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Impact of reimbursement limits on patient access to direct-acting antivirals in Italy: analysis of data from national registries

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Abstract. – OBJECTIVE: Hepatitis C virus (HCV) infection is a global epidemic, still highly prevalent in Europe. Given efficacy and safety of HCV therapy by Direct Antiviral Agents (DAA), World Health Organization called for actions to eliminate HCV infection. A limit is represented by access to care, mostly due to the high costs of medicines. In Italy, in 2015, the access to DAA therapy was reimbursed for patients with advanced disease, whereas in 2017 universal access was granted. The aim of this study was to analyse changes in patient recruitment trends treated with DAA with or without limitations to access to therapy.

PATIENTS AND METHODS: 165,105 patients treated with DAA in Italy from 2015 to December 2018 were analysed. Daily patient treatment rate was obtained by segmented regression of interrupted time series analysis.

RESULTS: 74,199 patients with advanced disease (62% with cirrhosis) had access to the therapy during the time period from 2015 to 2017. Following the extension of reimbursement criteria, 90,906 additional patients were treated (43.2% with F0-F1 and 22.9% with F2), with an absolute reduction of 59.9% of patients with advanced disease (cirrhosis decreased to 18.5%). Segmented regression of interrupted time series analysis of daily patient treatment rate showed a progressive reduction of patients with advanced disease, offset by those with initial disease. Notably, elimination of restrictions to therapy did not change the overall treatment rate.

CONCLUSIONS: This study showed that a no-limit reimbursement policy for DAAs prescriptions to HCV infected individuals in Italy widened the types of treated patients, but the process towards elimination of HCV infection was not significantly changed.

Key Words:
Hepatitis C, HCV treatment, Direct-acting antivirals, Registry-based data, Patient access, Reimbursement.

Abbreviations

HCV = Hepatitis C Virus; DAA = Direct Antiviral Agents; WHO = World Health Organization; AIFA = Agenzia Italiana del Farmaco (Italian Medicine Agency).

Introduction

Chronic viral hepatitis today still represents a major global clinical challenge, causing over 1.3 million deaths per year[1]. It is estimated that 360 million people are infected by hepatitis viruses, 71 million of which by chronic Hepatitis C Virus (HCV) hepatitis[1]. Chronic hepatitis C retains a relevant mortality, with 400,000 deaths on an annual basis, with liver decompensation or hepatocellular carcinoma being responsible for 96% of all liver-related mortality[1].

HCV infection is a global epidemic, with incidence and prevalence differing by countries and regions. The global prevalence of HCV infection is estimated to be 1%. Generally speaking,

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however, HCV infection is mostly associated to unsafe health-care-related injections and, therefore, with lower social/economic conditions, HCV infection is still highly prevalent in European countries, ranging from 1.2 to 1.5%[1]. The European region is second only to the Eastern Mediterranean Region as far as HCV prevalence is concerned[1].

The natural history of chronic hepatitis C has changed after the introduction of second-generation Direct Antiviral Agents (DAAs), which resulted effective in safely eliminating HCV infection in 95% of treated patients[2,3]. This has prompted major international institutions to elaborate strategies to eliminate HCV from communities. One of the most important of such strategies has been proposed by the World Health Organization (WHO), in which treatment is one of the three pillars[1].

Italy has a high HCV prevalence, estimated to be one of the highest in Europe. Studies conducted in local cohorts showed that HCV prevalence might range from 8% among those born in the thirties of the twentieth century to less than 1% in those born during the second half[4]. However, at a national level, so far there has been no implementation of an Italian epidemiological registry which could have facilitated a more precise definition of the number and disease severity of patients affected by HCV.

Difficulty in accessing care is a well-known obstacle for the implementation of an effective global plan for disease eradication. This is even more relevant in the case of HCV, given the high costs of drugs especially at time of their first negotiation and even more relevant in countries like Italy, offering a universal public healthcare system. During 2015, in a condition of a presumed high number of patients to be treated and financial constraints given by the high cost of therapy, full drug reimbursement was granted only to HCV patients at higher risks of disease progression or complications. Later, in 2017, thanks to the decrease in pricing due to competition from new DAAs, the criteria for reimbursement were expanded in the market, allowing access to therapy for all patients infected by HCV.

This study aims at analysing changes in patient recruitment trends treated with DAA with or without limitations to access to therapy. We specifically asked the following questions: 1) did the expansion of DAA reimbursement criteria change the clinical background of the patient population who would access therapy?; (2) did the expansion of DAA reimbursement criteria change the rate of patients treated per week?; (3) did the expansion of DAA reimbursement criteria favour the treatment of patients with more advanced diseases?

Patients and Methods

The first product for the treatment of chronic C hepatitis belonging to the pharmacological class of DAAs was reimbursed by the Italian National Health Service (NHS) in December of 2014. During 2015, more products were gradually considered for reimbursement. Initially, considering the prevalence of HCV infection in the country, the reimbursement of all DAAs in Italy was limited on the basis of detailed criteria (Table I) which identified the specific clinical conditions allowing patient access to new innovative treatments. To begin with, reimbursement criteria focused on less frequent HCV patients, with more severe clinical conditions. In particular, patient access to DAAs treatment was granted to cirrhotic patients, or having a hepatocellular carcinoma (i.e., first reimbursement criterion); or HCV patients managed by transplant centres (i.e., second, fifth and sixth reimbursement criteria); or patients having severe HCV-related extra-hepatic manifestations (i.e., third reimbursement criterion); or patients having severe to middle hepatic fibrosis (i.e., fourth and seventh reimbursement criteria, respectively).

From March 31st, 2017 (Table I), the Italian Medicines Agency AIFA expanded the reimbursement criteria of DAAs allowing treatment for less severely affected HCV patients. The new criterion allowed DAAs treatment of HCV patients having slight or none hepatic fibrosis (i.e., eighth reimbursement criterion), health workers (i.e., nineth reimbursement criterion), patients under haemodialysis (i.e., tenth reimbursement criterion) and patients on waiting lists for any kind of transplant (i.e., eleventh reimbursement criterion).

Considering the high prevalence of infected individuals in Italy with estimates ranging between 400,000 to 600,000 HCV patients, the extension of reimbursement to DAAs was expected to significantly increase patient access, speeding up the process towards the eradication of HCV infection. Therefore, the null hypothesis of this study states that h_0 = daily patient rate starting DAA treatment remains unchanged after the addition of four new reimbursement criteria.

Table I. Reimbursement criteria for starting DAAs in Italy. Number and frequency of patients starting DAAs for each reimbursement criteria before and after introduction of new criteria.

Criterion number	Criterion definition	Before new reimbursement criteria (until to April 2017)		After new reimbursement criteria (until to December 2018)		% difference
		No.	%	No.	%	
1	Patients having cirrhosis in Child A or B class and/or having HCC with complete response to surgical resection or loco-regional therapies not eligible for hepatic transplantation in which hepatic disease is determinant for prognosis	46,338	62.5%	16,837	18.5%	-44.0%
2	Recurrent HCV-RNA hepatitis of the transplanted liver in a clinically stable patient and with optimal levels of immunosuppression	1,958	2.6%	2,277	2.5%	-0.1%
3	Chronic hepatitis with severe HCV-related extra-hepatic manifestations (cryoglobulinemic syndrome with organ damage, B-cell lymphoproliferative syndromes, renal failure).	3,626	4.9%	4,635	5.1%	0.2%
4	Chronic hepatitis with fibrosis METAVIR F3 (or corresponding Ishak).	20,974	28.3%	11,742	12.9%	-15.4%
5	Patient on the waiting-list for liver transplantation having MELD cirrhosis < 25 and/or having HCC within the Milan criteria, with possibility of a waiting in the list for at least 2 months.	300	0.4%	35	0.0%	-0.4%
6	Chronic hepatitis after solid organ transplantation (non-liver) or bone marrow in clinically stable patient and with optimal levels of immunosuppression.	375	0.5%	233	0.3%	-0.2%
7	Chronic hepatitis with METAVIR F2 fibrosis (or corresponding Ishak) and/or co-morbidity at risk of progression of hepatic injury*	628	0.8%	20,825	22.9%	22.1%
8	Chronic hepatitis with fibrosis METAVIR F0-F1 (or corresponding Ishak) and/or co-morbidity at risk of progression of hepatic injury* **New criterion legally introduced from 31st March 2017**			39,240	43.2%	43.2%
9	Infected health workers. **New criterion legally introduced from 31st March 2017**			262	0.3%	0.3%
10	Chronic hepatitis or liver cirrhosis in patients having chronic renal failure under haemodialysis. **New criterion legally introduced from 31st March 2017**			384	0.4%	0.4%
11	Chronic hepatitis in the patient on the waiting-list for solid organ transplantation (non-liver) or marrow transplantation. **New criterion legally introduced from 31st March 2017**			14	0.0%	0.0%
Total		**74,199**	**100.0%**	**90,906**	**100.0%**	

*HBV coinfection, HIV coinfection, chronic non-viral liver disease, diabetes mellitus in pharmacological treatment, obesity (body mass index ≥ 30 kg/m^2), hemoglobinopathies and congenital coagulopathies.

To test the null hypothesis, we conducted a retrospective review of Italian national data from December 2015 to December 2018, collecting the number of patients starting DAA treatments due to an HCV infection before and after the expansion of the reimbursement criteria. Daily rates were calculated for patients starting DAAs according to each clinical criterion of reimbursement defined by the NHS. The source of data was represented by the monitoring reports of DAA treatments of patients with HCV+ chronic hepatitis, published weekly on AIFA registries through their institutional website http://www.aifa.gov.it[5]. The overall number of patients starting DAAs, was collected from each report published between 21 December 2015 to 24 December 2018, together with the distribution for each reimbursement criterion.

Since we intended to retrospectively evaluate patient access to treatment after a public health decision on patient DAAs reimbursement criteria, the segmented regression of interrupted time series analysis was chosen as an appropriate design by which daily patient rate before and after implementation of the decision could be compared, while taking into account also potential confounders[6,7]. The segmented regression analysis is the most commonly used approach to analyse interrupted time series data[8]. This regression requires data collected regularly over time and organized at equally spaced intervals. However, in few cases, a linear interpolation was used to get the number of patients starting DAAs exactly for each week, along the entire three-year time series. The time series of the daily patient rate starting a DAAs is used to ascertain an underlying trend, which may be interrupted by the regulatory decision to enlarge the coverage of patient access to treatment, at a known time-point. With respect to the legally valid date (31 March 2017), actual patient access to DAA treatments according to new reimbursement criteria started one month later, from 1 May 2017. This last date was considered as reference of the point in time for all following analysis. The outcome of interest of the current study was the variable Y_t that corresponds to the daily patient rate starting DAA treatments before and after the introduction of new reimbursement criteria. The time series of weekly number of patients starting DAA treatments was aggregated considering a time span of two-weeks. Thus, the daily patient rates were calculated at each time point as the number of patients starting DAA treatments per two-weeks.

Statistical Analysis

The regression model was specified to estimate the level and trend in the daily patient rate starting DAAs before the introduction of new reimbursement criteria and the changes in level and trend following the introduction of new criteria. Details of the statistical analysis and regression model are available in the **Supplementary Method section**.

Results

Changes in the Features of the Patients Accessing Therapy According to Reimbursement Criteria

From the introduction of the first DAA in 2015 to December 2018, overall 165,105 patients started a fully reimbursed DAA treatment in Italy, corresponding to a mean of about 41,276 patients per year. About half of them (i.e., 74,199) started the DAA treatment according to the initial reimbursement criteria (Table I). Access to DAAs was mostly for patients with cirrhosis, or for those having a hepatocellular carcinoma (i.e., first reimbursement criterion, 62.5% corresponding to 46,338 out of 74,199), followed by patients having severe hepatic fibrosis (i.e., fourth reimbursement criterion, 28.3% corresponding to 20,974 out of 74,199).

After the expansion of reimbursement criteria, between May 2017 and December 2018, 90,906 patients started a DAA treatment (Table I). The most frequent category of patients treated with DAAs became HCV patients with F0-F1 disease stage (i.e., eighth reimbursement criterion, 43.2% corresponding to 39,240 out of 90,906), followed by patients having a mild disease (F2, seventh reimbursement criterion, 22.9% corresponding to 20,825 out of 90,906). Even if the reimbursement criterion for F2 patients (seventh) was included among initial reimbursement criteria, the actual access to DAAs for those patients started only after the introduction of new reimbursement criteria, after April 2017 (**Supplementary Figure 1**). This is to be ascribed to the fact that the initial reimbursed treatment for those patients was the PegIFN + simeprevir combination only, which was indeed employed only in sporadic cases.

As a whole, after the expansion of reimbursement criteria, there was an absolute reduction of 59.9% in the incidence of patients starting DAAs treatment according to initial criteria

Table II. Parameter estimates, standard errors and *p*-values from segmented regression models predicting daily patient rate starting DAA treatment, adjusted for first-order autocorrelation of data.

Overall patients (R-square = 0.08; *p* = 0.121; Durbin-Watson's d = 2.1)	**Coefficient**	**SE**	***t***	***p*-value**
Intercept β_0	2.916	7.890	0.370	0.713
Baseline trend β_1	-0.431	0.377	-1.145	0.256
Level change after enlargement of reimbursement criteria β_2	22.932	9.852	2.328	0.023
Trend change after enlargement of reimbursement criteria β_3	0.125	0.461	0.272	0.787

(i.e., from the first to the sixth criterion). In the same period, there was an absolute increase of 66.0% in the incidence of patients starting DAAs treatment according to new reimbursement criteria (i.e., from the seventh to the eleventh criterion).

Effect of Expansion of Reimbursement Criteria on the Rate of Treated Patients

Table II illustrates the results of the segmented regression of interrupted time series analysis of daily patient rate starting DAA treatment in Italy, it shows the impact of expansion of reimbursement criteria on patient access. The model analysed the rate of overall patients starting DAA treatments at each time point, with all reimbursement criteria, the intercept β_0 was 2.9 patients per day, not statistically significant (p = 0.713). As the baseline trend, the unstandardized β_1 suggests a decreasing daily rate of patients of -0.431 per two-weeks, again not statistically significant (p = 0.256). The unstandardized β_2 was 22.9, indicating a significant level change in the rate immediately after the enlargement of reimbursement criteria (p = 0.023). The unstandardized β_3 was 0.125, indicating that there was an increasing trend albeit not statistically significant (p = 0.787) of the two-weeks rate after the expansion of reimbursement criteria compared with the previous trend. The proportion of explained variance by regression model was very low and not statistically significant (R square value was 0.08; p = 0.121). The Darbin-Watson'd value was 2.1.

Although an overall increase of the daily patient rate immediately after the expansion of reimbursement criteria may be observed (**Supplementary Table I** and **Supplementary Figure 2**), the data autocorrelation substantially biased the results (Darbin-Watson'd value was 0.438 in **Supplementary Table I**), determining an overestimation of the statistical significance of the effects. After adjustment for the first-order autocorrelation, the interruption of the time series by expansion of reimbursement criteria explained a very low variance proportion, not statistically significant (Figure 1).

Reduction of the Treatment Rate of Patients With More Advanced Disease After Expansion of Reimbursement Criteria

Table III shows the results of the segmented regression of interrupted time series analysis of daily patient rate starting DAA treatment according to each initial criterion (in **Supplementary Table II** the same results on data not adjusted for first-order autocorrelation). The highest daily patient rate was registered among patients with cirrhosis and/or hepatocellular carcinoma [reimbursement criterion one; the intercept β_0 being 9.8 patients per day (p = 0.010)]. As the baseline trend, the unstandardized β_1 suggests a decreasing daily rate of patients of -0.382 per two-weeks, statistically significant (p = 0.033). The unstandardized β_2 was 2.7, indicating that there wasn't a significant level change in the rate of patients

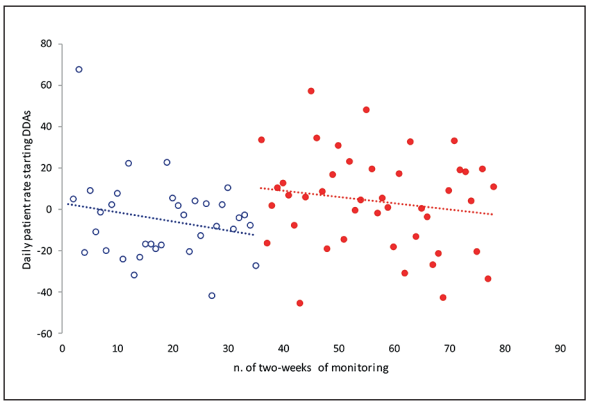

Figure 1. Daily patient rate starting DAAs, before (*circle indicators*) and after extension of reimbursement criteria (*black circle indicators*). The graph shows daily rate of overall patients starting DAA treatments at each time point, with all reimbursement criteria.

Table III. Parameter estimates, standard errors and *p*-values from segmented regression models predicting daily patient rate, adjusted for first-order autocorrelation of data, and performed for patient subgroups starting DAA treatment according to each reimbursement criteria. The criteria are ordered on the base of decreasing level of daily patient rate..

Criterion No. 1 (R-square = 0.11; *p* = 0.032; Durbin-Watson's d = 2.6)	**Coefficient**	**SE**	***t***	***p*-value**
Intercept β_0	9.776	3.685	2.653	0.010
Baseline trend β_1	-0.382	0.176	-2.173	0.033
Level change after enlargement of reimbursement criteria β_2	2.663	4.601	0.579	0.564
Trend change after enlargement of reimbursement criteria β_3	0.328	0.215	1.526	0.131
Criterion No. 4 (R-square = 0.11; *p* = 0.032; Durbin-Watson's d = 2.4)	**Coefficient**	**SE**	***t***	***p*-value**
Intercept β_0	3.480	2.140	1.626	0.108
Baseline trend β_1	-0.075	0.102	-0.734	0.465
Level change after enlargement of reimbursement criteria β_2	-0.971	2.673	-0.363	0.717
Trend change after enlargement of reimbursement criteria β_3	0.005	0.125	0.040	0.968
Criterion No. 3 (R-square = 0.10; *p* = 0.046; Durbin-Watson's d = 2.5)	**Coefficient**	**SE**	***t***	***p*-value**
Intercept β_0	0.672	0.468	1.436	0.155
Baseline trend β_1	-0.012	0.022	-0.521	0.604
Level change after enlargement of reimbursement criteria β_2	-0.422	0.584	-0.722	0.473
Trend change after enlargement of reimbursement criteria β_3	0.002	0.027	0.088	0.930
Criterion No. 2 (R-square = 0.08; *p* = 0.093; Durbin-Watson's d = 2.3)	**Coefficient**	**SE**	***t***	***p*-value**
Intercept β_0	0.386	0.165	2.347	0.022
Baseline trend β_1	-0.016	0.008	-2.021	0.047
Level change after enlargement of reimbursement criteria β_2	0.083	0.206	0.403	0.688
Trend change after enlargement of reimbursement criteria β_3	0.017	0.010	1.718	0.090
Criterion No. 5 (R-square = 0.23; *p* < 0.001; Durbin-Watson's d = 2.8)	**Coefficient**	**SE**	***t***	***p*-value**
Intercept β_0	0.180	0.047	3.800	<0.001
Baseline trend β_1	-0.007	0.002	-3.001	0.004
Level change after enlargement of reimbursement criteria β_2	0.063	0.059	1.068	0.289
Trend change after enlargement of reimbursement criteria β_3	0.005	0.003	1.654	0.102
Criterion No. 6 (R-square = 0.08; *p* = 0.094; Durbin-Watson's d = 2.3)	**Coefficient**	**SE**	***t***	***p*-value**
Intercept β_0	-0.024	0.077	-0.316	0.753
Baseline trend β_1	0.004	0.004	1.098	0.276
Level change after enlargement of reimbursement criteria β_2	-0.078	0.097	-0.808	0.422
Trend change after enlargement of reimbursement criteria β_3	-0.008	0.005	-1.697	0.094

starting DAA treatments with first criterion, immediately after the expansion of reimbursement criteria (p = 0.564). The unstandardized β_3 was 0.328, indicating that expansion of reimbursement criteria did not determine a significant increase in the rate of patients with cirrhosis and/or HCC treated with DAA (p = 0.131). The proportion of explained variance by regression model was low, but it was statistically significant (R square value was 0.11; p = 0.032). The Darbin-Watson'd value was 2.6. The described pattern is graphed in the Figure 2A.

With the exception of patients with advanced fibrosis (stage F3, reimbursement criterion 4, the intercept β_0 was 3.5 patients per day, p = 0.108), mean values of less than one patient started DAA treatment with all remaining initial reimbursement criteria. Among these criteria, in patients starting a

DAA treatment according to the fifth criterion (i.e., patient on the waiting-list for liver transplantation having MELD cirrhosis <25 and/or having HCC within the Milan criteria, with the possibility of being in the waiting-list for at least 2 months) a decreasing baseline trend of the daily rate along the time span was registered (the unstandardized β_1 = -0.007 per two-weeks, p = 0.004). The proportion of explained variance by regression model was 23% (R square value was 0.23; $p < 0.001$). The Darbin-Watson'd value was 2.8. The described pattern is depicted in Figure 2B.

As a whole, these findings suggest that, after the expansion of the reimbursement criteria, the baseline trend (β_1) in daily patient recruitment rate decreased for almost all the initial reimbursement criteria, attaining however statistical significance only for the first and the fifth criteria. As a matter of fact, the incidence of the first criterion (i.e., reimbursement of DAAs in cirrhotic patients, or having a hepatocellular carcinoma) decreased from 62.5% of the overall patients starting a DAAs treatment up to April 2017, to 18.5% after the enlargement of the criteria until to December 2018 (Table I). To summarize, the decreasing baseline trend of daily patient rate according to initial reimbursement criteria, involving patients having a more severe disease burden, has offset the patient access with new reimbursement criteria, involving patients having a less severe disease (e.g., with a METAVIR F0-F2).

Discussion

This study intended to produce a broad analysis of the fluxes of patients accessing DAA therapy in Italy, showing that: (1) the expansion of the reimbursement criteria produced an increased access to therapy by patients with low grade disease at the expenses of those with advanced disease; (2) the overall number of patients treated each week remained stable; (3) there was a decrease in the treatment rate of patients with advanced disease treated per week.

Availability of second generation DAA significantly changed the clinical scenario for patients with HCV, transforming a chronic, difficult-to-treat and potentially lethal disease into a short-term treatable one. Since the very beginning, a major concern was availability of medications to the general population, given the high costs of the new drugs and the disease prevalence. As a matter of fact, this issue was much more sensitive in countries with public, universal access to care, and a significant prevalence of HCV infected individuals, such as Italy.

A plan for early access to therapy for patients with more advanced disease was put in place with the intention to combine DAA availability with affordability. This was followed in Italy at a later stage by universal extension of treatment. This approach was implemented with the utmost caution, in consideration of the fact that a precise epidemiological registry of patients affected by HCV did not exist, making any estimate on the potential number and the severity of patients rather loose. Studies that investigated disease prevalence provided only a broad, age-dependent estimated prevalence[4]. Moreover, since they had been conducted years earlier, they did not reflect the actual situation at the time of first negotiation.

In Italy, full coverage of medication costs is granted on the basis of legislation in place and through criteria defined by the Italian Medi-

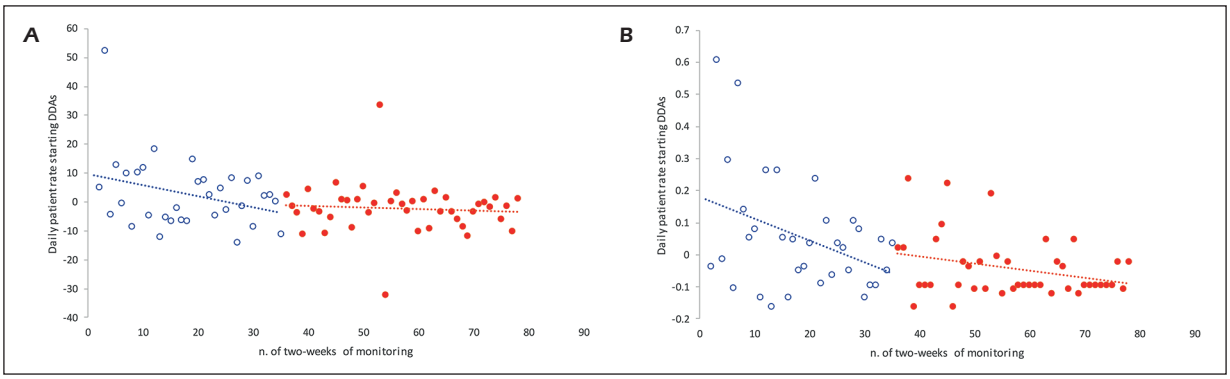

Figure 2. Daily patient rate starting DAAs, before (*circle indicators*) and after extension of reimbursement criteria (*black circle indicators*). The (**A**) graph shows daily rate of patients starting DAAs according to the first reimbursement criteria; (**B**) graph shows daily patient rate starting DAAs according to the fifth reimbursement criteria.

cines Agency (AIFA). Public funds provide full coverage of medication costs on the basis of specific reimbursement criteria. During 2015, in the case of HCV therapy, initial reimbursement criteria included patients at higher risk of disease progression or complications, such as patients with F3 disease stage or above (individuals who had cirrhosis, HCC, transplanted, transplanted in waiting lists and other more specific and severe conditions). As reported in Table I, more than 70,000 patients falling into the original reimbursement criteria were treated in less than two years in one of probably largest public funded HCV treatment programs in the world. Follow up studies based on AIFA registries found that treatment success in those patients was not different from what reported in pivotal studies[9-14].

Reimbursement criteria were expanded during 2017, granting access for DAAs therapy to all patients affected by HCV irrespectively of disease severity stage. Broadening the number of eligible patients on the basis of prevalence data led to hypothesize that medication uptake would ramp up after the elimination of restrictions for reimbursement. Notably, the current study shows that a completely different scenario occurred. As depicted in Figure 1, the treatment rate did not change after the extension of the reimbursement criteria. A minimal increase in the treatment rate occurred only during the first few weeks shortly after the extension, while the overall increase was not statistically significant. In order to confirm such evidence, the global number of patients treated within the same periods did not prove to be different (Table I). Clinical characteristics of the patients accessing to therapy showed clear changes. There was an increase in the number of patients with mild disease (F0-F2) in parallel with a decrease in the number of patients with advanced disease (Table I, Figure 2 and **Supplementary Figure 1**).

Those results can be explained in different ways. From an epidemiological point of view, it could be speculated that the total number of patients affected by HCV in Italy could be much less than what initially hypothesized. Since this can be considered a diseases with high prevalence but low incidence, which has spread out in this country mostly during the 50s-70s of the XX century[4], it could be postulated that the majority of infected people were not alive any longer at the time of the availability of DAAs. However, this hypothesis is in contrast with mortality data and, mostly, with recent data published by a patient advocacy group (EpaC Onlus, epac.it), which showed that patients who have an active medical costs exemption based on HCV infected status were more than 300,000. Patients with a certified diagnosis can be exempted and granted free access to diagnostic tests for the disease (i.e., no co-payment implied). Considering that the majority of people infected by HCV are unaware of their disease, this means that the current number of individuals residing in Italy and affected by HCV might be between 400,000 and 600,000 individuals, depending on the modelling used.

Another explanation for the absence of a significant increase in the HCV treatment rate after the approval of the new criteria is the absence in Italy of a national plan for case finding. Chronic HCV infection is a subtle disease that goes asymptomatic for the majority of its natural history[1-3], with a large proportion (up to 60%) of patients who remain undiagnosed[15,16]. Large scale testing and treatment are considered pillars of HCV elimination strategies[1]; therefore, the absence of screening/case finding programs limits the number of patients who could access therapy.

An additional factor which could explain the lack of treatment increase in Italy after the expansion of access criteria is the fact that only selected clinical centres with experience in hepatology can allow the prescription and reimbursement of DAAs. This was the approach taken at the time of first generation DAAs (boceprevir/telaprevir), given the complexity of that type of treatment. This was confirmed when marketing approval was granted for second generation DAAs since during the early access phases patients were more complex because of advanced disease. Such cautionary measure which was logical and effective when enforced within its original scopes, became a limiting factor for treatment uptakes when centres capacity, in a condition of less stringent criteria, was not adjusted to allow the increase in the number of patients managed in a given time frame.

Expansion of access criteria reduced mostly the number of patients with advanced disease (Figure 2). This result could be explained by an operational selection by prescribing centres, which put less serious patients on hold waiting for the introduction of more efficient second generation DAAs, than those initially authorized. This determined a so called "warehouse effect"[17], with the majority of the known patients with advanced disease treated immediately. The observed reduction in the treatment rate of severe patients before

the expansion of the access criteria (Figure 2) confirms this hypothesis.

The Italian experience in the ongoing government funded eradication program for HCV infection is certainly unique in terms of the prevalence of the disease, treated patients (almost 190,000 as of July 2019), and public expenditure of treatment costs. A recent study[18] performed in Greece on a limited number of patient (500 individuals) hypothesised that expansion of access to treatment to mild disease (F2) would increase the number of treated patients by 10%. Our study shows, by contrast, that in the absence of restrictions, between 22 and 43% will fall within the F2 and F0-F1 disease stages, respectively (Table I).

Medications costs and disease stage-based restrictions to therapy are thought to be the major limiting factors to comply with WHO goals for HCV elimination by 2030 in European countries[19-21]. The present findings only partially confirm the WHO assumptions, showing instead that more determinant factors for HCV eradication are effective screening programs[22] and capillarization of drug prescription and availability.

The results discussed here should be analysed within the international context of prices variability and reimbursement in several countries. The initial very high price of new DAAs constituted a barrier to patient access and is probably still delaying optimal access to treatment especially in countries with high prevalence of HCV infection. A recent WHO analysis showed that DAAs prices are overall still unaffordable and unrelated to potential market size and/or GDP per capita[23]. This finding is confirmed in low and middle-income countries, even where the prices of DAAs are much lower than those paid in high-income[24]. As a consequence, many developed countries adopted restricting measures to DAAs prescription, limiting it to patients with most severe disease conditions[19,21,24].

An interesting example of international HCV eradication programs was run in Australia, where the DDAs have been available for all individuals with chronic HCV infections aged 18 years and older, regardless of disease stage, drug and alcohol use, and prescriber restrictions[25]. The national HCV treatment programme allows treatment to be prescribed not only by specialists (gastroenterology and infectious diseases) but by all other medical practitioners. The scheme has specifically ensured access for prisoners and has no restrictions for treatment of HCV reinfection. A recent epidemiological study[26] conducted in the Australian healthcare context showed a relevant impact of this approach on hospitalization and mortality. Results show between 2015 and 2017 the declines of 21% and 17% in decompensated cirrhosis diagnoses and liver-related deaths, respectively. In the same three years' period the expected 34% in HCC diagnoses and 19% increase in all-cause mortality without DAAs therapy introduction, were decreased to 8% and 3%, respectively. However, it is worth to note that in Australia, after an initial spread of patients treated with DAAs, 70,260 patients were enrolled over the period of March 2016 to December 2018, corresponding to about 24,777 patients per year[27]. This figure is substantially lower than what registered in Italy where, in a four-year period (i.e., December 2014 to December 2018) a mean of 41,276 patients started a DAA every year.

In Germany, all patients with chronic HCV infection are eligible for treatment, regardless of their clinical stage, a provision similar to the one adopted in Italy after May 2017. However, after the introduction of new DAAs, only a moderate increase of monthly prescriptions of HCV treatment, lower than what expected, was registered and is currently summing up to only 20,000 patients per year. The authors speculated that the most probable causes of the difficulties in treating HCV infected individuals in Germany could be ascribed to the high prices of the DAAs[28].

Prices of DAAs are high all over the world and poorly correlated with the actual payment capacity of the healthcare systems. In fact, there are cases, such as that of Australia, which adopted an unrestricted access model, but achieved an annual number of treated patients much lower and with a less impacting economic burden than countries like Italy.

Overall, the lesson that we can learn from the patient access to DAAs is that in the case of high-priced medicines, even if in the presence of highly innovative products, the constrains of public budget expenditure may tend to prevail over those of health protection. Even when this line of reasoning does not seem to hold, it is only because there is a low yearly uptake of patients for DAA treatments that, despite high prices, would be still affordable. The first price negotiations of DDAs for the NHS were very efficient with respect to other developed countries, due to also to the high prevalence of HCV infected people in Italy. As a consequence, Italy has shown the highest annual rate of patients treated with DAAs in the last four years.

Some limitations of the study should be considered. Firstly, the possibility that some Italian

patients having an early phase of HCV infection (Metavir score F0/F1), initially excluded by a reimbursed DAA treatment, have sought abroad the treatment. In particular, it was reported that some Italian citizens travelled in low income countries (such as India) to purchase medications to lower costs. Although there is no indication that this was a prevalent and a statistically significant phenomenon, the loss of traceability of these DAA treatments in the AIFA monitoring registers would have increased the total number of patients prior to March 2017. Another limitation of the study is that the relationship between patient rate and treatment outcomes in terms of sustained virologic response (SVR) was not analysed. In this regard, several observational studies[9-14] based on real world evidence data have already found that the treatment outcomes in Italy did not differ from the outcomes published in pivotal study results. Furthermore, the inclusion of data, such as SVR within a real world monitoring registry many months after the conclusion of clinical monitoring, may be critical and in many cases incomplete[5], while the AIFA registries collect data on DAA treatments on a daily basis, with a coverage of all Italian approved prescribing centres.

Conclusions

Our study showed that in spite of the fact that a no-limit reimbursement policy for DAAs prescriptions to HCV infected individuals in Italy widened the types of patients who could have access to innovative treatments, the process toward the eradication of HCV infection in Italy did not significantly change. The evidence provided in this study are useful to support future strategies in reaching goals set by the WHO to fight HCV infections in large communities.

Conflict of Interest

The Authors declare that they have no conflict of interests.

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