Scientific Research Publishing

Health, 2017, 9, 1482-1493
http://www.scirp.org/journal/health
ISSN Online: 1949-5005
ISSN Print: 1949-4998

Managing Hepatitis C Patients in Greece: A Budget Impact Analysis of Simeprevir plus Pegylated Interferon/Ribavirin Regimen at Early Stages of the Disease

Mary Geitona[1*], Hara Kousoulakou[1], Ioannis Goulis[2], Spilios Manolakopoulos[3], Themistoclis Vasiliadis[2], Dimitrios Christodoulou[4], Charalabos Gogos[5], Spyridon Dourakis[3], Ioannis George Koskinas[3], Alexandra Papadokostopoulou[6], Aris Lathouris[6], George Papatheodoridis[3]

[1]University of Peloponnese, Corinth, Greece
[2]Aristotle University of Thessaloniki, Thessaloniki, Greece
[3]National and Kapodistrian University of Athens, Athens, Greece
[4]University of Ioannina, Ioannina, Greece
[5]University of Patras, Patra, Greece
[6]Janssen-Cilag Pharmaceutical SACI, Athens, Greece
Email: *marygeitona@gmail.com

How to cite this paper: Geitona, M., Kousoulakou, H., Goulis, I., Manolakopoulos, S., Vasiliadis, T., Christodoulou, D., Gogos, C., Dourakis, S., Koskinas, I.G., Papadokostopoulou, A., Lathouris, A. and Papatheodoridis, G. (2017) Managing Hepatitis C Patients in Greece: A Budget Impact Analysis of Simeprevir plus Pegylated Interferon/Ribavirin Regimen at Early Stages of the Disease. *Health*, **9**, 1482-1493.
https://doi.org/10.4236/health.2017.911109

Received: May 2, 2017
Accepted: October 20, 2017
Published: October 23, 2017

Abstract

Objectives: To identify local resource use such as pharmaceutical treatment, medical follow-up, and patient hospitalization and estimate the budget impact of simeprevir (SMV) plus pegylated interferon (P)/ribavirin (R) as a treatment option in the early stages of the disease in Greece. Methods: A budget impact tool was developed with a two-year time horizon, which estimated the impact on the Social Insurance Funds (SIFs) of introducing SMV + PR in the management of the early disease stages. Total direct and indirect costs were estimated for each of the following health states: non-cirrhotic chronic Hepatitis C (and within that by fibrosis stage), compensated cirrhosis, decompensated cirrhosis, and hepatocellular carcinoma. Data gaps on treatment algorithms, resource use and productivity losses were covered via an expert panel of eight leading hepatologists. Epidemiology data were taken from the published literature. Unit costs were obtained from the Ministry of Health and SIFs. The perspective was that of the SIF and the cost base year was 2015. Results: The total (direct and indirect) cost per patient per year (excluding cost of antiviral treatment) was estimated at €647, €703, €5,753, €16,313 and €37,237 for non-cirrhotic CHC, compensated cirrhosis, decompensated cirrhosis, HCC and liver transplantation, respectively. The budget impact analysis showed that

adding SMV to PR in the early stages of the disease would lead to an increase in the cost of antiviral treatment by €2.03 million. Conclusions: Costs of managing CHC increase dramatically with disease severity. SMV + PR for naive patients at early disease stages has a significant but manageable budget impact, and could prevent high costs in advanced stages.

Keywords

Hepatitis C, Budget Impact Analysis, Simeprevir, Greece

1. Introduction

Hepatitis C virus (HCV) is a leading cause of chronic liver disease, end-stage cirrhosis, and liver cancer [1]. According to the World Health Organization (WHO), about 3% of the world's population is infected with HCV, with prevalence ranging from 0.1% - 5% in different European countries [2] [3]. Approximately 15% - 25% of HCV infections are estimated to progress to severe liver disease, which may take more than 30 years to develop [4] [5].

HCV-specific burden of disease data for Europe are scarce [2]. According to available data, an estimated 7.3 - 8.8 million people (1.1% - 1.3%) are infected in Europe. Although the exact prevalence of HCV infection in Greece is not well known [6], it is estimated that approximately 1.5% - 2% of the general population have chronic HCV infection with a wide geographical variance of seropositivity (0.5% - 7.5%) [7] [8] [9] [10] [11]. Over the recent years, the epidemiology of the disease is changing owing to immigrants and intravenous drug users [12].

The burden associated with the management of chronic Hepatitis C (CHC) is significant [13]. A study conducted by Wong *et al.* had estimated that from the year 2010 through 2019, 165,900 deaths from chronic liver disease will occur in the US [14]. The study also forecasted that direct medical expenditure for HCV would rise to $10.7 billion [14]. Since 2011, new treatments have been introduced for chronic HCV infection with a cure rate of about 90% [15], which open a new era in the disease management [16] but also significantly affect related costs.

Simeprevir (Olysio®) is an HCV NS3/4A protease inhibitor that received a marketing authorization from the European Medicines Agency (EMA) in May 2014. It is indicated either in combination with pegylated-interferon and ribavirin (triple regimen) or in IFN free regimens for the treatment of CHC in adult patients.

In Greece, chronic patients, including those suffering from HCV, are fully covered by the work-related Social Insurance Funds (SIFs). In particular, the National Organization for Health Care Services Provision (EOPYY), which is the Reimbursement Agency of all SIFs, is responsible for reimbursing health care goods and services received by chronic patients, while SIFs are responsible for providing disability pensions to chronically ill patients that can no longer work.

Economic evaluation is becoming increasingly important in Greece, as the recently established Negotiation Committee which contributes to reimbursement decision making, requires an estimate of the budget impact to be included in the reimbursement dossier submitted by pharmaceutical companies. In this context, the aim of this study was to identify local resource use (health care resources associated with pharmaceutical treatment, medical follow-up, and hospitalization) and estimate the budget impact of simeprevir triple regimen as a treatment option in the early stages of the disease in Greece.

2. Methods

In order to estimate the budget impact on Social Insurance Funds (SIFs) of introducing simeprevir in combination with pegylated interferon and ribavirin (SMV + PR) in the management of the early stages of the disease, a budget impact analysis (BIA) was undertaken. A simplistic tool in Excel, a cost calculator with a 2-year time horizon, was developed in order to estimate the budget impact of the introduction of a new drug over the first two years into the Greek market.

In the health economics and HTA field budget impact analysis as well as other economic evaluation analyses are usually taking place in order to explore potential/future costs and related benefits depending on the analysis chosen. The study focused on genotype 1 patients. Total direct and indirect costs associated with the disease management were estimated for each of the following health states: non-cirrhotic chronic Hepatitis C (CHC) (and within that by fibrosis stage), compensated cirrhosis, decompensated cirrhosis, and hepatocellular carcinoma (HCC). A comprehensive search of the international and local literature was performed to identify data on patient demographics, disease epidemiology (prevalence, incidence), resource use associated with medical, pharmaceutical and hospital care and productivity losses associated with the disease in Greece.

Data gaps on treatment algorithms, resource use and productivity losses were covered via an expert panel of eight leading hepatologists, who have co-authored the local guidelines. The panel covered geographically the largest District Health Authorities and the Hospital Liver Units treating the majority of patients with HCV. For the purposes of the panel, a questionnaire was developed, structured by health state and validated by a clinical expert. The elicitation method used during the expert panel was the Delphi technique [17].

The direct medical costs considered in the analysis were hospitalization, lab and imaging tests, medical consultation and pharmaceutical care. The cost base year was 2015. Unit costs were retrieved from officially published sources. In particular, for non-antiviral pharmaceutical treatments, prices based on the positive reimbursement list were used [18]. Prices for antiviral drugs were retrieved from the Price Bulletin issued by the Ministry of Health [19]. As antiviral treatments are under Law 3816/2010 for high cost drugs, they are only available through hospitals, thus the NHS Hospital prices were used, after being reduced by 5% which is the obligatory discount provided to EOPYY. For costs of labora-

tory and imaging tests and hospitalization, the prices reimbursed by EOPYY and the diagnosis-related groups (DRGs) were used, respectively [20] [21].

Productivity losses for patients were estimated as absence from work due to illness (disease symptoms) and/or in order to receive treatment and medical consultation—these data were elicited from the panel. Costs associated with productivity losses were estimated based on per capita Gross Domestic Product (GDP) data in Greece [22]. Per capita GDP was projected to year 2015 based on the mean annual growth rate (MAGR) of the OECD time series data for the period 2008-2014. Disability benefits were obtained from the Disability Certification Centres of the Social Insurance Institute (KEPA-IKA [23]).

All costs refer to first year of treatment at the specific disease stage (*i.e.* when patients are on treatment or when the procedure takes place, e.g. the liver transplant). Population data were taken from OECD [22], and patient numbers for years 2015 and 2016 were estimated based on the literature and input from the expert panel. The expert panel also determined the treatment algorithm and standard of care in the early stages of the disease (F0 - F2) and provided input for the estimation of market shares for the antiviral drugs and projections for those market shares in year 2016.

3. Results

3.1. Lab & Imaging Costs

Patients with non-cirrhotic disease were grouped into patients with F0 - F2 before initiation of treatment and patients with F2 - F3 after they have started treatment. Total lab and imaging test costs were weighted for frequency and percentage of patients undergoing each test and are presented by disease stage in **Table 1**. Costs increase as the patient progresses to more severe disease stages.

3.2. Hospitalization Costs

The results show that patients in stages prior to decompensated cirrhosis do not require hospitalization. All patients (100%) with decompensated cirrhosis are hospitalized on average 2 - 3 times per year. The expert panel provided data on the percentage of patients being hospitalized under each diagnosis-related group (DRG) relating to cirrhosis. The average per patient cost of hospitalization for decompensated cirrhosis was estimated at €2,670 (**Table 2**).

HCC also requires hospitalization in 100% of the patient population (approx. 2 - 3 times per year). The average hospitalization cost per HCC patient was estimated at €6,751.13 (**Table 3**). The unit cost for liver transplantation (DRG code E01A) is €28,900.

3.3. Medical Consultation and Non-Antiviral Pharmaceutical Costs

With regards to medical consultation, the vast majority of patients (>95%) across all fibrosis stages visits hospital outpatient wards for medical follow up. This entails no cost to SIFs. In addition, pharmaceutical treatment (other than

Table 1. Cost of lab & imaging tests per disease stage and per patient (€).

Test	F0 - F2, from diagnosis to initiation of treatment	F2 - F3 while on treatment	F4 (compensated cirrhosis)	Decompensated cirrhosis	HCC
FBC	2.88	28.80	8.64	11.52	8.64
SGOT, SGPT	6.98	69.80	20.94	27.92	20.94
T3, T4, TSH		11.02	11.02	11.02	11.02
ALP, GGT, albumin, bilirubin, creatinine	18.16		36.32	72.64	36.32
Prothrombin time	12.00		8.10	48.00	8.10
AFP			3.71	12.38	
Hepatitis C antibody	9.00				
Liver biopsy	0.39				
Upper abdomen U/S	15.68		33.44	33.44	7.32
Upper abdomen CT			6.68	20.03	133.52
Gastroscopy				28.18	
MRI					165.00
Total cost	**65.09**	**109.62**	**128.85**	**265.13**	**390.86**

AFP: alpha-fetoprotein; ALP: alkaline phosphatase; CT: computed tomography; F0, 1, 2, 3, 4: Fibrosis stage 0, 1, 2, 3, 4; FBC: full blood count; GGT: gamma-glutamyltransferase; HCC: hepatocellular carcinoma; MRI: Magnetic resonance imaging; SGOT: Serum glutamic oxaloacetic transaminase; SGPT: serum glutamic-pyruvic transaminase; TSH (T3, T4): thyroid-stimulating hormone (T3, T4); U/S: Ultrasound.

Table 2. Hospitalization costs for decompensated cirrhosis per patient per year.

DRG code	Description	Unit cost (€)	% of patients hospitalized under each DRG	Frequency (number of hospitalizations per year)	Weighted average cost (€)
H40Mα	Cirrhosis with catastrophic (systematic) comorbidities/complications	1700.00	40%	2.5	1700.00
H40Mβ	Cirrhosis with moderate to severe comorbidities/complications	717.00	50%	2.5	896.25
H40X	Cirrhosis without comorbidities/complications	296.00	10%	2.5	74.00
Total cost					**2670.25**

DRG: diagnosis-related group.

Table 3. Hospitalization costs of HCC per patient per year.

DRG code	Description	Unit cost (€)	% of patients	Average cost per event (€)
H41M	Malignancy of the hepatic system with catastrophic comorbidities/complications	1754.00	70%	3663.50*
H41X	Malignancy of the hepatic system without catastrophic comorbidities/complications	792.00	30%	
H01M	Hepatic surgeries with catastrophic comorbidities/complications	5296.00	7%	370.72
	Angiography with chemoembolization^		30%	2048.78
	RF ablation^		15%	668.14
Total cost				**6751.13**

DRG: diagnosis-related group; RF: Radiofrequency; *Based on input from the expert panel that HCC patients are hospitalized 2 - 3 times per year under H41M & H41X; ^Related cost not included in DRGs-estimated with input from the expert panel.

antiviral treatment) was sought for all fibrosis stages and disease states; however, the expert panel concluded that the only disease states that require additional pharmaceutical treatment are advanced disease stages (compensated cirrhosis and HCC).

Patients with decompensated cirrhosis require additional pharmaceutical treatment (on top of antiviral therapy) for the management of disease symptoms and infections. This mainly consists of beta blockers (€28.08), diuretics (€169.13) and antibiotics (€37.61), summing up to €234.82 per patient per year. Approximately 10% of patient with HCC are also treated with sorafenib, 40% of whom receive full recommended by SPC dose and 60% receive half dose due to AEs, with an average cost (weighted with the probability of receiving sorafenib) of €1,136.41.

3.4. Indirect Costs

Patients with HCC and liver transplant go on full disability pension (>80% disability), which entails an average monthly per patient cost to SIFs of €650. Indirect costs for all other disease stages were based on the number of days lost from work due to illness or treatment, which were estimated via the expert panel at 10 days for non-cirrhotic CHC and compensated cirrhosis and 45 days for decompensated cirrhosis.

3.5. Overall Costs of Managing CHC Patients

The average cost of managing patients in each of the CHC disease states is presented in Table 4. Non-cirrhotic CHC patients (in fibrosis stages F0 - F3) have very limited costs, mainly consisting of the costs of lab and imaging tests. Both direct and indirect costs increase with disease severity.

3.6. Budget Impact of SMV + PR

The budget impact analysis was based solely on the antiviral treatments and the number of eligible patients for treatment with SMV + PR in the early stages. The total number of eligible patients was estimated at 372 (Table 5).

Table 4. Total cost per patient per health state (€).

Resource category	Non-cirrhotic CHC (F0-F3)	Compensated cirrhosis (F4)	Decompensated cirrhosis	HCC	Liver transplant
Lab & imaging tests	73.41	128.85	265.13	390.86	537.00
Other medication (non-CHC related)			234.82	1371.23	
Hospitalization (including procedures*)	-	-	2670.25	6751.13	28900.00
Direct cost	73.41	128.85	3170.20	8513.22	29437.00
Indirect costs	573.89	573.89	2582.50	7800.00^	7800.00^
Total costs	647.30	702.74	5752.70	16313.22	37237.00

CHC: chronic Hepatitis C; F0, 1, 2, 3, 4: Fibrosis stage 0, 1, 2, 3, 4; HCC: hepatocellular carcinoma; *Procedures: liver transplant, hepatectomy, chemoembolisation RF ablation etc.; ^Indirect costs for HCC and liver transplant refer to the average annual disability pension.

Under the assumptions that, the market share of SMV in the triple regimen could increase from 5% in 2015 to 50% in 2016, the average per patient cost would increase from €10,973 to €16,444 (Table 6). The total budget impact of managing 50% of the naïve, F0-F2 patients with SMV + PR is estimated at approx. €2.03 million.

Table 5. Estimation of eligible patient population.

	2015	2016	Source
Total population	10858018	10855694	Hellenic Statistical Authority [24]*
Prevalence	1.2%	1.2%	Hatzakis *et al.* 2015 [11]
Prevalent cases	126713	126686	
% of diagnosed patients	20.0%	20.0%	Papatheodoridis *et al.* 2015 [25]
Number of patients diagnosed	25343	25337	
% of G1 patients	33%	33%	Manolakopoulos *et al.* 2013 [26]
G1 patients	8363	8361	
% of Q80K patients	2.3%	2.3%	Expert panel data
Number of patients after excluding Q80K	8169	8167	
% of F0 - F2 patients	70%	70%	Expert panel data
F0 - F2 patient population	5718	5717	
% of treatment naïve patients at F0 - F2	65%	65%	Expert panel data
Treatment naïve F0 - F2 patient population	3717	3716	
% of patients initiating treatment	10.0%	10.0%	Expert panel data^
Patient population	372	372	

F0, 1, 2: Fibrosis stage 0, 1, 2; G1: Genotype 1; *Data projected to year 2016 based on the MAGR of the time series 2002-2015; ^The percentage of patients initiating treatment refers only to IFN-containing regimens.

Table 6. Budget impact of SMV + PR (€).

			Cost per year (€)		Difference (€)
	Duration of treatment (weeks)	**Cost per year (€)**	**2015**	**2016**	
PR	48	7204.1	5763.3	3241.9	
TVR + PR	TVR (12) + PR (48)*	27267.5	1363.4	0.0	
BOC + PR	BOC (24) + PR (48)	17855.0	892.7	0.0	
SMV + PR	SMV (12) + PR (24)	22774.8	1138.7	11387.4	
SOF + PR	12	36288.8	1814.4	1814.4	
Average cost per patient			10972.6	16443.7	5471.1
Patient population			372	372	
Total budget impact			4078168	6110293	2032124

BOC: boceprevir; PR: pegylated interferon; SMV: simeprevir; SOF: sofosbuvir; TVR: telaprevir; *This is a conservative approach reflecting the longest treatment duration (and thus highest cost), as some patients under treatment with TVR + PR might receive PR for 24 weeks.

4. Discussion

The present study showed that both direct and indirect costs of CHC increase with disease severity. The cost of managing CHC at the compensated cirrhosis stage is 75.5% higher than the cost in previous stages, while the cost of decompensated cirrhosis is 24.6 times higher than the compensated. Similarly, productivity losses are 3.5 times higher in the decompensated cirrhosis compared with respective costs in stages F0 - F4, and almost 13 times higher if the patient develops HCC or undergoes liver transplant. The major cost driver is hospitalization.

These findings are consistent with other studies conducted in Greece. In particular, Athanasakis *et al.* have estimated the costs per disease stage, and results support an increase in the economic burden in patients with advanced liver disease [27] [28]. Also, the study by Yfantopoulos and colleagues estimated the cost of lab and imaging tests in patients with HCV [29]. However, this study had a different perspective and focused on the cost comparison between the public and private health care sector, and results are not comparable with our findings.

With respect to the international literature, our study findings are also consistent with the study by Solomon *et al.*, which highlights the cost increase in the management of advanced liver disease, reaching €35,000 in the first year of liver transplant [30]. However, the range of costs for liver transplant varies significantly, with the study by Younossi *et al.* providing an estimate of $168,643 (€129,412, adopted to reflect 2015 euro) in the first year of liver transplantation [13].

The present study also showed that treating half of the eligible patients with SMV + PR has a budget impact of €2.03 million on the SIF budget. It should be noted that this cost does not take into consideration additional discounts on drug prices, rebates and clawbacks, which significantly reduce the costs incurred by SIFs. In addition, given the reductions in prices overtime, this budget impact is expected to be reduced in the future, thus currently reflects the maximum possible budget impact under the specific assumptions of the analysis.

Furthermore, the budget impact of increasing the use of SMV + PR in 2016 is associated with long-term benefits for SIFs, as SMV + PR has a significantly improved effectiveness profile compared with PR alone. More specifically, the sustained virological response (SVR) of SMV + PR in this patient population (naïve, F0 - F2 patients) is 84% versus 52% in patients treated with PR [31]. Therefore, from the 372 patients estimated to undergo treatment at this stage, if 50% is treated with SMV + PR (186 patients), 156 can be cured and exit the health care system, whereas, of the 45% patients treated with PR (167), only 87 will be cured, while the remaining 80 will progress to advanced disease stages and seek more costly treatment. Since approximately 25% of chronic HCV patients ultimately develop cirrhosis, and annually 1.6% of them develop hepatocellular carcinoma (HCC) [32], treatment in earlier stages should be considered mandatory, in order to avoid increased health care costs for the SIFs at a later stage.

The current study only focuses on the economic impact of treating patients at early disease stages with SMV + PR and does not take into consideration the treatment's effectiveness, as it was out of scope. However, it was recently shown by Westerhout and colleagues that, within the UK health care setting, SMV + PR is cost-effective versus PR, for all fibrosis stages, with an incremental cost-effectiveness ratio of £9,725/QALY for treatment-naïve and £7,819/QALY for treatment-experienced patients [31].

This study has some limitations. First, resource use and associated costs are based on expert panel data rather than real world or registry evidence. Expert panels as a source of determining resource use is weaker than evidence from clinical trials or patient files, however, given the lack of such data for Greece, it was deemed as the most appropriate method to elicit such information. Delphi panels are widely recognized as valid evidence generation methods for eliciting resource use in health care, and have been widely accepted by health technology assessment agencies globally [17].

Another limitation of the study is that in the present analysis the cost of medical consultation has been set to zero, due to the fact that consultations in hospital outpatient wards (where 100% of the consultations for this disease take place) are covered by the hospital budget that are not incurred by SIFs. This however, does not mean that there is no cost to the health care system. Therefore, it could be argued that the total direct cost of the disease management is not fully reflected due to the perspective adopted in this analysis. In addition, it should be highlighted that prices reimbursed by EOPYY for lab and imaging tests and hospital care do not properly capture true costs, as most of these prices have not been updated for at least the past 5 - 6 years (for example, the cost of DRGs has not been updated since March 2012). Therefore, total cost estimated in this analysis could be underestimated.

Furthermore, there are certain aspects of the disease - related costs that have not been investigated in the present study, such as presenteeism (*i.e.* going to work despite illness), social care, patients' shorter life-expectancy, time and productivity losses of non-paid care-givers (from patients family and friendly environment). Clinical and quality of life considerations have been excluded from the analysis as out of scope.

Despite limitations, the present study provides a view of the cost of managing CHC through all disease stages without pharmaceutical treatment, and the costs of curing patients—rather than just managing disease symptoms—in the early stages. Also, to the best of our knowledge, this is the first study to estimate indirect costs associated with the disease by stage.

The estimated budget impact of SMV + PR reflects the cost of complete patient cure, which can bring additional savings from allowing patients to exit the health care system and not seek treatment at later, more costly disease stages. Therefore, the results of the present study can provide valuable input to evidence based decision making in health care. Especially under current economic envi-

ronment, decision makers in Greece need to seek treatment options that can provide future savings. Further research is required at the local level in order to determine the cost-effectiveness of SMV + PR in the management of CHC in Greece.

5. Conclusion

Costs of managing CHC increase dramatically with disease severity. SMV + PR as a treatment option for naive patients at early disease stages has a significant but manageable budget impact, and could prevent high costs at advanced stages.

Role of the Funding Source

Funding for this project was provided from Janssen Cilag to the University of Peloponnese. Publication of the study results was not contingent upon sponsor's approval.

References

[1] Mühlberger, N., Schwarzer, R., Lettmeier, B., Sroczynski, G., Zeuzem, S. and Siebert, U. (2009) HCV-Related Burden of Disease in Europe: A Systematic Assessment of Incidence, Prevalence, Morbidity, and Mortality. *BMC Public Health*, **9**, 34. https://doi.org/10.1186/1471-2458-9-34

[2] Zanetti, A.R. (1999) Global Surveillance and Control of Hepatitis C. Report of a WHO Consultation Organized in Collaboration with the Viral Hepatitis Prevention Board, Antwerp, Belgium. *Journal of Viral Hepatitis*, **6**, 35-47.

[3] European Association on the Studies on the Liver (EASL) (1999) EASL International Consensus Conference on Hepatitis C. Paris, 26-27 February 1999, Consensus Statement. *Journal of Hepatology*, **31**(Suppl. 1), 3-8.

[4] Lauer, G.M. and Walker, B.D. (2001) Hepatitis C Virus Infection. *The New England Journal of Medicine*, **345**, 41-52. https://doi.org/10.1056/NEJM200107053450107

[5] Alter, H.J. and Seeff, L.B. (2000) Recovery, Persistence, and Sequelae in Hepatitis C Virus Infection: A Perspective on Long-Term Outcome. *Seminars in Liver Disease*, **20**, 0017-0036. https://doi.org/10.1055/s-2000-9505

[6] Raptopoulou, M., Touloumi, G., Tzourmakliotis, D., Nikolopoulou, G., Dimopoulou, M., Giannoulis, G. and Manolakopoulos, S. (2011) Significant Epidemiological Changes in Chronic Hepatitis C Infection: Results of the Nationwide HEPNET-GREECE Cohort Study. *Hippokratia*, **15**, 26-31.

[7] Gogos, C.A., Fouka, K.P., Nikiforidis, G., Avgeridis, K., Sakellaropoulos, G., Bassaris, H. and Skoutelis, A. (2003) Prevalence of Hepatitis B and C Virus Infection in the General Population and Selected Groups in South-Western Greece. *European Journal of Epidemiology*, **18**, 551-557. https://doi.org/10.1023/A:1024698715741

[8] Goritsas, C., Plerou, I., Agaliotis, S., Spinthaki, R., Mimidis, K., Velissaris, D. and Labropoulou-Karatza, C. (1999) HCV Infection in the General Population of a Greek Island: Prevalence and Risk Factors. *Hepato-Gastroenterology*, **47**, 782-785.

[9] Koulentaki, M., Spanoudakis, S., Kantidaki, E., Drandakis, P., Tzagarakis, N., Biziagos, E. and Kouroumalis, E.A. (1999) Prevalence of Hepatitis B and C Markers in Volunteer Blood Donors in Crete. A 5-year Study. *Journal of Viral Hepatitis*, **6**, 243-248.

[10] Malliori, M., Sypsa, V., Psichogiou, M., Touloumi, G., Skoutelis, A., Tassopoulos, N. and Stefanis, C. (1998) A Survey of Bloodborne Viruses and Associated Risk Behaviours in Greek Prisons. *Addiction*, **93**, 243-251.

[11] Hatzakis, A., Chulanov, V., Gadano, A.C., Bergin, C., Ben-Ari, Z., Mossong, J., Schréter, I., Baatarkhuu, O., Acharya, S., Aho, I., Anand, A.C., Andersson, M.I., Arendt, V., Arkkila, P., Barclay, K., Bessone, F., Blach, S., Blokhina, N., Brunton, C.R., Choudhuri, G., Cisneros, L., Croes, E.A., Dahgwahdorj, Y.A., Dalgard, O., Daruich, J.R., Dashdorj, N.R., Davaadorj, D., de Knegt, R.J., de Vree, M., Estes, C., *et al.* (2015) The Present and Future Disease Burden of Hepatitis C Virus (HCV) Infections with Today's Treatment Paradigm Volume 2. *Journal of Viral Hepatitis*, **22**, 26-45. https://doi.org/10.1111/jvh.12351

[12] Giannousis, I.P., Papatheodoridis, G.V., Deutsch, M.J., Manolakopoulos, S.G., Manesis, E.K., Koskinas, J.S. and Archimandritis, A.J. (2010) The Burden and Recent Epidemiological Changes of the Main Chronic Liver Diseases in a Greek Referral Tertiary Centre. *European Journal of Gastroenterology & Hepatology*, **22**, 172-179. https://doi.org/10.1097/MEG.0b013e328331115b

[13] Younossi, Z.M., Singer, M.E., Mir, H.M., Henry, L. and Hunt, S. (2014) Impact of Interferon Free Regimens on Clinical and Cost Outcomes for Chronic Hepatitis C Genotype 1 Patients. *Journal of Hepatology*, **60**, 530-537.

[14] Wong, J.B., McQuillan, G.M., McHutchison, J.G. and Poynard, T. (2000) Estimating Future Hepatitis C Morbidity, Mortality, and Costs in the United States. *American Journal of Public Health*, **90**, 1562. https://doi.org/10.2105/AJPH.90.10.1562

[15] Kowdley, K.V., Lawitz, E., Poordad, F., Cohen, D.E., Nelson, D.R., Zeuzem, S., Xie, W., *et al.* (2014) Phase 2b Trial of Interferon-Free Therapy for Hepatitis C Virus Genotype 1. *New England Journal of Medicine*, **370**, 222-232. https://doi.org/10.1056/NEJMoa1306227

[16] Mohamed, A.A., Elbedewy, T.A., El-Serafy, M., El-Toukhy, N., Ahmed, W. and Ali El Din, Z. (2015) Hepatitis C Virus: A Global View. *World Journal of Hepatology*, **7**, 2676-2680. https://doi.org/10.4254/wjh.v7.i26.2676

[17] Hsu, C.C. and Sandford, B.A. (2007) The Delphi Technique: Making Sense of Consensus. *Practical Assessment, Research & Evaluation*, **12**, 1-8.

[18] Ministry of Health: Positive Reimbursement List. Governmental Gazette 333-16.2.16.

[19] Ministry of Health. http://www.moh.gov.gr

[20] National Organization for Health Care Services Provision. http://www.eopyy.gov.gr

[21] Ministry of Health (2012) Diagnosis Related Groups and Related Tariffs. Governmental Gazette 946, 27/3/2012.

[22] OECD: Data Extracted in Apr 2016 from OECD. Stat. http://www.oecd.org/els/health-systems/health-data.htm

[23] KEPA-IKA. https://www.ika.gr/gr/infopages/kepa/home.cfm

[24] http://www.statistics.gr

[25] Papatheodoridis, G., Sypsa, V., Kantzanou, M., Nikolakopoulos, I. And Hatzakis, A. (2015) Estimating the Treatment Cascade of Chronic Hepatitis B and C in Greece using a Telephone Survey. *Journal of Viral Hepatitis*, **22**, 409-415. https://doi.org/10.1111/jvh.12314

[26] Manolakopoulos, S. (2013) Greek Final Outcomes of the Multicentered Study GUARD-C in Chronic Hepatitis C. *Annals of Gastroenterology*, **26**, 45.

[27] Athanasakis, K., Arzoumanidou, D., Petrakis, I., Karampli, E., Theodoropoulou, T., Retsa, M. and Kyriopoulos, J. (2013) A Cost-of-Illness Analysis of Hepatitis C in Greece. *Value Heal*, **16**, A323-A636.

[28] Athanasakis, K., Ferrante, S.A., Kyriopoulos, I.I., Petrakis, I., Hill, M., Retsa, M.P. and Kyriopoulos, J. (2015) Boceprevir for Chronic Genotype 1 Hepatitis C Virus in the Current Health Care Setting in Greece: A Cost-Effectiveness Analysis. *Clinical Therapeutics*, **37**, 1529-1540.

[29] Yfantopoulos, J., Papagiannopoulou, V., Kaligeros, K., Manolakopoulos, S., Charos, A. and Koskinas, J. (2008) Economic Evaluation of Hepatitis C in Greece. *Arch Hell Med*, **1**, 191-200.

[30] Solomon, M., Bonafede, M., Pan, K., Wilson, K., Beam, C., Chakravarti, P. and Spiegel, B. (2011) Direct Medical Care Costs among Pegylated Interferon plus Ribavirin-Treated and Untreated Chronic Hepatitis C Patients. *Digestive Diseases and Sciences*, **56**, 3024-3031. https://doi.org/10.1007/s10620-011-1802-z

[31] Westerhout, K., Treur, M., Mehnert, A., Pascoe, K., Ladha, I. And Belsey, J. (2015) A Cost Utility Analysis of Simeprevir Used with Peginterferon+ Ribavirin in the Management of Genotype 1 Hepatitis C Virus Infection, from the Perspective of the UK National Health Service. *Journal of Medical Economics*, **18**, 838-849. https://doi.org/10.3111/13696998.2015.1044457

[32] Global Burden of Hepatitis C Working Group (2004) Global Burden of Disease (GBD) for Hepatitis C. *The Journal of Clinical Pharmacology*, **44**, 20-29. https://doi.org/10.1177/0091270003258669