

Effectiveness and safety of sofosbuvir/velpatasvir ± ribavirin vs glecaprevir/pibrentasvir in genotype 3 hepatitis C virus infected patients

Luis Margusino-Framiñán^{1,2}, Purificación Cid-Silva^{1,2}, Sandra Rotea-Salvo¹, Álvaro Mena-de-Cea^{2,3}, Francisco Suárez-López⁴, Pilar Vázquez-Rodríguez^{2,3}, Manuel Delgado-Blanco^{2,4}, Ana Isabel Sanclaudio-Luhia⁵, Isabel Martín-Herranz¹, Ángeles Castro-Iglesias^{2,3}

1. Pharmacy Service, University Hospital of A Coruña, A Coruña, Spain
2. Division of Clinical Virology, Biomedical Research Institute of A Coruña (INIBIC), University Hospital of A Coruña (CHUAC), Sergas, University of A Coruña (UDC), A Coruña, Spain
3. Infectious Diseases Unit, Internal Medicine Service, University Hospital of A Coruña (CHUAC), A Coruña, Spain
4. Hepatology Unit, Digestive System Service, University Hospital of A Coruña (CHUAC), A Coruña, Spain
5. Information Systems Department, University Hospital of A Coruña, A Coruña, Spain

Abstract

Objectives

Sofosbuvir/velpatasvir±ribavirin (SOF/VEL±RBV) and glecaprevir/pibrentasvir (GLE/PIB) are the drug combinations of choice for treating individuals with genotype 3 hepatitis C virus (G3-HCV) infection. The objective of this study was to evaluate the effectiveness and safety of SOF/VEL±RBV compared with GLE/PIB for treating G3-HCV infection under routine clinical practice conditions.

Methods

We conducted a prospective observational cohort study of individuals with G3-HCV infection who initiated treatment with SOF/VEL +/-RBV or GLE/PIB between April 2017 and July 2018. Prisoners and children were excluded. The outcome variable of effectiveness was sustained virological response 12 weeks after completing treatment (SVR12). The safety variable was withdrawal secondary to severe adverse events (SAEs). Covariates included sex, age, HIV co-infection, previous liver transplant, cirrhosis, hepatic fibrosis and previous antiviral treatment. Statistical significance was calculated using Fisher's exact test or the Mann-Whitney U-test.

Results

A total of 76 patients were included in the analysis, of whom 46 were treated with SOF/VEL±RBV and 30 were treated with GLE/PIB. No baseline differences were observed between treatment groups with respect to age, sex, HIV co-infection, fibrosis stage, cirrhosis and previous antiviral treatment. Of the patients treated with SOF/VEL±RBV and GLE/PIB, 95.7% and 96.7% reached SVR12, respectively (P=0.7). Of patients with and without cirrhosis, 83.3% and 98.4% reached SVR12, respectively (P=0.09). Of the patients with low-grade hepatic fibrosis (F0-2) and advanced fibrosis (F3-4), 100% and 85.7% reached SVR12, respectively (P=0.03). In treatment-naïve and treatment-experienced patients, 95.7% and 100% reached SVR12, respectively (P=0.57), without significant differences independent of the treatment group (P=0.28 for SOF/VEL±RBV; P=0.18 for GLE/PIB). The incidence of AEs was 21.1% (95% CI 11.3% to 30.9%). None of the patients developed an SAE or required antiviral treatment withdrawal.

Conclusions

SOF/VEL±RBV or GLE/PIB are safe and effective for treating G3-HCV-infections, with a lower effectiveness in patients with advanced fibrosis F3-4.

Introduction

It is estimated that the prevalence of chronic hepatitis C virus (HCV) infection in Europe is approximately 1.1%, with a total affected population of 5.6 million people.¹ The prevalence of HCV genotypes varies among regions, with genotype 3 (G3) being the second most prevalent in Europe after genotype 1 (G1), accounting for approximately 25% of cases of chronic hepatitis C (CHC).² Compared with G1-HCV, G3-HCV chronic infection has a faster progression to liver cirrhosis³⁻⁶ and hepatocellular carcinoma (HCC),⁷ and is associated with a higher incidence of hepatic steatosis.⁸⁻¹¹ Furthermore, compared with other genotypes, G3-HCV has been reported to exhibit lower rates of sustained virologic response (SVR) with direct-acting antivirals (DAAs), particularly in patients with advanced liver fibrosis and non-responders to previous treatment.¹² Therefore, the evaluation of the effectiveness of antiviral treatment against G3-HCV chronic infection under clinical practice conditions in the era of DAAs is of special interest.

The treatment of G3-HCV recommended by scientific societies has changed in recent years. Taking the results of clinical studies into account, the European Association for the Study of the Liver (EASL) has repeatedly updated its recommendations, which have advised the use of peginterferon (PegIFN)+ribavirin (RBV) (2011), sofosbuvir (SOF)+PegIFN+RBV, SOF+RBV (2013, 2015), SOF+daclatasvir (DAC)±RBV, SOF/velpatasvir (VEL)±RBV (2016), SOF/VEL, glecaprevir/pibrentasvir (GLE/PIB) and SOF/VEL/voxilaprevir (VOX) (2018).¹³⁻¹⁷ The Infectious Diseases Society of America (IDSA) and American Association for the Study of the Liver (AASLD) have also updated their treatment recommendations, with the most recent update being in 2018.¹⁸ Table 1 provides a summary of the current treatment recommendations by EASL and IDSA/AASLD.^{17 18} However, there have been no studies published that compare the safety and effectiveness of these therapies in individuals with G3-HCV infection.

Table 1. Adaptation of the treatment recommendations of EASL and IDSA/AASLD of patients infected with genotype 3 of the hepatitis C virus, without cirrhosis or with compensated cirrhosis. recommended treatments. Update 2018 *†‡^{17 18}

Genotype 3-infected patient	EASL ¹⁷	IDSA/AASLD ¹⁸
Naïve-non cirrhotic	SOF/VEL 12 w GLE/PIB 8 w	SOF/VEL 12 w GLE/PIB 8 w
Treatment experienced-non cirrhotic‡	SOF/VEL 12 w GLE/PIB 12 w	SOF/VEL±RBV 12 w
Naïve-cirrhotic	GLE/PIB 12 w SOF/VEL/VOX 12 w	SOF/VEL 12 w GLE/PIB 12 w
Treatment experienced-cirrhotic‡	SOF/VEL/VOX 12 w GLE/PIB 16 w	ELB/GRZ+SOF 12 w SOF/VEL/VOX 12 w

*This table is a simplified adaptation. It is recommended to consult the direct references.

†Ribavirin addition is recommended in some subgroups of patients.

‡Recommendations in experienced patients are different and vary depending on whether the previous treatment was based on peginterferon or DAAs.

AASLD, American Association for the Study of the Liver; EASL, European Association for the Study of the Liver; ELB, elbasvir; GLE, glecaprevir; GRZ, grazoprevir; IDSA, Infectious Diseases Society of America; PIB, pibrentasvir; RBV, ribavirin; SOF, sofosbuvir; VEL, velpatasvir; VOX, voxilaprevir.

The objective of this study was to evaluate the effectiveness and safety of 8- to 24-week treatment regimens of SOF/VEL±RBV and GLE/PIB for treating G3-HCV infection under routine clinical practice conditions.

Methods

Study design and patient selection

We conducted an observational, prospective, cohort study of patients with G3-HCV infection who started HCV treatment with SOF/VEL±RBV or GLE/PIB between April 2017 and July 2018 and had reached week 12 post-treatment by January 2019. Infectious disease specialists and hepatologists chose the antiviral treatment regimen, taking into account not only the prevailing clinical practice conditions and international recommendations,^{17 18} but also variables such as concomitant treatment, lifestyle habits or patient preferences. The therapeutic regimen was a daily fixed combination of SOF 400 mg/VEL 100 mg (Epclusa; Gilead Sciences International Ltd) with or without the addition of RBV (Ribavirina Normon; Normon Laboratory), adjusted according to body weight and patient characteristics for 12 to 24 weeks, or three GLE 100 mg/PIB 40 mg fixed-dose combination tablets (Maviret; Abbvie Spain) administered for 8–16 weeks. The length of treatment was adjusted to the therapeutic guidelines, taking the patient characteristics, including the presence of cirrhosis, previous antiviral treatment and hepatic decompensation, into account.^{17 18} The inclusion criteria selected adult patients (≥18 years of age) with G3-HCV chronic infection. The patients included in the analysis were permitted to be naïve or treatment-experienced to peg-INF+RBV or DAAs, in all stages of hepatic fibrosis, including patients with decompensated cirrhosis or portal hypertension. Patients with HIV co-infection and those who had had a previous liver transplant were included.

Effectiveness and safety variables

Antiviral effectiveness and safety evaluation were carried out through SiMON,¹⁹ a local intelligent artificial monitoring system designed specifically for CHC patients. This system records data from the clinical history, related virological response and adverse events (AE). Additional data regarding hospitalisations or admissions to the emergency room were collected from patients' electronic clinical records.

HCV viral load was measured using the real-time PCR technique, with the Cobas AmpliPrep platform (Roche Molecular Systems, Basel, Switzerland) and the HCV Quantitative Test, version 2.0. The limits of detection and quantification in plasma were 11 IU/mL (95% CI): 10–13 IU/mL for the lower limit of detection (LOD), with a 95% positivity rate and 15 UI/mL as the LOD with positive results. Viral load was measured at baseline, on completion of treatment and 12 weeks after completion of treatment. Transient elastography was used for the staging of liver fibrosis (Fibroscan, Echosens, Paris, France), and patients were stratified according to stiffness results into fibrosis F0-1 (<7.6 kPa), F2 (7.6–9.5 kPa), F3 (9.6–14.4 kPa) or F4 (>14.4 kPa in HCV mono-infected patients and >14.0 kPa in HIV co-infected patients).^{20 21}

Adherence rates were calculated following continuous measurement of the medication acquisition (CMA) method,²² during the monthly visits to the Hospital Pharmacy Service where the study was conducted. This method measured cumulative days' supply obtained over a series of intervals/total days from the beginning to the end of the time period. Drug-drug interactions (DDIs) were identified by the clinical team (clinical pharmacists, hepatologists and infectious disease specialists) using the Hep Drug Interactions database of the University of Liverpool,²³ recommended as reference by EASL.¹⁷ If there was no information available in this database, Lexicomp Drug Interactions,²⁴ IBM Micromedex,²⁵ analysis of pharmacokinetic parameters available in the technical data sheet and consultation with the DAA manufacturing laboratory were employed.

The primary effectiveness endpoint was the proportion of patients with SVR12, defined as an undetectable HCV ribonucleic acid (HCV-RNA) 12 weeks' post-treatment. Secondary efficacy variables included treatment failure (detectable HCV-RNA in a patient with previous undetectable HCV-RNA on treatment), relapse (detectable HCV-RNA 12 weeks' post-treatment in a patient with undetectable HCV-RNA at the end of treatment), virological failure (HCV-RNA level remaining above the LOD throughout treatment) or missing HCV-RNA data 12 weeks' post-treatment due to on-treatment withdrawal secondary to severe AEs (SAEs) or death.

The primary safety endpoint was the percentage of treatment withdrawal secondary to SAEs. Secondary variables included the patients' self-referred AEs (stratified into mild, moderate or severe), emergency room consultation and hospital admissions secondary to SAEs.

Statistical analysis

Data of baseline variables, primary or secondary effectiveness variables, and safety end-points were collected and analysed by an intention-to-treat analysis according to the treatment regimen. Quantitative variables were expressed as the mean \pm SD deviation (SD) and were analysed using the Student's t-test or the Mann–Whitney U-test according to data distribution. Qualitative variables were expressed as counts and percentages, 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 CI. To determine the influence of baseline factors on the primary end-points, relative risk with a 95% CI (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 outcome events. To detect differences between treatment subgroups and predictors of response, univariate and multivariate analyses were performed. The results were considered to be statistically significant when the P-value was <0.05 . Statistical analysis was carried out using the Epidat 4.2 software.

Ethical aspects

This study complied with the Declaration of Helsinki of Good Clinical Practices. It was classified as 'Observational Post-Authorisation Study with Human Medicines' by the Spanish Agency of Medicines and Medical Devices (AEMPS) (LMF-NAA-2019–01), and was approved by the Clinical Research Ethics Committee (CREC) of the Regional Health Service (number 2016/161). Patients provided written informed consent and all study data were anonymised.

Results

Baseline patient demographics and characteristics

A total of 539 adult patients started antiviral treatment during the study period at our institution, of which 76 (14%) were infected with G3-HCV, and were treated with SOF/VEL \pm RBV or GLE/PIB. Figure 1 shows the study flow design. Forty-six patients were treated with SOF/VEL \pm RBV for 12 weeks and 30 with GLE/PIB for 8–16 weeks. The average adherence to SOF/VEL \pm RBV and GLE/PIB were 99.5 \pm 1.54 vs 99.9 \pm 0.67, respectively (P=0.13). Between concomitant treatments, 26% of patients in the SOF/VEL \pm RBV group, and 3% of patients in the GLE/PIB group, presented with DDIs (P=0.02). With both drug regimens, there was a potential for DDIs with omeprazole. DDIs were managed according to reference recommendations,²³ either by temporary suspension of omeprazole or by SOF/VEL administration with food: they were taken 4 hours before omeprazole at a maximum dose of 20 mg. The majority of patients were men (74%) with a median age of 65 years, naïve to antiviral treatment, with HCV mono-infection and without advanced fibrosis (74% F0-2). Only one patient (3%) suffered hepatic decompensation before the start of antiviral treatment. Only one patient had a liver transplant. Of the patients, 98% of those treated with SOF/VEL, and 100% of those treated with SOF/VEL+RBV completed 12 weeks of treatment, and 80% of those treated with GLE/PIB completed 8 weeks of treatment. Table 2 shows the main baseline patient characteristics of both cohorts.

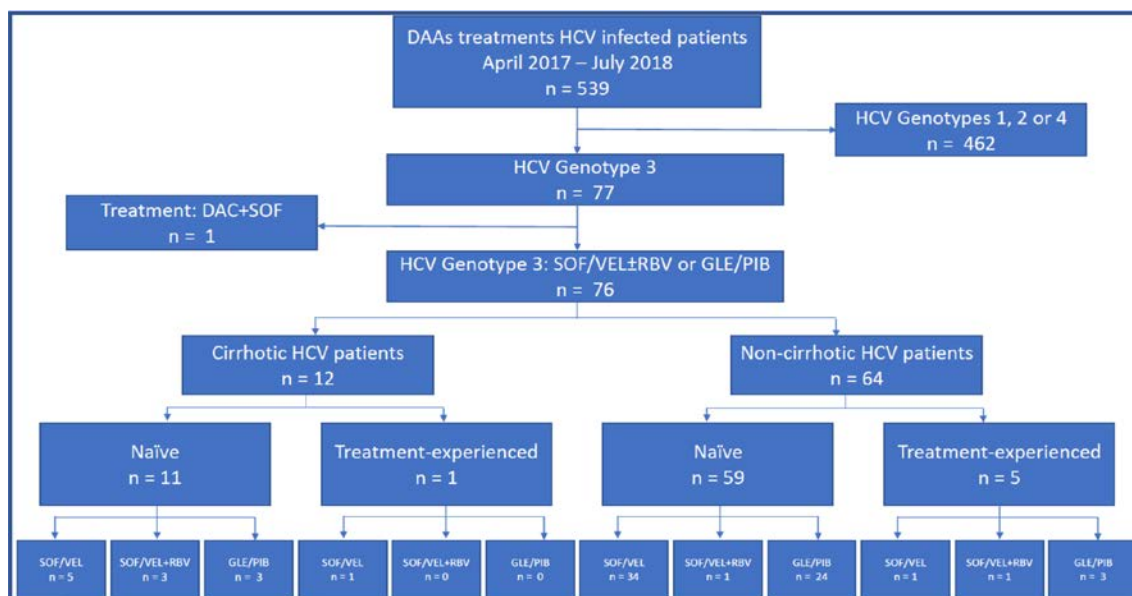


Figure 1. Study flow design. DAAs: direct-acting antivirals; HCV: hepatitis C virus; DAC: daclatasvir; SOF: sofosbuvir; VEL, velpatasvir; RBV: ribavirin; GLE: glecaprevir; PIB: pibrentasvir.

Table 2. Demographic and virological characteristics of the study population

Characteristic	Patients with SOF/VEL±RBV	Patients with GLE/PIB	P-value
Population, % (n)	60.5% (46)	39.5% (30)	
Males, % (n)	78.3% (36)	66.7% (20)	0.39
Age, mean (years±SD)	48,72±9,41	47,03±11,32	0.5
Age≥65 years, % (n)	4.3% (2)	6.6% (2)	0.93
HIV co-infection, % (n)	13.0% (6)	0.0% (0)	0.1
Fibrosis stage, % (n)			
F0-1	54.3% (25)	53.3% (16)	0.88
F2	19.6% (9)	16.7% (5)	0.99
F3	6.5% (3)	20.0% (6)	0.16
F4	19.6% (9)	10.0% (3)	0.43
Previous clinical decompensation, % (n)	2.2% (1)	0.0% (0)	0.83
CTP classification, % (n)			
A	19.6% (9)	10.0% (3)	0.43
B	0.0% (0)	0.0% (0)	>0.99
C	0.0% (0)	0.0% (0)	>0.99
Hepatocellular carcinoma, % (n)	4.3% (2)	0.0% (0)	0.67
Liver transplant, % (n)	2.2% (1)	0.0% (0)	0.83
HCV viral load, log IU/mL (mean±SD)	6,13±0,80	5,97±0,95	0.45
Estimated glomerular filtration rate<60 mL/min, % (n)	2.2% (1)	0.0% (0)	0.83
Previous antiviral treatment, % (n)			
Naïve	93,5% (43)	90,0% (27)	0.91
Treatment-experienced	6,5% (3)	10% (3)	
Response to previous antiviral treatment, % (n)			
Recidivant	0.0% (0)	6.7% (2)	0.3
Reinfection	2.2% (1)	0.0% (0)	0.83
Null responder	2.2% (1)	0.0% (0)	0.83
Unknown	2.2% (1)	3.3% (1)	0.67

CPT, Child-Pugh-Turcotte; GLE/PIB, glecaprevir/pibrentasvir; HCV, hepatitis C virus; HIV, human immunodeficiency virus; SOF/VEL±RBV, sofosbuvir/velpatasvir±ribavirin.

Effectiveness outcomes

All patients achieved virologic suppression at the end of treatment, but three of them relapsed within 12 weeks of follow-up, so the overall SVR12 was 96%. The SVR12 was 96% in patients treated with SOF/VEL±RBV compared with 97% in patients treated with GLE/PIB ($P=0.7$) (table 3). The SVR12 was 83% in cirrhosis patients, compared with 98% in patients without cirrhosis ($P=0.09$). The SVR12 was 100% in patients with low fibrosis, compared with 86% in those with high fibrosis ($P=0.03$). The SVR12 was 96% in all treatment-naïve patients, compared with 100% in treatment-experienced patients ($P=0.57$). Both of the patients who experienced viral rebound were treated with SOF/VEL+RBV and completed 12 weeks of treatment, but both had severe fibrosis (one F3, and one F4). The patient who showed treatment failure with GLE/PIB was treated for 12 weeks but also had severe fibrosis (F4). Figure 2 shows the SVR12 according to the basal fibrosis stage. The cirrhosis patient with hepatic decompensation, and the patient who had had a liver transplant both achieved SVR12. The SVR12 was 83% in the six patients with HIV co-infection, compared with 97% in patients with mono-infection ($P=0.57$). No other baseline patient or treatment factors that could influence treatment effectiveness were identified, and there were no significant differences in SVR12 according to the patient's sex, basal HCV viral load, platelet count or serum albumin concentration.

Multivariate analysis of the influence of the presence or absence of cirrhosis, previous hepatic decompensation, previous antiviral treatments based on PegIFN and current antiviral treatment (SOF/VEL±RBV or GLE/PIB) did not identify any variables that were independently associated with SVR12.

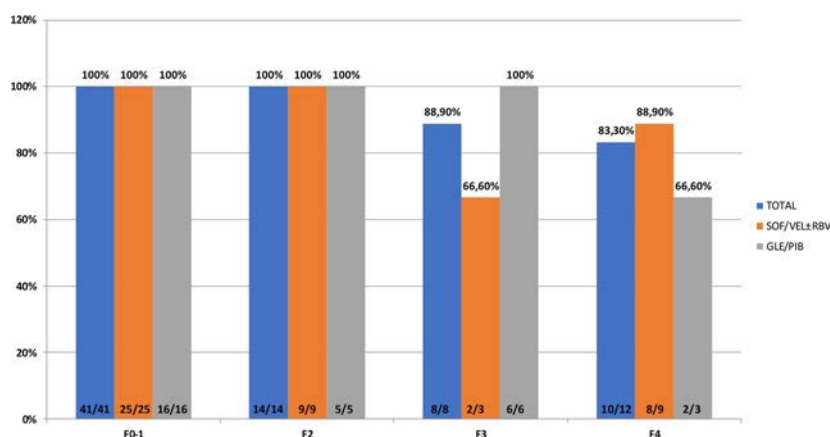


Figure 2. SVR12 according to basal fibrosis stage. SVR12, sustained virologic response 12 weeks' post-treatment; SOF/VEL±RBV, sofosbuvir/velpatasvir±ribavirin; GLE/PIB, glecaprevir/pibrentasvir.

Safety outcomes

During follow-up, 21% of patients experienced an AE, and 9% of patients experienced a moderate AE. The incidence of any degree AE was 26% in patients who received SOF/VEL±RBV vs 13% in patients who received GLE/PIB ($P=0.30$). Moderate AEs secondary to SOF/VEL±RBV included fatigue/asthenia, ocular pain, anxiety, dry skin, irritability and insomnia. Moderate AEs secondary to GLE/PIB included only fatigue/asthenia. The incidence of moderate AEs was higher in patients with cirrhosis (33%) compared with those without cirrhosis (5%, $P=0.009$). The incidence of AEs was not associated with sex, age or having previously been treated. Table 3 shows the main safety data. No patients experienced an SAE or required withdrawal, attention in the Emergency Department or hospitalisation as a result of an AE, and none of the patients died during the study period.

Table 3. Effectiveness and safety according with DAA

Characteristic	Total n=76 % (n; CI95%)	Patients SOF/VEL±RBV n=46	Patients GLE/PIB n=30	P-value
Virologic response				
SVR12 (main)	96,1 (73; 88.9 to 99.2)	95.7% (44)	96,7% (29)	0.7
Relapse	3,9 (3; 0.82 to 11.1)	4,3% (2)	3,3% (1)	
Treatment failure	0.0 (0)	0.0% (0)	0.0% (0)	>0.99
Virologic failure	0.0 (0)	0.0% (0)	0.0% (0)	>0.99
Missing date	0.0 (0)	0.0% (0)	0.0% (0)	>0.99
Any grade drug-related AE	21.1 (16; 11.3 to 30.9)	26,1% (12)	13,3% (4)	0.3
Moderate drug-related AE	9.2 (7; 2.1 to 16.4)	8,7% (4)	10.0% (3)	0.83
Any grade AE with global incidence>1.0%:				
Fatigue/asthenia	15.8 (12; 6.9 to 24.7)	17,4% (8)	13,3% (4)	0.88
Insomnia	2.6 (2; 0.3 to 9.2)	2,2% (1)	3,3% (1)	0.67
Gastrointestinal upset	1.3 (1; 0.0 to 7.1)	0,0% (0)	2,2% (1)	0.83
Headache	1.3 (1; 0.0 to 7.1)	2,2% (1)	0.0% (0)	0.83
Anxiety	1.3 (1; 0.0 to 7.1)	2,2% (1)	0.0% (0)	0.83
Diarrhoea	1.3 (1; 0.0 to 7.1)	2,2% (1)	0.0% (0)	0.83
Irritability	1.3 (1; 0.0 to 7.1)	2,2% (1)	0.0% (0)	0.83
Constipation	1.3 (1; 0.0 to 7.1)	2,2% (1)	0.0% (0)	0.83
Ocular pain	1.3 (1; 0.0 to 7.1)	2,2% (1)	0.0% (0)	0.83
Blurry vision	1.3 (1; 0.0 to 7.1)	2,2% (1)	0.0% (0)	0.83
Dry skin	1.3 (1; 0.0 to 7.1)	2,2% (1)	0.0% (0)	0.83
Dizziness	1.3 (1; 0.0 to 7.1)	2,2% (1)	0.0% (0)	0.83

AE, adverse event; DAA, direct-acting antiviral; GLE/PIB, glecaprevir/pibrentasvir; SOF/VEL±RBV, sofosbuvir/velpatasvir±ribavirin; SVR12, sustained virologic response week 12.

Discussion

DAAAs currently recommended by international reference guidelines for individuals with G3-HCV infection include the use of four options of combinations of second-generation direct-acting antivirals, SOF/VEL±RBV, GLE/PIB, SOF/VEL/VOX or GZR/EBR+SOF, depending on the baseline characteristics of the patient.^{17 18} These recommendations are based on the results of pivotal phase III clinical trials, where SVR12 rates obtained by any of these antiviral combinations are around 90%–100%, depending on the presence of cirrhosis and previous treatment (namely, variables that determine the antiviral selection, treatment length and/or RBV addition).^{26–32} Other variables that have been shown to influence the response to treatment, although not clinically significant, include the patient's sex, initial HCV viral load, serum albumin, platelet level and HIV co-infection.^{33 34} Our study has compared the effectiveness and safety of SOF/VEL±RBV vs GLE/PIB in routine clinical practice, and assessed the baseline and demographic characteristics of the patients in each treatment group to identify potential selection biases. No clinical differences between the treatment groups were observed at baseline in the proportion of treatment-naïve patients or patients with cirrhosis, so the two treatment groups were comparable. Likewise, both cohorts were balanced in relation to the patients' sex, age, liver elastography, baseline viral load and response to previous treatment among patients who had experienced previous treatment.

Based on the results of our real clinical practice study, SOF/VEL±RBV or GLE/PIB show a high antiviral effectiveness in individuals infected with G3-HCV, with an overall SVR12 rate of 96% and no significant differences in the effectiveness or the safety of the two treatment regimens. Our results are similar to those observed in the pivotal phase III clinical trials ASTRAL-3 for SOF/VEL±RBV²⁷ and ENDURANCE-3 for GLE/PIB,²⁹ where the overall SVR12 rate was 95%. Although there are no direct comparative observational studies in the routine clinical practice between both fixed combinations of antivirals in G3-HCV-infected patients, some studies have independently evaluated their effectiveness in clinical practice, and most studies found SVR12 results comparable to those found in our study.^{35–40} In addition to the consistency of these results in different populations, it is informative to analyse the virologic response according to the presence of cirrhosis, advanced fibrosis and previous treatment because these factors are used to stratify treatment protocols in international treatment guidelines.^{17 18} In

relation to the effectiveness of both drugs in cirrhosis patients in our study and in contrast with other previous observational studies,^{38 39 41 42} we observed a lower SVR12 than in non-cirrhosis patients, although no significant differences were observed between the two drug combinations. This is probably due to the small number of cirrhosis patients included in our study. Therefore, no definitive conclusions can be drawn regarding this subpopulation. However, with respect to cirrhosis patients included in our study, it should be noted that the cut-off point of the FibroScan which we used to categorise patients as cirrhosis was >14.4 kPa in HCV mono-infected patients and >14.0 kPa in HIV co-infected patients, whereas in the pivotal clinical studies of SOF/VEL±RBV or GLE/PIB it was 12.5 kPa. Therefore, patients in our study with advanced F3 fibrosis could have been included in the F4 category according to the criteria used in pivotal clinical trials. In this sense, we observed a significantly lower effectiveness (P=0.03) of SOF/VEL±RBV and GLE/PIB in patients with advanced fibrosis F3-4 (86%), compared with patients with low fibrosis F0-2 (100%). We observed a high effectiveness of both treatments in treatment-naïve and treatment-experienced patients, without statistically significant differences between SOF/VEL±RBV vs GLE/PIB, although it should be considered that only six patients included in this study had received previous antiviral treatment and that only one of them had cirrhosis.

In relation to safety, it is noteworthy that no patient experienced SAEs, visited the Emergency Department, was hospitalised or discontinued antiviral treatment, secondary to SAEs, so we consider that SOF/VEL±RBV and GLE/PIB are safe in G3-HCV-infected patients treated in real clinical practice. No significant clinical differences in safety were observed when the two treatment regimens were compared. The rates of any grade of AEs and moderate AEs was lower than those observed in pivotal clinical trials, for both SOF/VEL±RBV and GLE/PIB, although the types of AEs reported were similar. In the case of SOF/VEL±RBV, any degree of AEs observed in clinical trials was 50%,²⁷ whereas in our study it was about half of this figure (26%), and in the rate of moderate-to-severe AEs was also considerably lower in our study. In relation to GLE/PIB, the rates and the nature and degree of any AEs observed in the patients of our study (13%) were similar to those observed in the pivotal clinical trials (8%–11%).²⁹

There was a high adherence to antiviral treatment observed in our study, as has been documented in previous studies,⁴³ without differences by drug regimen, and therefore the effectiveness and safety shown by our results were not biased by patients not receiving the intervention. However, surprisingly, a higher incidence of DDIs was observed with SOF/VEL±RBV than with GLE/PIB. The latter could be expected to be associated with a higher incidence of DDIs because it contains a protease inhibitor (GLE) that usually has a higher rate of interactions.⁴⁴ We consider that there may have been a selection bias in favour of SOF/VEL±RBV in the presence of potential interactions between the basal pharmacological treatment and GLE/PIB, but that this did not have a significant clinical effect because the main interaction was a weak interaction with omeprazole.

This study has the inherent limitations of its design, and it was not possible to perform a multivariate analysis of predictors of response due to the high effectiveness of the treatment and the limited number of study participants. Also, the limited size of the two treatment groups did not allow us to demonstrate clinically significant differences regarding the safety of the two treatments, considering that one included ribavirin (SOF/VEL). Of the HCV genotypes, genotype 3 had a lower prevalence in our health area (around 15%), than that observed in Europe as a whole (25%).² In addition, most G3-HCV patients, especially cirrhosis patients, have already been previously treated and virologically cured using sofosbuvir+ribavirin or sofosbuvir+daclatasvir. These factors limited the size of our study population. Another limitation is the unavailability of data on the Y93 mutation for treatment selection, length of treatment or RBV addition: genotypic resistance testing is not a standard practice in our country before using DAAs to treat cirrhosis. However, currently IDSA/AASLD Recommendations for Testing, Managing, and Treating Hepatitis C¹⁸ indicates that NS5A RAS testing is recommended for treatment-naïve patients with cirrhosis infected with g3-HCV, and treatment-experienced patients (with or without cirrhosis) being considered for 12 weeks of sofosbuvir/velpatasvir. Furthermore, if Y93H is present, weight-based ribavirin should be added or sofosbuvir/velpatasvir/voxilaprevir should be used. However, this study has the strength of being the first comparative study in routine clinical practice.⁴⁵

SOF/VEL±RBV and GLE/PIB are both highly effective and safe drug combinations for treating patients with G3-HCV infection, with no significant differences between the two antiviral combinations. Antiviral treatment is less effective in patients with advanced fibrosis.

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