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Research Article

High Efficacy of Recommended Regimens in HCV Genotype 4 Advanced Disease

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Abstract

Aim: To analyze the efficacy of direct acting antivirals (DAAs) regimens in HCV genotype 4 patients, especially those with advanced liver fibrosis or cirrhosis.

Methods: All HCV genotype 4 patients who received DAAs in the "HERACLIS" cohort were included. All patients who fulfilled the national criteria for DAA reimbursement [F4 naive, F3-F4 retreated, decompensated cirrhosis, orthotopic liver transplantation, severe extrahepatic manifestation] were analyzed in this cohort. Sofosbuvir+simeprevir+ribavirin (SOF+SMV ± R), sofosbuvir+daclatasvir+ribavirin (SOF+DCV ± R), ledipasvir/sofosbuvir+ribavirin (LDV/SOF ± R), ombitasvir/paritaprevir/ritonavir+ribavirin (2D+R), sofosbuvir/velpatasvir+ribavirin (SOF/VEL ± R) and elabsvir/grazoprevir+ribavirin (EBR/GZR ± R) considered as currently recommended regimens according to the international and local guidelines. The primary efficacy endpoint was sustained viral response 12 weeks after end of treatment (SVR12); predictors of response to treatment were also assessed.

Results: 259 patients with genotype 4 (males 58%, age 55+10 years) were treated with DAA regimens; SOF+SMV+R in 33 (12.7%), SOF+DCV+R in 15 (5.8%), LDV/SOF+R in 42 (16.3%), 2D+R in 139 (53.7%), SOF/VEL+R in 3 (1.2%), EBR/GZR+R in 7 (2.7%). SVR12 rates for the first 189 patients who completed post-treatment follow-up was 90% for SOF+SMV+R, 93% for SOF+DCV+R, 89% for LDV/SOF+R and 97% for 2D+R and 100% for EBR/GZR. SVR12 was 97.4% for F3, 92.6%, for F4, and 82.6% for decompensated cirrhosis. Patients without than with SVR12 had higher BMI [(28.5 vs 26.2 kg/m^2); p = 0.01]], lower platelets (p = 0.018), or albumin (p = 0.061), and more frequently decompensated cirrhosis (26.7% vs 10.1%, p = 0.072) and use of non-recommended regimens [33.3% vs 7.9%; p = 0.006]. SVR12 rates in those with decompensated cirrhosis treated with currently recommended DAAS was 81% (17/21). Logistic regression analysis showed that lower SVR12 rate was independently associated only with the use of non-currently recommended regimens (OR: 0.2163, 95% CI: 0.033 - 0.81; p = 0.027).

Conclusion: The combinations of two DAA+R for 12 weeks achieve 95%-100% SVR12 rates in genotype 4, F3 fibrosis or compensated cirrhosis patients; optimization is required in decompensated cirrhosis.

Keywords: *HCV Infection; Genotype 4; Cirrhosis; Antiviral Therapy; Direct Acting Antivirals*

Introduction

Hepatitis C virus (HCV) represents a major cause of liver disease worldwide and a potential cause of substantial morbidity and mortality in the future [1]. Natural history of the disease shows that 5% - 20% among HCV patients will go on to develop cirrhosis over a period of 20 - 30 years and 1% - 5% will die from the consequences of chronic infection HCV genotype 1 is the most prevalent worldwide (49.1%), followed by genotype 3 (17.9%), 4 (16.8%) and 2 (11.0%). Genotypes 5 and 6 are responsible for the remaining < 5% [2]. While genotypes 1 and 3 are common worldwide, the largest proportion of genotype 4 is prevalent in lower-income countries [3] being more common in the Middle East and Africa, where it accounts for more than 80% of HCV infections. Egypt, a country with a massive HCV-related disease burden (15%), has the highest prevalence of HCV-4. In recent years, HCV-4 has spread to parts of the world where it was previously rare and especially in some European countries, such as Spain, France, and Greece [4]. In Greece, prevalence of HCV-4 has been reported to be as high as 13.2 - 15.2% in some series, and presenting a moderately increasing trend over time, due to immigration from Northern Africa. Subtype 4a is the most prevalent (78%) [4-6].

Generally, genotype 4 has been less extensively studied, as for epidemiology, natural disease history and therapeutic endpoints. Treatment advances are deficient and efficacy rates low using conventional interferon monotherapy or combination with ribavirin [7]. In a Greek cohort of patients treated with Pegylated interferon (Peg-IFN) along with ribavirin, SVR rates were 43.5% [8]. Even in the new era of Direct Acting Antivirals (DAAs), patients with genotype 4 are significantly underrepresented in phase 3 clinical trials. Undoubtedly, results from real-life cohorts from regions with increased prevalence, such as Greece, would add important knowledge to the management of these patients.

In our cohort we analyzed data from patients with HCV genotype 4 to assess the efficacy of different regimens of DAAs. Particularly we present data on patients with advanced liver fibrosis and cirrhosis, pooled from a larger cohort conducted in 14 Greek centers.

Materials and Methods

Study characteristics

This study represents a sub-analysis of the national, multicenter, observational cohort "HERACLIS" including HCV patients from 14 Greek centers. We prospectively studied patients with HCV-4 presenting in the hepatology clinics around the country for treatment be-

tween June 2014 and February 2017. We analyzed all patients treated with DAAs fulfilling the Greek national criteria for DAA reimbursement during the study period. We therefore included adult (> 18 years old) chronic hepatitis C patients with a) METAVIR F3 stage of fibrosis based on liver biopsy or liver elastography who were treatment experienced, b) F4 stage of fibrosis (treatment naïve or experienced), c) decompensated cirrhosis, d) orthotopic liver transplantation, or e) severe extrahepatic manifestation.

The therapy schedule was according to the national guidelines of the Greek Association for the Study of the Liver and in agreement with the international guidelines. Treatment duration was 12 or 24 weeks depending on the disease features (i.e. severity, treatment experience) and the required DAA regimen. According to the international and local guidelines the recommended regimens during the study period were: Peg-IFN +ribavirin +simeprevir (PR+SMV), Peg-IFN +ribavirin +sofosbuvir (PR+SOF), sofosbuvir +ribavirin (SOF+R), sofosbuvir +simeprevir ± ribavirin (SOF+SMV ± R), sofosbuvir +daclatasvir ± ribavirin (SOF+DCV ± R), sofosbuvir/ledipasvir ± ribavirin (SOF/LDV ± R), ombitasvir-paritaprevir-ritonavir +ribavirin (2D+R), sofosbuvir/velpatasvir ± ribavirin (SOF/VEL ± R) and elbasvir/grazoprevir ± ribavirin (EBR/GZR ± R). Since the first 3 regimens are not currently recommended by the local and international guidelines, we considered as currently recommended regimes for HCV-4 all regimens except for the first three (PR+SMV, PR+SOF, SOF+R).

The diagnosis of cirrhosis was based on the results of liver biopsy or liver elastography (liver stiffness > 12 kPa). Decompensated cirrhosis was diagnosed in cirrhotic patients with a history (current or previous) of variceal bleeding, ascites, hepatic encephalopathy, and/or jaundice of non-obstructive origin.

At baseline we recorded for every patient a complete medical history, including demographic and clinical features. HCV genotype analysis was conducted. HCV RNA was quantified at baseline, end of treatment (EOT) and 12 weeks post EOT to detect sustained viral response (SVR12). Patients were followed with clinical examination and laboratory parameters at baseline, every 4 weeks during therapy, at EOT and 12 weeks post EOT.

The primary objective was to evaluate the efficacy of the DAAs regimens in the HCV-4 infected Greek patients. Subsequently, the primary endpoint was the proportion of patients with undetectable HCV RNA at 12 weeks after the completion of treatment (SVR12 rates). We also assessed factors associated with the response to treatment.

The study protocol was approved by our Institutional Review Board and conformed to the ethical guidelines of the 1975 Declaration of Helsinki.

Statistical analysis

We conducted an intention-to-treat analysis including every patient enrolled in our cohort to receive DAA therapy. Results were presented using descriptive statistics and primary outcomes were identified as SVR12 rates. Continuous variables were presented as mean ± standard deviation (normally distributed) or median with interquartile range (non-normally distributed). Categorical variables were expressed as frequencies or percentages. Comparisons between regimens and SVR12 rates were performed using chi-square or Fisher's exact test for categorical variables. Logistic regression analysis was carried out to identify independent factors associated with the SVR12 rates. P value < 0.05 was considered statistically significant. Statistical analysis was conducted by SPSS (version 23.0 IBM).

Results and Discussion

Two hundred fifty nine patients (males 58%, age 55+10 years) with HCV-4 from a total of 1309 HCV patients consisting "HERACLIS" cohort (19.8%) were studied prospectively. Their baseline characteristics are shown in table 1. Seventy three patients (28.5%) mentioned a history of parenteral drug abuse (PDU) and 164 (63.3%) were treatment experienced. Nineteen patients (7.5%) had a previous DAA failure history. Sixty six percent (172 patients) of our genotype 4 cohort were cirrhotics (METAVIR stage F4), while 27 (10.4%) had decompensated disease.

Variable	Patients, n = 259
Age (mean ± SD, years)	55 ± 10
Sex, male n, (%)	151 (58%)
Source of infection, n, (%)	
PDU	73 (28.5)
Transfusion	81 (31.6)
Iatrogenic/Egypt	25 (9.8)
Sexual	1 (0.4)
Unknown	79 (29.7)
History of past treatment, n, (%)	
Yes	164 (63.3)
No	95 (36.7)
Type of previous treatment, n, (%)	
IFN	20 (7.6)
IFN+RBV	28 (10.8)
PR	180 (69.6)
PR+TPV	2 (0.6)
PR+SOF	11 (4.4)
PR+SMV	3 (1.3)
SOF+RBV	3 (1.3)
SOF+SMV	5 (1.9)
SOF+SMV+RBV	2 (0.6)
LDV/SOF+RBV	2 (0.6)
Other	3 (1.3)
METAVIR stage, n, (%)	
F0-2	8 (3.1)
F3	52 (20.1)
F4	172 (66.4)
Decompensated cirrhosis	27 (10.4)
HCV RNA (median, range, IU/mL)	876,841 (550 - 1,500,000,000)
BMI (mean ± SD, kg/m^2)	26 ± 4.5
Hemoglobulin (mean ± SD, g/dL)	13.4 ± 2.2
ALT (median, range, IU/L)	54 (6 - 478)
White blood cells (median, range, /ml)	6240 (1600 - 19800)
Platelets (median, range, x 10^3/μL)	186 (35 - 803)
Albumin (mean ± SD, g/dL)	3.9 ± 0.5
Creatinine (median, range, mg/dL)	0.9 (0.4 - 10)

Table 1: *Baseline clinical and laboratory characteristics of the 259 patients with HCV genotype 4.*

PDU: Problematic Drug Abuse; IFN: Interferon; RBV: Ribavirin; PR: Pegylated Interferon+Ribavirin; TPV: Telaprevir; SOF: Sofosbuvir; SMV: Simeprevir; LDV: Ledipasvir; BMI: Body Mass Index; ALT: Alanine Transaminase.

Our patients received different regimens of DAAs based on guidelines and clinician preference. One hundred twenty nine patients (49.8%) were treated with 2D+R (Figure 1). Treatment duration was 12 weeks for all combinations except for the PR+SMV combination and 6 cirrhotic patients (24 weeks; 2 patients under SOF+R, 2 patients under LDV/SOF+R, 2 patients under 2D+R).

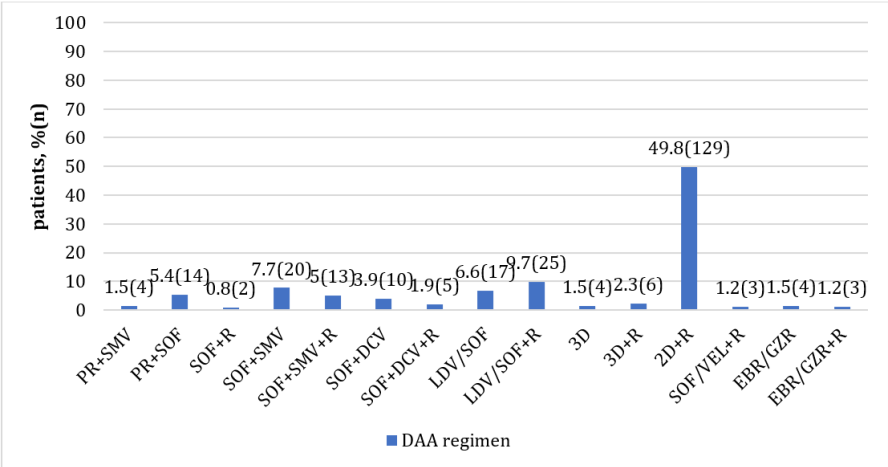

Figure 1: *Type of treatment administered.*

Primary outcome assessment

We investigated the primary efficacy endpoint for the first 204 patients who completed post-treatment follow up. Overall, 189 patients (about 93%) achieved SVR12. SVR12 rates were 100% for PR+SMV, 64% for PR+SOF, 100% for SOF+R, 90% for SOF+SMV+R, 93% for SOF+DCV+R, 89% for LDV/SOF+R and 97% for 2D+R and 100% for EBR/GZR+R (Figure 2). SVR12 rates for different stages of hepatic injury were 100% for F0-F2 patients, 97.4% for F3, 92.6%, for F4, and 82.6% for decompensated cirrhosis.

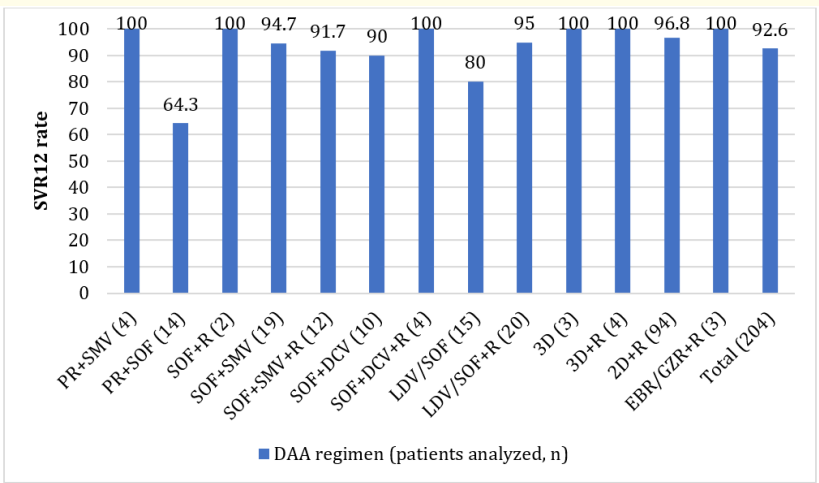

Figure 2: *SVR12 rates corresponding to each regimen.*

Predictors of the outcome

We further analyzed our patients and antiviral treatment characteristics to find factors associated with the outcome. Type of administered regimen showed significant association with SVR12 rates, p = 0.04. On the other hand, fibrosis stage was not associated with the

outcome, p = 0.153. Regarding our patients descriptive variables, those without than with SVR had higher BMI (28.5 vs 26.2 kg/m^2; p = 0.01), lower PLT (p = 0.018), or albumin (p = 0.061), and more frequently albumin < 3.5 g/dl (41.7% vs 15.3%; p = 0.032), PLT < 100 x 10^3/μL (33.3% vs 14.1%; p = 0.063). Moreover, they had more frequently decompensated cirrhosis (26.7% vs 10.1%, p = 0.072) and were treated with non-recommended regimens (33.3% vs 7.9%; p = 0.006) (Table 2). SVR rate in patients with decompensated cirrhosis treated with currently recommended DAAS was 82.6% (19/23).

Variables	Group 1 (n = 15, 7.4%)	Group 2 (n = 189, 92.6%)	p value
Sex, male (n, %)	8 (46.7)	114 (39.7)	0.79
Age (mean ± SD, years)	57 ± 7	55 ± 9	0.45
BMI (mean ± SD, kg/m^2)	28.5 ± 2.6	26.2 ± 4.6	0.01
Presence of diabetes (n, %)	3 (20)	24 (12.7)	0.69
Treatment experience (n, %)	10 (66.7)	124 (65.6)	1.0
Decompensated cirrhosis (n, %)	4 (26.7)	19 (10.1)	0.072
Hemoglobulin (mean ± SD, g/dl)	12.3 ± 1.8	13.5 ± 2.1	NS
WBC (median, range, /ml)	4450 (3100 - 7280)	6260 (2190 - 19800)	NS
Platelets (median, range, x10^3/μL)	117 (66 - 305)	160 (35 - 803)	0.018
< 100 (x10^3/μL, n, %)	5 (33.3)	26 (13.7)	0.063
> 100 (x10^3/μL, n, %)	10 (66.7)	158 (83.6)	
ALT (median, range, IU/L)	53 (23 - 93)	55 (10 - 261)	NS
Bilirubin (median, range, mg/dL)	1.4 (0.5 - 3.8)	0.8 (0.14 - 6.4)	NS
Albumin (median ± SD, g/dL)	3.6 ± 0.6	3.9 ± 0.48	0.061
<3.5 (g/dl, n, %)	5 (33.3)	25 (13.2)	
>3.5 (g/dl, n, %)	7 (46.6)	142 (75.1)	0.032

Table 2: *Clinical and laboratory characteristics of patients who did not achieve (group 1) or achieved SVR12 (group 2).*

Factors associated with the outcome: multivariate analysis

Conducting further data analysis, we included all the above mentioned factors found to be significant by univariate analysis in a multivariate model, to identify those related with lower possibility of achieving viral clearance. Logistic regression multivariable analysis showed that lower SVR rates were independently associated only with the use of non-currently recommended regimens (OR: 0.2163, 95% CI: 0.033 - 0.81; p = 0.027).

We pooled data from 259 HCV genotype 4 patients with advanced liver fibrosis or cirrhosis, from the large Greek cohort "HERACLIS", to assess the treatment efficacy of DAAs and establish factors associated with the outcome. Our analysis was conducted on the first 204 patients who had completed the therapeutic schedule and the minimum post-treatment follow-up. Based on this, HCV-4 can be treated with the currently recommended combinations of two DAAs+R; 2D+R or EBR/GZR+R administered for 12 weeks showed excellent efficacy in patients with F3 fibrosis and those with compensated cirrhosis, achieving SVR rates 95% - 100%. In contrast patients with decompensated cirrhosis presented lower SVR12 rates, reaching about 83%, which is a common finding in real world cohorts of different genotypes

In Greece, where estimation of the current prevalence of hepatitis C ranges from 0.5% to 2%, there is increased distribution of HCV-4 averaging 20% [9]. Traditionally, HCV-4 has been considered a difficult to treat genotype [4]. Until 2014, the standard treatment was Peg-IFN plus ribavirin for 24 or usually 48 weeks [10], with low SVR rates confirmed by Elefsiniotis., *et al.* in a previously published Greek cohort [8]. The development of DAAs has led to impressive results for the majority of HCV patients both in clinical trials and the real world setting.

However, data for the efficacy of the majority of these regimens in patients with genotype 4 are generally lacking from the literature. This is due to the low prevalence of patients with this genotype in countries where the large clinical trials as well as the real life reports

are held. According to older reports, data on 12 weeks treatment with SOF+PR showed acceptable outcomes of this regimen only in treatment naïve patients; treatment experienced patients with a history of non-response to PR treatment and patients with advanced fibrosis were at increased risk for a virological failure, instead [11]. We confirmed that the PR+SOF combination has only moderate efficacy with SVR12 rates about 64%, even in non-cirrhotic patients. These rates are not acceptable in the current environment of HCV treatment with DAAs. The SOF+R combination has been studied in several studies, mainly in Egyptian population, with mixed results even for the 24 week duration of treatment where SVR rates are reported between 71% and 97% [12-14]. This combination is not recommended by the current treatment guidelines and it was used only in 2 patients in our cohort.

Furthermore, OSIRIS study presented SOF+SMV for 12 weeks as a highly effective and well-tolerated treatment regimen for HCV-4 in treatment-naïve and Peg-IFN/ribavirin-experienced patients with or without compensated cirrhosis [15]. In our cohort, SOF+SMV+R had noteworthy performance with an SVR12 rate around 90%, in compensated and decompensated cirrhotic patients. Based on the latest European guidelines [16], we administered the combination SOF+DCV+R which had 93% efficacy and could be used in HCV-4 patients. In a small cohort of 21 genotype 4 patients, the 12 week regimen of oral combination SOF/LDV seemed to be effective with 100% SVR12, including patients with and without cirrhosis and those who were treatment naive and interferon treatment experienced [17]. In a recently published report of real world from Spain this combination achieved very good SVR results both in the overall population (SVR 95.4%) and the cirrhotic patients (SVR 93.2%) [18]. In fact, our findings showed 89% SVR12 in 35 HCV-4 patients who received LDV/SOF+R, including 13 decompensated cirrhotics. The large trials PEARL-I and AGATE I established the use of all oral regimen 2D+R, having high SVR12 rates in both non-cirrhotic and cirrhotic patients with HCV genotype 4 either naïve or treatment experienced [19,20]. Our findings supported the use of 2D+R too, showing 97% efficacy in a large subgroup of 129, mainly F4, patients. Finally, the use of the EBR/GZR combination has been tested in only a small group of genotype 4 patients in the registration trials yielding questionable data. This is reflected in the most recent international guidelines where a more conservative approach was selected for this population, especially in cirrhotic treatment experienced patients [21]. Although we treated only 7 compensated cirrhotic patients with EBR/GZR+R, results showed no virological failure and 100% SVR12 rate, which could be promising for this combination if confirmed.

Further analysis on the patients who failed to clear the virus showed they had more frequently indications of cirrhosis or even established decompensated disease, for whom SVR12 was 82.6% (19/23 patients). In fact, our multivariate analysis outlined the importance of treating each patient with a recommended regimen in order to achieve the highest SVR12 rates.

This study provides robust evidence on the management of HCV-4 patients based on real-life practice. It represents a sub-analysis of the large Greek cohort "HERACLIS" which consists of all Greeks treated with DAAs in the hepatology clinics around the country. To our knowledge, our study is one of the largest to be presented in patients with HCV genotype 4. Nonetheless the limitations of the study are the inherent for this type of real word practice studies, i.e. observational design, potential bias in patient selection by the treating physician and finally absence of data for the more recent combination of SOF/VEL which achieved 100% SVR rates in the ASTRAL-1 registration trial [22].

Conclusion

In conclusion, our study shows that the currently recommended combinations of two DAAs+R, 2D+R and EBR/GZR+R, for 12 weeks has excellent efficacy in HCV-4 patients with F3 fibrosis and compensated cirrhosis. In accordance to existing data, further treatment optimization seems to be required in HCV genotype 4 patients with decompensated cirrhosis.

Conflict of Interest

Ioannis Goulis: Advisor/lecturer for Abbvie, Bristol-Myers Squibb, Gilead, Janssen, Merck Sharp and Dohme, Novartis, Roche; research grants Abbvie, Bristol- Myers Squibb, Gilead, Merck Sharp and Dohme.

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