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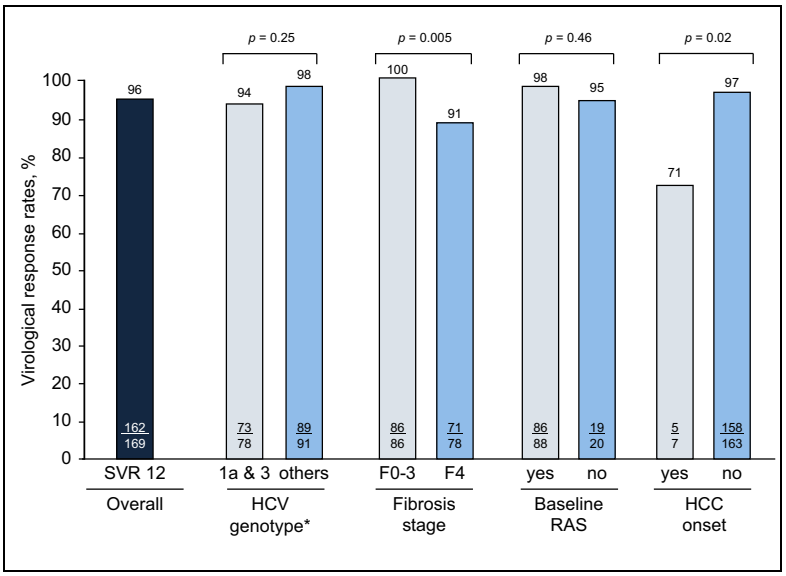
Real-life effectiveness and safety of sofosbuvir/velpatasvir/voxilaprevir in hepatitis C patients with previous DAA failure

Graphical abstract



Highlights

- SOF/VEL/VOX demonstrated excellent effectiveness in patients with HCV and previous DAA failure in a real-life study.
- Cirrhosis ($p = 0.005$) and hepatocellular carcinoma onset ($p = 0.02$) were the only features associated with treatment failure.
- Treatment failures (4%) occurred in patients with cirrhosis, with genotypes HCV-1a and 3 the most represented.

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Lay summary

This is the largest European real-life study evaluating effectiveness and safety of sofosbuvir/velpatasvir/voxilaprevir (SOF/VEL/VOX) in a large cohort of consecutive patients with hepatitis C virus infection and a prior direct-acting antiviral failure, who were treated within the NAVIGATORE Lombardia and Veneto Networks, in Italy. This study demonstrated excellent effectiveness (98% and 96% sustained virological response rates at week 4 and 12, respectively) and an optimal safety profile of SOF/VEL/VOX. Cirrhosis and hepatocellular carcinoma onset were the only features associated with treatment failure.

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Real-life effectiveness and safety of sofosbuvir/velpatasvir/voxilaprevir in hepatitis C patients with previous DAA failure

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Background & Aims: Sofosbuvir/velpatasivr/voxilaprevir (SOF/VEL/VOX) is approved for retreatment of patients with HCV and a previous failure on direct-acting antivirals (DAAs), however real-life data are limited. The aim of this study was to assess the effectiveness and safety of SOF/VEL/VOX in a real-life setting.

Methods: All consecutive patients with HCV receiving SOF/VEL/VOX between May-October 2018 in 27 centers in Northern Italy were enrolled. Bridging fibrosis (F3) and cirrhosis (F4) were diagnosed by liver stiffness measurement: >10 and >13 kPa respectively. Sustained virological response (SVR) was defined as undetectable HCV-RNA 4 (SVR4) or 12 (SVR12) weeks after the end-of-treatment.

Results: A total of 179 patients were included: median age 57 (18–88) years, 74% males, median HCV-RNA 1,081,817 (482–25,590,000) IU/ml. Fibrosis stage was F0-F2 in 32%, F3 in 21%, F4 in 44%. HCV genotype was 1 in 58% (1b 33%, 1a 24%, 1nc 1%), 2 in 10%, 3 in 23% and 4 in 9%; 82% of patients carried resistance-associated substitutions in the NS3, NS5A or NS5B regions. Patients received SOF/VEL/VOX for 12 weeks, ribavirin was added in 22% of treatment schedules. Undetectable HCV-RNA was achieved by 74% of patients at week 4 and by 99% at week 12. Overall, 162/179 (91%) patients by intention to treat analysis and 162/169 (96%) by per protocol analysis achieved SVR12, respectively; treatment failures included 6 relapsers and 1 virological non-responder. Cirrhosis ($p = 0.005$) and hepatocellular carcinoma ($p = 0.02$) were the only predictors of treatment failure. Most frequent adverse events included fatigue (6%), hyperbilirubinemia (6%) and anemia (4%).

Conclusions: SOF/VEL/VOX is an effective and safe retreatment for patients with HCV who have failed on a previous DAA course in a real-life setting.

Lay summary: This is the largest European real-life study evaluating effectiveness and safety of sofosbuvir/velpatasvir/voxilaprevir (SOF/VEL/VOX) in a large cohort of consecutive patients with hepatitis C virus infection and a prior direct-acting antiviral failure, who were treated within the NAVIGATORE Lombardia and Veneto Networks, in Italy. This study demonstrated excellent effectiveness (98% and 96% sustained virological response rates at week 4 and 12, respectively) and an

Keywords: Retreatment; Direct-acting antivirals; Sofosbuvir; HCV; RAS; Resistance.
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optimal safety profile of SOF/VEL/VOX. Cirrhosis and hepatocellular carcinoma onset were the only features associated with treatment failure.

Introduction

The development of direct-acting antivirals (DAA) for the treatment of HCV has dramatically increased rates of sustained virological response (SVR) to antiviral therapy, reaching more than 95–98% in all patient groups.[1] Despite optimal efficacy and safety, approximately 2% of patients still fail to achieve an SVR and need alternative treatment options.[1] Retreatment of patients with DAA failure could be challenging, as emergence of resistance-associated substitutions (RASs) in HCV nonstructural (NS) regions can negatively impact on the chances of SVR.[2,3] Indeed, RASs have been shown to confer cross-resistance among DAAs of the same class.[4,5] Moreover, due to preserved viral fitness, RASs in the NS5A region have been shown to persist long-term, being detectable even many years after treatment completion.[5] Recently, the approval of the protease inhibitor voxilaprevir (VOX) combined with the NS5B inhibitor sofosbuvir (SOF) and the NS5A inhibitor velpatasvir (VEL) has provided a potent retreatment option targeting all steps of HCV replication. The SOF/VEL/VOX combination has been evaluated in more than 800 patients enrolled in phase II and phase III studies, where it demonstrated excellent safety and efficacy, achieving overall SVR rates of more than 95%.[6–10] The POLARIS-1 and 4 phase III trials also included a significant proportion of patients with cirrhosis (46%) and/or carrying multiple RASs (49–83%). Despite this difficult-to-treat population, the POLARIS trials achieved 96% and 97% SVR rates, and led to approval of SOF/VEL/VOX, which is currently recommended as the first-line retreatment option for compensated HCV patients by EASL and AASLD recommendations.[1,11] More recently, the first real-life experiences with SOF/VEL/VOX have been published in US Veterans and in Spanish patients, reporting dismal effectiveness in patients who previously failed on SOF/VEL and in those with HCV genotype 3 infection.[12,13] However, data about SOF/VEL/VOX in clinical practice are still limited. Therefore, the aim of this study was to assess the effectiveness and safety of SOF/VEL/VOX in a large real-life patient cohort in Northern Italy.

Materials and methods

Patient population

All patients with HCV, consecutively starting antiviral treatment with SOF/VEL/VOX between May and October 2018 in 27 Centers in Northern Italy (Lombardia and Veneto Networks) were enrolled in a retrospective longitudinal multicenter real-life study. Data were collected through 2 electronic web-based platforms (NAVIGATORE-Lombardia and NAVIGATORE-Veneto), based on REDCap (Research Electronic Data Capture; http://project-redcap.org), including all patients treated with DAA in Lombardia and Veneto regions since December 2014. All patients provided informed consent to make available their medical records for the study, which was approved by the Institutional Board of the coordinating Center (Ethical Committee Milan Area 2) and conformed to the 1975 Declaration of Helsinki ethical guidelines.

Assessments

Clinical and virological characteristics were recorded at baseline, during and after the end-of-treatment (EOT). Adverse events (AEs) occurring after treatment start were also recorded. Fibrosis was staged non-invasively by transient elastography. Liver stiffness measurement (LSM) cut-offs >10 and >13.0 kPa identified bridging fibrosis (F3) or cirrhosis (F4), respectively.[1]

When available, resistance testing for baseline and treatment-emergent RASs was performed by direct sequencing analysis using the Sanger method (ABI PRISM 3100 genetic analyzer DNA Sequencer, Applied Biosystems, Foster City, CA, USA), with a 15% threshold.

Patients received SOF/VEL/VOX 400/100/100 mg/day for 12 weeks; ribavirin (RBV) was added at investigator's discretion. Treatment monitoring included blood examinations during (weeks 4 and 12) and after (weeks 4 and 12) treatment. Compliance was assessed according to clinician's judgment. AEs were reported at physician's discretion. On-treatment virological response was defined as HCV-RNA below the limit of quantification (LLOQ) or undetectable by either the Abbott-RT PCR (lower limit of detection 12 IU/ml) or COBAS TaqMan assay (lower limit of detection 15 IU/ml) at treatment week 4 (4-week virological response) and at EOT (EOT response). SVR was defined as undetectable HCV-RNA 4 (SVR4) and 12 (SVR12) weeks after treatment completion.

According to international recommendations, F3 and F4 patients underwent 6-month abdominal ultrasound surveillance for hepatocellular carcinoma (HCC);[14] upper gastrointestinal endoscopy (EGD) was performed according to Baveno recommendations for varices screening.[15]

Statistical analysis

Categorical variables were reported as frequencies (percentages) and continuous variables as median (range). Categorical variables were compared using the $\chi 2$ or the Fisher's exact tests; continuous variables were compared using the Student's *t* test, the Mann-Whitney *U* test or the Kruskall-Wallis test, when appropriate. All tests were 2-sided and used a significance level of 0.05. Data handling and analysis were performed with StataView package (SAS Institute Inc., Cary, NC).

Results

Patient population

Between May and October 2018, 179 patients with HCV consecutively starting SOF/VEL/VOX were enrolled. Patient characteristics are shown in Table 1. Median age was 57 (18–88) years; they were mostly males (74%), with a median BMI of 25 (16–45) kg/m^2. Median LSM was 10.2 (3.5–63.9) kPa and fibrosis stage was classified F0-F2 in 32%, F3 in 21%, F4 in 44%. At baseline, 78 out of 79 (99%) cirrhotic patients were Child-Turcotte-Pugh (CTP) score A; 16 (9%) patients had a previous history of HCC, and 2 compensated cirrhotics were on the liver transplant (LT) waiting-list for HCC. Gastro-esophageal varices were detected at EGD in 32% of cases. HCV genotype was 1 in 58% of the patients (1b 33%, 1a 24%, 1 nc 1%), 2 in 10%, 3 in 23% and 4 in 9%, respectively. At baseline, median HCV-RNA was

1,081,817 (482–25,590,000) IU/ml; median estimated glomerular filtration rate (eGFR) according to the MDRD (modification of diet in renal disease) formula was 93 (41–150) ml/min/1.73 m^2.

Baseline features according to previous DAA courses and resistance testing

Features of the last DAA treatment course before SOF/VEL/VOX are represented in Table S1. Most patients had failed SOF/VEL (20%), SOF/ledipasvir (LDV) (20%) or ombitasvir/paritaprevir-r (OBV/PTV-r) + dasabuvir (DSV) (17%). Overall, 94% of patients had failed an NS5A- and 39% an NS3-containing regimen. Overall, previous DAA courses conformed to the latest international recommendations at the time of DAA treatment in 159 (89%) patients, whereas 20 (11%) patients had received suboptimal DAA regimens.

Resistance testing at baseline (SOF/VEL/VOX start) was available in 115 (64%) patients (Table 2). Overall, RASs were detected in 94 (82%) patients: a single RAS was detected in 52 (46%) patients (NS5A 42%, NS3 3%, NS5B 1%), whilst combined RASs were detected in 40 (35%) of them (NS5A + NS3 in 16%, NS5A + NS5B + NS3 in 10%, NS5A + NS5B in 10%). Overall, NS5A RASs were detected in 77% of patients with available data, Y93H being the most frequent (50%).

All patients received SOF/VEL/VOX for 12 weeks; RBV was added in 39 (22%) of them, at a median dose of 1,000 (600–1,200) mg/day. Patients receiving RBV more frequently carried RASs at baseline (overall RAS: 72% *vs.* 47%, $p = 0.01$; NS5A RAS: 64% *vs.* 44%, $p = 0.006$), whereas other clinical features such as prevalence of cirrhosis (44% *vs.* 44%, $p = 1.00$), HCV genotype (1a *vs.* 3 *vs.* others: $p = 0.94$) and type of previous DAA course (SOF *vs.* non-SOF: 59% *vs.* 40% compared to 61% *vs.* 38%, $p = 0.85$) did not significantly differ between the 2 groups.

Table 1. Baseline characteristics of the 179 patients included in the study.

Characteristics	n = 179
Age, years	57 (18–88)
Males	132 (74%)
BMI, kg/m^2	25 (16–45)
IFN experienced	52 (29%)
LSM, kPa	10.2 (3.5–63.9)
Fibrosis	
F0-F2	57 (32%)
F3	38 (21%)
F4	79 (44%)
n.a.	5 (3%)
CPT score A*	78 (99%)§
A5	64 (81%)
A6	14 (18%)
Oesophageal varices	25 (32%)§
Previous HCC	16 (9%)
HCV genotype	
1	103 (58%)*
2	18 (10%)
3	42 (23%)
4	16 (9%)
HCV-RNA, IU/ml	1,081,817 (482–25,590,000)
ALT, U/L	54 (10–538)
GGT, U/L	53 (9–428)
PLT, 10^3/mm^3	154 (35–539)
Bilirubin, mg/dl	0.7 (0.3–5.7)
Albumin, g/dl	4.2 (2.8–5.1)
INR	1.0 (0.9–3.5)
Creatinine, mg/dl	0.8 (0.4–1.7)
eGFR (MDRD), ml/min/1.73 m^2	93 (41–150)
HIV positive	27 (15%)
HBsAg positive	2 (1%)
Diabetes	25 (14%)
Arterial hypertension	47 (26%)

Values expressed as n (%) or median (range).
ALT, alanine aminotransferase; BMI, body mass index; CTP, Child-Turcotte-Pugh; GGT, gamma-glutamyltransferase; HCC, hepatocellular carcinoma; IFN, interferon; INR, international normalized ratio; LSM, liver stiffness measurement; MDRD, modification of diet in renal disease; n.a., not available; nc, not classified; PLT, platelets. Categorical variables were compared using the $\chi 2$ or the Fisher's exact tests; continuous variables were compared using the Student's *t* test, the Mann-Whitney *U* test or the Kruskall-Wallis test, when appropriate.
* HCV genotype: 1b 58 (33%), 1a 43 (24%), 1nc 2 (1%).
§ Calculated in 79 F4 patients.

Treatment effectiveness

All 179 patients included in the study completed the 12-week treatment course: overall, on-treatment virological response at week 4 was achieved by 108 out of 145 (74%) patients with available on-treatment data: HCV-RNA was <LLOQ in 45 (31%) and undetectable in 63 (44%), respectively. Median HCV-RNA at week 4 in patients testing HCV-RNA positive was 25 (10–72,284) IU/ml. Cirrhosis ($p = 0.01$), higher baseline viral load ($p = 0.008$), lower eGFR ($p = 0.007$) and RBV use ($p = 0.006$) were associated with a lack of on-treatment response at week 4 (Table 3). An EOT response was achieved by 161/162 (99%) patients with available HCV-RNA assessment.

SVR data were available for 172 patients at SVR4 and 169 patients at SVR12, respectively: overall 10 patients completing treatment were lost to follow-up (3 between EOT and SVR4, 7 between SVR4 and SVR12 time-points) Fig. 1.

By intention to treat (ITT) analysis, 169/179 (94%) patients achieved the SVR4 and 162/179 (91%) the SVR12: by analyzing SVR rates according to HCV genotype, treatment effectiveness was suboptimal in HCV-3 patients, as 98/103 (95%) HCV-1, 17/18 (94%) HCV-2, 33/42 (79%) HCV-3 and 14/16 (88%) HCV-4 patients achieved the SVR12, respectively ($p = 0.02$). At per protocol (PP) analysis, 169/172 (98%) patients achieved the SVR4 and 162/169 (96%) the SVR12: in the PP analysis, SVR rates in HCV-3 patients were not significantly lower compared to other genotypes, as 98/101 (97%) HCV-1 patients, 17/17 (100%) HCV-2, 33/36 (92%) HCV-3 and 14/15 (93%) HCV-4 achieved the SVR12 ($p = 0.40$) (Fig. S1).

Table 2. RAS at baseline (SOF/VEL/VOX start) in the 115 patients with available resistance testing.

Resistance testing	n = 115
No RAS	21 (18%)
Any RAS	94 (82%)
Single RAS	
NS5A	48 (42%)
NS3	3 (3%)
NS5B	1 (1%)
Combined RAS	
NS5A + NS3	18 (16%)
NS5A + NS5B + NS3	12 (10%)
NS5A + NS5B	10 (9%)
Any NS5A RAS	88 (77%)
Y93H	57 (50%)

RAS, resistance-associated substitutions; SOF/VEL/VOX, sofosbuvir/velpatasvir/voxilaprevir.
Categorical variables were compared using the $\chi 2$ or the Fisher's exact tests.

Table 3. Factors associated with week 4 virological response.

	Week 4 response (n = 108)	Non-week 4 response (n = 37)	*p* value
Age, years	56 (18–88)	59 (28–81)	0.10
Males	82 (76%)	27 (73%)	0.83
BMI, kg/m^2	24 (16–41)	26 (19–45)	0.07
Diabetes	12 (11%)	7 (19%)	0.26
Arterial hypertension	29 (27%)	13 (35%)	0.40
IFN experienced	30 (28%)	16 (43%)	0.10
Previous DAA course			0.25
SOF-based	60 (56%)	25 (68%)	
Non-SOF-based	48 (44%)	12 (32%)	
LSM, kPa	10.0 (3.5–63.9)	11.0 (5.8–34.8)	0.77
Fibrosis			0.01
F0–F2	42 (39%)	6 (16%)	
F3	28 (26%)	7 (19%)	
F4	37 (34%)	24 (65%)	
n.a.	1 (1%)	–	
HCV Genotype			0.20
1	56 (52%)[#]	25 (67%)°	
2	11 (10%)	4 (11%)	
3	30 (28%)	4 (11%)	
4	11 (10%)	4 (11%)	
HCV–RNA, IU/ml	942,150 (482–25,590,000)	1,989,549 (163,512–14,740,187)	0.008
ALT, U/L	53 (13–387)	59 (15–327)	0.86
GGT, U/L	53 (9–367)	73 (10–428)	0.23
PLT, 10^3/mm^3	168 (35–508)	140 (51–539)	0.11
Bilirubin, mg/dl	0.7 (0.3–5.7)	0.7 (0.3–3.8)	0.79
Albumin, g/dl	4.2 (3.0–5.1)	4.0 (2.8–5.0)	0.92
INR	1.0 (0.9–3.5)	1.1 (1.0–1.5)	0.88
Creatinine, mg/dl	0.8 (0.5–1.2)	0.9 (0.5–1.7)	0.62
eGFR (MDRD), ml/min/1.73 m^2	96 (57–148)	85 (41–124)	0.007
HIV	19 (18%)	5 (16%)	0.79
RBV use	18 (17%)	15 (41%)	0.006

Numbers are expressed as n (%) or median (range).
Categorical variables were compared using the $\chi 2$ or the Fisher's exact tests; continuous variables were compared using the Student's *t* test, the Mann-Whitney *U* test or the Kruskall-Wallis test, when appropriate.
ALT, alanine aminotransferase; BMI, body mass index; DAAs, direct-acting antivirals; EOT, end-of-treatment; GGT, gamma-glutamyltransferase; IFN, interferon; INR, international normalized ratio; LSM, liver stiffness measurement; MDRD, modification of diet in renal disease; n.a., not available; PLT, platelets; RBV, ribavirin; SOF, sofosbuvir.
[#] 1b in 33, 1a in 23; °1b in 14, 1a in 10, nc in 1; §1b in 46, 1a in 35, nc in 2; ^1b in 1, 1a in 1.

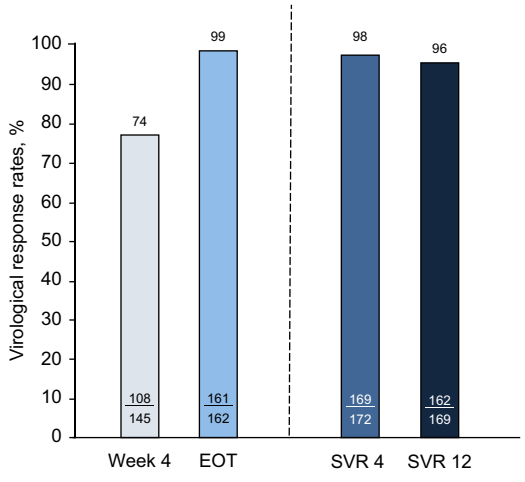

Fig. 1. Rates of on-treatment (week 4 and EOT) and off-treatment (SVR) virological response in the overall population. EOT, end-of-treatment; SVR, sustained virological response.

At PP univariate analysis, cirrhosis and HCC onset were the only features associated with a lack of SVR (Table 4). Indeed, SVR12 rates were 100% *vs.* 91% in F0-F3 *vs.* F4 patients ($p = 0.005$) and 71% *vs.* 97% in patients with or without HCC onset after treatment start ($p = 0.02$). On the contrary, treatment effectiveness was not affected by other baseline and on-treatment features considered, such as gender ($p = 1.00$), BMI >25 kg/m^2 ($p = 1.00$), HCV genotype (HCV-1a *vs.* 1b, $p = 0.57$; HCV-1a *vs.* others, $p = 1.00$; HCV-1 *vs.* non-1, $p = 0.44$; HCV-3 *vs.* others, $p = 0.16$; HCV-1a and 3 *vs.* others, $p = 0.25$), baseline HCV-RNA (<800,000 IU/ml *vs.* 800,000–6,000,000 *vs.* >6,000,000 IU/ml, $p = 0.78$), baseline RAS (yes *vs.* no, $p = 0.46$), RBV use (yes *vs.* no, $p = 0.64$) or detectable HCV-RNA viral load at treatment week 4 (yes *vs.* no, $p = 0.32$) (Fig. 2). Also when combining HCV genotype and fibrosis stage, SVR rates were similar in patients with or without cirrhosis across all HCV genotypes: indeed, by comparing F0-F3 *vs.* F4 patients, SVR rates were 100% *vs.* 93% in HCV-1 ($p = 0.06$), 100% *vs.* 100% in HCV-2 ($p = 1.0$), 100% *vs.* 84% in HCV-3 ($p = 0.09$) and 100% *vs.* 89% ($p = 0.39$) in HCV-4, respectively (Fig. S1).

Moreover, treatment effectiveness was not affected by the type of previous DAA regimen patients were exposed to: indeed, SVR12 rates were 100% in patients previously failing on OBV/PTV-r, glecaprevir/pibrentasvir (G/P), grazoprevir/elbasvir or SOF + simeprevir; 97% in patients failing OBV/PTV-r + DSV; 94% in patients experienced to SOF/LDV or SOF/VEL, and 92%

Table 4. Per protocol analysis of clinical factors associated with an SVR.

	SVR (n = 162)	Non-SVR (n = 7)	*p* value
Age, years	57 (18–88)	55 (50–73)	0.78
Males	119 (73%)	5 (71%)	1.00
BMI, kg/m^2	25 (16–45)	26 (22–33)	0.38
Diabetes	22 (14%)	2 (29%)	0.26
Arterial hypertension	42 (26%)	3 (43%)	0.38
IFN-experienced	46 (28%)	3 (43%)	0.41
LSM, kPa	10.0 (3.5–63.9)	14.2 (8.0–18.4)	0.73
Fibrosis			0.005
F0–F3	86 (53%)	–	
F4	71 (44%)	7 (100%)	
Previous HCC history	16 (10%)	–	0.38
HCV genotype			0.40
1	98 (60%)	3 (43%)	
2	17 (10%)	–	
3	33 (21%)	3 (43%)	
4	14 (9%)	1 (14%)	
Baseline HCV–RNA, IU/ml	1,010,000 (482–17,900,000)	856,033 (33,022–8,020,000)	0.80
ALT, U/L	53 (10–538)	50 (43–102)	0.73
GGT, U/L	54 (9–428)	44 (39–89)	0.89
PLT, 10^3/mm^3	159 (35–539)	126 (51–211)	0.16
Bilirubin, mg/dl	0.7 (0.3–5.7)	0.7 (0.3–3.2)	0.86
Albumin, g/dl	4.2 (3.0–5.1)	4.2 (2.8–4.4)	0.84
INR	1.0 (0.9–3.5)	1.1 (1.0–1.4)	0.38
Creatinine, mg/dl	0.8 (0.4–1.7)	0.9 (0.7–1.0)	0.89
eGFR (MDRD), ml/min/1.73 m^2	92 (41–150)	87 (56–118)	0.57
RAS			
NS5A	80 (49%)	2 (29%)	0.28
Y93H	50 (31%)	–	0.08
Multiple RAS	40 (25%)	1 (14%)	0.53
Detectable HCV–RNA			0.34
Week 4	34 (21%)	3 (43%)	
RBV use	24 (21%)	2 (29%)	0.32
HCC onset after treatment start	5 (3%)	2 (30%)	0.02

Numbers are expressed as n (%).
ALT, alanine aminotransferase; BMI, body mass index; eGFR, estimated glomerular filtration rate; GGT, gamma-glutamyltransferase; HCC, hepatocellular carcinoma; IFN, interferon; INR, international normalized ratio; LSM, liver stiffness measurement; PLT, platelets; RAS, resistance-associated substitutions; RBV, ribavirin; NS, non-structural; SVR, sustained virological response.
Categorical variables were compared using the $\chi 2$ or the Fisher's exact tests; continuous variables were compared using the Student's *t* test, the Mann-Whitney *U* test or the Kruskall-Wallis test, when appropriate.

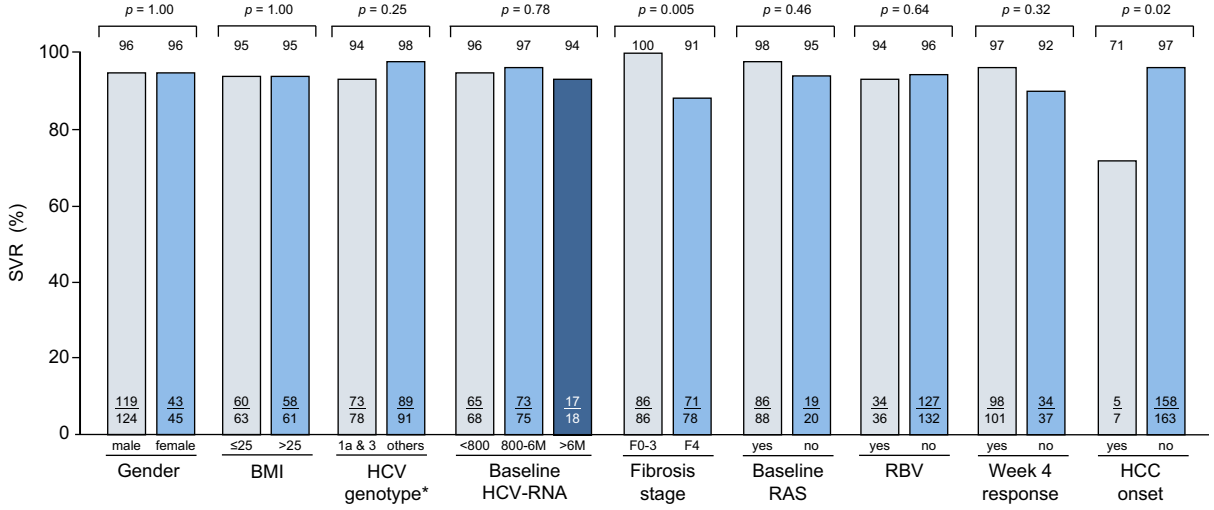

Fig. 2. Rates of SVR according to the most important baseline and on-treatment features. Categorical variables were compared using the $\chi 2$ or the Fisher's exact tests; continuous variables were compared using the Student's *t* test, the Mann-Whitney *U* test or the Kruskall-Wallis test, when appropriate. SVR, sustained virological response. *HCV-1a *vs.* 1b: 40/42 (95%) *vs.* 58/59 (98%), $p = 0.57$; HCV-1a *vs.* others: 40/42 (95%) *vs.* 122/127 (96%), $p = 1.00$ HCV-1 *vs.* non-HCV-1: 98/101 (97%) *vs.* 64/68 (94%), $p = 0.44$; HCV-3 *vs.* others: 33/36 (92%) *vs.* 129/133 (97%).

in patients previously receiving SOF + daclatasvir ($p = 0.88$) (Fig. S2).

Finally, as RAS testing was available at baseline for 115 patients, we also analyzed treatment outcome not only according to presence or absence of RAS, but also considering RAS features in more depth: again, SVR was not affected by the type of baseline RAS (NS5A RAS yes *vs.* no, $p = 0.28$; Y93H RAS yes *vs.* no, $p = 0.08$; Multiple RASs yes *vs.* no, $p = 0.53$) (Table 4). This also held true when restricting the analysis to SOF/VEL/VOX-specific RASs, SVR12 being 97% both in patients with or without SOF/VEL/VOX RASs, $p = 1.00$.

A treatment failure was reported in 7 (4%) patients: 6 of them had a virological relapse (2 at post-treatment week 4 and 4 at post-treatment week 12, respectively), while 1 patient failed to achieve 1 Log HCV-RNA decline at treatment week 4. The main features of virological failure are listed in Table 5. All patients had cirrhosis; 3 had HCV genotype 3, 2 had genotype 1a, and the other 2 patients had genotype 1b and 4. Two patients were HIV and 1 HBV-coinfected; all patients had received an NS5A-containing regimen, SOF-based in 6 cases. Two out of 7 patients received RBV during the SOF/VEL/VOX course. RAS testing before the start of SOF/VEL/VOX was available in 3 patients: 1 patient had no detectable baseline RAS, 1 had detectable RAS both in NS3 and NS5A regions, while the third patient carried RAS only in the NS5A region. At SOF/VEL/VOX failure, the first 2 patients maintained the same RAS features with respect to baseline, while in the third case RAS testing was not available. Concerning the only patient without RAS emergence after virological failure, correct adherence to antiviral therapy was reported by the treating physician: the patient received SOF/VEL/VOX plus RBV and showed moderate anemia during therapy, thus indirectly suggesting correct RBV intake, although SOF/VEL/VOX drug monitoring by plasmatic dosage was not available.

Treatment safety

Overall, any AEs were reported in 45 (25%) patients (Table 6): fatigue (6%), hyperbilirubinemia (6%) and anemia (3%) were the most frequent and were considered drug-related in 28 (16%) patients. AEs were mostly mild to moderate. Anemia was treated with RBV dose reduction and discontinuation in 1 (0.5%) and 2 (1%) patients, respectively. Eleven (6%) serious adverse events (SAEs) occurred in 8 patients, not drug-related in all cases: HCC development (*de novo* HCC n = 6, recurrent

Table 6. Prevalence of adverse events.

Adverse events	n = 179
Patients with any AEs	45 (25%)
Fatigue	11 (6%)
Hyperbilirubinemia	11 (6%)
>1.5–3.0 ULN (Grade 2), mg/dl	7 (4%)
>3.0–10.0 ULN (Grade 3), mg/dl	4 (2%)
Anemia	8 (4%)
Nausea	3 (2%)
Headache	1 (0.5%)
Drug–related AEs	28 (16%)
Serious AEs:	11 (6%)
HCC development[#]	7 (4%)
Liver transplantation (listed for HCC)	2 (1%)
Hip fracture	1 (0.5%)
Death[*]	1 (0.5%)

Values are expressed as n (%).
AEs, adverse events; HCC, hepatocellular carcinoma; ULN, upper limit of normal.
[#] HCC *de novo* (n = 6), HCC recurrence (n = 1).
[*] Pulmonary embolism resulting from deep vein thrombosis following HCC recurrence.

Table 5. Features of patients with virological failure.

	Patient #1	Patient #2	Patient #3	Patient #4	Patient #5	Patient #6	Patient #7
Age, years	73	61	54	50	55	67	55
Gender	female	male	female	male	male	male	male
BMI, kg/m^2	26	29	33	25	22	25	25
HCV genotype	1b	1a	4	1a	3	3	3
HBV/HIV co–infection	no	no	HIV	HBV	HIV	no	no
Fibrosis stage	F4	F4	F4	F4	F4	F4	F4
Previous treatments	BOC + PR OBT/PTV–r + DSV	TVR + PR SOF/LDV	– SOF/LDV	SOF/LDV SOF/VEL	SOF + DCV	SOF/VEL	SOF + DCV
HCC history	no	no	no	no	no	no	no
Adherence	yes	yes	yes	yes	yes	yes	yes
RBV use	yes	yes	no	no	no	no	no
HCV–RNA, IU/ml							
Baseline	547,066	1,536,215	455,000	1,165,000	8,020,000	102,546	30,022
Week 4	72,284	15	57	undetected	undetected	undetected	n.a.
EOT	–	undetected	undetected	undetected	undetected	undetected	n.a.
SVR4	–	undetected	3,800	1,160,000	undetected	undetected	
SVR12	–	387,675	–	–	4,741,000	198,300	undetected
NS3 RAS							
Baseline	none	176S	n.a.	n.a.	n.a.	none	n.a.
At failure	none	176S	n.a.	n.a.	n.a.	n.a.	n.a.
NS5A RAS							
Baseline	none	30R, 31 M	n.a.	n.a.	n.a.	Y93H	n.a.
At failure	none	30R, 31 M	n.a.	n.a.	n.a.	n.a.	n.a.
HCC after EOT	no	yes	no	no	no	no	yes

BMI, body mass index; BOC, boceprevir; DCV, daclatasvir; DSV, dasabuvir; EOT, end-of-treatment; HCC, hepatocellular carcinoma; LDV, ledipasvir; n.a., not available; NS, non-structural; OBV/PTV-r, ombitasvir/paritaprevir-ritonavir; PR, pegylated-interferon + ribavirin; RAS, resistance-associated substitutions; RBV, ribavirin; SOF, sofosbuvir; TVR, telaprevir; VEL, velpatasvir.

HCC n = 1), liver transplantation for HCC indication in compensated cirrhosis (n = 2), hip fracture (n = 1) and death (n = 1). *De novo* HCC occurred in 6 patients at a median of 1 (0–3) month after EOT: it was single in 3 (50%), median size 30 mm, alpha-fetoprotein at diagnosis 69 (7–1,500) ng/ml. One patient developed liver decompensation concomitantly to HCC diagnosis, while cirrhosis was compensated in the remaining cases, allowing for radical HCC treatments (liver resection n = 2, radiofrequency ablation n = 3). HCC recurred 1 month after EOT in 1 patient with a complete response to a previous HCC treatment (4 months before SOF/VEL/VOX start): at HCC recurrence, cirrhosis was compensated, and the tumor was multinodular but susceptible to transarterial chemoembolization. In the 2 patients who underwent LT for HCC, LT was performed 2 weeks after EOT in 1 case and at treatment week 10 in the other, leading to premature SOF/VEL/VOX discontinuation in the latter. Both patients tested HCV-RNA undetectable for at least 4 weeks before LT, and achieved HCV-RNA undetectability post LT, thus preventing HCV recurrence.

Discussion

To the best of our knowledge, this is the largest European report on retreatment of patients with HCV using the SOF/VEL/VOX combination in clinical practice. Our longitudinal real-life study, conducted in 179 consecutive patients enrolled in 2 large networks in Northern Italy, reported overall 98% SVR4 and 96% SVR12 rates: cirrhosis and HCC onset were the only predictors of treatment failure.

As expected in a real-life setting, our study included a heterogeneous patient population with high prevalence of difficult-to-treat patients with advanced (F3-F4) fibrosis, which accounted for 65% of patients enrolled. Moreover, cirrhotic patients included both CTP stage A5 and A6 and a subset of patients with endoscopic signs of portal hypertension, as well as previous HCC history. Comorbidities such as arterial hypertension, type 2 diabetes and HIV coinfection were also well represented in our population. Such comorbidities were generally less prevalent in phase II and III registration trials,[6–10] thus suggesting good effectiveness of the SOF/VEL/VOX combination even in a difficult-to-treat population in real-life practice. Indeed, our SVR rates are in line with the 95–100% effectiveness reported in preliminary real-life experiences across the US and Europe.[12,13,16–20; Table S2]

Besides SVR rates, our study also provided extensive information about treatment course and tried to identify predictors of on-treatment and off-treatment responses. In our patient population, on-treatment virological response at week 4 was achieved by 74% of patients, compared to 88–93% of patients treated in the POLARIS-1 and 4 trials; again, this could result from the particular setting of a real-life study, where patients are enriched by comorbidities and the prevalence of advanced fibrosis is higher. Indeed, not surprisingly, cirrhosis and higher baseline viral load were associated with a lack of on-treatment viral response at week 4.

Overall, 7 patients did not achieve the SVR: HCV genotypes 3 and 1a accounted for the majority of treatment failures (5 out 7) and all patients had cirrhosis. These characteristics are common to the other treatment failures reported both in POLARIS-1 and 4 trials as well as in real-life settings, where genotype 1a, 3 and cirrhosis were the most prevalent features among patients with virological failure.[12,13,16–20] Indeed, in the Spanish experience, SVR in HCV-3 patients with cirrhosis dropped to 69%.[13] In our study, in the ITT analysis, HCV-3 emerged as significantly associated with treatment failure, whereas this was not confirmed at PP analysis, although these results could be partially affected by the fact that 7 HCV-3 patients were lost to follow-up. Whilst our HCV-3 patient group was larger than the Spanish group and the prevalence of cirrhosis was higher (45%), we think that these small numbers are insufficient to provide definitive conclusions and that this issue should be furtherly evaluated. Unlike in the Belperio study, we could not find any influence of the previous DAA treatment on SOF/VEL/VOX outcome,[12] as we reported 94% SVR12 rates in patients with a previous failure on SOF/VEL. Due to our study enrollment period, we had the possibility to include many SOF/VEL-failures in our cohort; SOF/VEL represented the most frequent previous treatment, accounting for 20% of the patient population. In addition to cirrhosis, our study also identified HCC as the other main feature associated with treatment failure, SVR rates falling to 71% in patients with HCC onset, while SVR rates were not affected in patients with a previous HCC history before SOF/VEL/VOX course. Indeed, in our study 7 patients (2 patients with subsequent virological failure) had a diagnosis of HCC after SOF/VEL/VOX course; as HCC onset was reported very early after EOT (median 1 month), it can be assumed that these patients were treated with active HCC. The report of reduced antiviral treatment effectiveness in our study parallels the Belperio study, where SVR fell to 76% in patients with HCC, and also confirms previous reports in patients treated with other DAA-based regimens.[12,21,22]

As RAS testing at baseline was available in 115 patients, our study had the unique opportunity to extensively analyze RASs influence on-treatment outcome. In line with the sub-analysis of POLARIS trials by Sarrazin and colleagues, in our study the baseline presence of RAS was not associated with treatment outcome.[23] Despite RAS testing not being required for a SOF/VEL/VOX prescription in Italy, resistance testing was available for 64% of patients in our study, as many treating physicians performed RAS analysis in order to better guide retreatment decisions, according to EASL recommendations.[1] As expected in the setting of previous DAA failures, RASs were detected in 82% of patients tested, NS5A RAS accounting for 77%. The Y93H RAS, conferring high-level resistance to NS5A inhibitors, was present in 50% of the population and 35% patients had multiple RASs before SOF/VEL/VOX treatment. Despite this complex RAS profile, SVR rates were independent from RAS prevalence and features in our patient population, even when considering SOF/VEL/VOX-specific RASs.

Overall, 65% and 35% of total patient population carried predictors of lower response, such as advanced liver disease and complex NS5A RAS profile, respectively. Moreover, 9% fulfilled the EASL definition of "very-difficult-to-cure", (*i.e.* NS5A RAS and 2 failures on a protease- and/or a NS5A inhibitor-containing regimen). According to EASL recommendations, patients with predictors of lower response could benefit from the SOF + G/P combination,[1] which is currently off-label in Italy, but has been evaluated in 2 studies reporting excellent overall SVR rates in DAA-experienced patients.[24,25] On the other hand, EASL recommendations suggest that very-difficult-to-cure patients could benefit from an intensified treatment including RBV,[1] whereas AASLD guidelines do not endorse RBV addition to SOF/VEL/VOX, except from genotype 3 patients with cirrhosis and failure on an NS5A regimen.[11] In our study, RBV was added in 22% of treatment courses: not surprisingly, RBV was more

often prescribed in patients carrying a higher prevalence of RAS. Accordingly, RBV administration was associated with lower rates of virological response at week 4, confirming that RBV was prescribed in more complex patients, characterized by slower HCV-RNA decay. Concerning HCV-3 patients, only 10 HCV-3 patients received RBV in our study (2 with cirrhosis); all 7 patients with available SVR12 data reached this endpoint. According to our complete results, our study does not support the use of RBV, however, we think that no strong conclusions can be drawn due high heterogeneity in RBV administration in real-life studies, as well as small numbers of patients treated with RBV. More studies are needed in order to better investigate the role of RBV, especially in HCV-3 patients with advanced fibrosis. In the POLARIS trials, and the real-life reports from the US and Spain, none of the patients received RBV.[12,13] In the remaining clinical practice studies, RBV administration varied from 4% in the TRIO Network to 22% in the French experience, with criteria for RBV use not detailed.[16–20]; Table S2]

Concerning safety, in our study SOF/VEL/VOX administration was very well tolerated, resulting in low rates of AEs, which were mostly mild to moderate. None of the SAEs reported were drug-related and none of the patients discontinued treatment because of SOF/VEL/VOX-related AEs.

We acknowledge that our study could suffer from some limitations typical of its real-life design, first of all the potential risk of under-reporting both baseline features and comorbidities in the patient population, as well as treatment-emergent adverse events. Nevertheless, we believe that all SAEs were correctly reported by treating physicians. Another limitation of the study is the lack of some information concerning both the on-treatment and post-treatment period: although only 10 patients were lost to follow-up, many of them had HCV genotype 3, potentially preventing us from observing a stronger effect of genotype 3 on treatment outcome. Finally, evaluation of treatment adherence was based on clinical judgment, as no other more objective methods (pill counters) were available.

However, our study has a number of strengths, including the availability of information concerning patient characterization at baseline, such as clinical features and RAS analysis. Moreover, the specific Italian drug reimbursement rules that allowed treatment prescription only following a case-by-case authorization by the Italian Medicines Agency (AIFA, *Agenzia Italiana del Farmaco*), allowed for homogeneous patient enrollment.

In conclusion, our study reports excellent effectiveness and safety of the SOF/VEL/VOX combination in a large cohort of patients with HCV and a prior DAA failure treated in an Italian real-life setting. We identified cirrhosis and HCC onset as the main predictors of SOF/VEL/VOX failure.

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Conflicts of interest

Elisabetta Degasperi: Speaker: AbbVie, Gilead, MSD; Research Grants: Gilead; Travel Support: AbbVie; Luisa Pasulo: Advisory Board: AbbVie; Massimo Puoti: Speaker's bureau and Advisory: AbbVie, BMS, Boehringer Ingelheim, Janssen, Gilead, MSD, Roche; Reasearch Grant: Gilead, MSD; Maria Vinci: Advisory Board: AbbVie; Grant: AbbVie; Alessandro Soria: Consultation fees: AbbVie; Speaker: MSD, AbbVie; Travel Support: Gilead, MSD, Abbvie; Alessio Aghemo: Speaker's bureau and Advisory: AbbVie, Gilead, Intercept, Alfasigma, MSD; Alessia Giorgini: Speaker: AbbVie, MSD, Gilead; Advisory Board: AbbVie; Paolo Bonfanti: Speaker: MSD, Gilead; Advisory Board MSD, Gilead; Antonietta Romano: Speaker: Abbvie, Gilead, BMS; Pietro Lampertico: Speaker's bureau and Advisory: AbbVie, BMS, Gilead, GSK, Janssen, MSD, Roche; Stefano Fagiuoli: Speaker's bureau and Advisory for AbbVie, Bayer, Gilead, MSD, Kedrion, Novartis

All authors have nothing to disclose.

Please refer to the accompanying ICMJE disclosure forms for further details.

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Supplementary data

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