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Original Research

HCV elimination plan leads to significant benefits in managing liver-related diseases and hospital interventions: a regional simulation

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ABSTRACT

Objectives: This article presents a 3-year budget impact simulation on the effects of a chronic Hepatitis C (HCV) eradication plan in real-life costs incurred by the Regional Health Service in the Liguria Region (in Northern Italy).

Methods: The Liguria Region network performed a prospective 3-year (2017–2019) timeframe horizon trends simulation analysis focusing on management interventions and costs. It involved all the eight prescribing centres in the region, starting from retrospective historical performance data and assuming impact of sustained viral response rates for patients treated for HCV. Data on hospital admissions, medical visits, number of patients and deaths were collected through the healthcare database.

Results: At the beginning of 2017, 2,940 patients were eligible for HCV treatment with direct-acting antivirals. Assuming to treat this entire population with a success rate of 90%, the events related to liver complications in the 3-year horizon would decrease to 5,538 cumulatively (-35%), with a 27% reduction of direct costs, showing a global savings of 24,779.024 Euros.

Conclusion: Treating the entire eligible HCV population would lead to significant benefits and savings in managing liver-related diseases and their direct costs, opening opportunities to re-think new settings for the future organisation of liver disease management in the regional health system.

Keywords: HCV, liver disease costs, budget impact, hospital services, DAA

1. Introduction

Chronic hepatitis C has affected about 200 million people around the world. The recent advances in treating such a severe disease show a dramatic change in morbidity and mortality related to HCV. Accordingly, not only patients' perspectives have changed radically but also the improvements have had such an effective impact that the global eradication of HCV has been introduced in the "wish list" of the World Health Organisation (1).

The most recent treatment schedules are offering a sustained virological response (SVR) in about 90% of patients in only 8 weeks of treatment, with a minimal impact on patients' quality of life. The goal of antiviral treatment is to reduce the onset of disease complications, including liver cirrhosis and hepatocellular carcinoma. Starting from their introduction in 2014, the new wave of direct-acting antiviral (DAA) regimens have provided dramatic improvements in clinical outcomes, surpassing a 90% SVR (2,3). As of June 2017, the following DAA regimens are available and reimbursable in Italy: (sofosbuvir/velpatasvir, ombitasvir/paritaprevir/ritonavir and dasabuvir, ~~/~~elbasvir/grazoprevir).

Several economic analyses have evaluated the impact of the HCV patient journey in different Italian settings (4,5). However, up to now, no studies had investigated the potential effects on overall liver-related resources that the clinical utilisation of a new generation of DAAs will have on the HCV national elimination plan supported by the National Health System (NHS) innovative drug fund (€ 500 million/year for 2017, 2018 and 2019). This paper aims to estimate the impact and consequences of treating HCV in managing liver diseases and other liver-related direct costs.

2. Methods

2.1 Model structure

To reach the main objective, we initially performed a retrospective analysis concerning liver-related patient management interventions and their costs during the 2014–2016 timeframe across the Liguria Region network, involving the eight prescribing centres.

Figures (data/numbers/facts) on hospital admissions, medical visits, number of patients and deaths were collected through the healthcare database (6). Subsequently a prospective 3-year horizon trends simulation analysis was conducted on the same services and cost lists; the study was approved by the Liguria Region Local Ethical Committee (approval ID 268REG2016). All patients eligible for therapy, according to the new Italian Drug Agency (AIFA) criteria (2,940 people – Table 1), were enrolled. For the prospective analysis, we assumed SVR rates not inferior to the ones obtained in real clinical practice (7). Since the NHS special funds cover 100% of the drug supply, DAA costs were excluded, and we focused on the consequences of other liver-related direct costs.

2.2 Data sources

Data was analysed from the point of view of the Regional Health Service (RHS). Treatment costs included outpatient services, attended visits and inpatient service admissions. Hospitalisation was classified using ICD-9 codes, and the financial costs considered were calculated from the Italian NHS rate table. According to the AIFA, DAAs are fully reimbursable for all fibrosis stages, therefore providing complete coverage of the entire eligible population (8). The criteria defined by the AIFA have been summarised in Table 2.

2.3 Statistical analysis

At this point, we performed an additional analysis evaluating the weighing of different diagnosis-related group (DRG) codes on the expected trends in 2017–2019. While the sensitivity analysis described the impact of variations of the base case on the obtained results, the univariable sensitivity analysis was conducted to define the impact of SVR rates on liver

and the related direct costs. SVR rates varied over a range of 2–5%, assuming a high performance of success as demonstrated in several studies (7).

3. Results

3.1 Population

During the 2014–2016 period, 8,464 patients were assisted for liver-related complications (Table 2). At the beginning of 2017, 2,940 people were eligible for HCV treatment with DAAs. By assuming to treat this population with a cure success rate of > 90%, the patients assisted due to liver-related complications in the 3-year horizon should decrease to 5,538 patients (-35%). This reduction is remarkably higher among the less severely affected population (no cirrhosis or hepatocellular carcinoma (HCC), -89%.

3.2 Hospitalisation and day hospital care

A detailed analysis of hospitalisation (Table 3) showed a significant reduction in the number of activities. Overall, inpatient visits declined from 10,683 (2014–2016 period) to 6,830 (2017–2019 period), -36%, with a greater reduction in hospitalisation and a stronger focus on the less complicated cases (-89%). Days of hospitalisation declined from 87,514 to 65,725, (-25%); a similar trend was noticed on day hospital admissions, declining from 17,603 to 5,033 accesses (-71%), with a peak of -97% for patients with less severe conditions.

3.3 Deaths

Another major consequence of treating people for HCV resulted in an overall -21% of deaths among liver-related disease conditions (846 vs 1,077).

3.4 Health economic resources analysis

The overall direct cost sustained for the treatment of 5,538 patients with liver disease was

€ 24,779.024, showing a -27% decrease compared to previous costs. HCV direct costs accounted for a low proportion of these costs (€1,430.377; 5.8%). Code 203 "neoplasia" was the one absorbing the highest amount of resources (€ 14,252.459; -8% vs. previous period), followed by code 202 (€ 7,747.694; -38%), while codes 205 (liver disease no neoplasms/cirrhosis – complicated) and 206 (Liver disease no neoplasms/cirrhosis - not complicated) were those with the lowest impact. Notably, the expected expenses for patients with less severe conditions will decline by -95% as opposed to the same amount of resources needed during the 2014–2016 period.

This is clearer if we look closely at the HCV reduction in the population stratified by fibrosis scores. Overall, the variance of the liver-related direct interventions and health resource consumption is higher in the F0-F2 segment compared to the F3-F4 segment. With the exception of the number of deaths (-24% vs.-9% in favour of F3-F4), greater benefits and reductions are expected among F0-F2 patients, hospitalisations, day hospital activities and expenditures (-61%, -63%, -34%, -95% and -54%, respectively) vs. F3-F4 sub-population (-24%, -28%, -23%, -65% and -22%, respectively).

We explored additional findings by looking at the mean DRGs weighting and the related mean costs. The purpose was to explore any variance that may affect the case-mix management of the different liver disease conditions. We decided to calculate the weight for each one of the DRG codes using the NHS official statistics (Table 4a). Based on the calculation, we found out that the numbers of hospitalisations and day hospital activities are expected to increase (by 3.7% and 5.7%, respectively), despite the overall performance decrease (Table 4b).

In addition, we examined the patients' mean costs by DRG code (Table 2b). The overall mean cost per patient increased by 11% (€ 4,026.94 in the 2014–2016 period vs. € 4,474.69 in the 2017–2019 period, respectively). Looking at each single DRG code, we noted that all but the 203 one (i.e., the most severe patient's condition) are expected to decline over time. Both

analyses together tend to suggest that treating HCV will also help to decrease liver management economic expenses and, at the same time, allow us to concentrate more efforts on the most complex and severe cases.

Sensitivity analysis (Table 5) confirms the SVR rate as the major contributor to the total cost. Excluding anti-HCV treatment costs, as we assumed an "ad-hoc" budget for them, an increase in SVR rate led to a major reduction in overall costs.

4. Discussion

The use of DAA therapies is reducing the burden of HCV disease in Italy. As of early August 2017, more than 86,000 patients have already been treated. Ad-hoc funds for the innovative drugs (DAAs are included in this list) will facilitate treating patients with less stress on the regional healthcare resources. New generation DAAs will further improve the SVR rates. Several studies demonstrated that DAA regimens (9) such as sofosbuvir/velpatasvir are *undeniably* cost effective (10); however, no study reported the impact on workload for the overall liver disease interventions in the hospital setting and their effects in terms of direct costs and resource consumption.

Our paper is well aligned with a recent paper by Deuffic-Burban, addressing the cost-effectiveness of different screening strategies in France. In fact, this paper reported that universal screening is the most effective strategy, and it is cost effective when treatment is initiated regardless of fibrosis stage (11). The results observed in the long term will be very similar to those observed in the field of HIV therapy. In particular, the introduction of modern antiretroviral therapy, which determines the control of the HIV-RNA load and the gain in the T lymphocyte CD4+ count, led to a dramatic reduction in hospitalisations, admissions to day hospital services and access to outpatient services (12). Considering that drug cost is the main element in the hepatitis C drugs (7), the advent of generics in the future, characterised by the same results in order of SVR of branded molecules (13), is a crucial element that will play a

role in changing all economic evaluations and promising further savings for national health services across Europe (14).

Our analysis was conducted starting from a "real-world data" cohort of 3-consecutive year patients affected by any liver disease condition, regardless of comorbidities, coinfections, age, gender or prior therapies. Yet, this study has its limitations. For instance, treatment costs for other antiviral agents in coinfected patients with HIV or for HBV therapies were not included. Similarly, laboratory tests as well as other examinations like FibroScan were not considered. Moreover, this paper assumed that the achievement of SVR was equivalent to a permanent cure for patients, which could overestimate the benefits of therapies in the long term.

Our analysis confirms that, over the next years, the total expenditure for liver intervention direct costs will be affected by HCV treatment. We also demonstrated that eliminating HCV, besides reducing liver disease costs in general, will also help in maximising efforts and resources on other more severe liver conditions.

In addition, the recently published by the European Association for Liver Diseases (EASL) guidelines (11) recommend that patients with moderate fibrosis (F0-F2) before treatment will not require further checks after the achievement of SVR, a further element in the reduction of follow-up related costs.

The sensitivity analysis conducted on the direct costs clearly shows that the greater the success in SVR rates of HCV treatment, the greater the savings will be for the NHS.

In a scenario of limited funds, our analysis could help the health system in planning its resources in order to treat liver disease efficiently while helping to face challenges in other therapeutic areas, such as chronic HBV or Nonalcoholic Steatohepatitis (NASH).

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Declaration of Interest

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

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Author contributions

ADB and GC designed the study. GC and LT drafted the paper. AP,DM an PO worked on the analysis and interpretation. All authors approved the paper in all aspects

Availability of data and material: The data sets used and/or analysed during the current study are available from the corresponding author on prior request.

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Table 1. Patients eligible for HCV treatment at 1 April 2017 (source DB-Rete Ligure HIV/HCV)

Staging of fibrosis	Estimate of patients
F0-F2	2,680
F3-F4	260
Total	2,940

Table 2. AIFA (Italian Agency for Drugs) Criteria for prescription/reimbursement of DAAs in Italy.

Criteria	Description
Criteria 1	Patients affected by liver cirrhosis (Child A or B) and/or Hepatocellular carcinoma already treated.
Criteria 2	HCV reinfection (HCV RNA positive) in clinically stable patients after liver transplantation and with excellent levels of immunosuppression
Criteria 3	Chronic hepatitis C with severe extra hepatic manifestations (e.gh. kidney failure, lymphoproliferative diseases, cryoglobulinemic syndrome) with organ damage
Criteria 4	Chronic Hepatitis C with METAVIR F3 stage
Criteria 5	Patients on liver transplantation list affected by liver cirrhosis MELD score<25 within the Milano criteria with at least a two-months waiting list
Criteria 6	Chronic Hepatitis after solid organ (not liver) or bone marrow transplantation on clinically stable patients and with optimum levels of immunosuppression
Criteria 7	Chronic Hepatitis with fibrosis METAVIR F 2 and/or other diseases at risk of worsening liver disease *[coinfection HBV, HIV, chronic non-viral liver diseases, patients with diabetes mellitus in treatment, obesity (body mass index ≥30 kg/m^2), haemoglobinopathies and congenital coagulopathy].*
Criteria 8	Chronic Hepatitis with fibrosis METAVIR F 0-F1 and/or other diseases at risk of worsening liver disease [*coinfection HBV, HIV, chronic non-viral liver disease, patients with diabetes mellitus in treatment, obesity (body mass index ≥30 kg/m^2), haemoglobinopathies and congenital coagulopathy].*
Criteria 9	NHS workers affected by liver disease.

Criteria 10	Chronic hepatitis in patients with chronic kidney disease in treatment with hemodialysis.
Criteria 11	Patients with chronic hepatitis waiting for solid organ transplantation (other than liver) or bone marrow transplantation

Table 3 - Liver-related direct interventions and health resource consumption.

	Historical Trends			Expected Trends		
	Year 2014	Year 2015	Year 2016	Total 2014-16	Total 2017-19	Diff (%)
Patients (n.)	**3.172**	**2.991**	**2.301**	**8.464**	**5.538**	**-35%**
202 Liver cirrhosis and alcoholic hepatitis	946	973	702	2.621	1.745	-33%
203 Hepatobiliary / pancreas tumors (HCC)	1.236	1.198	1.029	3.463	2.861	-17%
205 Liver disease no neoplasms/cirrhosis - complicated	453	417	307	1.177	796	-32%
206 Liver disease no neoplasms/cirrhosis - not complicated	537	403	263	1.203	136	-89%
Hospitalizations cases (n.)	**4.025**	**3.743**	**2.915**	**10.683**	**6.838**	**-36%**
202 Liver cirrhosis and alcoholic hepatitis	1.338	1.342	987	3.667	2.255	-39%
203 Hepatobiliary / pancreas tumors (HCC)	1.644	1.537	1.320	4.501	3.643	-19%
205 Liver disease no neoplasms/cirrhosis - complicated	484	450	333	1.267	809	-36%
206 Liver disease no neoplasms/cirrhosis - not complicated	559	414	275	1.248	131	-89%
Hospitalizations days (n.)	**32.223**	**29.010**	**26.281**	**87.514**	**65.725**	**-25%**
202 Liver cirrhosis and alcoholic hepatitis	11.145	10.200	9.641	30.986	21.533	-31%
203 Hepatobiliary / pancreas tumors (HCC)	14.636	13.013	11.760	39.409	32.938	-16%
205 Liver disease no neoplasms/cirrhosis - complicated	4.327	4.082	3.233	11.642	7.910	-32%
206 Liver disease no neoplasms/cirrhosis - not complicated	2.115	1.715	1.647	5.477	3.344	-39%
Day hospital activities (n.)	**6.948**	**7.573**	**3.082**	**17.603**	**5.033**	**-71%**
202 Liver cirrhosis and alcoholic hepatitis	2.122	2.700	988	5.810	1.395	-76%
203 Hepatobiliary / pancreas tumors (HCC)	2.861	3.479	1.714	8.054	3.451	-57%
205 Liver disease no neoplasms/cirrhosis - complicated	534	305	117	956	100	-90%
206 Liver disease no neoplasms/cirrhosis - not complicated	1.431	1.089	263	2.783	87	-97%
Deaths (n.)	**397**	**362**	**318**	**1.077**	**846**	**-21%**
202 Liver cirrhosis and alcoholic hepatitis	91	89	90	270	194	-28%
203 Hepatobiliary / pancreas tumors (HCC)	244	216	176	636	496	-22%
205 Liver disease no neoplasms/cirrhosis - complicated	60	56	51	167	156	-7%
206 Liver disease no neoplasms/cirrhosis - not complicated	2	1	1	4	0	-95%

Expenditure (€)	12.382.533	12.091.046	9.610.409	34.083.988	24.779.024	-27 %
202 Liver cirrhosis and alcoholic hepatitis	4.520.683	4.427.467	3.524.370	12.472.520	7.747.694	-38%
203 Hepatobiliary / pancreas tumors (HCC)	5.314.387	5.639.024	4.616.116	15.569.527	14.252.459	-8%
205 Liver disease no neoplasms/cirrhosis - complicated	1.630.384	1.515.801	1.142.404	4.288.589	2.690.324	-37%
206 Liver disease no neoplasms/cirrhosis - not complicated	917.079	508.754	327.519	1.753.352	88.546	-95%

Abbreviation: DRG, diagnosis related group.

Table 4a: Overall mean cost per patient/DRG

DRG code	Clinical category	2014-16 (years)	2017-19 (years)	Diff (%)
202	Liver cirrhosis and alcoholic hepatitis	4.758,69	4.440,45	-7%
203	Hepatobiliary / pancreas tumors (HCC)	4.495,97	4.980,94	11%
205	Liver disease no neoplasms/cirrhosis - complicated	3.643,66	3.381,50	-7%
206	Liver disease no neoplasms/cirrhosis - not complicated	1,457.48	652,04	-55%
All	Mean costs (€)	4,026.94	4.474,69	11%

Abbreviation: DRG, diagnosis related group.

Table 4b: Mean weigthing by DRG

Description	**2014-16 (years)**	**2017-19 (years)**	**Diff (%)**
Patients (n.)	8,464	5.538	-35%
Hospitalizations cases (n.)	1,22	1,26	3,7%
Hospitalizations days	1,24	1,25	0,6%
Day hospital activities (n.)	1,20	1,27	5,7%
Deaths (n.)	1,077	846	-21,4%
Expenditure (€)	34,083.988	24,779.024	-27%

*In examining the patient's mean cost by DRG code we found an overall per patient increase by 11% (€ 4,026.94 in the 2014-16 period vs. € 4,474.69 in the 2017-2019 timeframe, respectively).

Table5 Cost (in €) and sensitivity analysis. Table is simulating the total cost variations at the change of SVR rate (% is indicating the SVR rate change)

Variable	Liver disease direct costs
Baseline	24,779.024
SVR (%)	
−2	25,320.538
−5	25,617.959
+2	24,260.652
+5	23,522.177