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MAJOR ARTICLE

Efficacy and Safety of Sofosbuvir/Velpatasvir/Voxilaprevir for Hepatitis C Virus (HCV) NS5A-Inhibitor Experienced Patients With Difficult to Cure Characteristics

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(See the Editorial Commentary by Sulkowski and Wyles on pages e3296–9.)

Background. In clinical trials, hepatitis C virus (HCV) salvage treatment with sofosbuvir/velpatasvir/voxilaprevir (SOF/VEL/VOX) achieved an SVR12 rate of >95% in NS5A-experienced participants. Lower SVR12 rates have been reported in real-world studies, particularly for genotype (GT)3 infection and cirrhosis. We determined the efficacy and safety of SOF/VEL/VOX in a large real-world cohort.

Methods. We assessed the efficacy of salvage SOF/VEL/VOX for HCV infection in NS5A-inhibitor experienced participants with cirrhosis and portal hypertension, prior liver transplantation (LT) or severe extra-hepatic manifestations. SOF/VEL/VOX was available via an early access program. The primary outcome was SVR12. Secondary outcome was frequency of adverse events (AE).

Findings. Ninety-seven participants were included. Median age was 58, 82% were male, 78% had cirrhosis, most with portal hypertension (61%, n = 46/76), and 18% had prior-LT. Of the cirrhotic participants, 96% were Child-Turcotte-Pugh class A, and 4% were class B. Of the 72% with GT3, 76% were also cirrhotic. By intention-to-treat analysis, SVR12 rate was 85% (n = 82/97). Per protocol, the SVR12 rate was 90%, including 91% in GT1 (GT1a n = 18/18, GT1b n = 2/4), 89% in GT3 (n = 59/66) and 100% in GT6 (n = 3/3). SVR12 in participants with GT3 and cirrhosis was 90%. No predictors of non-SVR12 were identified. There were 4 serious AEs including 1 death and 3 hepatic decompensation events. NS5A resistance-associated substitutions detected at baseline did not affect SVR12.

Conclusions. This real-world study confirms high efficacy of SOF/VEL/VOX for the treatment of difficult-to-cure NS5A-inhibitor experienced patients, including those with GT3 and cirrhosis. Treatment was well tolerated in most; however, serious AEs can occur in those with advanced liver disease.

Keywords. hepatitis C; relapse; cirrhosis; genotype 3; sofosbuvir/velpatasvir/voxilaprevir.

Hepatitis C virus (HCV) infection affects approximately 71 million people worldwide and contributes significantly to liver-related morbidity and mortality [1, 2]. Direct acting antiviral (DAA) therapy has revolutionized HCV treatment, with cure rates exceeding 95% in registration trials [3–5]. Some patients, however, do not respond to their initial DAA therapy, more commonly those with HCV genotype (GT)3 infection and with cirrhosis [6, 7]. Virological failure is associated with the selection of HCV resistance associated substitutions (RAS), and ideal retreatment regimens should target the NS5A, NS5B, and NS3 proteins [8, 9].

The efficacy of sofosbuvir/velpatasvir/voxilaprevir (SOF/VEL/VOX) for relapsed HCV infection following treatment with an NS5A-inhibitor (NS5Ai) containing DAA regimen has been investigated in multiple clinical trials [10]. In the POLARIS-1

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registration trial, NS5A-experienced participants treated with SOF/VEL/VOX achieved a sustained virological response 12 weeks after end of treatment (SVR12) rate of 96%. Several real-world studies have subsequently suggested reduced efficacy in those with cirrhosis, prior SOF/VEL exposure, and HCV GT3 infection [11–14]. This included a SVR12 rate of 69% among the small number of participants with both HCV GT3 infection and cirrhosis in one Spanish cohort [11]. In most studies, a minority of participants had cirrhosis (35–41%), and only 1 included those with prior liver transplantation (LT), where complex drug-drug interactions must be considered [11–13].

In both registration and real-world trials, treatment with SOF/VEL/VOX was generally well tolerated, and adverse events (AE) were limited. It is important to note that NS3/4A PIs are not recommended in Child-Turcotte-Pugh (CTP) B/C cirrhosis due to concerns about hepatotoxicity related to higher VOX drug exposures. The Food and Drug Administration (FDA) has also recently cautioned practitioners to closely monitor patients with compensated cirrhosis during treatment with an HCV protease inhibitor (PI) due to the potential for hepatic decompensation, particularly in the setting of portal hypertension (PHT), hepatocellular carcinoma (HCC), or alcohol misuse [15]. As SOF/VEL/VOX is increasingly used as salvage treatment in patients with advanced disease to avoid LT, it is important that these risks are further explored and validated in real-world settings [16, 17].

In this study, we have evaluated the efficacy and safety of SOF/VEL/VOX in a difficult to cure population with advanced liver disease or prior-LT.

METHODS

This was a retrospective, nationwide study to evaluate the efficacy and safety of SOF/VEL/VOX for relapsed HCV infection among participants with advanced liver disease or LT, treated in 27 Australian centers. All participants were treated with fixed dose SOF 400 mg, VEL 100 mg, and VOX 100 mg for 12 weeks available via an early access program (EAP) supported by Gilead Sciences. The EAP permitted access to SOF/VEL/VOX before reimbursement on the national prescription drug scheme. As such, at this time, this regimen was only available to Australians via this EAP, where specific eligibility criteria were satisfied. Eligibility criteria for the EAP were (i) age >18 years; (ii) chronic HCV infection GT1–6; (iii) prior treatment failure on a NS5A-inhibitor DAA containing regimen; (iv) compensated liver disease with at least one of (a) CTP class A cirrhosis and clinically significant portal hypertension (hepatic venous portal gradient (HVPG) > 10mmHg or the presence of varices (radiologically / endoscopically) or platelets $<100 \times 10^9$/L, (b) prior-LT, or (c) severe extrahepatic manifestations; and (v) eGFR $\geq$30mL/min/1.73m^2. Exclusion criteria for the EAP included (i) hepatic decompensation (CTP class B/C), (ii) contraindication or known hypersensitivity to the active substances or to any other component of the tablets, and (iii) concomitant prescription of rifampicin and/or rosuvastatin. Participants with human immunodeficiency virus (HIV) and/or hepatitis B virus (HBV) coinfection were eligible for inclusion. Combination therapy with ribavirin was permitted.

Australian hospitals with 2 or more participants treated via the Gilead Sciences EAP were invited to participate in this study. The primary outcome was the frequency of participants achieving SVR12, defined as the absence of detectable HCV RNA at least 12 weeks after end-of-treatment (EOT). The secondary outcome was frequency of treatment related adverse events (AE). Participants were followed until the SVR12 time point.

Assessments

Participant data were collected at baseline, EOT, and SVR12 timepoints with SOF/VEL/VOX, as well as details of prior HCV treatments. Cirrhosis status was defined as transient elastography score ≥12.5 kPa, prior liver biopsy demonstrating METAVIR fibrosis score 4, or clinical/radiological evidence of cirrhosis. Clinical evidence of cirrhosis included signs of cirrhosis and baseline platelet count of $<100 \times 10^6$. PHT was defined by the presence of intra-abdominal and/or esophageal varices, splenomegaly, or ascites. CTP scores were recorded at all timepoints. Laboratory investigations recorded included full blood count, renal and liver biochemical tests, HCV RNA, HCV genotype, HIV and HBV serology. The presence of HCV NS5A RAS were investigated in a subset of participants where serum was available, utilizing Sanger sequencing with a threshold limit of 20% for variant detection. HCV NS5A RAS were defined as polymorphisms encoded by the NS5A gene associated with at least 2-fold reduced susceptibility to a registered NS5A inhibitor. Virological breakthrough (VBT) was defined as detectable HCV RNA on PCR testing at the EOT timepoint.

Adverse events (AE) related to treatment with SOF/VEL/VOX were recorded until the SVR12 timepoint. Serious AEs were particularly scrutinized including hepatic decompensation, and AEs leading to hospitalization, treatment discontinuation, and death.

Ethical Considerations

The study conformed to the ethical guidelines of the 1975 Declaration of Helsinki, Good Clinical Practice Guidelines, and regulatory requirements. The study was approved by the Human Research Ethics Committee at St Vincent's Hospital Melbourne.

Statistical Analysis

Statistical analysis was performed using STATA 12.0 (StataCorp LP, College Station, TX, USA). Normally distributed continuous data were analyzed with the Student *t* test, whereas

non-normally distributed data were analyzed using the Mann-Whitney *U* test. Categorical data were described as number and percentage and were analyzed using χ^2 or Fisher exact test, as appropriate. Variables associated with SVR12 were investigated using appropriate univariable statistical tests after considering distribution of data. A *P* value of < .05 was deemed statistically significant.

RESULTS

Patient Population

From June 2018 to March 2019, 97 patients were commenced on SOF/VEL/VOX across 27 Australian hospitals. Baseline characteristics are described in Table 1. In brief, the cohort was predominantly male (82%), the median age was 58 years, and the most common genotype was HCV GT3 (72%). Most of the cohort were cirrhotic (78%) or had previously undergone LT (18%). Of the cirrhotic participants, 50% were CTPA5, and 46% were CTPA6. Three participants were included with CTP class B7 (n = 1) and B8 (n = 2) as protocol deviations by the treating clinicians; none of these 3 participants were felt to be LT candidates. In total, 61% of the cirrhotic participants had PHT. HIV (n = 2) and HBV (n = 3) coinfection were uncommon. A prior history of HCC was present in 19% (n = 18), 6 of whom had undergone LT. There were no participants with HCC at baseline. SOF/VEL/VOX was prescribed with ribavirin (600–1200 mg daily) for 3 participants.

Table 1. Baseline Characteristics of Participants Commencing SOF/VEL/VOX

Baseline Characteristics	N = 97
Age, median [IQR]	58 [53–64]
Male sex, n (%)	80 (82)
HCV viral load IU/mL, median, [IQR] (75/97)	654 000 [160 000–2 870 000]
HCV genotype, n (%)	
- Genotype 1a	19 (20)
- Genotype 1b	4 (4)
- Genotype 3	70 (72)
- Genotype 4	1 (1)
- Genotype 6	3 (3)
ALT, U/mL, median [IQR]	85 [48–170]
Albumin, g/L, median [IQR]	37 [33–40]
Bilirubin, umol/L, median [IQR]	14 [10–21]
Platelet count, median [IQR]	125 [90–178]
INR, median [IQR]	1.1 [1–1.2]
HIV infection, n (%)	2 (2)
HBV serology, n (%)	
HBsAg +	3 (3)
HBcAb +	29 (30)
Cirrhosis, n (%)	76 (78)
CPA5	38/76 (50)
CPA6	35/76 (46)
CPB7	1/76 (1)
CPB8	2/76 (3)
Cirrhosis with portal hypertension, n (%) [a]	46/76 (61)
Post liver transplantation, n (%)	17 (18)
Noncirrhotic, n (%)	4 (4)
Prior hepatocellular carcinoma n (%)	18 (19)
Pegylated interferon ± ribavirin ± protease inhibitor experienced, n (%)	24 (25)
2+ DAA treatments prior to SOF/VEL/VOX, n (%)	15 (15)

Abbreviations: ALT, alanine aminotransferase; DAA, direct acting antiviral; HBV, hepatitis B virus; HCV, hepatitis C virus; HIV, human immunodeficiency virus; INR, international normalized ratio; IQR, interquartile range; SOF/VEL/VOX, sofosbuvir/velpatasvir/voxilaprevir.

[a]Portal hypertension defined as the presence of intra-abdominal and/or gastroesophageal varices, splenomegaly, or ascites.

Prior HCV Treatment Experience

All participants were HCV NS5Ai treatment experienced. The most recent HCV DAA treatments prescribed prior to SOF/VEL/VOX are detailed in Table 2. The most frequent common NS5Ai were daclatasvir (DCV, 56%), VEL (20%), and ledipasvir (LDV, 15%). And 15% of participants (n = 15) had received more than 1 NS5Ai-based treatment (range 1–4). Three participants were treated with an NS5Ai containing "lead-in" DAA regimen immediately prior to commencing SOF/VEL/VOX to optimize liver function, including 1 who was downgraded from CTP class B to A during this treatment. Four other participants had a history of prior hepatic decompensation that had recompensated during their preceding first-line DAA treatment. In total, 25% of participants had been treated with pegylated IFN-α + ribavirin with or without a first-generation PIs prior to their first all-oral DAA treatment course.

Efficacy

By intention to treat, 82 (85%) of the 97 participants who commenced on SOF/VEL/VOX achieved SVR12, and SVR12 rates were 95% (n = 18/19) for GT1a, 50% (n = 2/4) for GT1b, 84% (n = 59/70) for GT3, 0% (n = 0/1) for GT4, and 100% (n = 3/3) for GT6 infection. Three participants discontinued treatment due to AEs during treatment week (TW) 1, 2 participants were lost to follow-up after EOT, and 1 participant died while receiving treatment. Of these 6 participants, 4 had GT3 infection. As such, complete data were available for per protocol analysis for 91 participants. Therefore, the per protocol SVR12 rate was 90% (n = 82/91, Figure 1). Two participants had VBT at EOT, and 7 relapsed. Per protocol, the SVR12

Table 2. Most Recent DAA Regimen Prescribed Prior to SOF/VEL/VOX

Prior DAA course	N = 97
Sofosbuvir + daclatasvir ± ribavirin, n (%)	54 (56)
Sofosbuvir + velpatasvir ± ribavirin, n (%)	19 (20)
Sofosbuvir + ledipasvir ± ribavirin, n (%)	15 (15)
Elbasvir + grazoprevir, n (%)	3 (3)
Paritaprevir + ritonavir + ombitasvir + dasabuvir ± ribavirin, n (%)	2 (2)
Sofosbuvir + elbasvir + grazoprevir ± ribavirin, n (%)	2 (2)
Uprifosbuvir + ruzasvir, n (%)	2 (2)

Abbreviations: DAA, direct acting antiviral; SOF/VEL/VOX, sofosbuvir/velpatasvir/voxilaprevir.

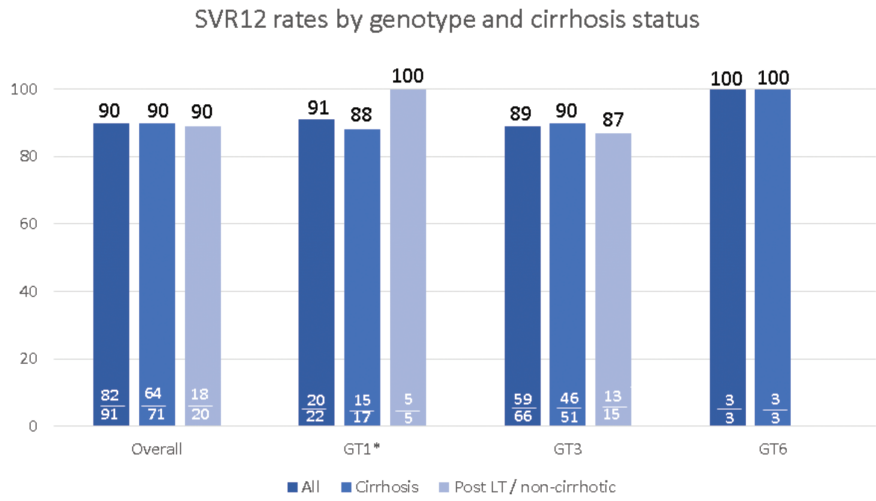

Figure 1. SOF/VEL/VOX per protocol treatment outcomes, presented by cirrhosis and post LT status. *GT1a SVR12 100% (n = 18/18) and GT1b SVR12 50% (n = 2/4). Abbreviations: LT, liver transplantation; SOF/VEL/VOX, sofosbuvir/velpatasvir/voxilaprevir.

rate for participants with GT1a infection was 100% (n = 18/18), 50% (n = 2/4) for GT1b, 89% (n = 59/66) for GT3, and 100% (n = 3/3) for GT6. The SVR12 rate was 90% (n = 64/71) for cirrhotic participants, 88% (n = 14/16) among those who were post-LT, and 100% (n = 4/4) in noncirrhotic, non-LT participants. SVR12 was achieved in 90% (n = 77/86) of participants previously treated with SOF + NS5Ai and 100% among those previously treated with other combination regimens (n = 5/5, Table 2).

Non-SVR Participants

Nine participants had detectable HCV RNA at the SVR12 timepoint (Table 3). All 9 participants reported adherence above 80%. Of the 2 participants with VBT, both had previously experienced VBT during their prior treatment with SOF + VEL. The remaining 7 participants relapsed. Of the treatment failures, 7 were cirrhotic, 5 of whom had PHT, and 2 were post-LT. Seven had HCV GT3, and 2 had HCV GT1b infection. HBV

Table 3. Characteristics of Non-SVR12 Participants

Characteristic	#1	#2	#3	#4	#5	#6	#7	#8	#9
Sex	M	F	M	M	M	M	M	M	M
Age	64	51	57	62	66	50	46	64	62
Cirrhosis status	F4	F4	Post LT (no cirrhosis)	Post LT (no cirrhosis)	F4	F4	F4	F4	F4
Relapse vs VBT	Relapse	Relapse	Relapse	VBT	VBT	Relapse	Relapse	Relapse	Relapse
HCV GT	1b	1b	3	3	3	3	3	3	3
ALT	103	64	50	126	110	91	73	305	82
Albumin	37	36	44	32	42	38	35	33	37
Platelets	151	125	106	177	117	216	60	131	73
Bilirubin	14	30	8	7	14	12	26	13	21
Portal hypertension[a]	Y	N	N	N	Y	N	Y	Y	Y
CTP score	5	5	5~	5~	5	5	6	6	5
HIV / HBV coinfection	HBV	N	N	N	N	N	N	N	N
Ribavirin	N	N	N	N	N	N	N	N	N
NS5A RAS at baseline	Y93H	NA	NA	NA	Y93H L31I	Y93H	NA	NA	Y93H
Prior treatment	PrOD	SOF / LDV	SOF / DCV	SOF / DCV	SOF / DCV	SOF / DCV	SOF / DCV	SOF / DCV	SOF / VEL
Prior VBT	N	N	N	Y	Y	N	Y	N	N
HCC at SVR12	N	N	N	N	N	N	N	Y	N
Non-HCC malignancy	N	NHL[#]	N	N	NHL[#]	N	N	N	N
DDI							PPI		
Other cofactors				Malabsorptive bariatric surgery					

Abbreviations: DAA, direct acting antiviral; DCV, daclastavir; DDI, drug-drug interactions; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; HIV, human immunodeficiency virus; LDV, ledipasvir; PrOD, paritaprevir/ritonavir/ozmbitasvir/dasabuvir; SOF, sofosbuvir; VBT, virological breakthrough; VEL, velpatasvir.

[a]Portal hypertension defined as the detection of intra-abdominal and/or gastrooesophageal varices, splenomegaly or ascites radiologically and/or endoscopically ~non-cirrhotic participants post LT.

[#] Non-Hodgkin's Lymphoma.

coinfection was present in 1 participant. HCV NS5A RAS testing was available for 4 non-SVR12 participants at baseline, in whom all had the Y93H RAS detected. One participant was diagnosed with de novo HCC at EOT. Two participants were treated with SOF/VEL/VOX following the recent diagnosis of non-Hodgkin lymphoma. Prior malabsorptive bariatric surgery was considered contributory to treatment failure in 1 participant. One participant was prescribed a proton-pump inhibitor with SOF/VEL/VOX, but no other concomitant medications were recorded that may have caused significant drug-drug interactions (DDI). No clinical or virological characteristics were associated with likelihood of SVR12 on univariate analysis (Table 4).

Table 4. Univariate Analysis of Factors Associated With SVR12

Variable	SVR12 (n = 82/91)	*P* value
Sex		.54
Male	68/76 (89%)	
Female	14/15 (93%)	
Age (years)	57.5	.86
>65	9/10 (90%)	
≤65	73/81 (90%)	
Non-LT		.63
Cirrhosis	64/71 (90%)	
No cirrhosis[a]	4/4 (100%)	
Prior LT		.66
No	68/75 (91%)	
Yes	14/16 (88%)	
HCV viral load, IU/mL (n = 70)		.25
>800 000	29/34 (85)	
≤800 000	34/36 (94)	
HCV genotype		.71
GT3 infection	59/66 (89%)	
Non-GT3	23/25 (92%)	
Baseline CTP score		.93
A5	31/36 (86%)	
A6	29/32 (91%)	
B7	1/1 (100%)	
B8	2/2 (100%)	
Portal hypertension[b]		.27
No	41/45 (91%)	
Yes	41/46 (89%)	
Albumin		.73
>35	50/56 (89%)	
≤35	32/35 (91%)	
Platelet count		.86
PI >150	25/28 (89%)	
PI ≤150	57/63 (90%)	
HCC, de novo recurrent		.27
No	80/88 (91%)	
Yes	2/3 (66%)	
HCV NS5A (n = 50)		1.0
RAS present	44/47 (94%)	
No RAS	3/3 (100%)	
>1 prior NS5A-containing DAA course		.59
No	70/78 (90%)	
Yes	13/13 (100%)	
Prior peginterferon/ribavirin		.68
No	63/69 (91%)	
Yes	19/22 (86%)	

Abbreviations: HCC, hepatocellular carcinoma; HCV, hepatitis C virus; LT, liver transplantation; RAS, resistance associated substitution.

[a]Excluding noncirrhotic participants with prior LT.

[b]PHT defined as the presence of intra-abdominal and/or gastroesophageal varices, splenomegaly or ascites.

HCV NS5A RAS Testing

HCV NS5A RAS testing results were available for 54 (56%) participants. Overall, 91% had detectable NS5A RAS at baseline (n = 49/54). Of those with detectable HCV NS5A RAS, 84% (n = 41/49) had a single NS5A RAS, and 16% (n = 8/49) had dual mutations identified (Table 5). The most frequent NS5A RAS was Y93H, which was detected in 84% of positive samples. On per-protocol analysis, the presence of baseline HCV NS5A RAS was not associated with treatment failure (SVR12 94% vs 100%, $P > .05$), nor was the presence of the Y93H RAS specifically associated (SVR 90% vs 100%, $P = .56$).

Safety

In most cases, treatment was well tolerated; however, AEs that led to treatment discontinuation and hepatic decompensation were observed in a minority (Table 6). SOF/VEL/VOX was discontinued during TW1 in 3 participants; 2 developed severe abdominal pain, and 1 individual's eGFR declined from 48 to 17 mL/min/m^2. There were 3 episodes of hepatic decompensation on treatment. Among the 18 participants with prior HCC (6 of whom had undergone LT), 1 had recurrent HCC identified between EOT and SVR12, and 1 discontinued therapy during TW1 due to abdominal pain, but otherwise no AEs were recorded in this group.

The first participant who developed hepatic decompensation on treatment had CTP class A5 cirrhosis with PHT at baseline secondary to HCV and prior alcohol misuse, with no history of hepatic decompensation. They did not attend review appointments while on treatment but presented at week 1 post-EOT with new ascites, bilirubin 119 umol/L and international normalized ratio (INR) 1·5, thought to be treatment related. This participant did not consume alcohol while receiving SOF/VEL/VOX. Alternate causes of hepatic decompensation were excluded. This participant subsequently had gastric variceal hemorrhage at week 5 post-EOT. SVR12 was achieved; however, they had persistent ascites and were assessed for LT. The second participant was CTP class A6 with PHT, with no prior episodes of liver decompensation, at baseline. This participant, who had a second diagnosis of autoimmune thrombocytopaenia thought to be related to HCV, developed new grade 3 ascites and presumed encephalopathy at TW3, which was attributed to SOF/VEL/VOX. The participant was immunosuppressed, and sepsis was considered as a secondary cause of decompensation, although bacterial cultures were negative. Treatment with SOF/

Table 5. Baseline NS5A Resistance Associated Substitutions (RAS), Available on a Subset of Participants

Baseline NS5A RAS	N = 54
No NS5A RAS detected	5 (9)
NS5A RAS detected	49 (91)
Single NS5A RAS detected	
Y93H	37/49 (76)
A30K	2/49 (4)
L31M/V	2/49 (4)
Dual NS5A RAS detected	
Y93H / A30K/H	3/49 (6)
A30K / L31M	2/49 (4)
L31M/I / H58P	2/49 (4)
Y93H / L31M	1/49 (2)

VEL/VOX was continued with weekly review. At week 6 post EOT, the participant recompensated, and diuretic and lactulose therapy were withdrawn. SVR12 was achieved. A third participant, who was CTP class A6 at baseline, presented at TW5 with esophageal variceal hemorrhage attributed by their clinician to significant recidivist alcohol consumption. Variceal surveillance was up to date prior to treatment. Bleeding was controlled endoscopically; however, the participant developed progressive hepatic decompensation and died 2 weeks later. At end of follow-up, 1 recurrent and 2 de novo HCCs were identified, which were detected between EOT and SVR12 timepoints. HCC surveillance was up to date in all 3 at baseline.

The 3 participants who were CTP class B at baseline tolerated treatment well, and no AEs were reported; their aggregate CTP scores were unchanged between baseline and SVR12 timepoints.

Table 6. Twenty Adverse Events Reported in 15 Patients.

Adverse events, n (%)	N = 97
Treatment related	
Nausea	4 (4)
Fatigue	3 (3)
Abdominal pain	2 (2)
Diarrhea	2 (2)
Headache	1 (1)
Vertigo	1 (1)
Weight gain	1 (1)
Mood disturbance	1 (1)
Serious adverse events	
Hepatic decompensation	3 (3)
Death	1 (1)
Deteriorating renal function	1 (1)
Leading to discontinuation of treatment	
Treatment related	
Abdominal pain	2 (2)
Deteriorating renal function	1 (1)

In 3 cases, adverse events led to treatment discontinuation.

The 5 participants who were CTP class A at baseline but who had had prior clinical decompensation, and a further 2 participants who were treated with an immediate "lead-in" regimen of SOF + NS5A-inhibitor, also tolerated SOF/VEL/VOX well; no AEs were recorded. Among participants with LT, there was no AEs on graft function or DDIs recorded.

DISCUSSION

This is the first Australian real-world study to investigate the efficacy and safety of SOF/VEL/VOX among participants with relapsed HCV infection following treatment with an NS5Ai-containing DAA regimen, and advanced liver disease or LT. Although the per protocol SVR12 rate of 90% was lower than top-line results in the registration trial, our sample was notable for "difficult-to-cure" characteristics including cirrhosis, PHT, and HCV GT3 infection.

The cohort is unique in its complexity including a high prevalence of cirrhosis (78%), the majority with PHT (61%, n = 46/76), which was notably higher than in POLARIS-1 and other SOF/VEL/VOX real-world studies (prevalence of cirrhosis 34–46%) [10–13]. The majority of participants also had HCV GT3 infection, which has been associated with increased likelihood of relapse after SOF/VEL/VOX in some real-world data, and approximately one-fifth had prior HCC [11]. It is the largest real-world study of relapsed patients with GT3 HCV. Our cohort also included the largest number of LT recipients outside of registrations trials, demonstrating that LT recipients can be safely treated and potential DDI appropriately managed. As expected, where virological testing was available, there was a high prevalence of HCV NS5A RAS at baseline (91%, n = 49/54), and 15% had previously failed multiple NS5Ai-containing DAA regimens, in some cases up to 4. Despite these difficult-to-cure characteristics, we show that 12 weeks SOF/VEL/VOX can achieve high rates of cure in clinical practice.

Our analysis did not identify any association between treatment outcomes and HCV genotype. The SVR12 rate was 89% among patients with GT3 HCV. This SVR12 proportion is similar to that observed in POLARIS-1, both in participants with GT3 HCV infection and cirrhosis, and in the overall cirrhotic population [10]. The rate of SVR12 observed in our GT3 patients is higher than that described by Llaneras and colleagues in Spain, who observed SVR12 rates of 80% (n = 24/30) in GT3 infection and 69% (n = 9/13) among GT3 cirrhotics, and from Degasperi and colleagues in Italy (SVR12 84% [n = 16/19] among GT3 cirrhotics) [11, 13]. The SVR12 data in our cohort are more similar to those with GT3 cirrhosis reported by Belperio in a Veteran's Affairs cohort (SVR12 = 91%, n = 21/23) [12]. The reasons for the differences between SVR12 rates reported in these respective cohorts is not clear, but our data provide reassuring evidence that in a large real-world cohort of

patients with GT3 cirrhosis and advanced disease, SVR12 rates remain high.

The high prevalence of participants with GT3 infection in this cohort, most of whom were cirrhotic, was notable. The community prevalence of GT3 HCV infection is approximately 39% in Australia [18]. The frequency of GT3 infection in our cohort exceeded 70%, consistent with GT3 remaining harder to cure than non-GT3 HCV after first-line DAA regimens, particularly in patients with cirrhosis (5). Most GT3 participants in our study were previously treated with SOF + DCV or SOF + VEL. GLE + PIB was not available in Australia at the time that this study was conducted. European guidelines no longer recommend 12 weeks SOF + VEL as a first-line treatment for GT3 infection and cirrhosis due to suboptimal outcomes in this group [19]. The high prevalence of GT3 in our study cohort highlight the importance of optimizing first-line DAA therapy for patients with GT3 infection and cirrhosis to minimize relapse and the need for salvage treatment.

Overall safety of SOF/VEL/VOX was acceptable; however, there were 3 episodes of hepatic decompensation in previously well-compensated CTP class A participants during treatment. As salvage triple therapy including PIs are increasingly prescribed to patients with advanced disease, the data highlight the need for regular clinical review and laboratory investigations to monitor for PI toxicity for at-risk patients during treatment. When toxicity is detected, treatment should be immediately discontinued. Where patients are LT candidates, we recommend review by a transplant board prior to commencing treatment.

Three participants with CTP class B disease were commenced on SOF/VEL/VOX, beyond the EAP criteria. Although no hepatic toxicity was noted in these cases, the use of NS3/4A PI in patients with CTP class B/C cirrhosis cannot be recommended. There were 5 other participants who were down-staged to CTP class A severity from CTP class B/C during prior treatment with SOF + NS5A (VEL/DCV), which was prescribed as a "lead-in" regimen immediately prior to SOF/VEL/VOX in one; all tolerated treatment well with close monitoring. In patients who are not candidates for LT, we believe the lead-in strategy regimen of SOF + NS5Ai to optimize liver function and downstage to CTP class A, prior to introducing VOX, warrants prospective evaluation given our positive experience.

Baseline RAS testing was available for 54 participants, and the presence of NS5A RAS was not associated with treatment failure. This is in keeping with results of a post hoc analysis of SOF/VEL/VOX registration data demonstrating that multitargeted combination therapy can overcome baseline resistance quasispecies [20]. There is thus a limited role for HCV NS5A sequencing in routine clinical management of these patients.

Second-line salvage therapies for the small number of patients who fail SOF/VEL/VOX are not well defined. As extension of treatment duration and regimen intensification with ribavirin was shown to improve SVR12 rates among DAA-experienced patients prior to the registration of relapse regimens including triple DAA therapy, we believe that both 24 weeks SOF/VEL/VOX ± ribavirin or 16 weeks SOF + GLE/PIB ± ribavirin present reasonable retreatment strategies for SOF/VEL/VOX failures [21]. Although ribavirin was included with SOF/VEL/VOX for 3 participants with GT3 and cirrhosis in our cohort, this number was too small to determine its effect.

In conclusion, SOF/VEL/VOX was an effective option for treatment of patients with difficult-to-cure characteristics who do not respond to a first-line DAA regimen, including patients with cirrhosis, GT3 HCV, and prior LT. Overall, this treatment regimen was well tolerated; however, serious AEs can occur in those with advanced liver disease.

Notes

Author contributions. All authors were involved in (i) substantial contribution to the conception and design; or the acquisition, analysis, or interpretation of the data and (ii) drafting and/or revision of the manuscript content, (iii) final approval of the version to be published, and (iv) agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the article are appropriately investigated and resolved.

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