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Financial and feasibility implications of the treatment of hepatitis C virus in Italy: scenarios and perspectives

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Background: Hepatitis C virus (HCV) affects an estimated number of people between 130 million and 210 million worldwide. In the next few years, the Italian National Health Service will face a growing trend of patients requiring HCV antiviral treatments. The aim of the analysis was to estimate the time horizon in which it would be possible to treat HCV-infected patients and the related direct medical costs (antiviral treatment and monitoring activities) from the Italian National Health Service point of view.

Methodology: In order to estimate the number of HCV-infected patients in Italy, we considered a top-down (considering published data) and a bottom-up approach. The number of years needed for treatment and related direct costs were estimated through the development of a static deterministic model.

Results: The estimated number of HCV-infected patients in Italy varies from 2.7 (estimated through a top-down approach) to 0.6 million (estimated through a bottom-up approach) and 0.3 million (measured through a bottom-up approach). Considering the last two scenarios and the use of interferon-free therapies for 50,000 patients per year, treatment for HCV-infected patients could be at a cost of €13.7 billion and €7.0 billion by 2030 and 2023, respectively.

Conclusion: The treatment for HCV-infected patients in Italy is a challenging target for the financial implications of patient care. HCV infection could be controlled or eliminated in a 10- to 15-year time horizon. The cost of treatment can hardly be dealt with using the traditional economic tools but should be faced through multiyear investments, as health benefits are expected in the long period. National Health Service stakeholders (industry, government, insurance, and also patients) will have to identify suitable financial instruments to face the new expenditure required.

Keywords: sustainability, financial disease scenario, budget impact model

Background

Epidemiology

Hepatitis C virus (HCV) is an asymptomatic disease and, as such, is treated mainly at an advanced stage.[1] However, the clinical evolution of HCV infection in the medium and long terms may lead to liver compensated and decompensated cirrhosis, hepatocellular carcinoma (HCC), liver transplant, and eventually to death. Among the patients who suffer from HCV infection, in fact, >90% become chronic carriers, among them 65%–95% develop chronic liver disease, and in 10%–30% of the cases, an evolution into cirrhosis is observed within 25–30 years.[2] Cirrhotic subjects have a yearly probability between 1% and 3% to develop HCC.[3]

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HCV affects an estimated number between 130 million and 210 million people worldwide.[4] According to the findings of a study conducted in 2014 by the European Centre for Disease Prevention and Control, Italy has the highest number of HCV-positive patients in Europe and the highest rate of death from cirrhosis and HCC.[5] The significant epidemiological impact of the disease will lead the Italian National Health Service (NHS) in the next 5–10 years to offer an increasing number of HCV-related health services to a growing number of patients.[2]

Management of chronic HCV

In the last 2 years, several new drugs have been authorized in the European market, with a therapy duration of few weeks, with less side effects than the first-generation protease inhibitors and with a high percentage of sustained virological response, defined as "undetectable HCV RNA 12 weeks or 24 weeks after treatment completion".[6] In 2015, the European Association for the Study of Liver published therapeutic recommendations for the treatment of HCV infection, divided by HCV genotype.[6]

In addition to the aforementioned treatment recommendations, in Italy further management tools were introduced in the regulation of drug treatment for HCV: a centralized log monitoring, the identification of HCV antiviral treatment prescribing centers by the Regional Health Services, and the identification of seven criteria by the Italian Medicines Agency (AIFA) to prioritize patients to be treated, and select the most appropriate antiviral therapy to be administered.[7] In the Italian context, all the health costs for the patients admitted to the pharmacological therapy for HCV are fully covered by the Regional Health Service.

At a regional level (the public payor), the management tools introduced for the disease are the identification of reference treatment centers (373 in Italy), setting of annual budgets (different in each region considering the estimated number of target patients), and the collection of bottom-up clinical information of each treated patient.

The cost of pathology

HCV is not only a considerable social burden but also an important chapter of NHS spending. In the next few years, the Italian NHS will face a growing trend of patients requiring HCV antiviral treatments (around 30,000 patients started antiviral treatment in 2015).[8] In terms of economic weight, new antiviral drugs for the treatment of HCV have increased their impact on the total NHS financing up to 0.45% in 2015 (considering the €0.5 billion allocated in 2015 for purchasing HCV antiviral treatments over the Italian NHS budget of €109.7 billion).

The literature highlights how treatment costs increase with the degree of severity of patients' condition:[9,10] per patient direct and indirect costs are mainly absorbed by cirrhotic patients and those affected by advanced forms of liver disease.[10] In the same study, the annual direct and indirect costs of the disease in Italy are estimated to be €418 million and €643 million, respectively, reaching a total of €1.061 billion. The total costs for chronic HCV patients are €256 million, cirrhotic patients €560 million, patients affected with HCC €50 million, and patients admitted to liver transplant €48 million, and costs due to patients' death equal to €146 million.

Vietri et al (2013)[11] assessed the indirect and direct costs of the pathology in 2010, comparing self-reported outcomes (absenteeism and presenteeism) and use of resources in a sample of 286 HCV-infected patients from five European countries (Italy, France, Germany, the United Kingdom, and Spain) with a matched control sample of patients with similar demographic and health characteristics. The results of the analysis for the Italian environment show higher working and activity impairments and health care use in the HCV-infected group compared with the control group. The indirect mean annual costs per patient were €7,532.54 in HCV-infected patients vs €4,576.43 in the control group (P=0.002), and the direct mean annual costs per patient (physician visits, emergency room visits, and hospitalizations) were €1,147.06 and €652.07 (P<0.001) in HCV-infected patients and control group, respectively.

In 2015, the research group of the University of Tor Vergata, Rome, published the first Italian pharmacoeconomic model that describes the epidemiological and economic burden (both direct and indirect medical costs) that HCV is expected to have up to 2020, 2030, and 2040 on the Italian NHS assuming the use of the first-generation protease inhibitors, boceprevir and telaprevir, of peginterferon-alfa + ribavirin and the second-generation treatments.[12] They also estimated that there will be a reduction of >156,000 HCV-related events and a reduction in health care costs between €13,000 and €18,000 per treated patient in a 10- to 30-year time horizon.

Objectives

Considering the lack of a structured study at a national level to assess the impact of the second-generation pharmacological treatments for HCV infection in Italy, the aim of the analysis presented was to estimate the total cost of the treatment and the related parameters (eg, time horizon for treatment period and NHS treatment capacity) referring to the most

recent treatment recommendations[6] by developing a static deterministic model and using both top-down and bottom-up approaches to identify the number of HCV-infected patients. The point of view considered is that of the Italian NHS.

Methodology

Epidemiology

The number of HCV-infected patients in Italy was estimated using two different approaches. First, a top-down approach was used considering the published data related to the Italian context in terms of regional prevalence,[13] genotype distribution,[14] and fibrosis stage[15] (Table 1).

Table 1 HCV prevalence, genotype distribution, and fibrosis stage distribution among the Italian HCV-infected population

Identification category	Partition	% value	Reference
Prevalence (age-adjusted analysis)	North	1.6	13
	Central	6.1	
	Southern	7.3	
Genotype	1	52.4	14
	2	26.6	
	3	9.8	
	4	10.5	
	5	0.7	
Fibrosis stage	F0–F1	42	15
	F2	15	
	F3	12	
	F4 and cirrhosis	31	

Abbreviation: HCV, hepatitis C virus.

The combination of the data referred to prevalence, genotypes, and liver fibrosis stages distribution among the Italian population (considering the Italian Resident Population on January 1, 2015)[16] (Table 1) leads to the regional estimation presented in Table 2. The total number of HCV-infected subjects in Italy using a top-down approach is estimated to be 2,688,444.

Second, a bottom-up approach was also used to estimate the emerged cases of HCV infection in Italy, identified through data available in literature that were collected thriough the records of the Italian NHS. The number of patients with an exemption from copayment due to HCV condition (which in the Italian NHS is certified by local health authorities) is 308,624.[17] Further patients should be included: 20,640 HIV coinfected patients (identified through the Italian Cohort Naive Antiretrovirals)[17] and 3,860 estimated patients in prison detention (number of persons in prison detention on December 31, 2015, and HCV prevalence among the prisoners).[18,19] Moreover, the number of HCV-infected patients, aware of their condition and who benefit from low-income exemption from copayment (total exemption from all copayments in the NHS than for only copayment for HCV-related treatments,

Table 2 Regional estimation of the number of hepatitis C virus-infected patients divided by genotype and fibrosis stage using a top-down approach

Top-down approach											
Region	**G1 F0–F2**	**G1 F3–F4**	**G2 F0–F2**	**G2 F3–F4**	**G3 F0–F2**	**G3 F3–F4**	**G4 F0–F2**	**G4 F3–F4**	**G5 F0–F2**	**G5 F3–F4**	**Total**
Piemonte[a]	21,144	15,951	10,734	8,097	3,955	2,983	4,237	3,196	283	213	70,791
Valle d'Aosta[a]	613	463	311	235	115	86	123	93	8	6	2,053
Lombardia[a]	47,801	36,061	24,266	18,305	8,940	6,744	9,578	7,226	638	482	160,042
Trentino-Alto Adige[a]	5,046	3,807	2,562	1,932	944	712	1,011	763	67	51	16,895
Veneto[a]	23,548	17,765	11,954	9,018	4,404	3,322	4,718	3,560	315	237	78,842
Friuli-Venezia Giulia[a]	5,864	4,424	2,977	2,246	1,097	827	1,175	887	78	59	19,634
Liguria[a]	7,566	5,708	3,841	2,897	1,415	1,068	1,516	1,144	101	76	25,332
Emilia-Romagna[a]	21,268	16,045	10,796	8,145	3,977	3,001	4,262	3,215	284	214	71,208
Toscana[b]	68,372	51,578	34,708	26,183	12,787	9,646	13,701	10,335	913	689	228,912
Umbria[b]	16,302	12,298	8,275	6,243	3,049	2,300	3,267	2,464	218	164	54,580
Marche[b]	28,255	21,315	14,343	10,820	5,284	3,987	5,662	4,271	377	285	94,599
Lazio[b]	107,357	80,988	54,498	41,112	20,078	15,147	21,512	16,229	1,434	1,082	359,438
Abruzzo[c]	29,033	21,902	14,739	11,118	5,430	4,096	5,818	4,389	388	292	97,205
Molise[c]	6,832	5,154	3,468	2,617	1,278	964	1,369	1,033	91	69	22,874
Campania[c]	127,803	96,412	64,877	48,942	23,902	18,031	25,610	19,319	1,707	1,288	427,892
Puglia[c]	89,180	67,275	45,271	34,151	16,679	12,582	17,870	13,481	1,191	899	298,578
Basilicata[c]	12,573	9,484	6,382	4,815	2,351	1,774	2,519	1,901	168	127	42,093
Calabria[c]	43,098	32,512	21,878	16,504	8,060	6,081	8,636	6,515	576	434	144,294
Sicilia[c]	111,026	83,756	56,361	42,517	20,765	15,664	22,248	16,783	1,483	1,119	371,722
Sardegna[b]	30,304	22,861	15,383	11,605	5,668	4,275	6,072	4,581	405	305	101,460
Italy	802,987	605,758	407,623	307,503	150,177	113,290	160,904	121,383	10,727	8,092	2,688,444

Notes: Prevalence data: [a]North; [b]Central; [c]South. G1–G5 are genotype distributions. F0–F4 are fibrosis stages.

which is more valuable for patients) should be estimated. In Italy, according to the Ministry of Health data, 6,930,000 patients are exempt from copayment because of low income (46.2% of the total exemptions from copayment for any reason in Italy).[20] Among them, using the national age-adjusted prevalence rate of 4.4%,[13] further 304,920 HCV-infected patients are estimated. Therefore, the total number of patients with a diagnosis of HCV infection in Italy is estimated to be within a range from 329,264 to 613,124.

Comparing the results of bottom-up and top-down analyses, we can state that the number of HCV-infected patients in Italy is between 0.3 million and 2.7 million. Considering the number of reference treatment centers activated in Italy at a regional level,[21] the average number of patients to be treated per center is estimated to be 7.208 for the 2.7 million prevalence scenario, 1.711 for the 0.6 million prevalence scenario, and 883 for the 0.3 million prevalence scenario.

Economic analysis

Starting from prevalence data and the European antiviral treatment guidelines (considering the information available on pharmaceutical companies' cost-volume agreements), we estimated the total direct medical costs that Italian NHS should tackle in order to eliminate the virus in terms of direct medical costs related to antiviral treatment and monitoring activities (treating the entire infected population regardless of the fibrosis stage), developing a static deterministic model to assess the time period in which it would be possible to treat these patients, until reaching a prevalence below 100 HCV infections.

At time 0, patients are distributed among health states, characterized by different stages of evolution of the pathology (ie, fibrosis stages from 0 to 4, decompensated cirrhosis, HCC, and patients eligible for liver transplant). The patient distribution at time 0 is presented in Table 3. Mühlberger et al (2009)[22] reported that in Italy, every year, 1,050 patients enter the model in fibrosis stage 0 (F0), considering a mean incidence of 1.75 cases per 100,000 inhabitants. Each year, patients may change their health state (F0, F1, F2, F3, F4, decompensated cirrhosis, HCC, transplant year 1, transplant year 2+, and death) using the following rates of transition: from F0 to F1, 0.077; from F1 to F2, 0.092; from F2 to F3, 0.145; from F3 to F4, 0.116; from F4 to decompensated cirrhosis, 0.039; from F4 to HCC, 0.014; from decompensated cirrhosis to HCC, 0.014; from decompensated cirrhosis to liver transplant, 0.030; from HCC to liver transplant, 0.030; from decompensated cirrhosis to death, 0.130; from HCC to death, 0.430; from liver transplant (year 1) to death, 0.210; from liver transplant (year 2 and following years), 0.057.[23–25]

Table 3 HCV-infected patient distribution in year 0

Health state	Number of patients			Source
	329,264	**613,124**	**2,688,444**	
F0	69,145	128,756	564,573	Calculated considering data from reference 15
F1	69,145	128,756	564,573	
F2	49,390	91,969	403,267	
F3	39,512	73,575	322,613	
F4	66,644	132,641	615,153	
Decompensated cirrhosis	22,215	44,214	205,051	Calculated considering a 3:1 ratio between compensated cirrhosis and decompensated cirrhosis[30]
HCC	12,850			Calculated considering the number of HCCs due to HCV, 60%,[31] from the 35,447 patients with HCC in Italy in 2015[32]
Liver transplant	364			Calculated considering the 34.5% liver transplants due to HCV[33] among the 1,056 liver transplants in Italy in 2014[34]

Note: F0–F4 are fibrosis stages.
Abbreviations: HCC, hepatocellular carcinoma; HCV, hepatitis C virus.

The distribution of patients in different health states in the baseline scenario (no patients treated) is compared with four different scenarios in which a fixed number of patients is treated with antiviral therapies in each yearly cycle: 25,000; 50,000; 75,000; and 100,000. Considering the number of reference treatment centers that were already authorized in Italy and the maximum number of weeks per treatment (24 weeks), we estimated an average number of patients to be managed by each center at the same time to be between 34 and 134 patients.

In the model, patients are treated starting from those associated with worst health states (eligible for a liver transplant the same year, HCC, decompensated cirrhosis, F4, F3, F2, F1, and F0). Based on the effectiveness of each antiviral treatment (as reported in Table 4), patients may reach a sustained virological response and exit the model or remain in the same health state and be retreated the following year.

The direct medical costs for treated patients include those of the antiviral treatment and of patient monitoring (ie, specialist visits, HCV-RNA test, alanine aminotransferase test, prothrombin time/international normalize ratio test,

Table 4 HCV therapies considered in the model and related effectiveness parameters

Scenario	Genotype	Antiviral treatment for noncirrhotic patients			Antiviral treatment for cirrhotic patients		
		Antiviral therapy	SVR 12	Source	Antiviral therapy	SVR 12	Source
All treatments available	Genotype 1	Peg-IFN-α + RBV + SOF for 12 weeks	89.38%[a,*]	35	Peg-IFN-α + RBV + SOF for 12 weeks	79.63%[b]	35
	Genotype 2	SOF + RBV for 12 weeks	97.14%[c,*]	35	Peg-IFN-α + RBV + SOF for 12 weeks	96.00%[d,*]	36
	Genotype 3	Peg-IFN-α + RBV + SOF for 12 weeks	90.00%[e]	37	Peg-IFN-α + RBV + SOF for 12 weeks	87.93%[f]	38
	Genotype 4	OMB/PAR/r + RBV for 12 weeks	100.00%[g]	39	OMB/PAR/r + RBV for 12 weeks	100.00%[g,*]	39
	Genotype 5	Peg-IFN-α + RBV + SOF for 12 weeks	97.14%[h,*]	35	Peg-IFN-α + RBV + SOF for 12 weeks	79.63%[b]	35
Only interferon-free treatments	Genotype 1	SOF + LDV for 8–12 weeks	98.60%[i,*]	40	SOF + LDV + RBV for 24 weeks	99.08%[j,*]	40
	Genotype 2	SOF + RBV for 12 weeks	97.14%[c,*]	35	SOF + RBV for 20 weeks	97.14%[c,*]	35
	Genotype 3	SOF + RBV for 24 weeks	86.51%[k]	38	SOF + DCV + RBV for 24 weeks	57.89%[l]	41
	Genotype 4	OMB/PAR/r + RBV for 12 weeks	100.00%[g]	39	OMB/PAR/r + RBV for 12 weeks	100.00%[g,*]	39
	Genotype 5	SOF + LDV for 12 weeks	98.60%[i,*]	40	SOF + LDV + RBV for 24 weeks	99.08%[j,*]	40

Notes: [a]Genotype 1 naïve cirrhotic and noncirrhotic patients. [b]Genotype 1, 4, 5, and 6 naïve cirrhotic patients. [c]Genotype 2 naïve cirrhotic and noncirrhotic patients. [d]Genotype 2 naïve and experienced cirrhotic and noncirrhotic patients. [e]Genotype 3 naïve noncirrhotic patients. [f]Genotype 3 naïve and experienced cirrhotic patients. [g]Genotype 4 naïve noncirrhotic patients. [h]Genotype 4, 5, and 6 naïve cirrhotic and noncirrhotic patients. [i]Genotype 1 naïve cirrhotic and noncirrhotic patients. [j]Genotype 1 naïve cirrhotic and noncirrhotic patients. [k]Genotype 3 naïve and experienced noncirrhotic patients. [l]Genotype 3 naïve cirrhotic patients. *Due to lack of published data concerning SVR at 12 weeks in the target population, the effectiveness values considered for noncirrhotic patients might be underestimated and the effectiveness values considered for cirrhotic patients might be overestimated.

Abbreviations: DCV, Daclatasvir; HCV, hepatitis C virus; LDV, Ledipasvir; OMB, Ombitasvir; PAR, Paritaprevir; Peg-IFN-α: peginterferon-alfa; r, Ritonavir; RBV, Ribavirin; SOF, Sofosbuvir; SVR, sustained virological response.

bilirubin test, and leukocyte count). Information concerning patient monitoring activities reflect the real clinical practice of two hospitals in Lombardy and Veneto regions, which are collected by interviewing key opinion leaders, and lead to a mean monitoring cost of €702 per treatment.

The cost of antiviral treatment was calculated considering the recommendations of the European Association for the Study of the Liver (2015),[6] divided by genotype and fibrosis stage, starting from the information available from the Italian Ministry of Health Official Gazette and official documentation. The costs related to each treatment recommended by the European Association for the Study of the Liver were then considered to select the less expensive antiviral therapy for each genotype and fibrosis stage (ie, genotype 1-infected patients with F0, F1, F2, F3, and F4 stages; genotype 2-infected patients with F0, F1, F2, F3, and F4 stages; etc). Two hypotheses were then considered: the possibility to use peginterferon within treatments and the sole use of interferon-free therapies.

The effectiveness parameters considered in the model, in terms of sustained virological response at 12 weeks, are those available in literature associated with the therapies considered per each genotype. The therapies within the two scenarios and the effectiveness parameters considered are reported in Table 4.

Effectiveness data were not available for all the direct-acting antiviral, genotype, and fibrosis conditions, therefore, overall effectiveness data for the unclustered patient population were considered in those cases. During the Social Affairs Commission of the Italian Parliament audition on November 16, 2015, the managing director of AIFA stated that price-volume agreement for Sofosbuvir considered a price of treatment of €750 million for 50,000 patients (€15,000 per treatment), with lower steps, down to €4,000 per treatment.[26] Considering the hypothetical cost batches, from €37,000 to €4,000, the mean cost per treatment of Sofosbuvir was estimated to be €16,353 (value-added tax inclusive). The cost of Sofosbuvir + Ledipasvir was considered to be 111.11% of the cost of Sofosbuvir as in the Italian Official Gazette documents,[27,28] equal to €19,987 (value-added tax inclusive).

Due to lack of data concerning the price-volume agreement for Ombitasvir/Paritaprevir/Ritonavir and Ombitasvir/Paritaprevir/Ritonavir + Dasabuvir, and assuming it to be similar to the one described earlier, we considered the same price of Sofosbuvir and Sofosbuvir + Ledipasvir, respectively. The costs per treatment considered in the analysis, value-added tax inclusive, are presented in Table 5.

Table 5 Cost of antiviral treatment considered in the analysis

Antiviral drug	Cost per treatment, € (VAT inclusive)	Source
Daclatasvir	18,700	42
Ombitasvir/Paritaprevir/Ritonavir	16,353	Assumption
Ombitasvir/Paritaprevir/Ritonavir + Dasabuvir	19,987	Assumption
Peginterferon-alfa^	186.1	43
Ribavirine^	84.1	44
Simeprevir*	19,800	45
Sofosbuvir	16,353	Assumption
Sofosbuvir + Ledipasvir	19,987	Assumption

Notes: ^Cost per week. *Cost of a 12-week treatment.

Abbreviation: VAT, value-added tax.

Results

Economic analysis

Considering the number of diagnosed HCV-infected patients emerged from the hypotheses presented in "Economic analysis" section (bottom-up assessment of 0.3 million patients, bottom-up estimation of 0.6 million patients, and top-down estimation of 2.7 million patients), it is possible to forecast the number of years required to treat the whole Italian HCV-infected population, starting from 2016. HCV treatments last for 8–12 weeks, up to 24 weeks, requiring a constant monitoring of patients during the whole curative process. In 2015, 30,000 HCV-infected patients were treated with antiviral treatments. Authorized referred centers have a higher capacity in terms of patients being treated yearly; therefore, different scenarios were considered in terms of number of annual treated patients: 25,000; 50,000; 75,000; and 100,000.

In Table 6, we report the estimated direct medical costs for antiviral treatment of the whole Italian HCV-infected population in the three scenarios presented and the year in which HCV prevalence would fall below 100 infected patients. The estimation has a 35-year time horizon, up to 2050.

The results of the strategy that consider the use of therapies with peginterferon-alfa lead to higher costs compared with the sole use of interferon-free antiviral therapies. This is due to the mean higher effectiveness of these treatments, leading to a lower number of retreatments. The 2.7 million HCV-infected patients scenario considering a number of yearly treated patients below 100,000 lead to a lack of treatment for all HCV-infected patients. In these scenarios, up to 2050, more than 0.16 million patients and up to 1.29 million patients would not have been treated with antiviral therapies.

Finally, in order to estimate the benefits deriving from the management of HCV infection, the number of deaths and the number of patients with HCCs and liver transplants due to HCV infection avoided due to treatments were estimated considering the most plausible hypothesis of prevalence and the number of treatments per year: 0.3 million and 0.6 million HCV-infected patients (derived from the bottom-up analysis) and 50,000 interferon-free treatments per year. The productivity condition (eg, human and structural resources) of the HCV antiviral treatments by authorized prescribing centers, in fact, could be enough to treat ~50,000 patients per year (with an estimated mean number of 67 patients to be managed per center at the same time). In order to deal with more patients, it would be necessary to activate further centers at a regional level.

Specifically, according to the aforementioned transition probabilities in the two scenarios (0.3 million and 0.6 million HCV-infected patients), the mean number of deaths avoided (compared with the do-nothing scenario) per year would be 3,518 and 7,657; the mean number of liver transplants avoided per year would be 606 and 1,220; and the mean number of HCCs avoided per year would be 1,013 and 2,411, respectively. Multiplying the annual average cost per patient affected by HCV-induced diseases (calculated by Marcellusi et al, 2015,[10] and converted to 2015 cost level using the annual average consumer prices inflation rate as calculated by the International Monetary Fund)[29] by the number of years spent by the estimated population with HCC, by the total number of avoided transplants and deaths, we estimated the direct

Table 6 Estimated direct medical costs (antiviral therapy and monitoring activities) to treat the whole HCV-infected Italian population and year in which HCV prevalence would fall below 100 infected patients (up to 2050)

Estimated HCV-infected patients	Patients treated per year	Sole use of interferon-free therapies		Use of interferon and interferon-free therapies	
		Year in which prevalence fall below 100 infected patients	Cost to treat the whole population (thousands of €)	Year in which prevalence fall below 100 infected patients	Cost to treat the whole population (thousands of €)
0.3 million	25,000	2030	7,177,964	2032	7,624,657
	50,000	2023	6,980,742	2025	7,331,094
	75,000	2021	6,918,471	2023	7,198,620
	100,000	2020	6,896,528	2022	7,115,776
0.6 million	25,000	2044	14,343,430	2046	15,418,509
	50,000	2030	13,742,639	2032	14,563,554
	75,000	2025	13,565,065	2027	14,280,134
	100,000	2023	13,484,796	2025	14,123,051
2.7 million	25,000	2050[a]	19,434,487	2050[b]	19,373,070
	50,000	2050[c]	38,868,973	2050[d]	38,746,140
	75,000	2050[e]	57,145,868	2050[f]	57,682,573
	100,000	2044	59,151,269	2048	63,639,349

Notes: [a]1,280,788 infected patients not treated; [b]1,292,860 infected patients not treated; [c]948,526 infected patients not treated; [d]1,048,528 infected patients not treated; [e]155,140 infected patients not treated; [f]339,839 infected patients not treated.

Abbreviation: HCV, hepatitis C virus.

and indirect costs saved due to antiviral treatments in the 0.3 million HCV-infected patients scenario to be equal to €4.21 billion in 8 years (direct costs of €0.14 billion and indirect costs of €4.07 billion), and in the 0.6 million HCV-infected patients scenario equal to €25.20 billion in 15 years (direct costs of €0.51 billion and indirect costs of €24.69 billion).

Discussion

The estimation of the number of HCV-infected patients in Italy shows a high spread between the top-down and bottom-up approaches, with a difference of around 2.4 million patients, and it is a relevant health problem in the Italian population. Considering the lack of publications of prevalence studies conducted among a significant sample of patients and/or accurate sampling distributions, the authors consider the estimation through the bottom-up approach to be more reliable to identify the costs to be incurred by the Italian NHS.

Moreover, we consider the topic of eradication and disease control as highly challenging in the absence of an accurate monitoring program to diagnose HCV infection in patients unaware of the infection. Italy has a rate of incidence between 1 and 2.5 per 100,000 and a lack of increase of prevalent cases is probably already reached.

The cost of treatment could be difficult to reconcile with an annual budget for pharmaceutical treatment for the country in case of elimination/controlling of HCV infection considering the prevalence data presented earlier, with a yearly cost of treatment of ~€1 billion (€0.87 billion and €0.92 billion) in the scenarios of bottom-up analysis (almost 5.5% of the total public financing for pharmaceutical treatments of the Italian NHS). HCV infection elimination requires a programmatic approach that probably fits better with a multiyear investment plan (treating all patients in a short-term horizon and paying the treatment costs in a medium-/long-term horizon).

Further research studies in this field should concentrate on the assessment of the prevalence and incidence of the pathology and on the effectiveness of antiviral treatments in different HCV-infected patient subgroups (considering virus genotypes and degree of severity of the pathology).

The results of the analysis might be overestimated due to the use of a fixed incidence rate, which might decrease with the reduction of infected patients. Moreover, the model does not consider deaths due to other causes than HCV; therefore, long-term results might be overestimated.

The treatment of the highest number of patients per year would be important to avoid the progression of the pathology, with a relevant impact on the quality of life of patients and on avoided direct and indirect medical costs for the Italian NHS. The opportunity to defer antiviral drug payment over a longer time period should be negotiated by the Italian Government with the pharmaceutical companies, to meet the objective of eliminating HCV with a sustainable multiyear payment schedule. The opportunity to control/eliminate the infection is in fact valuable, and the benefits for patients and for the Italian NHS would be maximized while treating the highest number of patients in a short-term horizon (considering the productive capacity of health care providers), deferring payments in the long-term. Health care sector in general and the pharmaceutical sector in particular will face further situations of this kind, for example, immunology discoveries, and then all the NHS stakeholders (industry, government and insurance, and also patients) will have to identify suitable financial instruments to face the new expenditure required.

The eradication of the disease in the 2.7 million infected people scenario would require a long time horizon, not compatible with the treatment of all patients, and also the capacity of treatment of the referring hospital centers could be questioned.

Conclusion

Italy has the highest prevalence of HCV-infected patients in Europe and the highest rate of deaths from cirrhosis and HCC, and the country needs a comprehensive approach to deal with this specific condition. The treatment of all HCV-infected patients in Italy (between 0.3 million and 2.7 million) is a challenging target for the financial implications of patient care, due to the number of specialist doctors needed and due to all other variables that affect the treatment of the disease.

In an environment with scarce resources, investments in health should be focused on those technologies that offer therapeutic efficacy rates high enough to allow the health services to amortize expenditures due to the savings induced by the treatments. In Italy, considering the two scenarios presented with 0.3 million and 0.6 million HCV-infected patients, HCV infection could be eliminated/controlled in a 10- to 15-year time horizon. In this framework, and in particular for chronic and potentially chronic diseases, a multidimensional approach such as Health Technology Assessment is strategic to support the evidence-based decision making. New highly expensive health technologies, both drugs and medical devices, will be available in different health care areas, determining the so-called competition between actions.

Finally, we observe that the relevant difference between patients conceivable through prevalence rates toward patients already aware of their HCV condition shows that the Italian

NHS could face serious difficulties due to possible emergence of unaware HCV-infected patients due to antiviral treatment costs, population treatment time, and hospital production capacity.

Disclosure

The authors report no conflicts of interest in this work.

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