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Real-life effectiveness of sofosbuvir/velpatasvir/voxilaprevir in hepatitis C patients previously treated with sofosbuvir/velpatasvir or glecaprevir/pibrentasvir

Juan Carlos Ruiz-Cobo[1,2] | Jordi Llaneras[1,2] | Xavier Forns[3,4,5,6] | Adolfo Gallego Moya[7] | Isabel Conde Amiel[8,9] | Ana Arencibia[10] | Moises Diago[11,12] | Javier García-Samaniego[6,13,14,15] | Jose Castellote[5,16,17] | Susana Llerena[18,19] | Elisa Rodríguez-Seguel[20,21,22,23] | Beatriz Mateos[24,25,26] | Manuel Rodríguez[27,28] | Jose Miguel Rosales Zabal[29] | Inmaculada Fernández[30] | Jose Luis Calleja[15,31,32] | Rosa María Morillas[6,33,34,35] | Silvia Montoliu[36,37] | Raul J. Andrade[6,38,39,40] | Ester Badia Aranda[41] | Manuel Hernández-Guerra[42] | Carlota Jimeno Maté[43] | Jesús M. González-Santiago[6,44,45] | Beatriz de Cuenca[46] | Vanesa Bernal-Monterde[47,48] | Manuel Delgado[49] | Juan Turnes[50] | Sabela Lens[3,4,5,6] | María Buti[1,2,6]

Correspondence
María Buti, Liver Unit, Department of Internal Medicine, Hospital Universitari Vall d'Hebron, Passeig Vall d'Hebron, Barcelona 119-129, Spain.
Email: mariaasuncion.buti@vallhebron.cat

Summary

Background: Sofosbuvir, velpatasvir and voxilaprevir (SOF/VEL/VOX) is the recommended rescue therapy for patients with chronic hepatitis C infection who fail direct-acting antivirals (DAAs). Data are limited on the effectiveness of this treatment after the current first-line therapies. Our aim was to analyse the effectiveness and safety of SOF/VEL/VOX among patients failing sofosbuvir/velpatasvir (SOF/VEL) or glecaprevir/pibrentasvir (GLE/PIB).

Methods: Retrospective multicentre study (26 Spanish hospitals), including chronic hepatitis C patients unsuccessfully treated with SOF/VEL or GLE/PIB, and retreated with SOF/VEL/VOX ± ribavirin for 12 weeks between December 2017 and December 2022.

Results: In total, 142 patients included: 100 (70.4%) had failed SOF/VEL and 42 (29.6%) GLE/PIB. Patients were mainly men (84.5%), White (93.9%), with hepatitis C virus genotype (GT) 3 (49.6%) and 47.2% had liver cirrhosis. Sustained virological response (SVR) was evaluated in 132 patients who completed SOF/VEL/VOX and were followed 12 weeks after end of treatment; 117 (88.6%) achieved SVR. There

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For affiliations refer to page 9.

were no significant differences in SVR rates according to initial DAA treatment (SOF/VEL 87.9% vs. GLE/PIB 90.2%, $p=0.8$), cirrhosis (no cirrhosis 90% vs. cirrhosis 87.1%, $p=0.6$) or GT3 infection (non-GT3 91.9% vs. GT3 85.5%, $p=0.3$). However, when considering the concurrent presence of SOF/VEL treatment, cirrhosis and GT3 infection, SVR rates dropped to 82.8%. Ribavirin was added in 8 (6%) patients, all achieved SVR.

Conclusion: SOF/VEL/VOX is an effective rescue therapy for failures to SOF/VEL or GLE/PIB, with an SVR of 88.6%. Factors previously linked to lower SVR rates, such as GT3 infection, cirrhosis and first-line therapy with SOF/VEL were not associated with lower SVRs.

1 | INTRODUCTION

The advent of pangenotypic direct-acting antivirals (DAAs) to treat chronic hepatitis C virus (HCV) infection has transformed the management of this condition and enabled the design of strategies aimed at achieving HCV eradication. Oral DAA regimens administered for 8–12 weeks have proven to eliminate HCV in more than 95% of patients in clinical trials and real-world cohorts.[1–3] Nonetheless, a subset of patients, mainly those with cirrhosis and GT3 infection, still experience treatment failure with DAAs. While previous studies have extensively characterised these patients in the context of earlier DAA regimens (e.g. sofosbuvir/ledipasvir, sofosbuvir/daclatasvir, ombitasvir/paritaprevir/dasabuvir), there remains limited data on HCV patients who have failed the first-line therapies in current use: sofosbuvir/velpatasvir (SOF/VEL) and glecaprevir/pibrentasvir (GLE/PIB).

International guidelines, such as those from the European Association for the study of the Liver (EASL) and the American Association for the Study of the Liver (AASLD), recommend use of the sofosbuvir/velpatasvir/voxilaprevir combination (SOF/VEL/VOX) as the retreatment of choice for patients who have not responded to previous DAA-containing therapies.[4,5] This combination includes a protease inhibitor (voxilaprevir), an NS5A inhibitor (velpatasvir) and an NS5B inhibitor (sofosbuvir) in a single tablet at fixed doses of 100, 100 and 400 mg, respectively, administered orally once daily for 12 weeks.[6,7]

The recommendation for using SOF/VEL/VOX as salvage therapy after DAA failure is based on the findings of the POLARIS-1 and POLARIS-4 studies. These clinical trials documented sustained virological response (SVR) rates of 96% and 98% in patients previously treated with DAA regimens with and without NS5A inhibitors, respectively. However, these trials included a limited number of patients, especially those with cirrhosis and HCV GT3 infection, and almost all the participants had failed treatments that are no longer recommended as first-line therapy. In addition, patients with decompensated cirrhosis or human immunodeficiency virus (HIV) coinfection were excluded.[6]

Several real-world studies have also evaluated SOF/VEL/VOX as a rescue therapy.[7–12] The majority of them included a small proportion of patients who had previously received SOF/VEL or GLE/PIB and were predominantly infected by GT1 HCV.[13] Even the most recent study, which assessed SOF/VEL/VOX in 746 European patients, mainly included individuals who had failed to HCV regimens not currently recommended in Europe, only 17% failed to SOF/VEL and 8% to GLE/PIB.[14] Notably, these latest publications found a significant association between GT3 HCV, liver cirrhosis, exposure to SOF/VEL and lower SVR rates to SOF/VEL/VOX.[13,14]

The aim of this study was to assess the efficacy and safety of SOF/VEL/VOX for HCV retreatment in a real-world cohort of patients who had failed to SOF/VEL or GLE/PIB. In addition, we conducted an analysis of the clinical characteristics of patients who failed HCV rescue treatment.

2 | PATIENTS AND METHODS

2.1 | Study design

This is an observational, retrospective, multicentre study to assess the efficacy and safety of SOF/VEL/VOX retreatment for HCV patients previously failing SOF/VEL or GLE/PIB in real-world clinical practice. Patients treated with SOF/VEL/VOX from 26 Spanish Hospitals from December 2017 to December 2022 were included. Some patients received ribavirin (RBV) in addition to SOF/VEL/VOX at their clinician's discretion. The inclusion criteria were: (1) patients older than 18 years; (2) chronic HCV infection and (3) unsuccessful response to a currently recommended first-line therapy with either SOF/VEL or GLE/PIB. Patients with decompensated cirrhosis or hepatocellular carcinoma (HCC) were not excluded, nor were those with hepatitis B virus (HBV) or HIV coinfection. Patients who experienced HCV reinfection after achieving SVR with first-line therapy were excluded. In all cases prior to starting SOF/VEL/VOX therapy, the physician reviewed patient's current medication regimen to ensure that there were no potential drug–drug interactions (DDI) with DAA treatment.

Patients were monitored following the recommendations in clinical guidelines. Adverse events were recorded during the course of SOF/VEL/VOX treatment and up to 12 weeks after the end of

treatment (EOT). The primary endpoint was the SVR rate, defined as an HCV RNA level below the lower limit of quantification at least 12 weeks after EOT.

Data were recorded in a National Registry (Hepa-C) under the aegis 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).

2.2 | Assessments

Information was collected on baseline characteristics, including demographic data (age, sex, body mass index, ethnicity), alcohol or injected drug abuse, pertinent comorbidities and concomitant medications, severity of liver disease, liver decompensations (ascites, hepatic encephalopathy, variceal haemorrhage), presence of HCC or liver transplantation. Data concerning previous HCV treatment and the corresponding treatment responses were also collected. When available, any resistance-associated substitutions (RASs) previously linked to treatment failure to NS3, NS5A or NS5B inhibitors were recorded.[11,15–18]

Laboratory testing was performed prior to initiation of first-line DAA therapy, at retreatment with SOF/VEL/VOX, and 12 weeks after retreatment EOT, when SVR was evaluated. The parameters recorded included creatinine, estimated glomerular filtration rate using the Chronic Kidney Disease Epidemiology Collaboration and Modification of Diet in Renal Disease formulas, albumin, total bilirubin, alanine and aspartate aminotransferase, haemoglobin, platelet count, leucocyte count, international normalised ratio, glucose, HCV GT and subgenotype and HCV RNA level. Virological failure was defined as detectable HCV RNA at least 12 weeks after EOT.

Liver fibrosis was noninvasively measured using serological fibrosis scores (FIB-4 and APRI) and transient elastography (Fibroscan; Echosens, Paris, France). Findings from liver biopsy analysis were recorded in patients who had undergone this procedure. Cirrhosis was defined by a transient elastography measurement of ≥12.5 kPa, METAVIR fibrosis score of 4 on liver biopsy or clinical evidence of cirrhosis (radiologic signs, oesophageal varices or prior liver decompensation). Child-Turcotte-Pugh (CTP) and model for end-stage liver disease (MELD) scores were recorded prior to first-line DAA therapy, at retreatment with SOF/VEL/VOX, and 12 weeks after retreatment EOT.

HCV RNA was determined using real-time PCR-based assays on the COBAS AmpliPrep/COBAS TaqMan system (Roche Molecular Systems, Pleasanton, CA, USA: lower limit of detection [LLOD], 15 IU/mL) or the m2000SP/m2000RT system (Abbott Molecular, Des Moines, IL, USA: LLOD, 12 IU/mL). HCV RNA levels were measured before starting and at completion (12 weeks) of first-line therapy, and at 12 weeks after retreatment EOT. HCV GT was established using the Abbott real-time HCV GT II assay. In a small number of patients, the presence of RASs before SOF/VEL/VOX administration was assessed by deep sequencing of the NS3, NS5A and NS5B coding regions.

Adverse events were recorded at the physician's discretion during treatment and 12 weeks after EOT. Severe events such as liver decompensation or HCC that resulted in death or hospitalisation were meticulously monitored.

2.3 | Statistical analysis

Statistical analyses were performed using the 2015 StataCorp Statistical Software, release 14.2 (StataCorp LP, College Station, TX). Normally distributed continuous variables are expressed as the mean ± standard deviation. Variables that were not normally distributed were compared using the Mann–Whitney *U* test and are expressed as the median and interquartile range. Categorical variables were analysed using the chi-square or Fisher exact test, as appropriate, and are expressed as frequencies (%). A p-value <0.05 was considered statistically significant in the comparisons. Variables associated with SVR were investigated using appropriate univariate statistical tests after considering the data distribution.

3 | RESULTS

3.1 | Patient population

In total, 142 patients retreated with SOF/VEL/VOX after failing SOF/VEL or GLE/PIB between December 2017 and December 2022 were included. Baseline characteristics are summarised in Table 1. Most patients were men (84.5%), White (93.9%), and median age was 54.6 years. Half the sample was infected with HCV GT3 and 47% had cirrhosis. Fifteen patients were coinfected with HIV and 2 with HBV. Fifteen patients had prior liver decompensation (ascites $n = 13$, variceal haemorrhage $n = 2$ or hepatic encephalopathy $n = 5$). However, at the initiation of SOF/VEL/VOX treatment, all had compensated liver disease except for three individuals who presented with mild ascites.

Overall, 67 patients had cirrhosis, 56 (83.6%) CTP-A, 8 (11.9%) CTP-B and 3 (4.5%) CTP-C. Regarding the initial therapy, 100 (70%) had received SOF/VEL and 42 (30%) GLE/PIB. Within our cohort, SOF/VEL had been administered as first-line therapy to 90.5% (38/42) of patients with CTP-A cirrhosis and no previous decompensation compared to only 52% (39/75) of non-cirrhotic patients ($p < 0.05$).

SOF/VEL/VOX was administered for 12 weeks. Ribavirin (600–1200 mg) was added in 8 (5.6%) patients at their clinician's discretion. Among the 142 patients included, 132 successfully completed the therapy, allowing for SVR evaluation. Of the 10 (7%) patients who did not complete treatment, 2 were diagnosed with advanced cancer in the interim (lung cancer and HCC, respectively) which precluded treatment completion. The remaining 8 patients did not attend the follow-up visits and could not be contacted.

None of the patients experienced hepatic decompensation during the study period. However, 6 (4.2%) patients with advanced

TABLE 1 Baseline characteristics of patients included.

	Total ($n = 142$)
Age, median, years (IQR)	54.6 (48.9–58.7)
Male sex, *n* (%)	120 (84.5)
BMI, median kg/m^2 (IQR)	25.6 (IQR 23.3–28.8)
Ethnicity, *n* (%)	
White	123/131 (93.9)
Hispanic	2/131 (1.5)
Asian	5/131 (3.8)
North Africa/Middle East	1/131 (0.7)
Alcohol abuse, *n* (%)	
No	55/117 (47)
Past	32/117 (27.4)
Active	30/117 (25.6)
IDU, *n* (%)	
No	60/123 (48.8)
Past	47/123 (38.2)
Active	16/123 (13)
Diabetes, *n* (%)	10/127 (7.9)
Cardiovascular disease, *n* (%)[a]	21/125 (16.8)
HBV coinfection, *n* (%)	3/133 (2.3%)
HIV coinfection, *n* (%)	15/133 (11.3%)
Concomitant medication, *n* (%)	
Diuretics	29/98 (29.6)
Proton-pump inhibitors	28/98 (28.6)
Anxiolytics	23/98 (23.5)
Antidepressants	22/98 (22.5)
Beta-blockers	20/98 (20.4)
Antiepileptics	9/98 (9.2)
HCV genotype, *n* (%)	
GT1	49/131 (37.4)
GT2	11/131 (8.4)
GT3	65/131 (49.6)
GT4	6/131 (4.6)
HCV RNA, IU/mL (IQR)	1,280,000 (249,000–3,230,000)
MELD, median (IQR)	7 (6–9)
Cirrhosis, *n* (%)	67/142 (47.2)
Child-Pugh, *n* (%)	
A	56/67 (83.6)
B	8/67 (11.9)
C	3/67 (4.5)
Previous episodes of liver decompensation, *n* (%)	15/142 (10.6)
Previous HCC, *n* (%)	9/136 (6.6)
Liver transplant prior to treatment, *n* (%)	8/142 (5.6)
First-line therapy, *n* (%)	
SOF/VEL	100/142 (70.4)
GLE/PIB	42/142 (29.6)

Abbreviations: BMI, body mass index; DAA, direct-acting antiviral; HBV, hepatitis B virus; HCV, hepatitis C virus; HCC, hepatocellular carcinoma; HIV, human immunodeficiency virus; IDU, injected drug user; IQR, interquartile range; MELD, model for end-stage liver disease; RNA, ribonucleic acid; SOF/VEL, sofosbuvir/velpatasvir; SVR, sustained virological response.

[a]This factor included coronary heart disease, cerebrovascular disease and peripheral artery disease.

fibrosis developed HCC after initiating VOX/VEL/SOF retreatment. Among these cases, 4 had achieved SVR. The median time from EOT with VOX/VEL/SOF to the diagnosis of HCC was 3.5 months (IQR 3.2–4.4).

3.2 | Efficacy analysis

By intention to treat analysis, SVR rate was 82.4% (117/142). However, at per protocol analysis, of the 132 patients who completed therapy and the 12 weeks of follow-up, 117 (88.6%) achieved SVR, while 15 (11.4%) did not respond to SOF/VEL/VOX despite completing treatment with optimal adherence. A flowchart of patient enrolment and outcomes is provided in Figure 1. SVR rates were 87.1% (54/62) in patients with cirrhosis and 90% (63/70) in those without cirrhosis ($p = 0.6$). SVR was achieved in 85.5% (53/62) of patients with GT3 HCV infection and in 91.9% (57/62) of those with other GTs ($p = 0.26$). In relation to prior treatment, SVR occurred in 90.2% (37/41) of failures to the GLE/PIB regimen and 87.9% (80/91) of failures to SOF/VEL, with no statistical differences ($p = 0.77$; Figure 2).

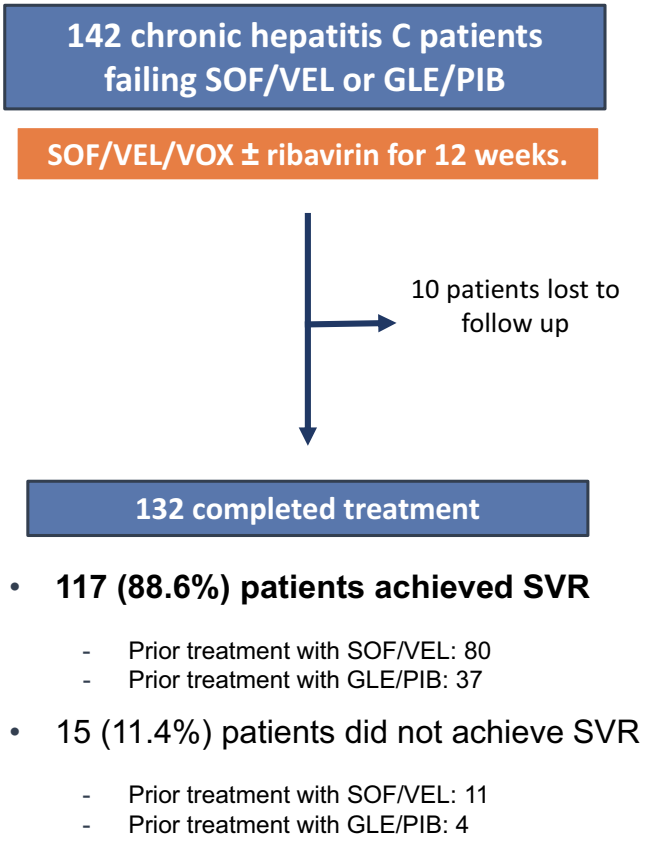

FIGURE 1 Flowchart with outcomes of the patients included. All individuals included received SOF/VEL/VOX, but 10 of them were lost to follow-up. Sustained virological response was evaluated as per protocol in the 132 patients who completed the treatment and SVR rate was 88.6% (117/132). GLE/PIB, glecaprevir/pibrentasvir; SOF/VEL, sofosbuvir/velpatasvir; SOF/VEL/VOX, sofosbuvir/velpatasvir/voxilaprevir; SVR, sustained virological response.

Among the 29 patients with cirrhosis and HCV GT3 who had failed to SOF/VEL, 24 were retreated with SOF/VEL/VOX, achieving SVR 79.2% of them, while all 5 who received SOF/VEL/VOX with RBV achieved SVR (100%). There were three patients with cirrhosis, HCV GT3, and failure to GLE/PIB, all of them received SOF/VEL/VOX and 2 (66.6%) achieved SVR. A total of 8 patients, including the five previously mentioned, received SOF/VEL/VOX with RBV and all of them reached SVR. Notably, five of them had liver cirrhosis, seven were infected with GT3 and 6 had received SOF/VEL as first-line therapy. Their main characteristics are displayed in Table 2.

3.3 | Characteristics of patients who did not achieve SVR with VOX/SOF/VEL

Main characteristics of 15 patients who did not achieve SVR after SOF/VEL/VOX are displayed in Table 3. They were mainly men (80%), median age 56 years, white (92.3%), 11 had previously received SOF/VEL, 9 had GT3 infection, and 8 had cirrhosis. There were not statistically significant differences between them and the patients who responded to SOF/VEL/VOX (Table 4).

3.4 | Resistance-associated substitutions

Results of RAS testing before initiation of SOF/VEL/VOX were available for 21 of the 132 patients with SVR data (15.9%). RAS were not detected in nine patients, while 12 (57.1%) had at least 1 RAS associated with resistance to DAAs: 9 (75%) to NS5A inhibitors (M31V, Y93H, A30S, A30K), 2 (16.7%) to NS5B inhibitors (S282T) and 2 (16.7%) to NS3 inhibitors (S122G). RAS were tested in only 3 patients who did not respond to SOF/VEL/VOX: 2 had a RAS related to NS5A inhibitors and 1 showed no RAS.

3.5 | Safety of SOF/VEL/VOX

No new or severe treatment-related adverse events that precluded treatment completion were reported, and no potential DDIs in patients with concomitant use of other medications were identified during therapy with SOF/VEL/VOX. No worsening of liver disease or decompensation was observed in patients with a previous episodes of decompensation. One patient with CPT-B that received RBV associated to treatment developed anaemia.

4 | DISCUSSION

This is one of the largest cohort of chronic HCV patients who failed to the currently recommended first-line DAAs (SOF/VEL or GLE/PIB) and subsequently received retreatment with SOF/VEL/VOX. Among those who completed rescue therapy, the SVR rate was 88.6% (117/132), slightly below the 90%–96% range

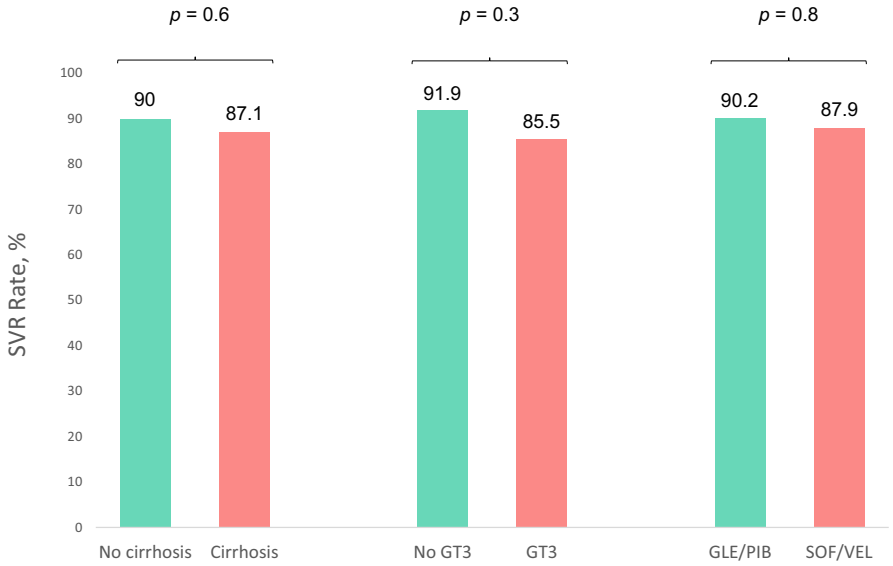

FIGURE 2 Bar graph representing sustained virological response rates according to the presence or not of cirrhosis, hepatitis C virus genotype 3 and first-line direct-acting antiviral regimen. Sustained virological response rates were lower in patients with factors reported to be related to sofosbuvir/velpatasvir/voxilaprevir failure, including cirrhosis, hepatitis C virus genotype 3 infection and prior failure to sofosbuvir/velpatasvir. However, none of the differences were statistically significant. GT3, genotype 3; GLE/PIB, glecaprevir/pibrentasvir; SOF/VEL, sofosbuvir/velpatasvir; SVR, Sustained virological response.

TABLE 2 Main characteristics of patients who received ribavirin in addition to sofosbuvir/velpatasvir/voxilaprevir.

	Age (years)	Sex	GT	Cirrhosis	Previous episode of liver decompensation	Child-Pugh	Prior treatment	SVR
1.	55	Male	3	No	No	A5	GLE/PIB	Yes
2.	59	Male	3	Yes	No	A5	SOF/VEL	Yes
3.	60	Male	3	Yes	No	A6	SOF/VEL	Yes
4.	58	Male	3	Yes	Ascites hepatic encephalopathy	A6	SOF/VEL	Yes
5.	59	Male	3	Yes	Ascites hepatic encephalopathy	A6	SOF/VEL	Yes
6.	43	Male	1	No	No	A5	GLE/PIB	Yes
7.	62	Male	3	No	No	A5	SOF/VEL	Yes
8.	57	Male	3	Yes	Ascites	B7	SOF/VEL	Yes

Abbreviations: GT, genotype; GLE/PIB, glecaprevir/pibrentasvir; SOF/VEL, sofosbuvir/velpatasvir; SVR, sustained virological response.

TABLE 3 Main characteristics of patients who did not respond to sofosbuvir/velpatasvir/voxilaprevir.

	Sex	Age	GT	Liver disease at baseline	First-line therapy	Decompensation at SOF/VEL/VOX initiation	RBV
1	Male	56	ND	Compensated cirrhosis	SOF/VEL	No	No
2	Male	54	3	Compensated cirrhosis	SOF/VEL	No	No
3	Female	59	1	Chronic hepatitis	SOF/VEL	No	No
4	Male	53	3	Compensated Cirrhosis	SOF/VEL	No	No
5	Male	53	3	Compensated cirrhosis	SOF/VEL	No	No
6	Female	59	1	Chronic hepatitis	SOF/VEL	No	No
7	Male	38	3	Compensated cirrhosis	SOF/VEL	No	No
8	Male	49	3	Chronic hepatitis	GLE/PIB	No	No
9	Female	81	1	Chronic hepatitis	GLE/PIB	No	No
10	Male	59	1	Chronic hepatitis	SOF/VEL	No	No
11	Male	57	3	Chronic hepatitis	SOF/VEL	No	No
12	Male	43	3	Compensated cirrhosis	GLE/PIB	No	No
13	Male	62	3	Compensated cirrhosis	SOF/VEL	No	No
14	Male	81	1	Compensated cirrhosis and CHC	SOF/VEL	No	No
15	Male	42	3	Chronic hepatitis	GLE/PIB	No	No

Abbreviations: GLE/PIB, glecaprevir/pibrentasvir; GT, genotype; HCC, hepatocellular carcinoma; ND, no data; RBV, ribavirin; SOF/VEL, sofosbuvir/velpatasvir; SVR, Sustained virological response.

TABLE 4 Factors associated with sustained virological response after treatment with SOF/VEL/VOX.

	SVR ($n = 117$)	Treatment failure ($n = 15$)	p-value
Age, median, years (IQR)	54.6 (49–58.8)	56 (49.3–59.9)	0.6
Male sex, *n* (%)	100/117 (89.3)	12/15 (80)	0.7
BMI, median kg/m^2 (IQR)	25.6 (IQR 23.2–28.6)	27.1 (IQR 24.4–29.2)	0.5
Ethnicity, *n* (%)			
White	103/110 (93.6)	12/13 (92.3)	0.99
Hispanic	2/110 (1.8)	0/13 (0)	0.99
Asian	4/110 (3.6)	1/13 (7.7)	0.4
North Africa/Middle East	1/110 (0.9)	0/13 (0)	0.99
Alcohol abuse, *n* (%)			
No	43/98 (43.9)	8/12 (66.6)	0.2
Past	27/98 (27.6)	3/12 (25)	0.99
Active	28/98 (28.5)	1/12 (8.3)	0.2
IDU, *n* (%)			
No	49/103 (47.6)	8/13 (61.5)	0.4
Past	42/103 (40.8)	4/13 (30.8)	0.6
Active	12/103 (11.6)	1/13 (7.7)	0.99
Diabetes, *n* (%)	8/106 (7.5)	2/13 (15.4)	0.3
Cardiovascular disease, *n* (%)[a]	16/104 (15.4)	3/13 (23.1)	0.4
HBV coinfection, *n* (%)	2/107 (1.9)	0/15 (0)	0.99
HIV coinfection, *n* (%)	13/110 (11.8)	1/13 (7.7)	0.99
Concomitant medication, *n* (%)			
Diuretics	25/87 (28.7)	2/6 (33.3)	0.99
Proton-pump inhibitors	26/87 (29.9)	2/6 (33.3)	0.99
Anxiolytics	22/87 (25.3)	1/6 (16.7)	0.99
Antidepressants	19/87 (21.8)	3/6 (50)	0.1
Beta-blockers	19/87 (21.8)	1/6 (16.7)	0.99
Antiepileptics	7/87 (8%)	1/6 (16.7)	0.4
HCV genotype, *n* (%)			
GT1	42/110 (38.2)	5/14 (35.7)	0.9
GT2	9/110 (8.2)	0/0 (0)	0.99
GT3	53/110 (48.2)	9/14 (64.3)	0.3
GT4	6/110 (5.4)	0/14 (0)	0.4
HCV RNA, IU/mL (IQR)	1,280,000 (300,477–2,935,000)	2,655,000 (679,155–7,575,570)	0.1
MELD, median (IQR)	7 (6–9)	7 (6–9)	0.8
Cirrhosis, *n* (%)	54/117 (46.2)	8/15 (53.3)	0.6
Child-Pugh, *n* (%)			
A	44/54 (81.5)	8/8 (100)	0.7
B	8/54 (14.8)	0/8 (0)	
C	3/54 (5.6)	0/8 (0)	
Previous episodes of liver decompensation, *n* (%)	13/117 (11.1)	0/15 (0)	0.4
Previous HCC, *n* (%)	6/112 (5.4)	1/15 (6.7)	0.6
Liver transplant prior to treatment, *n* (%)	8/117 (6.8)	0/15 (0)	0.6
First-line therapy, *n* (%)			
SOF/VEL	80/117 (68.4)	11/15 (73.3)	0.8
GLE/PIB	37/117 (31.6)	4/15 (26.6)	
GT3 HCV + Cirrhosis + prior SOF/VEL	20/112 (17.1)	5/15 (33)	0.17

Abbreviations: BMI, body mass index; DAA, direct-acting antiviral; HBV, hepatitis B virus; HCV, hepatitis C virus; HCC, hepatocellular carcinoma; HIV, human immunodeficiency virus; IDU, injected drug user; IQR, interquartile range; MELD, model for end-stage liver disease; RNA, ribonucleic acid; SOF/VEL, sofosbuvir/velpatasvir; SVR, sustained virological response.

[a]This factor included coronary heart disease, cerebrovascular disease and peripheral artery disease.

reported in previous studies.[8–11,13,14] The lower SVR in our patients might be related to the fact that in our cohort, all patients had failed to pangenotypic regimens (SOF/VEL or GLE/PIB), especially SOF/VEL (70%). This contrast to most previous studies, where only 6%–45% of the total populations had received SOF/VEL or GLE/PIB.[12–14]

In fact, the two previous largest studies reported SVR rates of 90% and 84.1% in patients treated with SOF/VEL, which aligns with our data (87.9%).[13,14]

Less data are available regarding failures to GLE/PIB, as only 58 cases of GLE/PIB failure were included in the Graf et al. study and no GLE/PIB failure was reported in the systematic review.[13] These studies associated prior exposure to SOF/VEL with worse SVR rates, mostly comparing it with outdated DAAs. Consequently, it remains unclear if prior treatment with SOF/VEL rather than GLE/PIB correlates with a lower SVR to SOF/VEL/VOX. In our cohort, SVR rates were 87.9% (SOF/VEL) and 90.2% (GLE/PIB), without statistically significant difference ($p=0.8$). This is consistent with results published by Graft et al (SVR 92% after GLE/PIB) and might suggest that not only patients failing SOF/VEL but also GLE/PIB are a particularly challenging-to-treat population.

As mentioned, GT3 HCV infection and the presence of cirrhosis, have also been associated with lower SVRs to SOF/VEL/VOX.[13,14] Thus, the high percentages of patients with cirrhosis (47.2%) and GT3 HCV (49.6%) in the present cohort could also explain the lower SVR rates. Nonetheless, we found a non-significant trend towards lower SVR rates between patients with cirrhosis versus without cirrhosis (87.1% vs. 90%, $p=0.6$) or GT3 HCV vs. other GTs (85.5% vs. 91.9%, $p=0.26$). Limited statistical power due to sample size, especially regarding non-responders, may have influenced these findings. Of note, however, the lowest SVR rate was observed in patients with all 3 concomitant risk factors. Only 82.8% achieved SVR and the rate dropped even further when patients receiving RBV were excluded (79.2%). These results suggest that this patient population may represent a profile of poorer responders, warranting further investigation.

The role of adding RBV to SOF/VEL/VOX in rescue therapy is still controversial.[13,14] The use of RBV in real-world studies depends on the criteria of the physician, thus probably selecting difficult to treat patients. In a randomised study including 315 Egyptian patients who primarily failed to sofosbuvir plus daclatasvir, adding RBV to SOF/VEL/VOX did not increase SVR but was associated with more side effects.[19] Caution is warranted when extrapolating these results, as sofosbuvir plus daclatasvir-based regimens are no longer considered first-line therapies.[19] Additionally, although GT data were lacking in this study, earlier studies have reported that 93% of HCV infections in Egypt are attributable to GT4, which represents only 13% of HCV patients worldwide.[20] In our limited experience, the eight patients treated SOF/VEL/VOX plus RBV achieved SVR despite having five cirrhosis, seven GT3 and six prior treatment with SOF/VEL, even five of them had the three concomitant factors. Our results support the EASL clinical guidelines recommendation of adding RBV on a case-by-case basis by expert clinicians.

Protease inhibitors are not recommended in patients with decompensated liver disease (CPT-B or C).[4,20] In our cohort, there were 15 patients with history of liver decompensation. However, at the time of retreatment, only 3 remained decompensated. Although, no relevant severe adverse events were reported, it should be noted that these were highly selected cases and they received therapy in experienced centres under strict monitoring.

Drug–drug interactions are one of the main limitations for DAA use, particularly when DAAs are co-administered with antiseizure medications. These drugs are potent inductors or inhibitors of cytochrome P450 enzymes, and in some cases, patients cannot be easily switched to an alternative. Evidence is limited concerning such interactions with SOF/VEL/VOX.[21] Within our cohort, nine patients were receiving antiseizure medications during retreatment, and seven achieved SVR (one was lost to follow-up and the other did not respond). No adverse events potentially associated with DDIs were reported.

An important point not answered in our study is the optimal rescue therapy for failures to SOF/VEL/VOX. The EASL Guidelines recommends the triple combination of GLE/PIB + Sofosbuvir for 24 weeks with RBV. This is based on the fact that pibrentasvir has a higher barrier to resistance than all other approved NS5A inhibitors in vitro. However, the number of patients retreated with SOF/VEL/VOX ± RBV is limited. Two retrospective studies showed a SVR of 79% (11/14) and 100% (10/10) in these individuals.[14,22]

Our study has some limitations. Firstly, the relatively small number of patients included, attributable to the high effectiveness of current first-line therapies for HCV. Secondly, the limited number of failures to SOF/VEL/VOX precluded a more detailed characterisation of these patients. Thirdly, being a retrospective study, there is a potential bias towards underreporting minor adverse events. Finally, RASs are not routinely tested in our setting. Consequently, only 21 patients (15.9%) were tested for RASs, and although no significant differences in SVR rates were observed, the limited sample size may have influenced this outcome.

In conclusion, our results provide evidence that SOF/VEL/VOX is an effective and safe rescue therapy for patients with HCV infection and nonresponse to SOF/VEL or GLE/PIB. Although there was a trend towards lower SVR rates in GT3 HCV infection, cirrhosis, and first-line therapy with SOF/VEL these were not statistically significant.

AUTHOR CONTRIBUTIONS

Juan Carlos Ruiz-Cobo: Methodology; data curation; validation; supervision; visualization; resources; writing – review and editing; writing – original draft; project administration; investigation. **Jordi Llaneras:** Formal analysis; writing – original draft; methodology; data curation; validation; supervision; visualization; resources; writing – review and editing; investigation. **Xavier Forns:** Writing – review and editing; data curation. **Adolfo Gallego Moya:** Data curation; writing – review and editing. **Isabel Conde Amiel:** Data curation; writing – review and editing. **Ana Arencibia:** Data curation; writing – review and editing. **Moises Diago:** Data curation;

writing – review and editing. **Javier García-Samaniego:** Data curation; writing – review and editing. **Jose Castellote:** Data curation; writing – review and editing. **Susana Llerena:** Data curation; writing – review and editing. **Elisa Rodríguez-Seguel:** Data curation; writing – review and editing. **Beatriz Mateos:** Data curation; writing – review and editing. **Manuel Rodríguez:** Data curation; writing – review and editing. **Jose Miguel Rosales Zabal:** Data curation; writing – review and editing. **Inmaculada Fernández:** Data curation; writing – review and editing. **Jose Luis Calleja:** Data curation; writing – review and editing. **Rosa María Morillas:** Data curation; writing – review and editing. **Silvia Montoliu:** Data curation; writing – review and editing. **Raul J. Andrade:** Data curation; writing – review and editing. **Ester Badia Aranda:** Data curation; writing – review and editing. **Manuel Hernández-Guerra:** Data curation; writing – review and editing. **Carlota Jimeno Maté:** Data curation; writing – review and editing. **Jesús M. González-Santiago:** Data curation; writing – review and editing. **Beatriz de Cuenca:** Data curation; writing – review and editing. **Vanesa Bernal-Monterde:** Data curation; writing – review and editing. **Manuel Delgado:** Data curation; writing – review and editing. **Juan Turnes:** Data curation; writing – review and editing. **Sabela Lens:** Conceptualization; investigation; project administration; writing – original draft; writing – review and editing; resources; visualization; supervision; validation; methodology. **María Buti:** Methodology; writing – review and editing; resources; validation; supervision; visualization; writing – original draft; project administration; conceptualization; investigation.

Affiliations

[1]Liver Unit, Hospital Universitari Vall d'Hebron, Barcelona, Spain

[2]Universitat Autònoma de Barcelona (UAB), Barcelona, Spain

[3]Liver Unit, Hospital Clínic, Barcelona, Spain

[4]Fundació de Recerca Clínic Barcelona-Institut d'Investigacions Biomèdiques August Pi i Sunyer (FRCB-IDIBAPS), Barcelona, Spain

[5]University of Barcelona (UB), Barcelona, Spain

[6]Centro de Investigación Biomédica en Red de Enfermedades Hepáticas y Digestivas (CIBERehd), Instituto de Salud Carlos III, Madrid, Spain

[7]Servicio de Patología Digestiva, Hospital de la Santa Creu i Sant Pau, Barcelona, Spain

[8]Hepatology and Liver Transplantation Unit, Hospital Universitario y Politécnico La Fe, Valencia, Spain

[9]Instituto de Investigación Sanitaria La Fe (IIS La Fe), Valencia, Spain

[10]Gastroenterology Department, Hospital Universitario Nuestra Señora de Candelaria, Santa Cruz de Tenerife, Spain

[11]Hospital General Universitario Valencia, Valencia, Spain

[12]Medicine Department, Universidad de Valencia, Valencia, Spain

[13]Liver Unit, Hospital Universitario La Paz, Madrid, Spain

[14]Instituto de Investigación Hospital Universitario La Paz (IdiPAZ), Madrid, Spain

[15]Universidad Autónoma de Madrid, Madrid, Spain

[16]Hepatology Unit, Gastroenterology Department, Hospital Universitari de Bellvitge, L'Hospitalet de Llobregat, Barcelona, Spain

[17]Instituto de Investigación Biomédica de Bellvitge (IDIBELL), Universitat de Barcelona, Barcelona, Spain

[18]Gastroenterology and Hepatology Department, Hospital Universitario Marqués de Valdecilla, Santander, Spain

[19]Instituto de Investigación Sanitaria Valdecilla (IDIVAL), Santander, Spain

[20]Liver Diseases, Instituto de Biomedicina de Sevilla (IBiS)/Hospital Universitario Virgen del Rocío/CSIC/Universidad de Sevilla, Seville, Spain

[21]Hospital Universitario Virgen del Rocío, Seville, Spain

[22]Digestive Diseases Research Unit, Virgen Del Rocío University Hospital, Seville, Spain

[23]Cell Biology Department, Faculty of Biology, University of Seville, Seville, Spain

[24]Gastroenterology Department, Hospital Universitario Ramón y Cajal, Madrid, Spain

[25]Instituto Ramón y Cajal de Investigación Sanitaria (IRYCIS), Madrid, Spain

[26]University of Alcala, Madrid, Spain

[27]Liver Unit, Gastroenterology and Hepatology Division, Hospital Universitario Central de Asturias, Oviedo, Spain

[28]University of Oviedo, Oviedo, Spain

[29]Gastroenterology Department, Hospital Universitario Costa del Sol, Marbella, Spain

[30]Gastroenterology Department, Hospital Universitario 12 de Octubre, Madrid, Spain

[31]Servicio de Gastroenterología y Hepatología, Hospital Universitario Puerta de Hierro, Madrid, Spain

[32]Instituto de Investigación Sanitaria Puerta de Hierro (IDIPHIM), Madrid, Spain

[33]Hepatology Unit, Hospital Universitari Germans Trias i Pujol, Badalona, Spain

[34]Institute for Health Science Research Germans Trias i Pujol (IGTP), Badalona, Spain

[35]Department of Medicine, Barcelona Autonomous University (UAB), Barcelona, Spain

[36]Gastroenterology Department Hospital, Universitari Joan XXIII, Tarragona, Spain

[37]Institut d'Investigació Sanitària Pere Virgili (IISPV), Tarragona, Spain

[38]Hospital Universitario Virgen de la Victoria, Málaga, Spain

[39]University Hospital-IBIMA Platform BIONAND, Málaga, Spain

[40]University of Malaga, Málaga, Spain

[41]Gastroenterology Department, Hospital Universitario de Burgos, Burgos, Spain

[42]Hospital Universitario de Canarias, Santa Cruz de Tenerife, Spain

[43]Gastroenterology Department, Hospital Universitario Virgen de Valme, Sevilla, Spain

[44]Gastroenterology and Hepatology Department, University Hospital of Salamanca, Salamanca, Spain

[45]Instituto de Investigación Biomédica de Salamanca (IBSAL), Salamanca, Spain

[46]Hospital Universitario de Getafe, Getafe, Spain

[47]Servicio de Aparato Digestivo, Hospital Universitario Miguel Servet, Zaragoza, Spain

[48]Instituto de Investigación Sanitaria de Aragón (IISA), Zaragoza, Spain

[49]Hospital Universitario La Coruña, La Coruña, Spain

[50]Department of Gastroenterology and Hepatology, Complejo Hospitalario Universitario Pontevedra & IIS Galicia Sur, Pontevedra, Spain

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AUTHORSHIP

Guarantor of the article: Sabela Lens & Maria Buti.

ORCID

Juan Carlos Ruiz-Cobo https://orcid.org/0000-0003-2239-4939
Jordi Llaneras https://orcid.org/0000-0001-9011-3954
Xavier Forns https://orcid.org/0000-0002-8188-1764
Adolfo Gallego Moya https://orcid.org/0000-0002-8423-6787
Isabel Conde Amiel https://orcid.org/0000-0001-7863-2233
Ana Arencibia https://orcid.org/0000-0002-7813-7563
Moises Diago https://orcid.org/0000-0002-8583-2433
Javier García-Samaniego https://orcid.org/0000-0002-9974-0855
Jose Castellote https://orcid.org/0000-0002-8528-3112
Susana Llerena https://orcid.org/0000-0002-5882-8404
Beatriz Mateos https://orcid.org/0000-0003-0326-4119
Manuel Rodríguez https://orcid.org/0000-0001-5763-7668
Jose Miguel Rosales Zabal https://orcid.org/0000-0001-6751-6720
Jose Luis Calleja https://orcid.org/0000-0002-2265-6591
Rosa María Morillas https://orcid.org/0000-0001-9117-5049
Silvia Montoliu https://orcid.org/0000-0002-3041-578X
Raul J. Andrade https://orcid.org/0000-0002-1565-0757
Ester Badia Aranda https://orcid.org/0000-0001-8774-0041
Manuel Hernández-Guerra https://orcid.org/0000-0002-3478-9981
Jesús M. González-Santiago https://orcid.org/0000-0003-4667-4492
Vanesa Bernal-Monterde https://orcid.org/0000-0002-4016-2165
Juan Turnes https://orcid.org/0000-0001-8426-6145
Sabela Lens https://orcid.org/0000-0003-4900-411X
María Buti https://orcid.org/0000-0002-0732-3078

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