



Liver, Pancreas and Biliary Tract

HCV novel therapeutic regimens in Wonderland: A budget impact analysis in the Lombardy Region



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ABSTRACT

Background: The advent of new HCV drugs has generated widespread economic concerns, particularly within the Italian setting, characterized by continuous linear cuts and spending review actions. The overall trade-off between investments and savings needs an in depth analysis.

Aims: The study aimed to estimate the budget impact of the introduction of the novel drugs approved during the year 2015, compared with the historical situation based on the different treatment options available prior to 2015.

Methods: A three-year budget impact model was developed, taking into consideration the Lombardy Region (Northern Italy) Health Service perspective. The degree of liver fibrosis, genotypes, presence of only HCV or HIV/HCV co-infections, presence or absence of sustained virological response, and direct healthcare total costs were the variables of the model.

Results: With the introduction of the novel regimens, a higher number of HCV patients achieved a sustained virological response (+20%). Further analysis showed that an investment in innovative technologies would have given the Regional System significant economic savings within the 36-month period (−6.64%/−7.15%).

Conclusions: Treating HCV-infected persons in the Lombardy Region with the new drugs would reduce healthcare expenditure on this specific disease, in each forecast implemented, thus reducing the economic burden of the pathology.

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1. Introduction

Hepatitis C virus (HCV) infection represents a major global public health problem, affecting approximately 160 million people worldwide [1]. Literature estimated that, in Italy, 2 million people have the infection. However, the actual burden of HCV may be underestimated due to the high number of undiagnosed infected subjects, often with latent disease, but at a significant stage [2].

Italian evidence now available [3,4], concerning the epidemiology and the prevalence of HCV, is inconsistent with reference to the administration of anti-HCV medications, as reported in real life

practice. Thus, an epidemiological gap emerged as a key issue to be considered for the management of HCV infection, leading to significant difficulties in the forecast and evaluation of the economic burden of disease for the Italian National Health Service (NHS).

The coverage of the mentioned knowledge gap could be relevant from a policy-making and pharmaco-economics point of view, allowing an efficient and effective economic resources allocation. Italian spending review imposed, over the last three years, a deep analysis of healthcare expenditures and required taking into particular consideration the assessment and introduction of healthcare technologies. In this regard, attention should be focused on the adoption of several new regimens made available in 2015 to clinical practices, that may represent important improvements if compared with traditional interferon-based HCV treatments (before May 2015).

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The standard of care, up to 2011, was “dual therapy” that used Pegylated Interferon and Ribavirin. The approval, in 2011, of the first generation of direct-acting anti-virals (DAAs), such as Boceprevir and Telaprevir, increased the effectiveness of previous treatments. However, in recent years (2014–2015), the landscape of anti-HCV medications has rapidly evolved, with several more effective alternative technologies introduced in the market, worldwide. While these treatments increased the rate of sustained virologic response (SVR), many patients were still unable to tolerate therapies with Pegylated Interferon [5,6]. If the significant increase of eligible patients were considered, the economic and budgetary implications would generate widespread concerns.

In 2015, with the Italian approval of novel combinations of DAAs, several expensive Interferon-free treatment options were made available: (i) Sofosbuvir/Ledipasvir; (ii) Daclatasvir + Sofosbuvir and (iii) Ombitasvir + Paritaprevir/Ritonavir + Dasabuvir, all assumed either alone or in association with Ribavirine.

An in-depth evaluation of the economic resources is therefore required for the proper and adequate treatment of HCV and HCV/HIV infected patients, in order to fill a literature gap.

To the best of the authors' knowledge, the present study is the first attempt to fully evaluate the budget impact of the above mentioned novel therapies, taking into consideration the Lombardy Region (Northern Italy) Health Service point of view, thus paving the way to allow planning for regional resources as providers and patients face a new context for HCV treatment decision-making.

2. Materials and methods

The study's objective was achieved using a budget impact analysis (BIA) approach, whose main purpose is to estimate and predict economic and financial consequences referring to the adoption and diffusion of new technologies into a healthcare system with finite resources [7].

The model was developed from the Lombardy Region Health Service perspective and represented the healthcare expenditure evolution over three years.

Two different comparative scenarios were simulated: the administration of the three interferon-free drugs approved during the year 2015 (innovative scenario) vs the historical situation of pharmacological alternatives consumption, considering both Interferon-free and Interferon-based strategies, representative of all treatments available prior to May 2015.

In accordance with this, (i) Sofosbuvir/Ledipasvir ± Ribavirine; (ii) Daclatasvir + Sofosbuvir ± Ribavirine and (iii) Ombitasvir + Paritaprevir/Ritonavir + Dasabuvir ± Ribavirine were included in the innovative scenario. Otherwise, (iv) Simeprevir + Sofosbuvir ± Ribavirine, (v) Simeprevir + Pegylated Interferon + Ribavirine, (vi) Sofosbuvir + Ribavirine, (vii) Sofosbuvir + Pegylated Interferon + Ribavirine, (viii) Pegylated Interferon + Ribavirine and (ix) PI old generation + Pegylated Interferon + Ribavirine, were part of the baseline/historical scenario.

To build up the model, four phases were developed:

1. *Input variables of the model.* All Lombardy Region subjects eligible to the treatments, entering the BIA, were defined and the related distribution was estimated considering (a) Metavir Score, determining the severity of the disease, (b) genotypes, (c) only HCV infection or HCV/HIV co-infection, and (d) previous medical history (naïve and treatment experienced patients), on the basis of literature, regional [8] and real-life data collected from two Infectious Disease Centres of Lombardy Region, involved in the analysis: “Ospedale di Circolo” of Busto Arsizio and “Luigi Sacco” of Milan Hospital Health Authorities (HHAs).

Since no clear consensus exists with reference to the number of HCV patients taken in charge in Lombardy Region, two different populations were hypothesized to be entered in the model, within the first year: (i) population related to the regional spending cap [9], and (ii) population related to the organizational and productive cap (starting from the Regional Decree 7826, 2015). These two assumptions were based on the declarations from the HHAs, taking into consideration only patients suffering from more severe stages of the disease (F3–F4), for whom the reimbursement indication was available, and estimating the F0–F2 population, potentially eligible to novel treatment, but assuming standard therapies.

The first hypothesis considered 13,658 infected patients of which 5395 were F3–F4 patients, for whom the Lombardy Region budget limitation was widely verified. In the second hypothesis, 31,722 HCV and HCV/HIV patients were considered, of which 12,530 subjects suffered from a severe stage of pathology (37,589 F3–F4 patients divided into three years of treatment due to capacity limit), this being consistent with the capacity of the Lombardy Region HHAs in terms of number of patients that could be treated per year.

The HCV prevalence rate was 2.45% [10], applied to verify the forecasts and hypotheses. The incidence of the disease was 0.016% per year [11], useful to enter new patients in the second and third year. Other relevant data used for the population progression, within the 24 and 36 months of analysis, were the number of deceased patients due to HCV-related causes (0.23%) and others due to hepatocellular carcinoma–HCC and decompensated cirrhosis–DCC (1.45% [12,13]), focusing on the fact that HCV is known to have an accelerated course in more than 30% of cases [6].

Furthermore, the model assumed that 30% of HIV infected patients had a concomitant HCV infection, on the basis of literature evidence [14,15] and in accordance with declarations from the HHAs involved.

The information regarding both the genotypes and the level of liver disease was retrieved by the Regional Decree 7826, and the related survey of November 2014. It was estimated that genotype 1 was the most common (60%), followed by genotypes 2 and 3 (15%). Patients affected by genotype 4 were less than 8%. These data were perfectly consistent with the most recent literature evidence [10,16].

With regard to the degree of liver fibrosis, the following rates were assumed (starting from the Regional Decree 7826 and validated with expert opinion): 28.50% (F0–F1), 32.00% (F2), 18.10% (F3) and 21.40% (F4). F4 patients were distinguished as follows [17]: 62.4% (Child–Pugh class A), 23.8% (Child–Pugh class B) and 13.8% (Child–Pugh class C).

The efficacy data was the sustained virological response, defined as the absence of detectable HCV RNA in the serum six months after the completion of treatment [18,19]. This information, together with the adverse events' incidence rates, was retrieved from the most recent clinical trials related to the different therapeutic regimens under assessment, as presented in Table 1.

2. *Budget impact model design.* The BIA design was dependent on: (i) the development of the population entering the model (point 1); (ii) the economic evaluation related to the patients pathways (point 3); and (iii) the scenarios compared in the assessment (point 4) (Fig. 1).

Patients could enter the model in one of the 138 possible health states, defined on the basis of: (i) genotype (1a, 1b, 2, 3, or 4), (ii) degree of liver fibrosis (F0, F1, F2, F3 or F4), (iii) previous clinical history, (iv) presence or absence of SVR (SVR vs NO SVR) at the end of the anti-HCV treatment, and related to the efficacy data, (v) presence of HCV infection or HCV/HIV co-infection. According to this, four different populations were assumed.

F2 individuals could develop DCC, HCC, receive a liver transplant, or die as a result of a liver-related cause: the higher the

Table 1
Efficacy rate sources of information, for HCV and HCV/HIV infected patients.

Treatment regimens	Clinical trials
Ledipasvir/Sofosbuvir ± Ribavirine	ION 1 [20], ION 2 [21], ION 4 [22], ELECTRON 2 [23], NIH SINERGY [24]
Daclatasvir + Sofosbuvir ± Ribavirine	A1444-040 [25], ALLY 2 [26], ALLY 3 [27]
Simeprevir + Sofosbuvir ± Ribavirine Ombitasvir + Paritaprevir/Ritonavir + Dasabuvir ± Ribavirine	COSMOS [28] PEARL I [29], PEARL III [30], PEARL VI [30], SAPPHIRE 1 [31], SAPPHIRE 2 [32], TURQUOISE [33]
Simeprevir + Pegylated Interferon + Ribavirine Sofosbuvir + Ribavirine	QUEST 1 [34], PROMISE [35], RESTORE [36], C212 [37] NIH-SPARE [38], FISSION [39], FUSION [40], Egyptian Ancestry Trial [41], PHOTON II [42]
Sofosbuvir + Pegylated Interferon + Ribavirine	NEUTRINO [39], NIH-SPARE [38], ELECTRON [43], LONESTAR 2 [44]
PI old generation + Pegylated Interferon + Ribavirine	SPRINT 2 [45], RESPOND 2 [46]

Metavir Score, or the Child–Pugh, the higher the probability that there will occur a disease progression and death. The evolution of the population at different stages of pathology decreased the number of patients in the model: at the end of each year of analysis, patients could either exit or enter the model (on the basis of the death and HCV prevalence rate). Patients who successfully moved to SVR health state remained in the model for the whole time-period (after achieving SVR, their annual economic value was composed of their monitoring only). On the other hand, patients not achieving SVR could remain in absence of cultural control, with a

higher risk of disease progression, or move to SVR population, in the second or third cycle (with a lower economic resources absorption). Both SVR and NO SVR patients could present the same incidence of adverse events, aspect totally related to the treatment regimen.

3. *Economic evaluation.* In order to conduct a complete BIA, the economic evaluation of the above mentioned different categories of patients (point 1), considering their whole clinical and diagnostic HCV pathway, was composed of the following aspects:

- i) Annual costs of HCV treatment, considering (a) different stages of disease, (b) presence or absence of co-infection, and (c) achievement of SVR, on the basis of the HCV Lombardy Region data [8] and standard clinical pathways carried out in the two HHAs involved (March–October 2015), with final approval from the clinicians of reference in accordance with the Delphi method [47]. The total amount of hematologic and cultural exams, diagnostic and surgical procedures, outpatients and medical examinations and hospital admissions were the investigated variables.
- ii) Cost of drugs during treatment that varied between 8 and 48 weeks, in accordance with liver fibrosis, HCV genotype, presence of HCV/HIV co-infection and pharmacological treatment scheme.
- iii) Cost of side effects management (in terms of laboratory exams, diagnostic and surgical procedures, medical examinations and hospital admissions), depending on the incidence and therapeutic strategy administered.

The presented three items of expenditure considered a time-horizon of 12, 24 and 36 months and were evaluated in accordance with the 2015 Lombardy Region outpatients and hospital admissions Reimbursement Tariffs. Drug costs derived from the

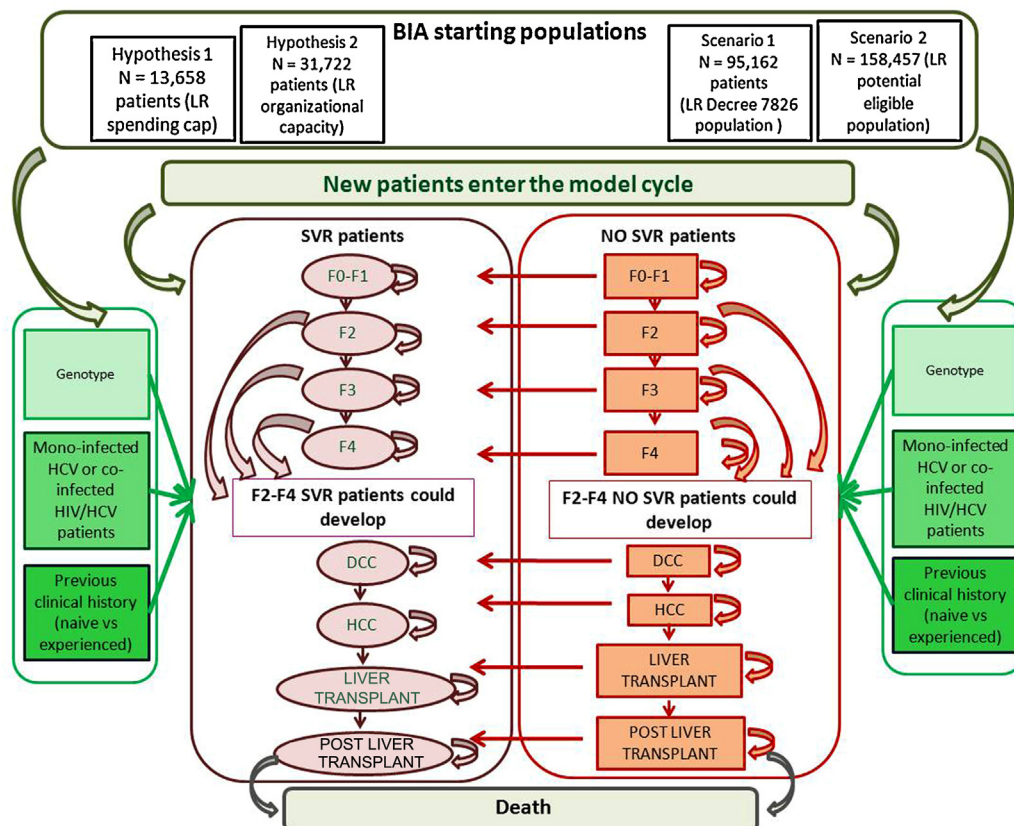


Fig. 1. Budget impact model design.

Table 2
Cost of the diagnostic and follow-up monitoring.

	F0–F1	F2	F3	F4
HCV patient				
BASELINE	€414.12	€414.12	€414.12	€414.12
SVR	€186.56	€245.49	€304.42	€1648.40
NO SVR	€373.12	€484.30	€595.48	€7658.76
HCV/HIV patient				
BASELINE	€414.12	€414.12	€414.12	€414.12
SVR	€186.56	€260.95	€335.33	€1888.34
NO SVR	€373.12	€499.76	€626.39	€7898.70

officially published NHS price list, and considering the Regional Decree 7826.

4. *Scenario and sensitivity analysis.* In addition to the above mentioned population hypotheses, four different scenarios were simulated: (i) 95,162 infected patients could enter the model [8]; (ii) the whole Lombardy Region population (158,457 patients) could be eligible to HCV anti-viral treatment [8]; (iii) non-responder patients included in the baseline scenario could receive innovative therapies; and (iv) the novel regimens could be administered to all the patients, independently from their level of liver fibrosis (application of a 0% market share to Interferon-based therapies).

After the implementation of the BIA and the scenario analysis, a sensitivity analysis was carried out by changing time-sensitive parameters (efficacy rates and drugs' prices). In order to account for lower SVR rates in practice vs clinical trials as conducted by Chhatwal and colleagues [48], a decrement of 2% and 5% was applied to each regimen. A decrease and an increase ($\pm 10\%$) in the drugs' market prices were applied, both in the historical and in the innovative scenario, in order to investigate if significant changes in the BIA occurred.

3. Results

3.1. Economic evaluation of the HCV patient clinical pathway

The economic evaluation of the HCV patient clinical pathway considered: (i) HCV diagnosis and follow-up, (ii) drugs cost, and (iii) the anti-viral monitoring and side-effect costs.

- i) **Table 2** shows the economic value related to the management of a standard HCV and HCV/HIV patient, stratified by level of liver fibrosis: the more severe the pathology, the more significant the amount of economic resources absorbed for the management of the patient.

The baseline value referred to the introduction of the patient into the taking in charge process, that requires hematologic and cultural exams useful to investigate the absence or the presence of HCV infection. SVR and NO SVR costs are related to the

follow-up of a patient who reaches, or does not reach, the virological control.

The difference between mono-infection and co-infection is due to the fact that an HCV/HIV patient requires more frequent controls both for HCV and HIV, since HIV is a leading cause of HCV rapid evolution.

- ii) The drugs' costs presented in **Table 3** are related to a single week of treatment. The complete therapy's administration was calculated, distinguished by level of disease progression.
- iii) Patients receiving the anti-HCV therapy should be monitored during the administration of the treatment, undergoing specific procedures and exams regarding the investigation of the strategy's efficacy and the possible development of drug-related adverse events. The differences presented in **Table 3** could be explained by the different number of exams, in particular with regard to the use of Ribavirine and Sofosbuvir that required more frequent controls of blood count and creatinine.
- In the real life setting, regional payers could take advantages from price-volume discounts concerning Ledipasvir/Sofosbuvir, Sofosbuvir, Ombitasvir + Paritaprevir/Ritonavir and Dasabuvir; in the model, this discount rate was applied on the basis of the overall treated population entering the BIA cycles, and the use of the previously mentioned drugs.
- iv) The procedures concerning the management of drug-related adverse event were evaluated, considering a 12-month period. The most common adverse events were (i) fatigue (€22.50), (ii) bilirubin increase (€84.75), (iii) insomnia (€81.30), (iv) anemia (€5629.31), (v) pruritus (€85.68), (vi) nausea (€52.74), (vii) rash (€110.34) and (viii) neutropenia (€1264.80).

3.2. Results from the budget impact analysis

The BIA was conducted with two different hypotheses' populations, for whom the same trend could be found, considering the decreasing of both the populations who could not reach the virological control and the overall economic resources needed for the entire management of the disease. With the introduction of the novel regimens, more effective than those available prior to May 2015, the progression of the disease could be stopped in a higher number of HCV and HCV/HIV patients.

Considering the first hypothesis of real-data drugs consumption, 13,658 patients entered the model in the first year, and 14,195 individuals were treated at the end of 36 months. In comparison with the baseline scenario, the innovative scenario reported an increase in +20.16% of the patients' virological control (equal to 1213 patients), over three years. The same trend was found in the second hypothesis, in which 31,722 patients were included in the model: a higher level of virological control was registered and 2815 patients (+20.15%), who in the baseline scenario were classified as "NO SVR" patients, became SVR.

Table 3
Cost of the therapeutic regimens and the related monitoring.

Therapeutic regimen	Cost of the drug (included VAT 10%)	Monitoring costs
Ledipasvir/Sofosbuvir	€3730.83	€868.75
Ledipasvir/Sofosbuvir + Ribavirine	€3745.68	€876.85
Daclatasvir + Sofosbuvir	€4950.00	€868.75
Daclatasvir + Sofosbuvir + Ribavirine	€4964.85	€876.85
Simeprevir + Sofosbuvir	€4766.67	€868.75
Simeprevir + Sofosbuvir + Ribavirine	€4781.52	€876.85
Ombitasvir + Paritaprevir/Ritonavir + Dasabuvir	€2475.00	€863.65
Ombitasvir + Paritaprevir/Ritonavir + Dasabuvir + Ribavirine	€2489.85	€871.75
Simeprevir + Pegylated Interferon + Ribavirine	€1615.35	€1082.95
Sofosbuvir + Ribavirine	€3406.52	€876.85
Sofosbuvir + Pegylated Interferon + Ribavirine	€3632.02	€1088.05
Pegylated Interferon + Riba	€240.35	€1082.95
PI old generation + Pegylated Interferon + Ribavirine	€1778.13	€1082.95

Table 4
Budget impact analysis and scenario analysis.

Treated HCV population	Time-horizon	NO SVR population		HCV management costs		Economic impact	
		Innovative vs baseline (N)	Innovative vs baseline (%)	Baseline	Innovative	Innovative vs baseline	Innovative vs baseline (%)
Hypothesis 1 (N = 13,658)	12-Month period	-688	-17.18	€394,946,618.80	€394,050,223.35	-€896,395.45	-0.23
	24-Month period	-402	-26.87	€127,327,739.83	€98,374,098.80	-€28,953,641.03	-22.74
	36-Month period	-123	-23.88	€43,444,752.10	€35,723,183.43	-€7,721,568.67	-17.77
	Total		-1213	€565,719,110.73	€528,147,505.58	-€37,571,605.15	
Hypothesis 2 (N = 31,722)	12-Month period	-1597	-17.17	€683,684,838.71	€695,397,772.61	€11,712,933.90	1.71
	24-Month period	-932	-26.82	€242,910,054.69	€177,189,910.41	-€65,720,144.28	-27.06
	36-Month period	-286	-23.91	€91,941,391.53	€73,166,191.10	-€18,775,200.43	-20.42
	Total		-2815	€1,018,536,284.94	€945,753,874.12	-€72,782,410.81	
Scenario analysis – increase of the population eligible to treatment							
Scenario 1 (N = 95,162)	12-Month period	-4791	-17.17	€2,050,968,255.43	€1,875,351,587.36	-€175,616,668.08	-8.56
	24-Month period	-2794	-26.81	€728,684,141.94	€490,843,086.37	-€237,841,055.57	-32.64
	36-Month period	-858	-23.93	€275,725,784.74	€202,482,454.21	-€73,243,330.53	-26.56
	Total		-8443	€3,055,378,182.12	€2,568,677,127.94	-€486,701,054.17	
Scenario 2 (N = 158,457)	12-Month period	-7979	-17.17	€3,415,126,935.99	€3,122,715,984.99	-€292,410,951.00	-8.56
	24-Month period	-4653	-26.82	€1,213,362,793.92	€817,280,737.62	-€396,082,056.30	-32.64
	36-Month period	-1426	-23.89	€459,045,184.70	€337,120,468.61	-€121,924,716.09	-26.56
	Total		-14,058	€5,087,534,914.62	€4,277,117,191.22	-€810,417,723.40	
Scenario 3 (N = 13,658)	12-Month period	-688	-17.18	€394,946,618.80	€394,050,223.35	-€896,395.45	-0.23
	24-Month period	-217	-16.55	€119,395,163.86	€98,374,098.80	-€21,021,065.06	-17.61
	36-Month period	-75	-16.06	€41,810,513.79	€35,723,183.43	-€6,087,330.35	-14.56
	Total		-980	€556,152,296.44	€528,147,505.58	-€28,004,790.86	
Scenario 4 (N = 31,722)	12-Month period	-1597	-17.17	€683,684,838.71	€695,397,772.61	€11,712,933.90	1.71
	24-Month period	-502	-16.49	€211,413,480.40	€177,189,910.41	-€34,223,569.98	-16.19
	36-Month period	-173	-15.97	€85,889,566.67	€73,166,191.10	-€12,723,375.57	-14.81
	Total		-2272	€980,987,885.77	€945,753,874.12	-€35,234,011.65	
Scenario 5 (N = 13,658)	12-Month period	-2444	-61.02	€294,362,509.80	€280,680,315.20	-€13,682,194.61	-4.65
	24-Month period	-992	-66.31	€104,578,125.93	€38,958,887.73	-€65,619,238.21	-62.75
	36-Month period	-344	-66.80	€39,581,306.29	€17,518,860.79	-€22,062,445.50	-55.74
	Total		-3780	€438,521,942.03	€337,158,063.72	-€101,363,878.31	
Scenario 6 (N = 31,722)	12-Month period	-5678	-61.04	€683,684,838.71	€651,906,633.99	-€31,778,204.72	-4.65
	24-Month period	-2305	-66.33	€242,910,054.69	€90,456,898.38	-€152,453,156.31	-62.76
	36-Month period	-799	-66.81	€91,941,391.53	€40,684,093.14	-€51,257,298.39	-55.75
	Total		-8782	€1,018,536,284.94	€783,047,625.51	-€235,488,659.42	

The introduction of the innovative technologies would, therefore, give the Health Service a significant economic saving, equal to -6.64% or -7.15% depending on the number of treated patients. The initial investment in innovative therapies could be covered in 24 months, generating relevant benefits for the Regional Service that could be consolidated in time. With the inclusion in the model of the 31,722 HCV and HCV/HIV patients, Lombardy Region would achieve an economic advantage, considering an overall baseline cost equal to €1,018,536,284.93 and an innovative scenario resources absorption of €945,753,874.12, over three years. Although the increase of the population to be treated would raise the HCV health budget at an investment equal to twice the resources made available by the Italian Ministry of Health, the situation would generate economic savings exactly twice as much with respect to the previous forecast.

While hypothesis 1 shows in the first year an immediate economic saving, hypothesis 2 shows an incremental, but moderate resources absorption of 1.71%; however, this is amply rewarded in the second cycle of the model. The two apparently different results in a short time-horizon clearly suggest the importance of monitoring the number of patients enrolled and treated, in order to maximize and optimize the discount policies, thus achieving the greatest benefit for the NHS.

Furthermore, six scenario analyses were performed, concerning the increase of HCV patients potentially eligible to treatment. The first scenario, based on the survey mentioned in the Decree

7826, recorded 37,589 patients with positive HCV-RNA, treated by the Lombardy Region HHAs. Moving on from this data (considering only F3 and F4 patients), the overall number of HCV infected patients was estimated to be 95,162. The second scenario analysis considered all the Lombardy Region HCV infected patients, on the basis of the HCV prevalence rate, resulting in a starting population entering the model of 158,457 patients. Hence, the introduction of the novel therapeutic regimens showed a significant increase of HCV patients who achieved the SVR (+20.15%), and a substantial economic saving of -15.93% in both cases (Table 4).

The results highlighted in the BIA did not vary significantly even if, in the baseline scenario, non-responder patients were treated with the innovative regimens in the second and in the third cycle (scenarios 3 and 4). The innovative scenario always represents the preferable "standard of care", decreasing the number of NO SVR patients by -16.95% and providing the regional health Service with an economic advantage reducing the amount of resources required for the treatment of all the eligible patients, considering a range variable from -3.59% (N = 31,722) to -5.04% (N = 13,658).

Moreover, if the innovative drugs were available for the treatment of all the patients (including F0-F2 individuals), with the consequent avoidance of Interferon-based combinations (scenarios 5 and 6), the related benefits would be significantly higher and would not present a difference in the case of 13,658 or 31,722 individuals treated. Over the three-year period, there emerged an

Table 5
Sensitivity analysis.

Treated HCV population	Time-horizon	NO SVR population		HCV management costs		Economic impact	
		Innovative vs baseline (N)	Innovative vs baseline (%)	Baseline	Innovative	Innovative vs baseline	Innovative vs baseline (%)
1. Efficacy rate –2% (N = 13,658)	12-Month period	–688	–16.08	€395,347,750.90	€394,451,355.45	–€896,395.45	–0.23
	24-Month period	–426	–25.30	€134,794,726.63	€105,857,764.38	–€28,936,962.25	–21.47
	36-Month period	–136	–22.33	€48,178,065.94	€39,854,714.48	–€8,323,351.46	–17.28
	Total		–1250	€578,320,543.47	€540,163,834.31	–€38,156,709.16	
2. Efficacy rate –2% (N = 31,722)	12-Month period	–1597	–16.07	€684,616,506.05	€696,329,439.95	€11,712,933.90	1.71
	24-Month period	–991	–25.33	€257,194,387.68	€190,653,598.66	–€66,540,789.02	–25.87
	36-Month period	–318	–22.47	€102,003,331.77	€81,525,220.21	–€20,478,111.56	–20.08
	Total		–2906	€1,043,814,225.50	€968,508,258.82	–€75,305,966.68	
3. Efficacy rate –5% (N = 13,658)	12-Month period	–687	–14.65	€395,949,449.05	€395,053,053.60	–€896,395.45	–0.23
	24-Month period	–465	–23.40	€146,040,112.52	€117,155,339.52	–€28,884,773.00	–19.78
	36-Month period	–161	–20.83	€55,900,531.56	€46,517,017.18	–€9,383,514.38	–16.79
	Total		–1313	€597,890,093.12	€558,725,410.30	–€39,164,682.83	
4. Efficacy rate –5% (N = 31,722)	12-Month period	–1597	–14.67	€686,014,007.05	€697,726,940.95	€11,712,933.90	1.71
	24-Month period	–1078	–23.36	€278,715,466.18	€210,940,641.98	–€67,774,824.20	–24.32
	36-Month period	–373	–20.77	€118,289,506.26	€95,180,721.09	–€23,108,785.17	–19.54
	Total		–3048	€1,083,018,979.49	€1,003,848,304.02	–€79,170,675.47	
5. Drugs' price –10% (N = 13,658)	12-Month period	–688	–17.18	€363,916,583.14	€362,486,336.67	–€1,430,246.47	–0.39
	24-Month period	–402	–26.87	€117,358,728.84	€90,586,980.30	–€26,771,748.54	–22.81
	36-Month period	–123	–23.88	€40,137,071.50	€32,992,805.21	–€7,144,266.28	–17.80
	Total		–1213	€521,412,383.48	€486,066,122.19	–€35,346,261.29	
6. Drugs' price –10% (N = 31,722)	12-Month period	–1597	–17.17	€634,976,644.31	€644,070,107.30	€9,093,462.98	1.43
	24-Month period	–932	–26.82	€225,038,744.70	€164,233,671.17	–€60,805,073.53	–27.02
	36-Month period	–286	–23.91	€85,155,586.94	€67,806,526.35	–€17,349,060.59	–20.37
	Total		–2815	€945,170,975.95	€876,110,304.81	–€69,060,671.14	
7. Drugs' price +10% (N = 13,658)	12-Month period	–688	–14.79	€426,926,835.37	€426,564,500.51	–€362,334.85	–0.08
	24-Month period	–464	–23.63	€156,420,094.59	€125,288,583.40	–€31,131,511.19	–19.90
	36-Month period	–161	–21.13	€59,474,785.48	€49,431,161.44	–€10,043,624.04	–16.89
	Total		–1313	€642,821,715.43	€601,284,245.35	–€41,537,470.08	
8. Drugs' price +10% (N = 31,722)	12-Month period	–1597	–17.17	€718,807,671.25	€733,942,331.86	€15,134,660.60	2.11
	24-Month period	–932	–26.82	€256,383,996.97	€186,022,355.64	–€70,361,641.33	–27.44
	36-Month period	–286	–23.91	€97,180,223.83	€76,954,135.19	–€20,226,088.64	–20.81
	Total		–2815	€1,072,371,892.05	€996,918,822.68	–€75,453,069.37	

important reduction of patients who did not achieve a sustained virological control (–62.84%), with an economic saving of –23.12%.

3.3. Sensitivity analysis

All results deriving from the sensitivity analysis show the robustness of the proposed BIA. Even with a decrease in all the treatments' efficacy rates (from –2% to –5%) Lombardy Region would achieve an economic saving of –6.60% and a consequent increase of responder patients (+18%), in the treatment of 13,658 or 31,722 infected individuals.

If the price of the drugs (excluding VAT –10%) were included in the model, the innovative regimens would result in an economic advantage variable from –6.78% (N = 13,658) to –7.31% (N = 31,722) over three years. By applying an increase of +10% to all the therapeutic strategies, the novel drugs would give cost reductions of –6.46% and –7.04%, with reference to the two different investigated populations respectively (Table 5).

4. Discussion

This model provides clinicians and policy makers with a rational method to allocate HCV patients to the correct alternatives, with a consistent economic forecast, in a general context of limited economic resources and dynamic changing options for HCV treatment.

The results showed that treating eligible HCV-infected F3–F4 persons in Lombardy Region with the new drugs would decrease

the related healthcare expenditure, thus reducing the economic burden of the pathology, disinvesting resources for the implementation of new technologies and/or guaranteeing the best treatment for a greater number of patients.

Therefore, the population potentially eligible for treatment has emerged as the main factor leading to a significant change in the overall HCV healthcare expenditure: the higher number of patients treated, the higher the possibility to take advantage from the innovative therapies' discount rate.

Indeed, the treatment of all the F0–F4 patients with the novel regimens would generate greater savings for the NHS, if compared with the historical situation. If the economic resources (first year) needed for the treatment of 13,658 patients (hypothesis 1) are compared with the overall HCV expenditure required for the treatment of the regional eligible population (scenarios 1 and 2), it emerges that the time for the return on investment is around three years. Such a result is impressive, but partial: the investment required for adapting the hospitals organizational capacity should be considered for a complete evaluation.

In addition, the model could be easily adapted with the inclusion of the entire Italian HCV population suffering from the disease. In particular, literature evidence [49] declared that, in the national setting, the estimated number of F3–F4 patients is about 187,756 (referring to the entire year 2015). Moving on from this information, the overall number of HCV infected Italian patients potentially eligible to treatment is equal to 475,332: in particular, 135,470 were F0–F1, 152,106 were F2, 86,035 were F3 and 101,721 were

F4. Considering the drugs' reimbursement indications (year 2015), the treatment of Italian HCV patients would lead the NHS to a significant economic saving (−15.93%), thus also increasing the effectiveness of the treatment strategies (−20.14% of NO SVR patients) within 36 months. This consideration is further strengthened if all the individuals (F0–F4) were treated with the innovative regimens, avoiding interferon-free therapies: given an increase of SVR patients (+10.57%), HCV Italian healthcare expenditure would present a reduction of −37.48%.

Despite the relevance of the results, the model has several limitations.

First, the SVR rates were retrieved from the clinical trials available for each strategy, targeting different patient cohorts, as the analysis was not based on an observational study. Second, within the national setting, there has been a lack of recent information related to both the prevalence/incidence of HCV infection, and the real patients distribution concerning the genotypes and the levels of liver fibrosis, that could contribute to a better control and appropriate care of infected individuals.

In conclusion, the model did not consider long-term benefits derived from the novel drugs' administration, leading to a reduction in the number of HCV-related deaths and of HCC or liver transplant occurrence [50].

Therefore, it could be an interesting topic for future research to study the update of the results, with the inclusion and the investigation of other different costs, impacting on the overall HCV healthcare expenditure as well as taking into consideration the number of Italian HCV patients treated in 2016 (representing precisely the first year, after the new DAAs approval).

Conflict of interest

None declared.

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