RESEARCH ARTICLE

Real-life cost of managing chronic HCV infection in Greece prior to Direct-Acting Antivirals (DAAs): an undeniable truth of spending more for less

Souliotis K[1,2], Siakavellas S[3], Golna C[4], Manesis E[5], Papatheodoridis G[3], Hatzakis A[6]

[1]Department of Social and Educational Policy, Faculty of Social and Political Sciences, University of Peloponnese, Corinth, Greece
[2]Health Policy Institute
[3]Department of Gastroenterology, Medical School, National and Kapodistrian University of Athens, Laiko General Hospital Athens, Greece
[4]Innowth Ltd, Larnaca, Cyprus
[5]Division of Internal Medicine, Hippokration General Hospital
[6]Department of Hygiene, Epidemiology and Medical Statistics
Medical School, National and Kapodistrian University of Athens, Athens, Greece

Abstract

Purpose: Chronic hepatitis C virus (HCV) infection is a major public health challenge across the world. Before the introduction of Direct-Acting Antivirals (DAAs), managing and treating the disease and its possible complications (cirrhosis, hepatocellular carcinoma) placed a considerable financial burden on public health resources. This study estimates the financial burden of managing HCV in Greece before the introduction of DAAs.

Patients and methods: We reviewed the clinical records of 146 consecutive patients with chronic HCV that were regularly followed-up at two tertiary hospitals in Athens. Public health resources utilization was recorded by category for consultations, hospitalizations, medications [for the pre-DAAs: pegylated interferon (PEG-IFN) and ribavirin (RBV) regimens), and laboratory and imaging tests. Overall disease burden was stratified according to fibrosis stage in four categories [F1-F2, F3-F4, decompensated cirrhosis, and hepatocellular carcinoma (HCC) - liver transplantation (LT)]. All cost calculations were based on current prices in the Greek Public Health System.

Results: The average cost per patient on treatment was €8,629 for F1-F2 patients, €13,302 for F3-F4 patients, €14,678 for patients with decompensated cirrhosis, and €48,152 for patients with HCC or LT. Main cost drivers were medications (75.6 % of total cost), laboratory and imaging tests (12.4 %) and hospitalizations (11.4 %). Hospitalization cost grew significantly as the disease progressed.

Conclusions: Chronic hepatitis C places a substantial economic burden on the Greek Public Health System. This burden is expected to increase exponentially as patients move to more advanced disease stages. Robust interventions to deter chronic HCV infection progression should be considered beneficial from a long-term economic perspective. HIPPOKRATIA 2018, 22(3): 127-131.

Keywords: Budget impact, cost of hepatitis, Direct-Acting Antivirals, real-world data

Corresponding author: Kyriakos Souliotis, 8 Agisilaou str., 15123 Maroussi, Greece, tel: +302106108720, fax: +3021061097540, e-mail: info@ksouliotis.gr, ksouliotis@uop.gr

Introduction

Hepatitis C virus (HCV) infection is a critical public health challenge. This was acknowledged recently by the World Health Organization (WHO), which referred to HCV as a "time bomb"[1]. It is estimated that almost 3 % of the world population (approximately 170 million people) is infected with HCV[2]. The disease is significantly underdiagnosed, due to lack of symptoms in the acute phase, and, subsequently, undertreated[3]. When left untreated, HCV infection may progress to liver cirrhosis and hepatocellular carcinoma (HCC)[4]. HCV-related liver cirrhosis is one of the primary causes of liver transplantation (LT)[5]. As such, HCV related morbidity places a substantial burden on public health services, especially as the necessity for LT and treatment of HCC increases.

In Greece, the epidemiological data on HCV infection are similar to those of the other Western countries. Prevalence was recently estimated at 1.87 % of the total population (approximately 200,000 people). The most vulnerable subgroup was People Who Inject Drugs (PWIDs)[6]. Of the total estimate, 29,000 HCV infected patients are aware of their condition but only 13,000 of them, have ever received antiviral treatment[6]. Of those infected, 9.2 % have developed cirrhosis and an additional 1.3 %

HCC. Age of patients was found to be the most important factor for developing HCV related complications. Sustained Virologic Response (SVR) was associated with a significantly reduced complication rate[7] and a substantial decrease in new cirrhosis and HCC cases[8]. Access to effective treatment that leads to an SVR is therefore critical in averting complications of HCV. An increase in the percentage of naïve patients that receive effective treatment with interferon-free (IFN-free) Direct-Acting Antivirals (DAAs) from 1.2 % to 10 % per annum was modeled to be able to reduce the cumulative cirrhosis and HCC incidence by 10.8-39.4 % and 12.8-39.8 %, respectively over the next 30 years[9]. To manage the future burden of disease, Greece would need to offer such treatment to a total of 86,500 chronic hepatitis C patients over the years 2016-2030[10].

The financial burden of HCV is equally substantial. The average annual cost per HCV patient in Greece in 2013 ranged from €12,685.1 for F0-F3 fibrosis stage patients [inclusive of pegylated interferon (PEG-IFN) and ribavirin (RBV) costs] to €21,890.1 for patients with HCC and €35,051.1 for patients with LT[11]. Data regarding cost in that study were derived from an Expert Panel Consensus and not from real life. Understanding the real-life burden and treatment cost of chronic HCV would provide a solid basis for negotiating and agreeing upon the future of HCV treatment. This study reports on the real-life cost of managing chronic HCV before the introduction of DAAs in Greece.

Material and methods

This was a retrospective, case note review, study of 146 patients with chronic HCV on treatment with PEG-INF/RBV (pre-DAAs) in two specialized tertiary Hepatology Centers in Athens, performed between June 2013 and July 2014. The study was contacted in a three-month period (August-October 2014). Patients' medical files were retrieved, and the full clinical pathway was reviewed. All available data were entered into case registration forms, and each registration form was encoded to ensure the anonymity of the study population. No exclusion criteria were applied. Entry date was the date of the first visit to the Hepatology center. Exit date was either i) date of last entry in the medical file, ii) date of treatment initiation with DAAs or iii) date of death. The time between entry and exit dates constituted the follow-up period. Patients were classified into different disease stages, using the METAVIR fibrosis score, either based on the histological (liver biopsy) or imaging (liver elastography) and the clinical data (diagnosis of variceal bleeding, ascites, hepatic encephalopathy or/and HCC marked the onset of advanced decompensated liver disease). When none of the above were available, fibrosis stage was estimated according to typical fibrosis progression rates in chronic HCV[12].

Health service utilization and cost was also recorded by fibrosis stage, including:

- Outpatient clinic visits (mainly in Hepatology clinics),
- Inpatient hospital stays (either day clinics e.g., gastrointestinal endoscopy or liver biopsy or more prolonged hospitalizations due to severe complications),
- Laboratory tests (blood tests performed in public hospitals or private diagnostic centers including serology and virology tests),
- Liver-related imaging (including liver stiffness evaluation with elastography),
- Histological evaluation with liver biopsy,
- Antiretroviral treatment (multiple lines in cases of failure to achieve SVR),
- Medical treatment for complications arising from disease progression (e.g., treatment for complications of antiretrovirals, diuretics for ascites, sorafenib in HCC).

Use of health resources not associated with HCV management or attributed to the personal patient initiative was excluded from the analysis. Costs for visits, tests, and pharmaceuticals were calculated according to the reimbursement list of the National Organization for Provision of Healthcare Services (EOPYY). Inpatient hospital costs were calculated according to the Ministry of Health Diagnosis Related Groups (DRGs). All costs reflect prices at the time of the study.

Ethics approval for this study was obtained from the Research Ethics Committee of the University of Peloponnese. Consent to participate was not necessary as data were anonymized and retrospectively collected. No sample size calculation was conducted since the goal of the study was to estimate the annual real-life cost of the HCV patient. The tertiary hepatology centers of Laiko and Hippokratio general hospitals were chosen due to their specialty on the field. Management of HCV patients is not expected to largely diversify in the other hepatology clinics across the country.

Continuous variables were described using mean (± standard error of the mean) and range values. Frequency and relative frequency tables of observations were calculated for every fibrosis stage (F1-F2, F3-F4, F4D, HCC-LT). Estimates were obtained for the mean duration of each successive disease stage and the mean cost value for each patient. Projections were then made for total cost per fibrosis stage for the diagnosed population and the total HCV-infected population in Greece.

Results

Of the sample of 146 patients, the majority (n: 110, 75.3 %) remained in the same fibrosis stage during the follow-up. Disease progression by two fibrosis stages during follow-up was found in 23 cases (15.8 %) and by three fibrosis stages in 13 cases (8.9 %). Classification of study sample by fibrosis stage is depicted in Table 1. Patients who changed fibrosis stage during the follow-up were classified in more than one fibrosis stages (195 medical records in total).

Mean time in each fibrosis stage ranged from 4.8 years for F1-F2, 5.7 years for F3-F4, 6.4 years for decompensated cirrhosis (F4D), and 2.2 years for HCC-LT.

The maximum time in HCC-LT was six years (Table 2).

Cost per patient increased with fibrosis stage and ranged from €8,629 for F1-F2 patients to €48,152 for HCC-LT patients. Costs for the HCC-LT group varied widely, mainly due to the extremely high price associated with sorafenib chemotherapy (Table 3).

The main cost drivers across the fibrosis stages were pharmaceuticals (Table 4, Table 5, and Table 6), followed by laboratory tests, and imaging in the earlier fibrosis stages (F1-F2 and F3-F4) and hospitalizations in F4D and HCC-LT. Pharmaceuticals related expenditure in the fibrosis stage F4D was reported at below 75 % of the total cost, as PEG-INF/RBV regimes are counter indicated in patients at this stage.

When projected to the total diagnosed and infected population in Greece[6], the total cost to the Greek Public Health System for managing HCV related morbidity was calculated at €302,239,552 and €1,357,892,963, respectively.

Table 1: The study population (146 consecutive chronic hepatitis C patients, regularly followed-up at two tertiary hospitals) according to their fibrosis stage.

Fibrosis stage	Number	%
F1-F2	81	41.5
F3-F4	72	36.9
F4D	27	13.8
HCC-LT	15	7.7
Total	**195**	**100.0**

Table 2: Mean time in each fibrosis stage and range, per fibrosis stage (in years).

Fibrosis stage	Mean	Min	Max	Range
F1-F2	4,877	1	23	22
F3-F4	5,736	1	16	18
F4D	6,444	1	23	22
HCC - LT	2,267	1	6	5

HCC: Hepatocellular carcinoma, LT: Liver transplantation.

Table 3: Mean and maximum hepatitis C (HCV)-related cost per patient, by fibrosis stage.

Fibrosis stage	Mean	Maximum
F1-F2	8,629 (± 824)	38,846
F3-F4	13,302 (± 1,682)	81,600
F4D	14,678 (± 3,132)	55,064
HCC – LT	48,153 (± 14,761)	202,458
Total	**14,233 (± 1,554)**	**202,458**

Costs are expressed in Euros (€).

Discussion

The current study is the first to estimate the financial burden of HCV-related morbidity on the Greek Public Health System, using real-life data. Such a burden is projected to increase over the coming years across the world[13], partly (and maybe mainly) due to the progression of the disease among an aging population towards end-stage, and partly because of new infections. As health systems struggle with sustainability and fiscal constraints, understanding the actual burden of the disease on the public health finances on the basis of real life, actual clinical practice data is critical to reaching optimal public health policy decisions.

All findings in our study refer to the full duration of treatment to exit from follow-up. Calculating a per annum cost for the patients under study might have been relevant in the pre-DAAs era, when many patients had no option but to stay on treatment for a number of years until achieving SVR, but is of limited value in the post-DAAs era, when the vast majority of patients will achieve SVR within 12-24 weeks. Therefore, if to correctly inform health policy planning, actual costs to be compared should refer to the full treatment duration to SVR and not a per annum cost.

Nonetheless, the majority of published studies in the field do mention a per annum cost, when discussing pre-DAAs treatment options. In this light and to facilitate discussion, Table 7 presents the mean per patient and per annum cost for each fibrosis stage.

Findings in Table 7 confirm those of previous studies and offer additional insights. In a previous study in Greece[11], which based its estimates of the burden of the disease on Expert Panel Consensus, the annual cost of a patient with chronic HCV was estimated at €12,685.1 for fibrosis stages F0-F3. This figure is 5-6 times higher than the one recorded in the current study on real-life data

Table 4: Total costs per cost category by fibrosis stage (in €)

Category	Fibrosis stage				
	F1-F2	F3-F4	F4D	HCC - LT	Total
Pharmaceuticals	564,749	757,248	221,462	554,470	2,097,930
Outpatient	5,460	6,240	4,140	1,110	16,950
Tests	103,313	137,102	83,390	19,023	342,828
Inpatient	25,45	57,163	87,325	147,689	317,627
Total	**698,972**	**957,754**	**396,317**	**722,292**	**2,775,335**

Costs are expressed in Euros (€). HCC: Hepatocellular carcinoma, LT: Liver transplantation.

Table 5: Participation of cost categories in the total cost, by fibrosis stage.

Category	Fibrosis stage				
	F1-F2	F3-F4	F4D	HCC - LT	Total
Pharmaceuticals	80.8 %	79.1 %	55.9 %	76.8 %	75.6 %
Outpatient	0.8 %	0.7 %	1.0 %	0.2 %	0.6 %
Tests	14.8 %	14.3 %	21.0 %	2.6 %	12.4 %
Inpatient	3.6 %	6.0 %	22.0 %	20.5 %	11.4 %
Total	**100 %**	**100 %**	**100 %**	**100 %**	**100 %**

HCC: Hepatocellular carcinoma, LT: Liver transplantation.

Table 6: Hepatitis C (HCV)-related cost synthesis per patient, by fibrosis stage.

Category	Fibrosis stage				
	F1-F2	F3-F4	F4D	HCC - LT	Mean
Pharmaceuticals	6,972 (± 763)	10,517 (± 1,477)	8,202 (± 2,355)	36,965 (± 12,257)	10,759 (± 1,280)
Outpatient	67 (± 6)	87 (± 9)	153 (± 33)	74 (± 11)	87 (± 7)
Tests	1,275 (± 118)	1,904 (± 226)	3,089 (± 657)	1,268 (± 228)	1,758 (± 140)
Inpatient	314(± 78)	794 (± 181)	3,234 (± 1,029)	9,846 (± 3,675)	1,629 (± 366)
Total	**8,629 (± 824)**	**13,302 (± 1,682)**	**14,678 (± 3,132)**	**48,153 (± 14,761)**	**14,232 (± 1,554)**

Costs are expressed in Euros (€). HCC: Hepatocellular carcinoma, LT: Liver transplantation.

Table 7: Mean and maximum annual hepatitis C (HCV)-related cost per patient, by fibrosis stage.

Fibrosis stage	Mean	Maximum
F1-F2	2,502 (± 270)	15,609
F3-F4	2,527 (± 272)	15,546
F4D	4,102 (± 281)	8,891
HCC - LT	18,035 (± 3,428)	39,096
Total	**3,927 (± 423)**	**39,096**

Costs are expressed in Euros (€). HCC: Hepatocellular carcinoma, LT: Liver transplantation.

(€2,501.9 for fibrosis stages F1-F2, and €2,526.5 for fibrosis stages F3-F4). This may be accounted for by the fact that the earlier study estimated costs based on completion of 24 or 48 weeks of treatment, whereas real-life data confirm that a significant percentage of patients do not start treatment due to difficulties in access or counter-indications or discontinue their treatment regime due to treatment-related complications. Moreover, reimbursement data in our study are derived from the 2015 lists in contrast to the 2012 lists used in the earlier study.

When compared to studies from other countries, and allowing for variability in patient classification by disease stage, cost components, list prices, and clinical practice, our findings are in line with previous research conclusions. For example, a recent UK study using "real-world data"[14] estimated the annual cost for F0-F3 patients at €2,980.7, including pharmaceutical cost. For cirrhotic patients, the annual cost was estimated at €4,869.7. These estimates are comparable to our analysis.

Another study from Belgium[15], based on the validated Razavi et al[16] model for transition to subsequent disease stages, estimated annual costs for the initial stages of disease (F0-F2: €1,919, F3: €1,690, F4: €2,276 inclusive of pharmaceutical costs) similar to those of the present study. Decompensated cirrhosis costs though were shown to be significantly higher, at €10,223 (versus €4,102 recorded in the present study).

A study from France[17] validated low annual costs for the initial fibrosis stages (F0-F3: €348 - €398, F4: €1,523, excluding pharmaceutical costs), and significant increases when HCV advances (F4D: €9,000 - €15,000, HCC: € 11,000 - €17,000). These findings are in line with our results.

Further, studies from Italy, Switzerland and Germany[18-20] all agree that the cost of managing HCV is bearable in the stages up to compensated cirrhosis, increasing exponentially after decompensation of cirrhosis, and HCC. Two Canadian studies[21,22] also report quite low annual costs for the initial fibrosis stages (F0-F3: €279, F4: €590, excluding pharmaceutical costs), increasing significantly after decompensation (€4,111 - €14,670, depending on the type of the cirrhotic complication) and/or HCC (€11,715). In the US, cost estimates range from €1,235, for fibrosis stages to F3, €3,690 for fibrosis stage F4, €9,775 for F4D and €38,899 € for HCC[23]. These significantly higher costs may be associated with higher prices for all cost components in the American health care system.

In all previous studies, as in this one, decompensation of cirrhosis appears to be the critical point in time, after which an array of complications necessitates repeated, costly hospital admissions. These admissions not only burden the health system but also impact negatively on the patient's quality of life.

The costs mentioned above reflect resource use and could not be correlated with an SVR, as such data were not readily available on the medical records. HCV-RNA laboratory tests are not reimbursed by the National Organisation for Health Services Provision (EOPYY), which covers 95 % of the population, and are therefore harder to perform, as their cost has to be covered out of pocket. Such a correlation would have allowed the study to estimate the actual cost per SVR, as well as provide insights into the percentage of people on treatment with non-DAAs that do not achieve SVR and have to go through multiple lines of treatment ("cost of non-SVR").

Conclusion

Overall, our study confirms a substantial increase in the financial burden of HCV on the Greek health system as the disease progresses among patients on treatment with PEG-INF/RBV. Delayed or no access to newer, effective DAAs that have a substantially higher probability of achieving SVR, impacts not only on the epidemiological burden of the disease but also on its economic burden on the health care system. To ensure that optimal numbers of patients are diagnosed and treated with a view to a cure, in line with WHO recommendations, it is critical to design an integrated HCV action plan that caters for treatment provision, to address not only the nominal cost of the present but also, and most crucially, the actual, overbearing cost of the future; investing now only to save later.

Conflict of interest

The authors declare no conflict of interest for this work.

References

1 Parry J. Viral hepatitis appears on World Health Assembly agenda for first time. BMJ. 2010; 340: c2420.
2 Negro F, Alberti A. The global health burden of hepatitis C virus

infection. Liver Int. 2011; 31 Suppl 2: 1-3.
3 European Centre for Disease Prevention and Control. Hepatitis B and C in the EU neighbourhood: prevalence, burden of disease and screening policies. Stockholm: ECDC; 2010. Available at: http://publications.europa.eu/resource/cellar/432783c9-2a62-4e52-a59d-fb6b27fca928.0001.02/DOC_1, date accessed: 02/04/2018.
4 Poynard T, Yuen MF, Ratziu V, Lai CL. Viral hepatitis C. Lancet. 2003; 362: 2095-2100.
5 Germani G, Tsochatzis E, Papastergiou V, Burroughs AK. HCV in liver transplantation. Semin Immunopathol. 2013; 35: 101-110.
6 Papatheodoridis G, Sypsa V, Kantzanou M, Nikolakopoulos I, Hatzakis A. Estimating the treatment cascade of chronic hepatitis B and C in Greece using a telephone survey. J Viral Hepat. 2015; 22: 409-415.
7 Manesis EK, Papatheodoridis GV, Touloumi G, Karafoulidou A, Ketikoglou J, Kitis GE, et al. Natural course of treated and untreated chronic HCV infection: results of the nationwide Hepnet. Greece cohort study. Aliment Pharmacol Ther. 2009; 29: 1121-1130.
8 Sypsa V, Touloumi G, Tassopoulos NC, Ketikoglou I, Vafiadis I, Hatzis G, et al. Reconstructing and predicting the hepatitis C virus epidemic in Greece: increasing trends of cirrhosis and hepatocellular carcinoma despite the decline in incidence of HCV infection. J Viral Hepat. 2004; 11: 366-374.
9 Sypsa V, Touloumi G, Papatheodoridis GV, Tassopoulos NC, Ketikoglou I, Vafiadis I, et al. Future trends of HCV-related cirrhosis and hepatocellular carcinoma under the currently available treatments. J Viral Hepat. 2005; 12: 543-550.
10 Gountas I, Sypsa V, Papatheodoridis G, Souliotis G, Razavi H, Hatzakis A. Is elimination of HCV possible in a country with low diagnostic rate and moderate HCV prevalence?: The case of Greece. J Gastroenterol Hepatol. 2017; 32: 466-472.
11 Athanasakis K, Arzoumanidou D, Petrakis I, Karampli E, Theodoropoulou T, Retsa MP, et al. A cost-of-illness analysis of hepatitis C in Greece. Value Health. 2013; 16: A496.
12 Thein HH, Yi Q, Dore GJ, Krahn MD. Estimation of stage-specific fibrosis progression rates in chronic hepatitis C virus infection: a meta-analysis and meta-regression. Hepatology. 2008; 48: 418-431.
13 Hatzakis A, Chulanov V, Gadano AC, Bergin C, Ben-Ari Z, Mossong J, et al. The present and future disease burden of hepatitis C virus (HCV) infections with today's treatment paradigm - volume 2. J Viral Hepat. 2015; 22 Suppl 1: 26–45.
14 Backx M, Lewszuk A, White JR, Cole J, Sreedharan A, van Sanden S, et al. The cost of treatment failure: resource use and costs incurred by hepatitis C virus genotype 1-infected patients who do or do not achieve sustained virological response to therapy. J Viral Hepat. 2014; 21: 208–15.
15 Vandijck D, Moreno C, Stärkel P, Van Damme P, Van Vlierberghe H, Hindman SJ, et al. Current and future health and economic impact of hepatitis C in Belgium. Acta Gastroenterol Belg. 2014; 77: 285-290.
16 Razavi H, Waked I, Sarrazin C, Myers RP, Idilman R, Calinas F, et al. The present and future disease burden of hepatitis C virus (HCV) infection with today's treatment paradigm. J Viral Hepat. 2014; 21 Suppl 1: 34-59.
17 Gerkens S, Nechelput M, Annemans L, Peraux B, Mouchart M, Beguin C, et al. A health economic model to assess the cost-effectiveness of PEG IFN alpha-2a and ribavirin in patients with mild chronic hepatitis C. J Viral Hepat. 2007; 14: 523-536.
18 Mennini FS, Marcellusi A, Andreoni M, Gasbarrini A, Salomone S, Craxì A. Health policy model: long-term predictive results associated with the management of hepatitis C virus-induced diseases in Italy. Clinicoecon Outcomes Res. 2014; 6: 303-310.
19 Sagmeister M, Renner EL, Mullhaupt B, Wong JB. Simulation of hepatitis C based on a mandatory reporting system. Eur J Gastroenterol Hepatol. 2002; 14: 25-34.
20 Stahmeyer JT, Rossol S, Bert F, Antoni C, Demir M, Hinrichsen H, et al. Cost of treating hepatitis C in Germany. Eur J Gastroenterol Hepatol. 2014; 26: 1278-1285.
21 Krajden M, Kuo M, Zagorski B, Alvarez M, Yu A, Krahn M. Health care costs associated with hepatitis C: a longitudinal cohort study. Can J Gastroenterol. 2010; 24: 717-726.
22 Myers RP, Krajden M, Bilodeau M, Kaita K, Marotta P, Peltekian K, et al. Burden of disease and cost of chronic hepatitis C infection in Canada. Can J Gastroenterol Hepatol. 2014; 28: 243-250.
23 Liu S, Cipriano LE, Holodniy M, Owens DK, Goldhaber-Fiebert JD. New protease inhibitors for the treatment of chronic hepatitis C: a cost-effectiveness analysis. Ann Intern Med. 2012; 156: 279-290.