for 12 weeks from 2015 to 2019 (scenario 1); the second one introducing in the base case scenario SOF + DCV + RBV for 24 weeks with the following annual market shares: 50% in 2015 and 2016, 55% in 2017 and 2018, and 60% in 2019 (scenario 2). The market shares were based on experts' opinions.

Patients enter the model in one of the following health states [15]: F3 (60%), F4 (16%), decompensated cirrhosis (3%), HCC (19%), liver transplant (2%). Each year patients may change their health states with probabilities based on previously published works [18,19], as presented in Table II.

Every annual cycle a percentage of patients, equal to the effectiveness of the antiviral treatment, reach a sustained virologic response (SVR). During the first year of treatment patients may experience treatment related adverse events (anemia and rash) with rates derived from literature. The effectiveness (SVR at 12 weeks after the end of the treatment) and adverse events rates are reported in Table III. Due to lack of data concerning the effectiveness and the efficacy of the treatments among patients affected with decompensated cirrhosis, HCC and eligible for liver transplant, the same effectiveness observed in patients with fibrosis stages 3 and 4 was considered.

The costs considered within the model are those of the antiviral therapy, direct medical costs for the management of the health state

Cost category	Cost yearly / per event / per treatment cycle (€)	Source
F3	302.0	[8]
F4	426.8	[8]
Decompensated cirrhosis	6,720.2	[8]
HCC	7,470.0	[8]
Transplant (year 1)	84,093.8	[8]
Transplant (year 2+)	4,958.7	[8]
Death	1,138.7	Reprocessed from [8,30]
Anemia	38.7	Expert opinion
Rash	34.6	Expert opinion
SOF + DCV + RBV – 24 weeks[1]	55,560.0	[26-29]
INF-α + RBV + SOF – 12 weeks[1]	39,809.0	[26-29]

Table IV. *Costs considered in the model*
[1] Ex-factory negotiated net price considering confidential agreements

Scenario	Cost category	Costs (€)					
		Year 2015	Year 2016	Year 2017	Year 2018	Year 2019	Total
Without DCV	Treatment	107,723,154	107,723,154	107,723,154	107,723,154	107,723,154	538.615.770
	HS and AE	9,705,386	14,603,436	14,835,723	15,056,818	24,168,852	78,370,216
	Total	117,428,540	122,326,590	122,558,877	122,779,972	131,892,006	616,985,986
With DCV	Treatment	129,034,257	129,034,257	131,165,367	131,165,367	133,296,478	653.695.726
	HS and AE	9,702,128	14,646,651	14,762,469	14,877,664	14,965,146	68.954.059
	Total	138,736,385	143,680,908	145,927,836	146,043,031	148,261,623	722.649.785
Budget impact	Treatment	21,311,103	21,311,103	23,442,213	23,442,213	25,573,324	115,079,956
	HS and AE	- 3,258	43,215	- 73,254	- 179,154	- 9,203,706	- 9,416,157
	Total	21,307,845	21,354,318	23,368,959	23,263,059	16,369,618	105,663,799

Table V. *Impact on the budget of the Italian NHS of the use of DCV for the treatment of HCV genotype 3 infected patients*

and direct medical costs for the management of the therapies' adverse events.

All costs refer to 2015, those derived from published articles were converted using the Italian yearly average inflation rates as reported by the International Monetary Fund [25]. The cost of the antiviral therapies considered were based on the price published in the Official Gazette of the Italian Medicines Agency [26-29]. The costs of the management of adverse events were calculated using an activity based costing approach, through interviews with clinical experts and are therefore based on the Italian real clinical practice. The cost of death was calculated by multiplying by 12.5 the average cost of 3 months in health states F3 and F4 [30]. The costs considered are reported in Table IV.

Univariate and multivariate sensitivity analyses were performed to test the robustness of the results. The parameters changed were the cost of DCV (±10%); the effectiveness of DCV (-5%) and the number of patients eligible for antiviral treatment (±10%).

RESULTS

The results of the analysis are reported in Table V.

The use of DCV would lead to an increase of the costs for the Italian NHS in the five years considered in the analysis. In details, the costs increase is due to the cost of treatment, while the costs related to the management of patients conditions in terms of health state and to the management of the adverse events decrease in the first year (- 3,258 €), increase in year 2 (+ 43,215 €) and exponentially decrease in the last three years of the analysis (-73,254 €, -179,154 € and -9,203,706 €, respectively). The total impact on the budget of the Italian NHS increase, compared to the previous year in the second and third year (+ 0.22% and + 9.43%) and decrease in the last two years (- 0.45% and -29.63%).

The sensitivity analysis results are reported in Table VI.

All scenarios show the same trends of the base case analysis and show a budget impact with yearly variations lower than 6 million euros.

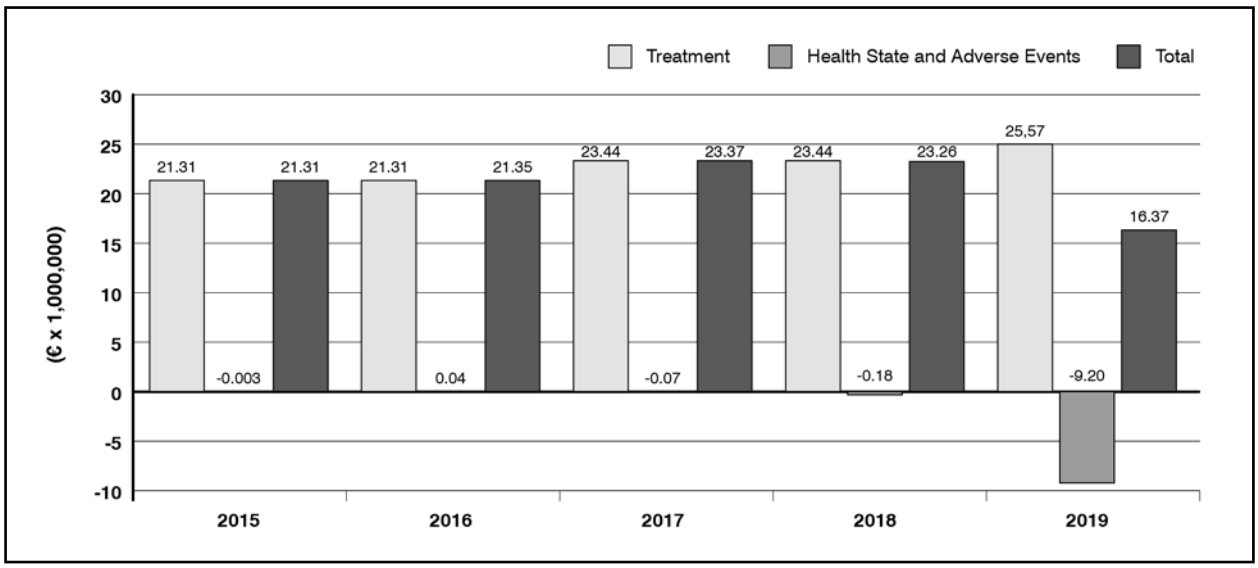

Figure 1. *Impact on the budget of the Italian NHS of the use of DCV for the treatment of HCV genotype 3 infected patients*

Scenario	Costs (€)				
	Year 2015	Year 2016	Year 2017	Year 2018	Year 2019
Base case	21,307,845	21,354,318	23,368,959	23,263,059	16,369,618
DCV cost -10%	19,007,745	19,054,218	20,838,849	20,732,949	13,609,498
DCV cost +10%	23,607,945	23,654,418	25,899,069	25,793,169	19,129,738
DCV effectiveness -5%	21,307,845	21,325,040	23,419,717	23,384,465	16,570,992
Number of patients eligible to antiviral treatments -10%	19,177,060	19,218,887	21,032,063	20,936,753	14,732,656
Number of patients eligible to antiviral treatments +10%	23,438,629	23,489,750	25,705,855	25,589,365	18,006,579
DCV cost -10% and DCV effectiveness -5%	19,007,745	19,024,940	20,889,607	20,854,355	13,810,872
DCV cost +10% and DCV effectiveness -5%	23,607,945	23,625,140	25,949,827	25,914,575	19,331,112
DCV cost -10%, DCV effectiveness -5% and number of patients eligible to antiviral treatments +10%	20,908,519	20,927,434	22,978,568	22,939,790	15,191,959
DCV cost +10%, DCV effectiveness -5% and number of patients eligible to antiviral treatments +10%	25,968,739	25,987,654	28,544,810	28,506,032	21,264,223
DCV cost -10%, DCV effectiveness -5% and number of patients eligible to antiviral treatments -10%	17,106,970	17,122,446	18,800,647	18,768,919	12,429,785
DCV cost +10%, DCV effectiveness -5% and number of patients eligible to antiviral treatments -10%	21,247,150	21,262,626	23,354,845	23,323,117	17,398,001
DCV cost +10%, and number of patients eligible to antiviral treatments +10%	25,968,739	26,019,860	28,488,976	28,372,486	21,042,711
DCV cost +10% and number of patients eligible to antiviral treatments -10%	21,247,150	21,288,977	23,309,162	23,213,852	17,216,764
DCV cost -10%, and number of patients eligible to antiviral treatments +10%	20,908,519	20,959,640	22,922,734	22,806,244	14,970,447
DCV cost -10% and number of patients eligible to antiviral treatments -10%	17,106,970	17,148,797	18,754,964	18,659,654	12,248,548

Table VI. *Yearly budget impact resulting from the sensitivity analysis performed*

DISCUSSION

New HCV antiviral treatments, due to their high effectiveness compared with previously available treatments, give the opportunity to cure the infection and substantially reduce its prevalence. Few studies investigated the cost effectiveness of DCV for the treatment of HCV genotype 3 infection [31,32], however to our knowledge its impact on national budget was not investigated so far. These economic evaluation may provide information on the efficiency of the resource allocation, but not on the sustainability of the treatment strategy.

The analysis performed show an increase of costs for the treatment of HCV genotype 3

infected patients for the Italian NHS in the five years considered. The cost increase is due to the cost of the antiviral treatment, while the direct medical costs related to the management of the patients' health state and of therapy related adverse events constantly decrease after the second year. The dynamics of cost reduction (-73,254 €, -179,154 € and -9,203,706 € in the last three years of the analysis) suggest the possibility to compensate over the years the higher cost of the treatment with the cost reduction for the management of patients improved health conditions.

The model is based on published data related to the Italian context. However, the number of HCV infected patients and the rate of genotype 3 infection are still discussed within the scientific community. Moreover, the effectiveness of therapies in genotype 3 HCV infected patients is based on studies with limited samples due to the lower prevalence of this genotype compared with other HCV genotypes.

The main limit of the analysis is related to the 5 year time horizon considered. The higher effectiveness of DCV+ SOF + RBV compared with INF-α + RBV + SOF, lead to a decrease in the number of patients infected with HCV. The direct medical costs of the management of HCV infection increase in the long period (due to decompensated cirrhosis, HCC and liver transplant), therefore the budget impact of the use of DCV+ SOF + RBV is likely to be overestimated in the analysis presented, not considering the therapy's long term benefits.

CONCLUSION

The use of DCV for the treatment of HCV genotype 3 infected patients in the Italian context is likely to have a short term impact on the budget of the Italian NHS increasing the resources use compared to the sole use of INF-α + RBV + SOF. However, in the five years analysis there is a trend of reduction in the cost of the management of health states and adverse events with DCV+ SOF + RBV, compared with INF-α + RBV + SOF, which may lead to the possibility to reduce costs in the long term.

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