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Effectiveness and safety of daclatasvir/sofosbuvir with or without ribavirin in genotype 3 hepatitis C virus infected patients. Results in real clinical practice

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Article history

Received: 15 October 2018; Revision Requested: 8 November 2018; Revision Received: 26 November 2018; Accepted: 9 January 2019

ABSTRACT

Objectives. Direct-acting antivirals have shown high efficacy in all hepatitis C virus (HCV) genotypes, but genotype 3 (G3) treatments continue to be a challenge, mainly in cirrhotic patients. The aim of this study is to analyse effectiveness and safety of daclatasvir associated with sofosbuvir with or without ribavirin in G3-HCV infected patients in real clinical practice.

Patients and methods. An observational, prospective, cohort study over 2.5 years, in G3-HCV infected adult patients, in all fibrosis stages including patients with decompensated cirrhosis. Treatment was a combination of sofosbuvir 400 mg/day + daclatasvir 60 mg/day, with or without a weight-adjusted dosing of ribavirin for 12 or 24 weeks. The primary efficacy endpoint was sustained virologic response rates 12 weeks after therapy (SVR12). The primary safety endpoint was treatment withdrawal rates secondary to severe adverse events.

Results. A total of 111 patients were enrolled, 32.4% cirrhotics and 29.9% treatment-experienced. The global SVR12 rate was 94.6%, while the SVR12 rate in F3-4 fibrosis stage patients was 90.8% versus 100% in patients with F0-2 fibrosis ($p=0.03$). In cirrhotic patients, SVR12 was 100% versus 40% depending on whether ribavirin was added or not to daclatasvir/sofosbuvir ($p=0.001$). No other patient or treatment basal variables influenced the treatment effectiveness. No patient treatment withdrawal secondary to severe adverse events was observed.

Conclusions. Daclatasvir/sofosbuvir \pm ribavirin is highly effective in G3-HCV infected patients. Advanced degrees of fibrosis significantly decrease the effectiveness of this treatment, which motivates the need for the addition of ribavirin in cirrhotic patients. The regimen was safe and well tolerated.

Keywords: hepatitis C; genotype 3; daclatasvir; sofosbuvir; ribavirin.

Efectividad y seguridad de daclatasvir/sofosbuvir con o sin ribavirina en pacientes infectados por el genotipo 3 del virus de la hepatitis C. Resultados en práctica clínica real

Objetivos. Los antivirales de acción directa han demostrado una alta eficacia en todos los genotipos del virus de la hepatitis C (VHC), pero los tratamientos para el genotipo 3 (G3) siguen siendo un desafío, principalmente en pacientes cirróticos. El objetivo de este estudio es analizar la efectividad y la seguridad del daclatasvir asociado con sofosbuvir con o sin ribavirina en pacientes infectados por G3-VHC en la práctica clínica real.

Pacientes y métodos. Estudio observacional, prospectivo, de cohorte de más de 2,5 años, en pacientes adultos infectados con G3-VHC, en todos los estadios de fibrosis, incluidos los pacientes con cirrosis descompensada. El tratamiento fue una combinación de sofosbuvir 400 mg / día + daclatasvir 60 mg / día, con o sin una dosis de ribavirina ajustada por peso durante 12 o 24 semanas. El criterio de valoración principal de eficacia fue la tasa de respuesta virológica sostenida 12 semanas después del tratamiento (RVS12). La variable principal de seguridad fue la tasa de suspensiones de tratamiento secundaria a eventos adversos graves.

Resultados. Se incluyeron 111 pacientes, 32,4% cirróticos y 29,9% con experiencia previa de tratamiento antiviral. La tasa global de RVS12 fue del 94,6%, mientras que la tasa de RVS12 en pacientes con estadio de fibrosis F3-4 fue del 90,8% frente al 100% en pacientes con fibrosis F0-2 ($p = 0,03$). En pacientes cirróticos, la RVS12 fue del 100% en comparación con el 40%, dependiendo de si se agregó o no ribavirina a daclatasvir / sofosbuvir ($p = 0,001$). Ninguna otra variable basal del paciente o del tratamiento influyó en la efectividad del tratamiento. No se observó ninguna suspensión del tratamiento secundario a eventos adversos graves.

Conclusiones. Daclatasvir / sofosbuvir \pm ribavirina es altamente efectivo en pacientes infectados por G3-VHC. Los

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grados avanzados de fibrosis disminuyen significativamente la efectividad de este tratamiento, lo que motiva la necesidad de la adición de ribavirina en pacientes cirróticos. El régimen fue seguro y bien tolerado.

Palabras clave: hepatitis C; genotipo 3; daclatastir; sofosbuvir; ribavirina

INTRODUCTION

World Health Organization (WHO) states that viral hepatitis is a major public health problem and that globally, in 2015, 71 million people were living with chronic hepatitis C virus (HCV) infection [1]. The distribution of HCV by viral genotype varies from one region to another, with genotype 3 (G3) being the second most prevalent worldwide after genotype 1, which implies around 30% of chronic hepatitis C (CHC) cases [2]. In addition, G3-HCV chronic infection is characterised by a faster progression to liver cirrhosis [3-6] and development of hepatocellular carcinoma (HCC) [7], as well as higher rates of hepatic steatosis development as the result of multiple mechanisms [8-11]. Another remarkable feature of G3-HCV is the lower rates of sustained virologic response (SVR) observed with direct-acting antivirals (DAAs), mostly in advanced liver fibrosis and/or non-responders to previous treatments, compared with other genotypes [12]. Therefore, the evaluation of the real-practice effectiveness of antiviral treatment against G3-HCV chronic infection in the era of DAAs is of special interest.

Treatment of CHC with DAAs in G3-HCV infected patients has rapidly evolved in accordance with the efficacy and safety results of clinical trials were known. Initially, the treatment of choice was based on the association of sofosbuvir (SOF) to ribavirin (RBV) [13] or peg-interferon (peg-IFN) and RBV, with discrete SVR rates; later, the combination of ledipasvir (LDV) and SOF, which achieved higher SVR12 rates. Nowadays, the American Association for the Study of Liver Diseases (AASLD) and the Infectious Diseases Society of America (IDSA) Guidance [14] recommends various therapeutic options based on the patient's previous treatments and the presence/absence of cirrhosis, among which is the association of daclatasvir (DCV) + SOF ± RBV [15], with a level of the evidence I that supports a strength of recommendation A; this recommendations are based on phase III pivotal clinical trials, where this association reached a SVR12 of 90% in naïve patients and 86% in treatment-experienced patients, and rates of SVR12 in non-cirrhotic patients of 96% versus 63% in patients with cirrhosis [16]. In addition, the analysis of viral response in patients with decompensated cirrhosis deserves special attention, due to the lower efficacy of antiviral treatment in this subgroup of HCV patients, especially in genotype 3 [16, 17], which translates into specific treatment recommendations in the main reference guides [14, 18]. However, in real clinical practice, few studies have evaluated the use of DCV/SOF ± RBV in G3-HCV infected patients, with a limited number of patients with advanced liver disease included. Therefore, more data about the use of this combination of DAAs will shed more light on clinical outcomes in real life.

Based on the above, the objective of this study is to analyse the effectiveness and safety of 12-24 weeks treatment regimens of DCV associated with SOF with or without RBV in a cohort of G3-HCV infected patients in real clinical practice.

PATIENTS AND METHODS

Study design and patient selection. We are looking at a unicentric, observational, prospective, cohort study of G3-HCV infected patients who started antiviral treatment with DCV/SOF±RBV between January 2015 and June 2017 and who had reached week 12 post-treatment before January 2018. Treatment decisions corresponded to the prescribing specialist (infectious diseases specialists or hepatologist), under usual clinical practice conditions valid during the study period. The therapeutic regimen was the one authorised by the European Medicine Agency (EMA) and consisted of a fixed combination of SOF 400 mg/day (Sovaldi®; Gilead Sciences International Ltd.) plus DCV 60 mg/day (Daklinza®; Bristol Myers Squibb Pharma EEIG), associated or not with the corresponding dose of RBV (Ribavirina Normon®; Normon Lab.), adjusted to body weight and patient characteristics. It was administered for 12 or 24 weeks, based on EMA recommendations. Inclusion criteria selected adult patients (≥18 years of age), with G3-HCV chronic infection, naïve or treatment-experienced to peg-IFN + RBV or DAAs, in all fibrosis stages (F0-4) including patients with decompensated cirrhosis or portal hypertension, human immunodeficiency virus (HIV) co-infected patients or liver transplant patients.

Effectiveness and safety variables. Pharmacological treatment effectiveness and a safety evaluation were carried out through SiMON [19], a local intelligent computerised monitoring system designed specifically for CHC patients on antiviral treatment. This system recorded, through an automated and anonymous way from clinical history data, the necessary effectiveness events for the evaluation of antiviral treatment based on algorithms previously defined by physicians and pharmacists responsible for CHC patients. These systems also allowing for registering patient reported outcomes as the adverse events (AEs).

The HCV viral load was determined using the real-time PCR technique with the Cobas® AmpliPrep platform from Roche; the kit is HCV Quantitative Test, version 2.0. The limits of detection and quantification in plasma (there is no significant difference in the serum) were 11 IU/mL (10-13 IU/mL, 95%CI) for the lower limit of detection (LOD) with a 95% positive result rate and 15 UI/mL for LOD with positive results. Viral load determinations were made at the baseline, week 4, at the end of antiviral treatment (week 12 or 24) and 12 weeks after antiviral treatment was completed. Transient elastography was used for the staging of liver fibrosis (Fibroscan®), stratifying patients according stiffness results in fibrosis F0-1 (<7.6 kPa), F2 (7.6-9.5 kPa), F3 (9.6- 14.4 kPa) or F4=cirrhosis (>14.4 kPa in HCV mono-infected patients and > 14.0 kPa in HIV co-infected patients).

Adherence rates were made following continuous measurement of the medication acquisition (CMA) method [20], during the monthly visits to the Hospital Pharmacy Service where the study was conducted, from the beginning to the end of the treatment.

The primary efficacy endpoint was the percentage of patients with SVR12, defined as the ribonucleic acid (RNA) HCV un-detectability 12 weeks post-treatment. Secondary efficacy variables were based on the analysis of covariates such as the presence of cirrhosis, fibrosis stage, previous antiviral treatments, hepatic decompensation, RBV addition to the combination of DAAs, HIV co-infection and liver transplantation. Treatment failure was defined as a lack of SVR12 due to a virologic breakthrough (RNA-HCV detectability in a patient with previous RNA-HCV un-detectability on treatment), relapse (RNA-HCV detectability 12 weeks post-treatment in a patient with RNA-HCV un-detectability at the end-of-treatment), virologic failure (no RNA-HCV un-detectability on treatment) or missing RNA-HCV data 12 weeks post-treatment due to on-treatment withdrawal secondary to severe AEs or death. The primary safety endpoint was the percentage of treatment withdrawal secondary to severe AEs; secondary variables included the patient reported AEs stratified into mild, moderate or severe and emergent haematological abnormalities stratified according to CTCAE v4.0 [21].

Statistical analysis. The Intention-To-Treat (ITT) evaluable population included all patients who took at least one dose of the prescribed treatment. Both baseline variables (demographics, clinical, histological and laboratory values and frequencies) and primary or secondary effectiveness and safety end-points were collected and analysed by a modified ITT (mITT) analysis, including ITT evaluable population patients and excluding patients without quantification of RNA-HCV 12 weeks post-treatment for reasons other than treatment failure. Quantitative variables were expressed as mean \pm standard deviation (SD) or as median and interquartile range if their distributions were normal or non-normal, respectively, and were analysed using the Student's t-test or the Mann-Whitney U-test according to data distribution. Qualitative variables were expressed as count and percentage, with confidence interval at 95% and were compared using a Chi-square test or Fisher's exact test. Primary end-points were expressed as a percentage and exact 95% binomial confidence interval. To determine any baseline factor influence on primary end-points, relative risk with a 95% confidence interval (Katz) for cohort studies was calculated using the Chi-square association test without Yates correction or Fisher's exact bilateral test according to the number of cases analysed. To detect differences between treatment subgroups and predictors of response, a univariate analysis was performed. Statistically significant results were considered when the p value was <0.05 . Statistical analysis was carried out using the Epidat 3.1 program.

Ethical aspects. This study complies with the Declaration of Helsinki of Good Clinical Practices. It was classified as "Ob-

servational Post-Authorization Study with Human Medicines" by the Spanish Agency of Medicines and Health Products (LMF-NAA-2016-01), dependent on the Ministry of Health and it was authorized by the Clinical Research Ethics Committee (CREC) of the Regional Health Service (number 2016/161). Patients signed an informed consent approved by the CREC for participation in the study and all their data was anonymised.

RESULTS

Baseline patient demographics and characteristics. A total of 950 adult patients started antiviral treatment during the study period at our institution, of which 132 were G3-HCV infected patients. Of these, 14 patients started antiviral treatment with different regimens of DCV/SOF \pm RBV and 7 patients who completed the therapeutic regimen did not attend their appointments for the determination of viral load 12 weeks post-treatment for reasons other than treatment failure. So, 111 patients constitute the study population for the mITT analysis. The average adherence to antiviral treatment was 99.3% (98.7% -99.9%, 95%CI). The patients were mostly men under 65 years of age, naïve to antiviral treatment, HCV mono-infected, with low HCV viral loads ($<6_1$ log IU/mL) and with advanced fibrosis (58.4% F3-4) although mostly non-cirrhotic (table 1). The majority of non-naïve patients had experienced recurrence to previous antiviral treatment based on Peg-Interferon + RBV and only one patient had received previous DAAs treatment. A small percentage of cirrhotic patients had suffered hepatic decompensation before the start of antiviral treatment. No patient had, at the beginning of treatment, a MELD score (Model of End-stage Liver Disease) higher than 10 points. Seven patients had a liver transplant. Also, 81.6% of cirrhotic patients had a treatment duration of 24 weeks compared to 6.7% of non-cirrhotic patients ($p<0.0001$). Meanwhile, 81.6% of cirrhotic patients associated RBV with DCV/SOF versus 13.3% of non-cirrhotic patients ($p<0.0001$).

Effectiveness outcomes. All patients achieved virologic response at the end of treatment, but 6 of them relapsed after 12 weeks of follow-up, so the SVR12 was 94.6% (89.9%-99.3%, 95%CI). One hundred per cent of patients with low fibrosis (F0-2) reached SVR12 (92.3%-100%, 95%CI) compared to 90.8% (83.0% - 98.6%, 95%CI) of patients with advanced fibrosis F3-4 ($p=0.03$) and the differences in effectiveness between F3 or F4 patients versus F0-2 patients were very similar ($p=0.10$ or $p=0.16$, respectively). No statistically significant differences were observed in SVR12 among cirrhotic patients with or without previous hepatic decompensation (84.6% vs 95.7%, $p=0.6$). SVR12 in naïve and pretreated patients was 96.2% and 90.3% respectively ($p=0.35$). One of the 4 patients with Child-Pugh-Turcotte (CPT) B grade did not reach SVR12 compared to 2 of the 32 CPT A grade patients. All patients treated after liver transplantation reached SVR12, including the patient with previous treatment based on DAAs; also, all HIV co-infected patients reached SVR12. SVR12 rates according to basal fibrosis stage are shown in figure 1. One hundred per cent (91.4%-100%, 95%CI) of patients treated with DCV/SOF with

Table 1 Baseline patient demographics and characteristics.

Characteristic	HCV-G3 infected patients (n=111)
Males, % (n)	78.4% (87)
Age, mean (years \pm SD)	50.21 \pm 6.98
Age \geq 65 years, % (n)	1.80% (2)
HIV co-infection, % (n)	24.3% (27)
Fibrosis stage, % (n)	
F0-1	9.0% (10)
F2	32.4% (36)
F3	26.2% (29)
F4	32.4% (36)
Elastography kPa, median (rank)	9.95 (4.0-72.1)
Previous clinical decompensation, % (n)	11.7% (13)
CTP classification, % (n)	
A	88.9% (32)
B	11.1% (4)
Hepatocellular carcinoma, % (n)	5.4% (6)
Liver transplant, % (n)	6.3% (7)
HCV viral load, log IU/mL (median)	6.13
\geq 6 ₁ IU/mL, % (n)	16.2% (18)
Platelets 10 ⁹ /mL (mean \pm SD)	155.5 \pm 61.5
Albumin mg/dL (mean \pm SD)	4.19 \pm 0.37
Bilirubin mg/dL (mean \pm SD)	0.77 \pm 0.70
Estimated Glomerular Filtration Rate \geq 60 ml/min, % (n)	92.8% (103)
Previous antiviral treatment, % (n)	
Naïve	72.1% (80)
Treatment-experienced	27.9% (31)
Response to previous antiviral treatment, % (n)	
Recurrent	54.8% (17)
Null responder	19.4 % (6)
Intolerant to treatment	12.9 % (4)
Unknown	12.9 % (4)
Treatment duration, % (n)	
12 weeks	67.6% (75)
24 weeks	32.4% (36)
RBV addition, % (n)	36.9% (41)

SD: standard deviation. kPa: kilopascals. HIV: human immunodeficiency virus. CPT: Child-Pugh-Turcotte. HCV: hepatitis C virus. RBV: ribavirin.

RBV reached SVR12, compared to 91.9% (85.0%-98.8%, 95% CI) of the patients who did not receive RBV ($p=0.083$). In the cirrhotic patients subgroup, SVR12 was 100% or 40.0% depending on the addition or not of RBV ($p=0.001$). Other potential baseline patient or treatment factors that could influence treatment effectiveness have not been identified, so no significant differences has been seen in SVR12 according to the patient's gender, HIV co-infection, previous liver transplanta-

tion, basal HCV viral load, platelets or albumin levels, previous antiviral treatment experience or treatment duration (table 2).

Safety outcomes. During follow-up, the rate of any degree of AEs secondary to DCV/SOF \pm RBV was 57.7% (48.0%-67.3%, 95%CI), although none of the patients required treatment withdrawal. Meanwhile, 4.5% of patients (1.5%-10.2%, 95%CI) developed serious AEs: three patients manifested severe headaches (which responded to the use of non-steroidal analgesics), one patient reported itching in lower limbs with bleeding (associated with grade II thrombocytopenia) and one patient presented constipation which required a visit to the Hospital Emergency Department and the use of a rectal enema. Beyond this, 9.9% (3.9%-15.9%, 95%CI) of patients developed moderate AEs: 5 with fatigue/asthenia, 3 with headache, 2 with anxiety and 5 with various symptoms (drowsiness, myalgia, insomnia, irritability and diarrhoea). Mild AEs were reported by 43.2% of patients (33.6%-52.9%, 95%CI), presenting a median of 1 event per patient, that usually disappeared after the first or second week of antiviral treatment. Table 3 shows the main safety data. Two patients required hospital admission, one secondary to hydropic decompensation and another due to respiratory infection. Both were cirrhotic patients, stage Child-Pugh-Turcotte (CTP) B and finally reached SRV12. During the antiviral treatment, no patient included in this study died.

Neither gender, HIV co-infection, liver transplantation, presence of liver cirrhosis, experience with previous antiviral treatments or treatment duration statistically had influenced on AEs development ($p>0.24$). However, RBV addition to DCV/SOF had a significant negative impact on treatment safety, both at the level of general or serious AEs, and, specifically, on the development of fatigue/asthenia or pruritus, although no patient required treatment withdrawal secondary to RBV addition. Also, 16.2% (8.9%-23.5%, 95%CI) of patients developed different degree cytopenias with respect to their baseline pretreatment situation: 2 patients experienced severe haematological alterations (one grade III neutropenia; other one thrombocytopenia grade III) and 11 patients minor alterations grade I-II (7 leukopenia, 6 thrombocytopenia, 3 anemia and 2 neutropenia). Cytopenia development is linked to liver cirrhosis with a relative risk of 4.2 (1.7-10.2, 95% CI, $p = 0.0016$) and to RBV addition to DCV/SOD, with a relative risk of 5.8 (2.1- 16.9, 95% CI, $p = 0.0002$). Also, 12 patients developed hyperbilirubinemia (8 grade I and 4 grade II).

DISCUSSION

Based on the results of our real clinical practice study, DCV/SOF \pm RBV shows a high antiviral effectiveness in G3-HCV in-

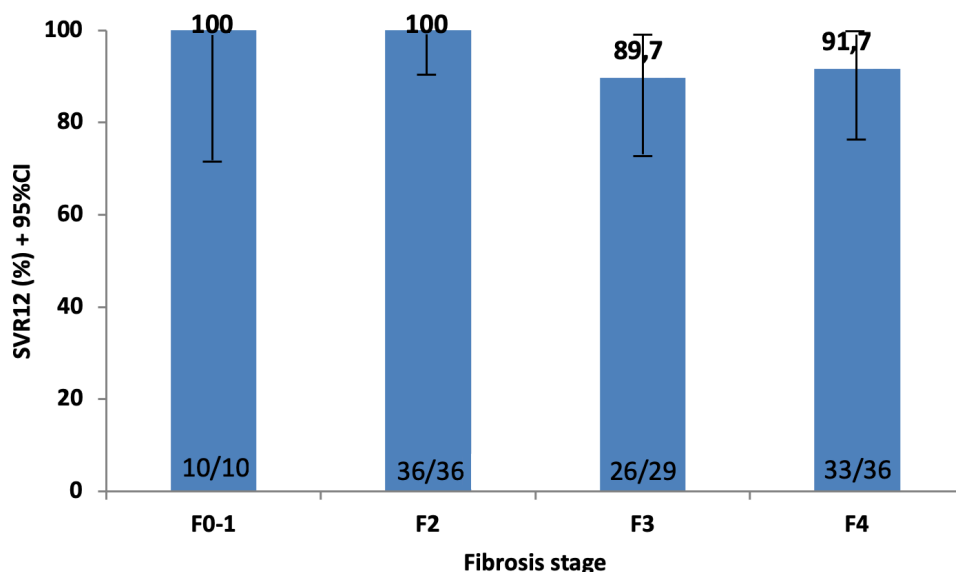


Figure 1 Sustained Virologic Response 12 (95%CI) according to basal fibrosis stage.

Table 2 Evaluation of basal factors associated with SVR12.

Basal factor	Relative risk ratio (CI 95%)	p
Gender: male vs female	1.07 (1.01 - 1.14)	0.19
HIV co-infection: yes vs no	1.08 (1.01 - 1.14)	0.15
Liver transplantation: yes vs no	1.06 (1.01 - 1.11)	0.99
HCV basal viral load $\geq 6_1$ UI/mL: yes vs no	0.93 (0.78 - 1.10)	0.24
Platelets 10^9 /mL: <100 vs ≥ 100	0.94 (0.80 - 1.10)	0.31
Albumin (mg/dL): <3.5 vs ≥ 3.5	0.88 (0.61 - 1.26)	0.32
Treatment-experienced patient: yes vs no	0.94 (0.83 - 1.06)	0.21
Treatment duration: 12 weeks vs 24 weeks	1.05 (0.94 - 1.18)	0.34

SVR12: sustained virologic response 12. HIV: human immunodeficiency virus. HCV: hepatitis C virus.

ected patients, with an overall SVR12 rate of 94.6%. This data is slightly higher than those observed in the pivotal phase III clinical trial ALLY-3 [16], where the SVR12 overall rate was 89% with a study population very similar to our study (25% of cirrhotic patients and 34% of previous non-responders to antiviral treatment). These differences in SVR12 are due to the high antiviral effectiveness shown in cirrhotic patients in our study compared with ALLY-3 (92% vs 66%), because we have implemented therapeutic strategies like 24 weeks treatment duration or RBV addition in cirrhotic patients ($p < 0.0001$), as the pivotal phase III clinical trial authors postulate to increase the effectiveness of DCV/SOF. Also, as ALLY-3 clinical trial, our study revealed higher rates of SVR12 in naïve compared to experienced patients, although this difference is not statistically significant.

We have observed a significantly lower effectiveness of DCV/SOF \pm RBV in patients with advanced fibrosis F3-4 compared to patients with low fibrosis F0-2 ($p = 0.03$). This is consistent with the results of the ALLY-3+ clinical trial [22], where SVR12 was 90% in a population of 50 patients with advanced fibrosis or compensated cirrhosis and also with the results observed in cirrhotic patients in the DCV European Compassionate Use Program (SVR12: 88-89%) [23], or in the DCV French Compassionate Use Program (SVR12: 85-90%) [24]. Studies in real clinical practice, such as the one published by Alonso et al [25] documented SVR12 rates of 94% in G3-HCV cirrhotic pa-

tients (both in CTP A and CTB B/C) and authors suggest that this high effectiveness in patients with advanced liver disease with regarding previous studies may be due to the fact that all cirrhotic patients were treated over 24 weeks with an RBV addition to the antiviral regimen. In fact, when analysing the influence of RBV on SVR12 in our study, it is observed that 100% of patients who have been added RBV to DCV/SOF reached SVR12 compared to 91.4% in those without RBV, and this superior effectiveness is a clinical and statistically significant difference when analysed in patients F4 (SVR12: 100% vs 40%, $p = 0.001$), confirming the importance of adding RBV to DCV/SOF in cirrhotic G3-HCV infected patients. This strategies are still necessary with the most recent DAAs, such as elbasvir/grazoprevir, sofosbuvir/velpatasvir (SOF/VEL), glecaprevir/pibentavir (GLE/PRI), that require an RBV addition and/or antiviral treatment prolongation when the G3-HCV infected patient is cirrhotic and/or is not naïve to antiviral treatment. Apart from the RBV addition, no other baseline factor dependent on the patient or treatment (except for advanced fibrosis) has been identified as significant on treatment effectiveness in this study.

Regarding the analysis in other patient subgroups (although with a limited sample), it is noteworthy that all liver transplant patients have achieved SVR12, in accordance with the high effectiveness of DCV/SOF \pm RBV observed in patients with advanced cirrhosis or post-liver transplantation recurrence, in which SVR12 rates of 83% and 91% have been reported respectively [26]. Likewise, treatment has been effective in all HIV co-infected patients, reproducing the results of other studies in these patients [27-29]. Patients with decompensated cirrhosis included in this study obtain an SVR12 around 85%, which, while not statistically inferior to the response obtained

Event (%)	GLOBAL (n=111)	DCV/SOF (n=70)	DCV/SOF+RBV (n=41)	p
Treatment withdrawal due to drug-related AE	0.0%	0.0%	0.0%	0.999
Any drug-related AE	57.7%	45.7%	75.6%	0.004
Any drug-related serious AE	7.2%	1.4%	17.1%	0.007
Hospitalization during treatment	1.8%	0.0%	4.9%	0.260
Death	0.0%	0.0%	0.0%	0.999
Any grade AE with global incidence > 2.5%:				
Fatigue/asthenia	36.0%	25.7%	53.7%	0.006
Headache	21.6%	18.6%	26.8%	0.435
Insomnia	9.0%	5.7%	14.6%	0.215
Gastrointestinal upset	7.2%	5.7%	9.8%	0.678
Nausea	5.4%	5.7%	4.9%	0.805
Anxiety	4.5%	4.3%	4.9%	0.742
Diarrhoea	4.5%	4.3%	4.9%	0.742
Myalgia	3.6%	1.4%	7.3%	0.281
Irritability	3.6%	1.4%	7.3%	0.281
Constipation	3.6%	2.9%	4.9%	0.981
Pruritus	3.6%	0.0%	9.8%	0.033
Emergent haematological abnormalities				
Leukopenia	6.3%	0.0%	17.1%	0.0007
Thrombocytopenia	5.4%	2.9%	14.6%	0.0498
Anaemia	2.7%	0.0%	7.3%	0.0481
Neutropenia	2.7%	2.9%	7.3%	0.3565
All	17.1%	5.8%	46.3%	<0.001

DCV: daclatasvir. SOF: sofosbuvir. RBV: ribavirin. AE: adverse event.

in patients with compensated cirrhosis (around 96%), could be considered clinically relevant in the current context of elevated effectiveness of antiviral treatment. Some previous studies have analysed the efficacy and safety of DAAs in HCV patients with decompensated cirrhosis. Curry MP et al [30] conducted an open phase 3 clinical trial (ASTRAL 4) that evaluated SOF associated with velpatasvir with or without RBV for 12 weeks or without RBV for 24 weeks in HCV patients genotype 1 to 6 with decompensated cirrhosis; RVS12 in the small group of 39 HCV genotype 3 patients was 50% if RBV had not been associated with DAAs and 85% in those who did associate it; these results are very similar to those of our study and reinforce the importance of the RBV addition to the antiviral regimen in patients with decompensated cirrhosis. Also, Foster GR et al [31] evaluated the response to a 12-week treatment with SOF+DAC or SOF/LPV associated or not with RBV (according to non-protocolized medical criteria) in 192 HCV genotype 3 patients with decompensated cirrhosis; SVR12 in regimens based

on LDP was around 40% or 60% (depending on the absence or presence of RBV) and in regimens with DAC of 61% or 73% respectively; this low effectiveness observed in this study, much lower than that achieved in our experience, reinforces the hypothesis of the importance of the addition of RBV to DAAs and treatment durations of 24 weeks in HCV genotype 3 patients with decompensated cirrhosis, as the authors conclude in their work.

It is also important to assess the results of our study in the context of the current reference therapeutic guidelines. European Association for the Study of the Liver (EASL) considers therapeutic options the association of SOF/VEL 12 weeks or GLE/PRI 8-12 weeks (according to previous therapeutic experience) for patients HCV genotype 3 without cirrhosis, GLE/PRI 12-16 weeks (according to previous therapeutic experience) or SOF/VEL/voxilaprevir (SOF/VEL/VOX) for 12 weeks for patients with compensated cirrhosis, and SOF/VEL + RBV 12 weeks or SOF/VEL 24 weeks (if intolerance or contraindication to RBV)

in patients with decompensated cirrhosis [18]; these recommendations can be considered in line with the results obtained in our study, since the observed SVR12 with SOF + DAC in patients F3 or F4 is improved with the therapeutic options proposed, although in decompensated cirrhosis (with due caution due to the limited population analysed) they are similar to the results observed with SOF/VEL. On the other hand, AASLD/IDSA Guidance still recommends SOF + DAC + RBV for 12 weeks in patients with decompensated cirrhosis, in line with the results of our study, in addition to SOF/VEL + RBV [14]. In both cases, the scientific societies consolidate the importance of the addition of RBV and/or prolongation of the antiviral treatment in patients with decompensated cirrhosis, also in agreement with the data of our study.

In relation to safety, it is noteworthy that no patient required antiviral treatment withdrawal secondary to severe AEs, even among patients who were hospitalised, so we consider DCV/SOF ± RBV safe in G3-HCV infected patients treated in real clinical practice. Rates of patients affected by any grade of AEs or serious AEs are very similar to those observed in clinical trials or observational studies, as well as in the recent review carried out by Cornberg et al [32]. Also, we must highlight the incidence of fatigue/asthenia, headache, insomnia and gastrointestinal upset. Our study has also detected the development of cytopenias, which is usually mild or moderate during antiviral treatment, associated with advanced liver disease. On the other hand, both in the case of general AEs and in the development of cytopenias, the RBV addition to DCV/SOF has a significant negative effect on treatment safety, as has been reflected by Ferreira et al in a meta-analysis about interferon-free treatments safety in CHC [33].

In summary, although our study has the inherent limitations of its design and the impossibility of performing a multivariate analysis on predictors of response due to the high effectiveness of the treatment, it has the strength to present results in a large population of patients in real clinical practice, and may conclude that DCV/SOF ± RBV is highly effective and safe for G3-HCV infected patients, with a lower effectiveness in patients with advanced fibrosis F3-4, as well as that RBV addition is determinant on the effectiveness of this antiviral treatment in cirrhotic patients, which also influences their safety.

FUNDING

None to declare

CONFLICT OF INTEREST

LMM: Honoraria for speaking at symposia. Gilead Sciences, Inc. Janssen. Abbvie Inc. Merck Sharp & Dohme. Financial support for attending symposia. Gilead Sciences, Inc. Janssen. Abbvie Inc. Merck Sharp & Dohme. Position on advisory board. Bristol Myers-Squibb. MDB: Honoraria for speaking at symposia. Gilead Sciences, Inc. Abbvie Inc. Merck Sharp &

Dohme. Bristol Myers-Squibb. IMH: Honoraria for speaking at symposia. Gilead Sciences, Inc. Janssen. Financial support for attending symposia. Janssen. Financial support for educational programs. Janssen. ACI: Financial support for attending symposia. Gilead Sciences, Inc. Abbvie Inc. Merck Sharp & Dohme. Position on advisory board. Gilead Sciences, Inc. Honoraria for speaking at symposia. Gilead Sciences, Inc. Abbvie Inc.

Rest of authors declare that they have no conflicts of interest.

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