Research Article
Viral Hepatitis

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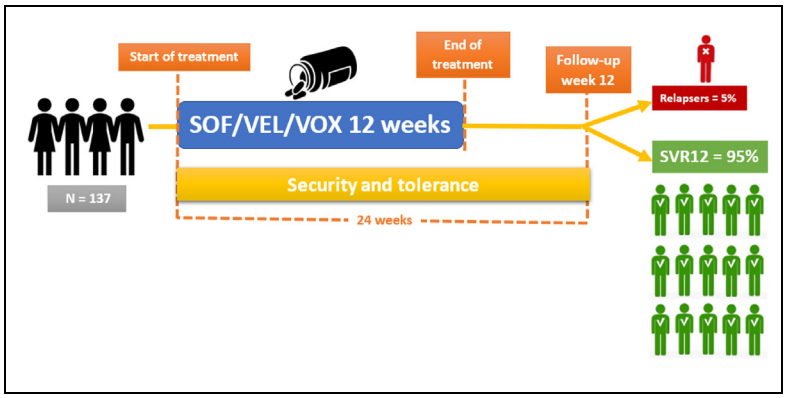
Effectiveness and safety of sofosbuvir/velpatasvir/voxilaprevir in patients with chronic hepatitis C previously treated with DAAs

Graphical abstract



Highlights

- Patients achieve high SVR12 rates with sofosbuvir/velpatasvir/voxilaprevir after prior DAA failures.
- Sofosbuvir/velpatasvir/voxilaprevir is a very safe and well tolerated combination.
- GT3 cirrhotic patients with previous treatment with NS5A-inhibitors are poor responders.
- GT3 is the only factor that impacts SVR12 rates in retreatment with sofosbuvir/velpatasvir/voxilaprevir.

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Lay summary

Treatment with sofosbuvir/velpatasvir/voxilaprevir (SOF/VEL/VOX) for 12 weeks is the current recommendation for the 5% of patients infected with HCV who do not achieve eradication of the virus under treatment with direct-acting antivirals. In a Spanish cohort of 137 patients who failed a previous combination of direct-acting antivirals, a cure rate of 95% was achieved with SOF/VEL/VOX. Genotypic characteristics of the virus (genotype 3) and the presence of cirrhosis were factors that decreased the rate of cure. Treatment with SOF/VEL/VOX is an effective and safe rescue therapy due to its high efficacy and very good safety profile.

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Effectiveness and safety of sofosbuvir/velpatasvir/voxilaprevir in patients with chronic hepatitis C previously treated with DAAs

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Background & Aims: Around 5% of patients with chronic hepatitis C virus (HCV) infection treated with direct-acting antiviral (DAA) agents do not achieve sustained virological response (SVR). The currently approved retreatment regimen for prior DAA failure is a combination of sofosbuvir, velpatasvir, and voxilaprevir (SOF/VEL/VOX), although there is little data on its use in clinical practice. The aim of this study was to analyse the effectiveness and safety of SOF/VEL/VOX in the real-world setting.

Methods: This was a prospective multicentre study assessing the efficacy of retreatment with SOF/VEL/VOX in patients who had experienced a prior DAA treatment failure. The primary endpoint was SVR 12 weeks after the completion of treatment (SVR12). Data on safety and tolerability were also recorded.

Results: A total of 137 patients were included: 75% men, 35% with liver cirrhosis. Most were infected with HCV genotype (GT) 1 or 3. The most common prior DAA combinations were sofosbuvir plus an NS5A inhibitor or ombitasvir/paritaprevir/r +dasabuvir. A total of 136 (99%) patients achieved undetectable HCV RNA at the end of treatment. Overall SVR12 was 95% in the 135 patients reaching this point. SVR12 was lower in patients with cirrhosis (89%, $p = 0.05$) and those with GT3 infection (80%, $p < 0.001$). Patients with GT3 infection and cirrhosis had the lowest SVR12 rate (69%). Of the patients who did not achieve SVR12, 1 was reinfected and 7 experienced treatment failure (6 GT3, 1 GT1a). The presence of resistance-associated substitutions did not impact SVR12. Adverse effects were mild and non-specific.

Conclusion: Real-world data show that SOF/VEL/VOX is an effective, safe rescue therapy for patients with prior DAA treatment failure despite the presence of resistance-associated substitutions. However, patients with liver cirrhosis infected by GT3 remain the most-difficult-to-treat group.

Lay summary: Treatment with sofosbuvir/velpatasvir/voxilaprevir (SOF/VEL/VOX) for 12 weeks is the current recommendation for the 5% of patients infected with HCV who do not achieve eradication of the virus under treatment with direct-acting antivirals. In a Spanish cohort of 137 patients who failed a previous combination of direct-acting antivirals, a cure rate of 95% was achieved with SOF/VEL/VOX. Genotypic characteristics of the virus (genotype 3) and the presence of cirrhosis were factors that decreased the rate of cure. Treatment with SOF/VEL/VOX is an effective and safe rescue therapy due to its high efficacy and very good safety profile.

Keywords: Sofosbuvir; Velpatasvir; Voxilaprevir; Hepatitis C; Treatment failures; HCV genotype 3.
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Introduction

Current treatments with direct-acting antivirals (DAAs) for hepatitis C virus (HCV) infection lead to elimination of the virus in more than 95% of patients, regardless of the HCV genotype or presence of advanced liver fibrosis.[1] The American Association for the Study of Liver Diseases (AASLD) and the European Association for the Study of the Liver (EASL) guidelines both recommend combinations including an NS5A inhibitor with either a NS3/4 protease inhibitor, such as grazoprevir/elbasvir or glecaprevir/pibrentasvir, or a nucleotide analogue plus an NS5A inhibitor, such as sofosbuvir/velpatasvir, for durations ranging from 8 to 12 weeks.[2–4] Sofosbuvir/velpatasvir and glecaprevir/pibrentasvir combinations are pangenotypic and therefore, they are the preferred regimens to simplify HCV therapy.[5–7] Despite the high efficacy of these new combinations, the options for patients who do not achieve a sustained virological response (SVR) are limited.[8] The latest approved retreatment regimen is combined therapy with sofosbuvir plus the NS55 inhibitor, velpatasvir, and the NS3/4 protease inhibitor, voxilaprevir (SOF/VEL/VOX),[9] which is recommended in the AASLD and EASL guidelines for retreating patients previously failing DAA regimens.[2–4]

The SOF/VEL/VOX combination, evaluated in 2 phase II trials including DAA-experienced patients, yielded very high SVR rates.[10,11] Later, the single-tablet SOF/VEL/VOX combination in a 12-week regimen was evaluated in 2 phase III trials including patients previously treated with a DAA-containing regimen.[12] In POLARIS-1, 300 patients with HCV genotype (GT)1 infection who had previously received a regimen containing an NS5A inhibitor were randomly assigned to receive either SOF/VEL/VOX (150 patients) or placebo (150 patients) once daily for 12 weeks. In addition, 114 patients infected with HCV other than GT1 were enrolled in the SOF/VEL/VOX group. In another study, POLARIS-4, patients with HCV GT1 to GT4 who had previously received a DAA regimen without an NS5A inhibitor were randomly assigned to receive SOF/VEL/VOX (182 patients) or sofosbuvir/velpatasvir (151 patients) for 12 weeks. A substudy was also carried out including 147 patients randomized to receive placebo in POLARIS-1 who did not achieve an SVR 12 weeks after completion of treatment (SVR12). These patients were retreated with 12 weeks of SOF/VEL/VOX and 97% achieved SVR12.[13] Four patients had virological relapse; all were infected with GT1a but only one had liver cirrhosis. In total, 96% of patients in POLARIS-1, 98% in POLARIS-4, and 97% in the POLARIS-1 substudy achieved SVR, suggesting high efficacy of SOF/VEL/VOX as a retreatment regimen.

In these trials, all patients underwent baseline deep sequencing of the NS3, NS5A, and NS5B coding regions of HCV to detect genetic changes associated with resistance to the treatment received. Resistance-associated substitutions (RASs) were reported when they were detected in more than 15% of the sequence reads. Nonetheless, the presence of RASs did not have a significant impact on the rates of SVR12. The POLARIS-1 and POLARIS-4 trials showed that treatment with SOF/VEL/VOX for 12 weeks is an effective and safe option for retreating patients with HCV, although the data on its use in clinical practice are limited.

The aim of this study was to evaluate in the real-world setting the efficacy and safety of the fixed-dose combination of SOF/VEL/VOX for 12 weeks in patients with chronic hepatitis C of any genotype and with different degrees of liver fibrosis who had previously failed oral DAA therapy.

Patients and methods

Study design

This is a prospective, nationwide, multicentre study evaluating the efficacy and safety of antiviral retreatment for HCV-infected patients who failed DAA regimens in routine clinical practice at 28 Spanish Hospitals. The inclusion criteria were adults with chronic hepatitis C, including those with compensated cirrhosis, who had previously failed combined therapy with 2 DAAs in an interferon-free regimen from January 2014 to December 2017. Patients coinfected with HIV and those with hepatocellular carcinoma (HCC) were also enrolled. All patients received a fixed-dose oral tablet containing 400 mg of sofosbuvir, 100 mg of velpatasvir, and 100 mg of voxilaprevir without ribavirin once daily for 12 weeks from March 2017 to September 2018.

The primary endpoint was the percentage of patients with a sustained virological response, defined as persistently undetectable HCV RNA at week 12 after completion of treatment (SVR12). The secondary endpoint was treatment-associated adverse events.

Data were collected through a National Registry (HEPA-C) under the auspices of the Spanish Association for the Study of the Liver (AEEH) and the Networked Biomedical Research Centre for the Study of the Liver and Digestive Diseases in Spain (CIBEREHD).

Measurements

Data were collected on the patients' baseline demographics, disease characteristics, prior treatment, and type of response. The degree of liver fibrosis was evaluated by transient elastography (FibroScan®; Echosens, Paris, France), and the Child-Turcotte-Pugh score (CTP) was recorded at the start of treatment. Laboratory tests included creatinine, albumin, total bilirubin, alanine and aspartate aminotransferase, international normalized ratio, haemoglobin, platelet count, estimated glomerular filtration rate (eGFR) using the Chronic Kidney Disease Epidemiology Collaboration formula (CKD-EPI), HCV genotype and subgenotype, and HCV RNA level. During the treatment period and over a 12-week follow-up, the clinical symptoms, virological determinations, adverse events, and drug-drug interactions were recorded. Variables classically associated with the virological response, such as age, sex, liver stiffness, platelet counts, HCV RNA level, and previous HCV treatment were analysed. Cirrhosis (F4) was established on a transient elastography score >14 kPa, or liver biopsy showing Metavir fibrosis 4, or clinical evidence of liver cirrhosis.

Virological failure was defined by an HCV RNA level ≥15 IU/ml. HCV RNA was determined using either the COBAS AmpliPrep/COBAS TaqMan (Roche Molecular Systems, Pleasanton, CA, USA; lower limit of detection [LLOD] 15 IU/ml) or the m2000SP/m2000RT (Abbott Molecular, Des Moines, IL, USA; LLOD 12 IU/ml) real-time PCR-based assays. HCV RNA levels were measured at baseline, week 12 (end of treatment), and 12 weeks after treatment completion. The Abbott RealTime HCV genotype II assay was used to determine HCV genotype at the time of retreatment.

Adverse events were recorded throughout the treatment period and 12-week follow-up. Special attention was placed on serious adverse effects that led to hospital admission or death, and severe conditions, such as HCC or liver transplant requirement. Treatment discontinuations related to adverse events were included in the safety analysis.

Deep sequencing of the NS3, NS5A, and NS5B coding regions was done at the time of failure in serum samples obtained from patients who did not achieve SVR. The HCV RNA sequences obtained at that time were compared with the baseline sequences in available cases to detect RASs that had emerged in association with treatment. RASs present in more than 15% of sequence reads were reported, as has been done in previous studies.[14–16]

The study was conducted in accordance with Good Clinical Practice Guidelines and was approved by the institutional review board or independent ethics committee at each site. All data were anonymized, and patients were asked to consent to contribute their data to the registries.

Statistical analysis

Normally distributed quantitative variables were compared with the Student *t* test and expressed as the mean ± standard deviation. Variables with a non-normal distribution were analysed with the Mann-Whitney *U* test and expressed as the median and interquartile range. Categorical variables were compared using the chi-square or Fisher exact test, as appropriate, and expressed as frequencies and percentages. Variables showing $p < 0.10$ in the univariate model were analysed in a multivariate logistic regression model. Odds ratios (ORs) and 95% CIs were calculated for the independent predictive factors of SVR. Only patients with complete data for all the variables were included in the multivariate logistic regression analysis. *P* values <0.05 were considered statistically significant. All analyses were carried out using the 2015 StataCorp Stata Statistical Software, release 14 (StataCorp LP; College Station, TX).

Results

Patient population

In total, 137 patients were included: 75% were men, median age was 56 years, 46 (34%) had compensated liver cirrhosis, and 6 (4%) were HIV coinfected. Most had HCV GT1 infection (1b 39%, 1a 22%, and non-subtyped 2%), whereas 22% had GT3, 10% GT4, and 5% GT2. Nine (7%) patients had a history of HCC, and 8 (6%) had received a liver transplant.

All patients had previously received a DAA-based interferon-free regimen with the following combinations: sofosbuvir-based regimen plus an NS5A inhibitor or NS3/4A inhibitor in 88 patients (64%), NS3/4A inhibitor-based regimen plus an NS5A inhibitor in 15 (11%), non-nucleoside NS5B plus NS5A plus NS3/4A inhibitor in 28 (20%), and other DAA combinations within clinical trials in 6 (4%). The main combinations in the 88 patients who had previously received sofosbuvir-based regimens were as follows: 52 (60%) combined with ledipasvir, 25 (28%) with daclatasvir, 8 (9%) with velpatasvir, and only 3 (3%) with simeprevir.[6,17,18] The 15 patients who failed NS5A-inhibitor plus NS3/4-inhibitor combinations included 9 (60%) with elbasvir/grazoprevir, 4 (27%) with ombitasvir/paritaprevir/r, 1 (7%) with glecaprevir/pibrentasvir, and 1 (7%) with simeprevir plus daclatasvir.[7,19,20] Finally, in the 28 patients receiving 3-inhibitor combinations, all were dasabuvir plus ombitasvir/paritaprevir/r.[21]

With regard to the latest approved DAA regimens (sofosbuvir/velpatasvir and glecaprevir/pibrentasvir), only 8 (6%) patients had previously failed sofosbuvir/velpatasvir (3 [38%] GT3 with cirrhosis) and 1 (1%) had failed glecaprevir/pibrentasvir (GT1a, no cirrhosis). In addition, 9 (7%) patients had failed elbasvir/grazoprevir (3 [33%] with cirrhosis).

In the 46 patients with liver cirrhosis, sofosbuvir/ledipasvir had been the previous combination most commonly used in GT1b (10 patients, 59%) and GT1a (7 patients, 70%). Sofosbuvir plus daclatasvir was the combination most often used in GT3 cirrhotic patients: in 7/13 (54%), followed by sofosbuvir/ledipasvir (n = 3) or sofosbuvir/velpatasvir (n = 3).

Previous treatment failures were evaluated according to whether the regimen was recommended in the 2014 EASL clinical guidelines[22] at the time of prescription. Most patients (111 of 137 [81%]) had received an optimal treatment regimen based on their clinical and virological characteristics, according to the EASL recommendations.

Previous DAA combination treatments by HCV genotype are shown in Table 1.

Efficacy analysis

All patients completed therapy and 135 were followed for 12 additional weeks. Two were lost to follow-up: 1 patient died and the other did not attend the control. End of treatment response was observed in 136 of 137 patients. The only patient with detectable viremia was a 62-year-old man with HCV GT3 infection and mild liver fibrosis who had previously failed treatment with sofosbuvir plus daclatasvir. The patient reported correct adherence throughout the treatment.

SVR12 was achieved in 95% (128/135). SVR12 rates by HCV genotype were 100% (29/29) in patients with GT1a, 100% (53/53) in GT1b, 80% (24/30) in GT3, 100% (7/7) in GT2 and 93% (13/14) in GT4. The SVR12 rate was 89% (41/46) in cirrhotic patients and 98% (87/89) in non-cirrhotic patients ($p = 0.05$). SVR rates combining HCV genotype and liver cirrhosis are shown in Fig. 1. Overall, SVR12 rates were higher in the non-3 genotypes (99%) than in GT3 (80%) (OR 26; 95% CI 3–226). GT3 patients with cirrhosis showed the lowest SVR12 rates: only 69% compared to 97% in non-GT3 cirrhotic patients (OR 24; 95% CI 2.7–213). SVR12 rates regarding the previous treatment regimen were as follows: 93% (81/87) in patients who had received a sofosbuvir-based regimen, 93% (14/15) in those previously treated with an NS3/4A-based regimen plus NS5A, and 100% (27/27) in patients who had received the 3-inhibitor combination therapy, with no significant differences between the groups ($p = 0.62$). There were no significant differences in SVR rates according to the CTP score ($p = 0.19$), presence of HCC ($p = 0.07$), co-infection with HIV ($p = 0.72$), or liver transplant recipient ($p = 0.66$). SVR12 rates were similar in patients whose previous therapy had followed the EASL recommendations and those whose therapy did not ($p = 0.26$)[22] Table 2.

Characteristics of patients who did not achieve SVR

Eight patients had detectable HCV RNA at 12 weeks following SOF/VEL/VOX treatment. Six had relapsed, 1 had a detectable viral load at completion of treatment, and the last patient had a reinfection. Six (75%) patients were infected with HCV genotype 3, and 4 (67%) of them had liver cirrhosis. All 6 relapsers had previously received a combination including sofosbuvir plus an NS5A inhibitor (5 daclatasvir and 1 velpatasvir). The patient with detectable viral load following SOF/VEL/VOX had HCV GT4 and liver cirrhosis and had previously failed elbasvir/grazoprevir therapy. The patient with HCV reinfection was an active intravenous drug user who initially had GT1 infection. At the time of reinfection, HCV genotype was found to have changed to GT3. All treatment failures had been previously treated in accordance with the EASL recommendations. The clinical

Table 1. Previous DAA combination treatment according HCV genotype.

	Overall (N = 137)	GT1a (n = 30)	GT1b (n = 54)	GT2 (n = 7)	GT3 (n = 30)	GT4 (n = 14)
Sofosbuvir-based regimen						
Sofosbuvir plus simeprevir	3 (2)	1 (3)	1 (2)	–	–	1 (7)
Sofosbuvir plus daclatasvir	25 (18)	–	2 (4)	1 (14)	22 (73)	–
Sofosbuvir/ledipasvir	52 (38)*	20 (67)	20 (37)	–	3 (10)	7 (50)
Sofosbuvir/velpatasvir	8 (6)	–	–	3 (43)	4 (14)	1 (7)
NS5A plus NS3/4A						
Simeprevir plus daclatasvir	1 (1)	–	1 (2)	–	–	–
Ombitasvir/paritaprevir/r	4 (3)	2 (7)	1 (2)	–	–	1 (7)
Elbasvir/grazoprevir	9 (7)	1 (3)	5 (9)	–	–	3 (21)
Glecaprevir/pibrentasvir	1 (1)	1 (3)	–	–	–	–
NS5A plus NS5B plus NS3/4A						
Dasabuvir plus ombitasvir/paritaprevir/r	28 (20)	4 (13)	24 (44)	–	–	–
Experimental combination	6 (4)	1 (3)	–	3 (43)	1 (3)	1 (7)

Data presented are: n (%).
DAA, direct-acting antiviral; GT, genotype; HCV, hepatitis C virus.
* Two patients were genotype 1 non-subtipable previously treated with a sofosbuvir plus ledipasvir.

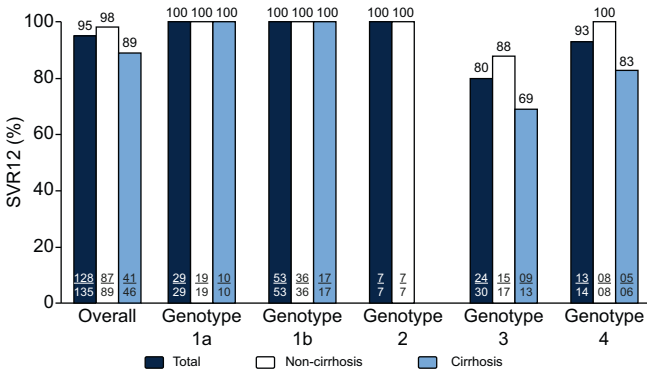

Fig. 1. SVR12 (%) by HCV genotype and presence or not of cirrhosis. Bars show SVR12 rates (at the top of each bar) in the overall cohort (first bar) and in the various HCV genotype subgroups. The fraction at the bottom of each bar represents the number of patients who achieved SVR12 over the total. HCV, hepatitis C virus; SVR12, sustained virological response 12 weeks after treatment completion.

and virological characteristics of patients who did not achieve SVR12 are shown in Table 3.

Resistance-associated substitutions

In patients treated with the SOF/VEL/VOX combination, RAS assessments were performed in 49 (52%) of 94 patients who had achieved SVR12. Among the total, 25% of these patients had RASs to NS3 inhibitors, 87% to NS5A inhibitors, and only 7% to NS5B inhibitors. Nonetheless, there were no significant differences in SVR12 rates between patients with documented RASs and those without ($p = 0.54$). Four of the 7 patients who failed SOF/VEL/VOX had a previous RAS, and all of them showed substitutions associated with resistance to NS5A inhibitors.

Adverse events

Treatment-related adverse effects were evaluated in 131 patients. Only 25 (19%) mild adverse episodes were reported during treatment. Headache was the most common (36%),

Table 2. Univariate and multivariate analysis of factors associated with the achievement of SVR12 (n = 135).

	SVR12 rates	Univariate *p* value	Multivariate	
			OR (95% CI)	*p* value
Gender		0.44		
Males	95/101 (94)			
Females	33/34 (97)			
Age (years)	56 (52–64)	0.45		
HIV coinfection	6/6 (100)	0.72		
Previous HCC	7/9 (78)	0.07		
Liver transplant	8/8 (100)	0.66		
ALT level (IU/L)	52 (37–84)	0.014		0.12
CTP score		0.19		
A (5–6)	125/131 (95)			
B (7–8)	3/4 (75)			
Cirrhosis	41/46 (89)	0.05		0.21
Genotype		<0.001	16 (1.7–152)	0.02
Non-GT3	104/105 (99)			
GT3	24/30 (80)			
Previous DAA combination		0.62		
Sofosbuvir-based	81/87 (93)			
NS5A + NS3/4A	14/15 (93)			
NS5A + NS5B + NS3/4A	27/27 (100)			
EASL 2014 guidelines recommendation (24)	102/109 (96)	0.26		

Data presented are: n of patients/total N (%), or median (range).
ALT, alanine aminotransferase; CTP, Child-Turcotte-Pugh score; DAA, direct-acting antiviral; EASL, European Association for the Study of the Liver; HCC, hepatocellular carcinoma; HIV, human immunodeficiency virus

Table 3. Clinical characteristics of patients who failed treatment with SOF/VEL/VOX.

Gender	Age (yr)	Genotype	Fibrosis	CTP*	Previous DAA treatment	Resistance-associated substitutions**
Male	55	3	F4	5	Sofosbuvir + daclatasvir + ribavirin/24w	L28S, M31L, D168G
Male	47	3	F4	5	Sofosbuvir + daclatasvir + ribavirin/24w	Not available
Male	62	3	F2	–	Sofosbuvir + daclatasvir/12w	Y93H
Male	54	3	F0-F1	–	Sofosbuvir + daclatasvir/12w	Not substitutions detected
Male	63	3	F4	7	Sofosbuvir + daclatasvir/12w	Not substitutions detected
Male	53	3	F4	5	Sofosbuvir/velpatasvir/12w	Not available
Female	50	4	F4	5	Elbasvir/grazoprevir/12w	Y93H

*CTP, Child-Turcotte-Pugh score.
**Analysis performed prior to receiving treatment with SOF/VEL/VOX for 8 weeks, 12 weeks or 24 weeks: Treatment for 8,12 or 24 weeks.

followed by asthenia (32%), diarrhoea (12%), and nausea (12%). Treatment discontinuation was not needed in any patient because of adverse effects. One patient developed *de novo* multicentric HCC. He was a 43-year-old man with HCV GT1a infection and compensated cirrhosis (CTP = 5) who had failed sofosbuvir/ledipasvir. At week 8 of retreatment he developed jaundice, and computed tomography examination showed diffuse HCC. The patient's clinical status rapidly worsened and he died during the study before achieving SVR12.

Discussion

The results of this real-world study show that the SOF/VEL/VOX combination is safe and effective for patients with previously treated HCV, supporting the results reported in clinical trials. The overall SVR12 rate was 95%, although GT3-infected patients, particularly those with underlying liver cirrhosis, had considerably lower SVR rates. Only 24 of 30 (80%) GT3-infected patients achieved SVR12, and this percentage decreased to 9 of the 13 (69%) with cirrhosis. Hence, GT3 can be considered a factor associated with a poor response to SOF/VEL/VOX rescue therapy (OR 16; 1.7–152). Although the differences were not statistically significant, the low SVR12 rate associated with rescue therapy for GT3-infected cirrhotic patients stresses the importance of selecting the best first-line treatment regimen for this population.

The EASL recommendation for DAA treatment failure is retreatment with SOF/VEL/VOX for 12 weeks as the first option for non-cirrhotic and compensated cirrhotic patients, regardless of the genotype. In patients with indicators of low response to treatment (advanced liver disease or complex NS5A RAS profile), 12 weeks of combination therapy with sofosbuvir plus glecaprevir/pibrentasvir is recommended, although supporting clinical evidence is weak.[2] This latter combination, evaluated in 2 studies including patients with GT1 to 4 infection and advanced fibrosis, yielded SVR rates of 90% to 100%.[23,24] The AASLD guidelines recommend SOF/VEL/VOX as the first option for GT1, -3, -4, and -5, regardless of the presence of cirrhosis and previous use of NS5A inhibitors. The second recommended option is glecaprevir/pibrentasvir.[3,4] However, a recent update of the AASLD guidelines recommends adding weight-based ribavirin to the SOF/VEL/VOX combination in GT3 patients with cirrhosis previously treated with an NS5A inhibitor-based regimen to minimize relapse risk. This regimen would likely have increased SVR12 rates in our study, as most relapsers were GT3 cirrhotic patients previously treated with regimens that included an NS5A inhibitor.

The baseline characteristics of our cohort were similar to those included in the POLARIS-1 and POLARIS-4 studies in terms of age, sex, percentage of patients with cirrhosis, HCV genotypes, and previous treatments.[12] The SVR12 rate was also similar to that of the POLARIS studies (95% *vs.* 96%, respectively), but there was a surprisingly lower rate in GT3-infected individuals (80% *vs.* 91%). In POLARIS-1, 2 of the 4 GT3 patients with cirrhosis who failed SOF/VEL/VOX had previously received sofosbuvir plus daclatasvir, and in our study, 5 (83%) of the 6 GT3 failures had previously received this combination. A potential explanation for the lower response in GT3 could be the presence of cirrhosis and the recent *in vitro* data suggesting that escape variants under daclatasvir at positions 28 and 93, and selected RAS at position 31 confer cross resistance to velpatasvir.[25]

The largest real-world cohort receiving rescue therapy with SOF/VEL/VOX was from the United States and included 573 treatment-experienced patients retreated with SOF/VEL/VOX for 12 weeks.[26] The majority had GT1 and GT3 infection. The cirrhosis rate was approximately 25% and the most common previous regimen was sofosbuvir/ledipasvir (66%). Overall SVR12 rates ranged from 93% in GT3 to 100% in GT2 and GT4. Advanced liver disease had no effect on SVR between genotypes. SVR was lower in patients previously treated with sofosbuvir/velpatasvir (GT1 82%, GT2 86%, and GT3 85%). In a study in France, including mainly sofosbuvir plus NS5 inhibitor failures, 43 patients were retreated with SOF/VEL/VOX plus ribavirin for 8 or 12 weeks (n = 9), or SOF/VEL/VOX without ribavirin for 12 weeks (n = 34).[27] Preliminary SVR12 findings yielded rates around 95%. The only 2 patients who failed were cirrhotic, previously treated with sofosbuvir plus daclatasvir, and infected with GT1 and GT3. In both studies, the lowest SVR rates were in GT3 patients with cirrhosis. The ongoing Trio Network cohort included 179 patients whose main previous treatment was with NS5A-contanining regimens. All 49 patients who had reached follow-up at 12 weeks achieved SVR.[28] The preliminary results of the first 54 patients included in the ongoing German cohort study (German Hepatitis C-Registry) also showed a high SVR12.[29]

An important question that arises from these findings is whether HCV resistance testing should be carried out before retreatment. Vermehren *et al.* performed resistance analysis in serum samples from 34 DAA-experienced patients treated with SOF/VEL/VOX (results from the Frankfurt Resistance Database).[30] Before starting SOF/VEL/VOX rescue therapy, all 10 GT1 patients and 80% of the 15 GT3 patients had NS5A RASs (in GT1, the predominant RAS were at positions Q30 and Y93, and in GT3, Y93H predominated). At the time of the data analysis, SVR12 results were 92% in HCV GT1 (n = 12/13), 90% in HCV GT3 (n = 9/10), and 100% in HCV GT4 (n = 2/2). No treatment-emergent RAS were observed in the 2 patients with SOF/VEL/VOX failure. These results support the notion that SOF/VEL/VOX is an effective rescue therapy in patients with prior DAA treatment failure despite the presence of high-level RAS and/or multiple previous DAA therapies.

Resistance testing is not available in all countries, and in some of them, including Spain, it is only available in academic centres. Nonetheless, more than half the patients included in our study had RAS testing before starting SOF/VEL/VOX treatment, and NS5A RASs were the ones most commonly found. However, the presence of RASs did not have an impact on the patients' overall SVR rates, in accordance with the analysis of patients included in the phase III POLARIS program.[31]

Regarding patients who failed glecaprevir/pibrentasvir, Pearlman *et al.* reported the results of a small cohort of 14 glecaprevir/pibrentasvir failures (5 GT1 and 9 GT3), predominantly with cirrhosis. Overall, 93% (13/14) achieved SVR12: 100% of the 5 GT1 and 89% (8/9) of the GT3 patients. SVR was 91% (10/11) in patients with no baseline NS5A RASs and 100% (5/5) in those with baseline NS5A RASs.[32] Due to the relatively recent authorization of glecaprevir/pibrentasvir in Spain, there are few patients with failure to this combination. The single patient in the present study who failed previous treatment with glecaprevir/pibrentasvir had an undetectable viral load at the end of treatment. The limited information from our current results does not suffice to consider SOF/VEL/VOX treatment a potential rescue option for patients failing therapy with glecaprevir/pibrentasvir.

The present study, performed in the largest real-life European HCV cohort, also included 6 HIV-HCV coinfected patients. All of them achieved SVR, which supports the idea that this is not a special population regarding HCV treatment. There is little data on retreatment of coinfected patients. In the RESOLVE study, including 71 HIV-HBV coinfected patients who had previously failed DAAs, the SVR12 rate by protocol was 98.5%.[33]

In our study, SOF/VEL/VOX therapy was found to be safe. Headache and asthenia were the most common adverse events, and no new side effects were reported. One patient was diagnosed with HCC during therapy.

The main limitation of this study was the relatively small number of patients, particularly patients with GT3 infection and liver cirrhosis, a key population for retreatment analysis. In addition, the previous regimens were quite heterogeneous, and only a few patients failing the most potent first-line pangenotypic regimens (sofosbuvir/velpatasvir and glecaprevir/pibrentasvir) were included. Another limitation is that RAS testing was performed in only half the patients and with different techniques; nonetheless, RAS analysis was not the purpose of the study.

In conclusion, the real-world data obtained here support the notion that SOF/VEL/VOX for 12 weeks is a safe, effective regimen for retreatment of HCV patients previously failing DAA therapy. However, lower SVR12 rates were documented in the subgroup of patients with HCV GT3 and liver cirrhosis who had been previously treated with sofosbuvir plus daclatasvir.

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Conflicts of interest

Jordi Llaneras has no potential conflicts of interest to report. Mar Riveiro-Barciela has served as speaker for Gilead and MSD and has received grants from Gilead. Sabela Lens has received speaker/advisory fees from Abbvie, Gilead, Janssen and MSD. Moisés Diago has served as speaker/advisory for Abbvie, MSD and Gilead. Alba Cachero reports personal fees from Gilead. Javier García-Samaniego is consultant and speaker for Gilead, Abbvie and MSD. Isabel Conde has no potential conflicts of interest to report. Ana Arencibia has no potential conflicts of interest to report. Juan Arenas reports personal fees from Gilead, Abbvie and MSD. Francisco Gea has no potential conflicts of interest to report. Xavier Torras is a speaker for Gilead, Abbvie and MSD and advisor for Abbvie and Gilead. José Luis Calleja is a speaker for Gilead, Abbvie and MSD. José Antonio Carrión has received speaker fees from Abbvie, Gilead and MSD. He is advisor for Abbvie. Inmaculada Fernández is a speaker and consultant for Abbvie, Gilead, Janssen and MSD. Rosa Maria Morillas is a speaker from Gilead, Merck, Abbvie and Intercept. She is advisor for Intercept. José Miguel Rosales has no potential conflicts of interest to report. Isabel Carmona has no potential conflicts of interest to report. Conrado Fernández-Rodríguez has served as speaker and advisor for Abbvie, MSD and Gilead. Manuel Hernández-Guerra has no potential conflicts of interest to report. Susana Llerena has no potential conflicts of interest to report. Vanesa Bernal has no potential conflicts of interest to report. Juan Turnes has no potential conflicts of interest to report. Jesús M. González-Santiago has no potential conflicts of interest to report. Silvia Montoliu has no potential conflicts of interest to report. Blanca Figueruela has no potential conflicts of interest to report. Ester Badia has no potential conflicts of interest to report. Manuel Delgado has served as speaker for Abbvie, Gilead and MSD. Miguel Fernández-Bermejo has no potential conflicts of interest to report. Mercedes Iñarraiaegui has no potential conflicts of interest to report. Juan Manuel Pascasio is advisor/lectures for Gilead and Abbvie. Rafael Esteban is an advisor and speaker for Gilead, MSD and Abbvie. Zoe Mariño is a speaker from Abbvie, Gilead, Janssen, MSD; Advisor for Gilead and BMS. Maria Buti is an advisor and speaker for Gilead, MSD and Abbvie. Please refer to the accompanying ICMJE disclosure forms for further details.

Authors' contributions

Jordi Llaneras, Mar Riveiro-Barciela, Rafael Esteban and Maria Buti: concept and design, experiments and procedures; discussing the results and writing of article. S. Lens, M. Diago, A. Cachero, J. García-Samaniego, I. Conde, A. Arencibia, J.I. Arenas, F. Gea, X. Torras, J.L. Calleja, J.A. Carrión, I. Fernández, R.M. Morillas, J.M. Rosales, I. Carmona, C. Fernández-Rodríguez, M. Hernández-Guerra, S. Llerena, V. Bernal, S. Daponte, J.M. González-Santiago, S. Montoliu, B. Figueruela, E. Badia, M. Delgado, M. Fernández, M. Iñarraiaegui, J.M. Pascasio and Z. Mariño: experiments and procedures and discussing the results.

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Supplementary data

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