



Research Article

Budget Impact Analysis of HCV Patients' Pathway: Past, Present and Future in the Italian Landscape

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Abstract

Objectives: The present study aims at analysing the budget impact related to the management of patients with Hepatitis C Virus (HCV) in Italy, over the years. Indeed, despite an increasing expenditure related to the novel HCV treatments was registered, due also to an increased therapeutic strategies efficacy, little is known about the expenditure related to the overall pathway, considering the capability of the novel therapies to improve the clinical management of HCV patients. **Methods:** Economic evaluation considered the biennial cost of 578 HCV patients' pathway, registered by three Hospitals in Lombardy Region (Italy), and considered the following items of healthcare expenditure: examinations, diagnostic procedures, outpatients and inpatients activities, and day-hospital events, also for the management of drug-related adverse events and complications. HCV population was stratified according to the two different waves of antiviral drugs available in the Italian market (before and after 2017, the year of the introduction and extension of new HCV treatment criteria in the Italian NHS), distinguishing also Sofosbuvir (SOF)-based regimes from the others. Three scenarios were simulated and compared, assuming the Italian NHS point of view, and estimating the NHS healthcare expenditure up to three years: 1) Retrospective projection considered the cost of the pathways related to the first wave of drugs and the HCV population effectively treated in the period 2015-2017 (108.887 patients); 2) Hypothetical retrospective projection considered the cost of the pathways related to the second wave of drugs, but the HCV population effectively treated in the period 2015-2017; 3) Perspective projection: considered the cost of the pathways related to the second wave of antiviral drugs, and the forecast HCV population treated in the period 2018-2020 (172.938 patients). **Results:** In the comparison between the two retrospective projections, NHS total costs devoted to the treatment of HCV patients decreased of -35%: if new treatments had been available since 2015, the economic saving would have been equal to 68,696,848€ (about 630€ per treated patient). Results from perspective projection revealed that the saving were confirmed in the long term (about 500€ per treated patient equal to -28%), despite the increase in the population assuming therapeutic strategies. If the SOF-based regimens market shares increased, savings up to 13% would be registered.

Conclusions: The results reported new evidence concerning the resources absorption related to HCV patients. Innovative drugs have increased the expenditure for drugs but ensuring an efficient management of the overall pathway (reduction of 63% in expenditure for hospitalizations), with a lower resource absorption per patient.

Keywords: HCV infection; Economic burden; Italian setting; Economic resources' absorption; Clinical management

Introduction

Hepatitis C Virus (HCV) infection represents a global public health problem, affecting million people worldwide, spreading a silent epidemic. Over the last few years, the epidemiological profile of HCV infection has evolved worldwide, due to the introduction of more effective antiviral drugs devoted to the management of HCV pathology, thus changing the HCV nature, from a chronic disease leading to a fatal condition, to a temporary condition of illness, especially if treated in an early stage of the pathology.

The standard of care, up to 2011, was the “dual therapy” composed by Pegylated Interferon and Ribavirin; then, in 2011, the first generation of Direct-Acting Antivirals (DAAs), such as Boceprevir and Telaprevir, appeared in the market and increased the effectiveness of treatments.

Another important revolution in this therapeutic landscape was represented by new regimens made available in 2015: these treatments increased the rate of Sustained Virological Response (SVR) and allowed the increase of eligible patients to treat, avoiding safety issue related to Pegylated Interferon based treatment [1-3]. Indeed, the advent of Direct-Acting Antivirals (DAAs) has significantly improved the pathway of patients with chronic HCV infection [4,5], due to the ability of these drugs to achieve high rates of Sustained Virological Response (SVR). As a result, the screening, diagnosis, and treatment of HCV infection continue to evolve with the availability of more effective, though with more costly, treatments, and the cost of care continues to rise.

The emergence of pangenotypic regimens, also in the Italian market, reported new opportunities, due to a greater coverage of population and an omission of resource-intensive genotyping [6], from a clinical point of view, and due to the simplification of the procurement processes, from a managerial perspective.

Thus, the landscape of anti-HCV medications has rapidly evolved, with several more effective alternative technologies introduced in the market, worldwide: both clinicians and policy makers are addressing the issue of overall trade-off among investments, savings, and economic sustainability due to the introduction of HCV treatments in the general management of this disease [7].

Based on this consideration, an increasing expenditure related to the HCV treatments is registered, but little is known about the absorption of economic resources of the overall patient pathway, thus requiring an answer to the following policy question: *is the cost of HCV patients' management reduced, due to the increased efficacy of HCV novel therapies, in terms of general clinical management of the patients?*

Literature evidence available on the topic focuses the attention only on the cost-effectiveness and cost-sustainability nature of both the innovative therapeutic regimens [8-13], and the potential institution of massive screening programs devoted to HCV detection [14-18]. Apart from these studies, no specific analysis has estimated the different components of the clinical HCV patients' pathway, assuming the Italian National Healthcare System to define the impact of the innovative drugs in the overall improvement of the patients' management. Moreover, no accurate distinctions concerning the HCV patients' clinical management, based on the liver fibrosis or the presence of a concomitant HIV infection are available, thus validated health economics information is required for the development of institutional forecast and precise cost models. As a direct consequence, an informative gap has emerged concerning the management costs of HCV disease within National Healthcare Service-based countries. While HCV is a significant economic burden for healthcare providers, limited country-oriented evidence is available about the economic resources absorption related to the patients, useful for supporting healthcare systems in the definition of action plans and strategies devoted to HCV management.

Moving on from these premises, the present study aims at fully evaluate the budget impact of the resources absorption in HCV management deriving from real world evidence, focusing on the comparison of the economic pathway related to the introduction of more inclusive treatment criteria in the Italian setting, proving the existence of real and measurable benefits from an economic point of view.

Materials and Methods

A Budget Impact Analysis (BIA) was implemented to achieve the above-mentioned study objective, thus being the reference methods to estimate and predict economic and financial consequences referring to the adoption and diffusion of new technologies into a healthcare system with finite resources [19].

To build up the model, three phases were developed, as follows.

Economic Evaluation of the HCV Clinical Pathway

To create economic inputs for the BIA model, an economic evaluation was conducted to estimate the medical pathway for each treated patients' assuming a 24-month time horizon from the first administration of the antiviral. Real-life data related to 578 HCV patients' pathways were collected from three Infectious Disease Centres of Lombardy Region (Northern Italy), involved in the analysis: “Valle Olona” of Busto Arsizio, “Fatebenefratelli Sacco” of Milan Hospital and “Policlinico San Matteo” of Pavia Hospitals, during the years 2017-2018.

To estimate the HCV management costs, the following health expenditure items were investigated, assuming the

NHS perspective: laboratory exams, diagnostic and specialist procedures, drugs directly purchased by the patients in accordance with a specialist prescription and an NHS co-payment (territorial drugs), and hospital admission. Economic information was evaluated in accordance with outpatient visits and examinations, hospital admission Reimbursement Tariffs, and the Italian NHS official drugs price list.

A clarification is needed here. Antiviral drugs costs were intentionally not included in this economic evaluation because, all over the world but especially in the Italian setting, the price of new drugs between the Italian Medicines Agency and industries, depended on many factors in the negotiation phase (i.e. target population, expected National Healthcare Service -NHS-expenditure, etc...) and it does not reflected the real amount of resources invested in the HCV patients care. Moreover, the Italian NHS has established a specific budget, with specific caps for "innovative drugs", and antiviral drugs were considered in this budget.

The results of the economic evaluation were stratified depending on the antiviral drugs assumed by HCV patients in this

specific time point: i) before 2017 (e.g. Ledispavir/Sofosbuvir, Sofosbuvir+Daclatasvir/Simeprevir, Ombitasvir+Paritaprevir/Ritonavir, Ombitasvir+Paritaprevir/Ritonavir + Dasabuvir, Simeprevir or Telaprevir with Peg Interferon, Peg Intefezone, with or without Ribavirine) and ii) after 2017 (e.g. Sofosbuvir/Velpatasvir/Voxilaprevir, Sofosbuvir/Velpatasvir, Glecaprevir + Pibrentasvir, Elbasvir/Grazoprevir, with or without Ribavirin). The year 2017 represented indeed a new era in the Italian HCV landscape, because new HCV treatments' criteria were introduced, allowing innovative antiviral drugs to be used more broadly, as is happening today in 2022.

Moreover, pathways were distinguished in SOF (Sofosbuvir)-based regimens and others therapeutic strategies.

Definition of the population: Data concerning treated population and drugs market shares were retrieved from the Italian Medicines Agency Registers, related to the administration of direct-acting antivirals (DAAs) and reported in Table 1. With regard to the degree of liver fibrosis, the following rates were assumed: 28.50% (F0-F1), 32.00% (F2), 18.10% (F3) and 21.40% (F4) [20].

Year	Population (active treatment)	Market share SOF-based regimens	Market share other regimens
2015	30,560	70.28%	29.72%
2016	33,667	75.04%	24.96%
2017	44,660	58.90%	41.10%
2018	56,499	37.40%	62.60%
2019	57,638	37.40%	62.60%
2020	58,801	37.40%	62.60%

Table 1: Population and drugs market shares considered in the BIA Model.

Budget Impact Analysis design

After the definition of the costs related to each antiviral under assessment, the BIA was conducted assuming the Italian National Healthcare System point of view and hypothesizing the healthcare expenditure evolution up to three years. The BIA design was dependent on the development of the population entering the model, the economic evaluation related to the patients' pathways, and the following projections.

1. Retrospective projection, considering the HCV pathways' costs and drugs before 2017 and number of HCV population treated in the period 2015-2017 in the Italian landscape (108,887 patients).

2. Hypothetical retrospective projection, considering the HCV pathways' costs and drugs available after 2017, and number of HCV population treated in the period 2015-2017 (108,887 patients). This projection was clearly unrealistic, but useful to measure the potential impact of new HCV treatments' criteria in case they were introduced earlier.

3. Perspective projection, considering the HCV pathways' costs and drugs, before and after 2017, and the HCV population forecast treated in the period 2018-2020 (172,938 patients). Part of population related to 2019 and 2020 population were estimated, concerning the trend registered in the first six months of 2019, assuming a linear trend. Drug markets' shares related to 2019 and 2020 were validated by expert opinion.

Scenario and Sensitivity Analysis

In addition to the abovementioned projections, other different scenarios were simulated, to investigate if significant changes in the results should occur.

Three different changes in market shares were simulated:

a) patients with degree of liver fibrosis equal to F0, F1, F2, F4 treated only with SOF-based regimens, while other patients (F3) treated both with SOF-based regimes and other strategies (considering the same market share of the Perspective projection);

b) patients with degree of liver fibrosis equal to F0, F1, F2 treated only with SOF-based regimens, while other patients (F3 and F4), treated both with SOF-based regimes and other therapeutic strategies (considering the same market share of the Perspective projection);

c) all population treated only with SOF-based regimens.

Results

Table 2 showed the average annual total cost of HCV patient pathway (considering the year of the treatment), stratified on degree of liver fibrosis and distinguished in SOF-based and other regimens before and after 2017, accordingly with the new HCV treatment criteria.

Total Cost Per Patient	F0+F1	F2	F3	F4	p-value
SOF-based regimens after 2017	€ 546.66	€ 527.87	€ 883.49	€ 913.23	0.001
SOF-based regimens before 2017	€ 4,062.85	€ 625.62	€ 1,077.03	€ 998.64	0.001
OTHER regimens after 2017	€ 892.44	€ 932.81	€ 608.73	€ 936.64	0.031
OTHER regimens before 2017	€ 4,318.66	€ 947.98	€ 833.87	€ 944.97	0.700

Table 2: Average total cost of HCV patient pathway, before and after 2017.

In general, the average total costs, associated with the most recent treatments (after 2017), presented a lower consumption of resources, especially for F0+F1 patients. In particular, F2 patients, treated with SOF-based regimens after 2017, reported the lowest costs (€ 527.87, p-value = 0.001).

The average total cost of the HCV patients' pathway considering the follow-up phase (i.e. the 12 months after the first antiviral treatment) amounted to € 477.05 for SOF-based regimens, and € 534.13 for other regimens. No differences were observed related to the degree of liver fibrosis.

Considering the retrospective projection (Table 3), the expenditure for the treated HCV population from 2015 to 2017 was equal to € 196 million. Considering the hypothetical retrospective projection, if new treatments had been introduced from 2015, the economic savings would have been more than € 68 million: this implied a saving of 630€ per diagnosed and treated patient, equal to a cost reduction of 35%.

	Retrospective projection	Hypothetical retrospective projection	Delta	Delta %
Total costs-Year 2015 [30,560 active treatments]	€ 55,087,446.62	€ 22,448,610.27	-€ 32,638,836.35	-59.25%
Total costs-Year 2016 [33,667 active treatments]	€ 75,591,771.49	€ 39,533,759.74	-€ 36,058,011.75	-47.70%
Total costs-Year 2017 [44,660 active treatments]	€ 65,375,392.21	€ 65,375,392.21	€ 0,00	0.00%
Total costs- from 2015 to 2017 [108,887 active treatments]	€ 196,054,610.32	€ 127,357,762.22	-€ 68,696,848.10	-35.04%

Mean total costs per patient- from 2015 to 2017	€ 1,800.53	€ 1.169.63	-€ 630.90	-35.04%
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Table 3: Total costs of HCV patients' pathways, from 2015 to 2017- Comparison between retrospective projection and hypothetical retrospective projection.

Analysing the perspective projection, the total costs from 2018 to 2020 were equal to € 225 million. In comparison with the previous projections, the global expenditure was increased due to a growth in the treated population, in the 2018-2020 period (+64,051 patients, +59%), but less than proportionally.

Indeed, the mean total costs per patient were equal to € 1,300: comparing this value with the retrospective projection, a saving of € 500 (-28%) was registered (Table 4). Table 5 showed the results of the scenario analyses: three different changes in market shares of the Perspective projection were performed. Increasing the use of SOF-based regimes, further savings could be observed (up to – 30 million euros, -13.44%, when patients with the degree of liver fibrosis F0+F1, F2, F4 were treated only with SOF-based regimes).

	Perspective projection
Total costs-Year 2018 [56,499 active treatments]	€ 44,909,446.65
Total costs-Year 2019 [57,638 active treatments]	€ 74,786,827.28
Total costs-Year 2020 [58,801 active treatments]	€ 105,266,722.53
Total costs from 2018 to 2020 [172,938 active treatments]	€ 224,962,996.46
Mean total costs per patient- from 2018 to 2020	€ 1,300.83
Savings per patient, compared with retrospective projection	-€ 499.70 -27.87%

Table 4: Total costs of HCV patients' pathway from 2018 to 2020- Perspective projection.

	Perspective projection Degree of liver fibrosis F0+F1, F2, F4 treated only with SOF-based regimes	Perspective projection Degree of liver fibrosis F0+F1, F2, treated only with SOF-based regimes	Perspective projection All degree of liver fibrosis stages treated only with SOF-based regimes
Total costs - Year 2018 [56,499 active treatments]	€ 36,663,754.79	€ 36,840,920.39	€ 38,422,685.81
Total costs - Year 2019 [57,638 active treatments]	€ 64,721,178.68	€ 65,334,012.07	€ 66,150,117.19
Total costs - Year 2020 [58,801 active treatments]	€ 93,344,415.51	€ 94,401,702.47	€ 94,436,706.80
Total costs from 2018 to 2020 [172,938 active treatments]	€ 194,729,348.98	€ 196,576,634.92	€ 199,009,509.80
Savings, compared with Perspective projection	-€ 30,233,647.48	-€ 28,386,361.54	-€ 25,953,486.66
Mean total costs per patient- from 2018 to 2020	€ 1,126.01	€ 1,136.69	€ 1,150.76

Savings per patient, compared with Perspective projection	-€ 174.82 -13.44%	-€ 164.14 -12.62%	-€ 150.07 -11.54%
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Table 5: Comparison between Scenarios *post* criteria enlargement.

Conclusions

Like other developed countries, Italy has agreed to meet the World Health Organization targets to reduce new cases of HCV infection by 90% and to treat 80% of eligible cases by 2030 [21]. The results of the present study represent an original contribution to the HCV literature stream, being something, that literature has not yet investigated thoroughly concerning “real-life” economic resources absorption for the annual HCV management, independently from the antiviral therapy administered to patients.

Indeed, in a general context of limited economic resources, dynamic changing alternatives for HCV treatment, and approaches to the reimbursement tariffs, a better understanding of HCV costs associated to the pathways and economic forecast can support the management of HCV patients, in the development of treatment strategies in the light of the emergence of several new and potent anti-HCV therapies. This is particularly important in the current era, where estimations have revealed that delaying treatment with DAAs due to the COVID-19 pandemic could determine over 500 deaths from HCV-related liver disease after five years [22].

In general terms, results showed that an economic sustainability for NHS could be achieved: the introduction of a specific budget for “innovative drugs” (as antiviral therapies), and new criteria for treatment eligibility, have increased the number of treated patients and consequently the global expenditure, but reducing the cost per patient thank to an efficient management of HCV patients, due to prescription and use of novel treatments (after 2017). Specifically, the cost of DAAs administered to patients in 2015-2016 was higher than that administered to patients in 2017-2019, suggesting that the return on investment decreased over time was also because of the decreasing price of treatment, and the optimisation of the HCV clinical management, thus being consistent to scientific evidence available on the topic [23].

Secondly, the projections suggested that, if new treatments had been available since 2015, the economic saving would have been equal to 630€ per patient. Results from perspective projection revealed that the savings are confirmed in the long run (about 500€ per patient, equal to a reduction of 28%), despite the number of patients treated growth. In case of SOF-based regimens usage increase, additional 13% of savings for the NHS would be registered.

The above economic saving should thus be reinvested in preventions activities, through the institution of mass screening activities devoted to HCV eradications, as has happened in other

European Countries, such as France, Great Britain, and the United Kingdom [18], and as suggested by Italian colleagues (XXX) [24,25].

Moreover, since 2017 the increase in drugs expenditure was offset by a lower resources' absorption per patient, assuring an efficient management of the overall HCV pathway (i.e. reduction of 63% in hospitalizations expenses). Thus, the present results should represent the baseline cost related to the overall HCV clinical managements, without considering the antiviral drug costs. The inclusion of such item of healthcare expenditure is critical, given the current company-hospital agreement that may expire in 2-3 years, requiring a new renegotiation. Within this specific setting, the estimation of the cost of illness is thus important for priority setting and forecasting activities [26], thus being useful for the achievement of the above-mentioned WHO objective related to HCV eradication.

Despite the relevance of the topic, the economic analysis revealed an important limitation, given the fact that long-term clinical outcomes have not been included in the evaluation of the clinical pathway. If the reduced occurrence rates of HCV-related liver disease would be included, the economic saving would become greater, as demonstrated in scientific evidence available on the topic [23].

In conclusions, the results obtained in the present study could help decision makers in the management and monitoring of the factors influencing the economic optimisation of the overall HCV pathways, and not limited to antiviral drugs costs to a correct planning [27,28].

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