Sofosbuvir/velpatasvir for patients with chronic hepatitis C virus infection and compensated liver disease: real-world data in Taiwan

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Abstract

Background

Data regarding the real-world effectiveness and safety of sofosbuvir/velpatasvir (SOF/VEL) for East Asian patients with chronic hepatitis C virus (HCV) infection and compensated liver disease are limited. We evaluated the performance of SOF/VEL for 12 weeks for HCV-infected patients with compensated liver disease in a large real-world cohort in Taiwan.

Methods

Between July 2019 and March 2020, 1,880 HCV-infected patients with compensated liver disease who received SOF/VEL 400/100 mg once daily for 12 weeks were included at 15 academic centers in Taiwan. The sustained virologic response at off-treatment week 12 (SVR₁₂) was assessed for evaluable (EP) and per-protocol populations (PP). The tolerance was also reported.

Results

The SVR₁₂ rates by EP and PP analyses were 95.6% (1,798 of 1,880 patients; 95% confidence interval (CI): 94.6%-96.5%) and 99.3% (1,798 of 1,811 patients; 95% CI: 98.8%-99.6%), respectively. Among 82 patients who failed to achieve SVR₁₂, 13 (15.9%) were attributed to virologic failures. The SVR₁₂ rates were comparable regardless of baseline characteristics. A total of 1,859 (98.9%) patients completed 12-week SOF/VEL treatment. Four (0.2%) patients discontinued treatment due to adverse events (AEs). All patients with serious AEs or deaths were judged not related to SOF/VEL. The AEs occurring in $\geq 10\%$ included headache (16.8%), fatigue (16.2%), nausea (11.8%), and insomnia (11.1%). Nine (0.5%) and 2 (0.1%) patients had grade 3 total bilirubin and alanine aminotransferase elevations.

Conclusions

SOF/VEL for 12 weeks is efficacious and well-tolerated chronic HCV-infected patients with compensated liver disease in Taiwan.

Introduction

Chronic hepatitis C virus (HCV) infection is the leading cause of cirrhosis, hepatocellular carcinoma (HCC), hepatic decompensation and liver transplantation. The estimated global prevalence of HCV infection is 1.0% and about 71 million people are living with HCV [1]. Patients with persistent HCV viremia are associated with an increased risk of various hepatic and extrahepatic manifestations, which compromise the overall morbidity and mortality [2, 3]. In contrast, the health-related outcomes are substantially improved following effective antiviral therapies for HCV [4]. Based on the high sustained virologic response (SVR) rate, low treatment-emergent adverse event (AEs) rate, and all-oral regimen with short treatment duration, the advent of interferon (IFN)-free direct acting antivirals (DAAs) has become the standard of care for managing HCV. Currently, DAAs with pangenotypic potency and fixed-dose combination (FDC) are recommended to be the first-line therapies because these regimens can simplify the care by obviating the needs for HCV genotype (GT) testing and intensive on-treatment monitoring [5–7]. Moreover, the World Health Organization (WHO) recommends the pangenotypic DAAs for HCV in order to move toward the viral elimination by 2030.

Sofosbuvir/velpatasvir (SOF/VEL) is formulated in the form of FDC by HCV non-structural protein 5B (NS5B) and NS5A inhibitors [8]. Clinically, SOF/VEL is administered once daily orally with pangenotypic and panfibrotic potency. In addition, this regimen has a high genetic barrier to viral resistance and has a lower potential for drug-drug interactions (DDIs) than protease-inhibitor (PI)-based regimens [9, 10].

The phase 3 global trials evaluating the performance of SOF/VEL for 12 weeks in patients with HCV GT 1–6 and compensated liver disease demonstrated that the SVR₁₂ rates were 99% for HCV GT 1, 2, 4, 5, and 6 and 95% for HCV GT 3 infections [11, 12]. The phase 3 Asian trial indicated that the SVR₁₂ rate was 97% for patients with HCV GT 1, 2, 3, and 6 infection and compensated liver disease receiving SOF/VEL for 12 weeks [13]. Furthermore, most patients tolerated treatment well. Recently, a meta-analysis recruiting 5,552 HCV-infected patients receiving SOF/VEL for 12 weeks from 12 real-world cohort studies in the USA, Canada and Europe revealed that the SVR₁₂ rates was 92.6% and 99.0% for those who received at least one dose of treatment and for those who had available data for off-treatment effectiveness analysis [14]. Based on the excellent safety and efficacy, most Western countries have approved the use of SOF/VEL for HCV-infected patients with compensated liver disease. In East Asia, China and Taiwan have approved the use of SOF/VEL for 12 weeks for patients with compensated liver disease, whereas Japan has approved this regimen only for patients with decompensated liver disease. Till now, data regarding the real-world effectiveness and safety of SOF/VEL for 12 weeks in East Asian chronic HCV-infected patients remain limited. Only 4 small-scale studies from China and Taiwan reported the effectiveness of brand-name and generic SOF/VEL for 12 weeks, showing that the SVR₁₂ rates ranged from 97.7–100% [15–18]. We

thus conducted a large-scale multicenter study to assess the performance of brand-name SOF/VEL for 12 weeks in chronic HCV-infected patients with compensated liver disease in Taiwan.

Materials And Methods

Patients

Between July 2019 and March 2020, we retrospectively recruited patients with chronic HCV infection and compensated liver disease who were aged ≥ 20 years and received SOF/VEL for 12 weeks at 15 academic centers in Taiwan. Chronic HCV infection was defined as the presence of detectable HCV antibody (anti-HCV; Abbott HCV EIA 2.0, Abbott Laboratories, Abbott Park, Illinois, USA) and quantifiable serum HCV RNA (Cobas TaqMan HCV Test v2.0, Roche Diagnostics GmbH, Mannheim, Germany, lower limit of quantification [LLOQ]: 15 IU/mL) for ≥ 6 months. Patients with compensated liver disease was defined as those without cirrhosis or with compensated cirrhosis (Child-Pugh A).

Study design

Patient demographics, hemogram, international normalized ratio (INR), serum albumin, total bilirubin (upper limit of normal [ULN]: 1.0 mg/dL), direct bilirubin, aspartate aminotransferase (AST), alanine aminotransferase (ALT) (ULN: 30 U/L for males and 19 U/L for females), estimated glomerular filtration rate (eGFR), anti-HCV, hepatitis B surface antigen (HBsAg) (Abbott Architect HBsAg qualitative assay, Abbott Laboratories, Abbott Park, Illinois, USA), anti-HIV (Abbott Architect HIV Ag/Ab Combo, Abbott Laboratories, Abbott Park, Illinois, USA), HCV RNA, HCV genotype (Roche Cobas HCV GT, Roche Diagnostics GmbH, Mannheim, Germany, or Abbott RealTime HCV Genotype II, Abbott Laboratories, Abbott Park, Illinois, USA) were assessed for all patients [19, 20]. The stage of hepatic fibrosis was graded by fibrosis index based on 4 parameters (FIB-4) and aspartate aminotransferase to platelet ratio index (APRI). Patients with a FIB-4 score of < 1.45 , $1.45\text{--}3.25$ and > 3.25 were categorized to have a fibrosis stage of F0-1 (no fibrosis, mild fibrosis), F2 (significant fibrosis), and F3-4 (advanced fibrosis, cirrhosis), respectively. Patients were further classified to have a fibrosis stage of F3 and F4 if the APRI scores were ≤ 2.0 and > 2.0 [21, 22]. In patients with compensated cirrhosis, the Child-Pugh score of A5 or A6 was calculated. Hepatic imaging studies, including ultrasonography, computed tomography or magnetic resonance imaging, were performed to detect HCC or ascites.

Patients received SOF/VEL (Epclusa®, FDC 400/100 mg per tablet, Gilead Sciences, Carrigtohill, Co. Cork, Ireland) 1 tablet once daily for 12 weeks. After the initiation of treatment, patients underwent monitoring at on-treatment weeks 4, 8 and 12 and at off-treatment week 12. Hemogram, total bilirubin, direct bilirubin, AST and ALT were assessed at on-treatment weeks 4 and 12. Hemogram, INR, albumin, total bilirubin, direct bilirubin, AST, ALT, eGFR and hepatic imaging studies were assessed at off-treatment week 12. Serum HCV RNA levels were assessed at on-treatment week 12 and at off-treatment week 12.

Drug adherence

The adherence was presented as the percentage of the total pills consumed during treatment divided by the 84 dispensed pills for SOF/VEL.

Effectiveness

We assessed the end-of-treatment virologic response and sustained virologic response at on-treatment week 12 and off-treatment week 12, respectively. All patients were judged not to achieve SVR₁₂ if the HCV RNA level was $> \text{LLOQ}$ at off-treatment week 12 (virologic failure) or if patients had missing SVR₁₂ data (non-virologic failure). The SVR₁₂ endpoints included evaluable population (EP) for patients who received at least one dose of SOF/VEL, and per-protocol population (PP) for patients who had available SVR₁₂ data.

Safety

In patients who prematurely discontinued treatment, or who had serious adverse events (AEs) including death, life-threatening condition, in-patient hospitalization, persistent disability, or important medical events requiring emergent intervention, the investigators reviewed the medical records and judged the causal-relationship between the events and SOF/VEL. We also reported common AEs with rates of $\geq 10\%$ and the proportion of patients with $\geq$ grade 2 total bilirubin or ALT elevation according to Common Terminology Criteria for Adverse Events (CTCAE) version 5.0. The eGFR changes between baseline and SVR₁₂ were compared for all patients.

Statistical analysis

All analyses were performed by Statistical Program for Social Sciences (SPSS Statistics Version 23.0, IBM Corp., Armonk, New York, USA). Baseline characteristics were shown in median (interquartile range, IQR) and numbers (percentages) when appropriate. The virologic response rates at on-treatment and off-treatment weeks 12 were shown in numbers (percentages) with 95% confidence interval (CI). We demonstrated the subgroup analyses of SVR₁₂ in number (percentage) with 95% CI according to PP analysis. The common AEs and laboratory abnormalities were shown in numbers (percentages) when appropriate. The eGFR at baseline and SVR₁₂ was shown in mean (standard deviation), and the changes of the eGFR were compared by paired t-test according to baseline CKD stage.

Results

Patient characteristics

A total of 1,880 chronic HCV-infected patients with compensated liver disease who received SOF/VEL for 12 weeks were included in the study. Among the 1,880 patients, 1,859 (98.9%) completed 12-week treatment, and 1,811 (96.3%) completed 12-week off-treatment follow-up (Fig. 1). The median age was 60 years, 933 (49.6%) were males and 1,751 (93.1%) patients were treatment-naïve. Among the 129 treatment-experienced patients, 14 (10.9%) had experienced to DAA treatment. Nine patients, who were all coinfecting with HIV, had confirmed reinfection after DAAs by documenting different HCV GT infections or HCV species from phylogenetic tree analysis. The remaining 5 patients relapsed from prior DAAs, including glecaprevir/pibrentasvir (GLE/PIB) (n = 2, HCV GT2), sofosbuvir/ledipasvir (SOF/LDV) (n = 2, HCV GT1b) and SOF plus daclatasvir (DCV) (n = 1, HCV GT1b). Seventy-eight (4.1%) patients with HCC had achieved complete tumor ablation, and 20 (1.1%) patients with active HCC before the initiation of SOF/VEL. Thirteen and 8 patients with active HCC had tumor stages of C and B according to Barcelona Clinic Liver Cancer (BCLC) staging system. One hundred forty-nine (7.9%) and 115 (6.1%) patients had HBV and HIV coinfection. With regard to GT distribution, 817 (43.5%), 838 (44.6%), 38 (2.0%), 1 (0.1%) and 134 (7.1%) patients were infected with HCV GT 1, 2, 3, 4, and 6, respectively. One hundred fifty-one (8.0%) patients had compensated cirrhosis, and 99 and 52 of them had Child-Pugh scores of A5 and A6 (Table 1).

Table 1
Baseline characteristics

Characteristics †	Patients (N = 1,880)
Age, yr, median (IQR)	60 (50–70)
Age > 60 yr	935 (49.7)
Male	933 (49.6)
Prior antiviral treatment	
Naïve	1,751 (93.1)
Experienced	129 (6.9)
PR	115 (89.1)
DAA ‡	14 (10.9)
History of HCC	
No	1,782 (94.8)
Yes	98 (5.2)
Ablated	78 (79.6)
Active	20 (20.4)
HCV RNA, log ₁₀ IU/mL, median (IQR)	6.2 (5.3–6.7)
HBV coinfection	149 (7.9)
HIV coinfection	115 (6.1)
HCV RNA > 6,000,000 IU/mL	364 (19.4)
HCV genotype	
1	22 (1.2)
1a	105 (5.6)
1b	690 (36.7)
2	838 (44.6)
3	38 (2.0)
4	1 (0.1)
6	134 (7.1)
Mixed	37 (2.0)
Indeterminate	15 (0.8)
Fibrosis stage §	
F0-1	686 (36.5)

IQR, interquartile range; PR, peginterferon plus ribavirin; DAA, direct acting antiviral; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; RNA, ribonucleic acid; HBV, hepatitis B virus; HIV, human immunodeficiency virus; INR, international normalized ratio; ALT, alanine aminotransferase; ULN, upper limit of normal; eGFR, estimated glomerular filtration rate; CKD, chronic kidney disease.

† Values are numbers (percentages) unless otherwise indicated.

‡ Nine patients were confirmed to have reinfection after achieving sustained virologic response by prior courses of direct acting antivirals. The other 5 patients had viral relapse following NS5A-containing DAA regimens, including glecaprevir/pibrentasvir (n = 2), sofosbuvir/ledipasvir (n = 2), and sofosbuvir plus daclatasvir (n = 1).

§ Assessed by FIB-4 index (fibrosis index based on 4 parameters), APRI index (aspartate aminotransferase to platelet ratio index) and clinical presentations. A FIB-4 score < 1.45 was categorized as F0-1, a FIB-4 score between 1.45–3.25 was categorized as F2, a FIB score > 3.25 was categorized as F3-F4. Among patients with a FIB-4 score > 3.25, those with a APRI score > 2 was categorized as F4, and those with a APRI score ≤ 2 was categorized as F3. For patients with a fibrosis stage of F4, the grade of cirrhosis was further assessed by Child-Pugh score.

¶ The ULN of total bilirubin is 1.0 mg/dL. The ULN of ALT is 30 U/L for males and 19 U/L for females.

Characteristics †	Patients (N = 1,880)
F2	805 (42.8)
F3	238 (12.7)
F4	151 (8.0)
Child-Pugh A5	99 (65.6)
Child-Pugh A6	52 (33.3)
Hemoglobin, g/dL, median (IQR)	13.8 (12.6–15.1)
White blood cell count, 10 ⁹ cells/L, median (IQR)	5.8 (4.8–7.1)
Platelet count, 10 ⁹ cells/L, median (IQR)	201 (158–246)
INR, median (IQR)	1.03 (0.98–1.09)
Albumin, g/dL, median (IQR)	4.2 (4.0–4.5)
Total bilirubin, ULN, median (IQR) ¶	0.7 (0.5–0.9)
ALT, ULN, median (IQR) ¶	1.8 (1.2–3.3)
eGFR, mL/min/1.73m ² , median (IQR)	91 (75–103)
CKD stage	
1 (eGFR ≥ 90 mL/min/1.73m ²)	997 (53.0)
2 (eGFR 60–89 mL/min/1.73m ²)	644 (34.3)
3a (eGFR 45–59 mL/min/1.73m ²)	106 (5.6)
3b (eGFR 30–44 mL/min/1.73m ²)	61 (3.2)
4 (eGFR 15–29 mL/min/1.73m ²)	54 (2.9)
5 (eGFR < 15 mL/min/1.73m ²)	18 (1.0)
IQR, interquartile range; PR, peginterferon plus ribavirin; DAA, direct acting antiviral; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; RNA, ribonucleic acid; HBV, hepatitis B virus; HIV, human immunodeficiency virus; INR, international normalized ratio; ALT, alanine aminotransferase; ULN, upper limit of normal; eGFR, estimated glomerular filtration rate; CKD, chronic kidney disease.	
† Values are numbers (percentages) unless otherwise indicated.	
‡ Nine patients were confirmed to have reinfection after achieving sustained virologic response by prior courses of direct acting antivirals. The other 5 patients had viral relapse following NS5A-containing DAA regimens, including glecaprevir/pibrentasvir (n = 2), sofosbuvir/ledipasvir (n = 2), and sofosbuvir plus daclatasvir (n = 1).	
§ Assessed by FIB-4 index (fibrosis index based on 4 parameters), APRI index (aspartate aminotransferase to platelet ratio index) and clinical presentations. A FIB-4 score < 1.45 was categorized as F0-1, a FIB-4 score between 1.45–3.25 was categorized as F2, a FIB score > 3.25 was categorized as F3-F4. Among patients with a FIB-4 score > 3.25, those with a APRI score > 2 was categorized as F4, and those with a APRI score ≤ 2 was categorized as F3. For patients with a fibrosis stage of F4, the grade of cirrhosis was further assessed by Child-Pugh score.	
¶ The ULN of total bilirubin is 1.0 mg/dL. The ULN of ALT is 30 U/L for males and 19 U/L for females.	

Table 2
On-treatment and off-treatment virologic responses

HCV RNA < LLOQ †	Patients (N = 1,880)	
	n/N (%)	95% CI
During treatment		
Week 12 ‡	1,853/1,859 (99.7)	99.3–99.9
After treatment		
SVR ₁₂ (EP) §	1,798/1,880 (95.6)	94.6–96.5
SVR ₁₂ (PP) ¶	1,798/1,811 (99.3)	98.8–99.6
Reason for failure to achieve SVR₁₂, n		
On-treatment		
Death	8	
Premature discontinuation	6	
Loss to follow-up	7	
Off-treatment		
Death	12	
Loss to follow-up	36	
Non-response	3	
Relapse	10	
LLOQ, lower limit of quantification; CI, confidence interval; SVR, sustained virologic response.		
† HCV RNA LLOQ = 15 IU/mL.		
‡ Eight patients who died, 6 patients who prematurely discontinued treatment, and 7 patients who were lost to follow-up before on-treatment week 12 did not have available data for the analysis.		
§ Evaluable population (EP) included patients receiving at least one dose of SOF/VEL.		
¶ Per-protocol population (PP) included patients with available SVR ₁₂ data.		

Drug adherence

One thousand eight hundred and fifty-nine (98.9%) patients consumed > 95% of the dispensed SOF/VEL pills. Among the 21 patients who consumed ≤ 95% of the dispensed SOF/VEL pills, 14 patients consumed < 33% and the other 7 patients consumed 58%-75% of the dispensed pills.

Effectiveness

At on-treatment week 12, 1,853 of 1,859 patients with available data (99.7%; 95% CI: 99.3%-99.9%) had serum HCV RNA level < LLOQ. By EP and PP analyses, the SVR₁₂ rates were 95.6% (1,798 of 1,880 patients; 95% CI: 94.6%-96.5%) and 99.3% (1,798 of 1,811 patients; 95% CI: 98.8%-99.6%). Among the 82 patients who failed to achieve SVR₁₂, 13 (15.9%) were attributed to virologic failures and the remaining 69 (84.1%) were attributed to non-virologic failures. The baseline characteristics of patients with virologic failures were summarized in Table 3. Among the 6 patients who had serum HCV RNA ≥ LLOQ at on-treatment week 12, 2 with on-treatment week 12 HCV RNA levels of 28 IU/mL and 51 IU/mL achieved SVR₁₂, 3 with on-treatment week 12 HCV RNA levels of 1,600 IU/mL, 1,500,000 IU/mL and 3,710,000 IU/mL remained viremic at off-treatment week 12, and one with on-treatment week 12 HCV RNA level of 838,000 IU/mL did not have available SVR₁₂ data due to loss to follow-up after stopping SOF/VEL. The SVR₁₂ rates of subgroups by PP analysis are shown in Fig. 2.

Table 3
Summary of patients with virologic failures

Patient Number	Type of failure	Age ₂	Sex	Prior antiviral Tx	History of HCC	HCV RNA, log ₁₀ IU/mL	HCV genotype	Fibrosis stage	HBV	HIV	CKD stage	Drug adherence (%)
1	Non-response	75	Female	No	No	6.41	2	F3	Yes	No	2	98
2	Non-response	61	Male	No	No	6.06	2	F1	No	No	1	100
3	Non-response	84	Male	No	No	7.37	1b	F3	No	No	2	95
4	Relapse	45	Male	No	No	3.05	1a	F4	No	Yes	1	100
5	Relapse	73	Female	No	No	5.70	2	F3	No	No	1	98
6	Relapse	30	Male	No	No	4.87	6	F1	No	Yes	1	100
7	Relapse	59	Male	No	No	6.79	Indeterminate	F2	No	No	2	100
8	Relapse	59	Male	Yes (PR)	No	5.09	2	F2	No	No	1	96
9	Relapse	68	Male	Yes (PR)	No	7.41	2	F2	No	No	2	99
10	Relapse	43	Male	Yes (PR)	No	7.20	6	F1	No	No	1	100
11	Relapse	66	Female	No	No	5.49	2	F2	No	No	2	98
12	Relapse	42	Male	No	No	6.54	3	F4	No	No	2	99
13	Relapse	36	Male	No	No	6.35	6	F1	No	No	1	100
Tx, treatment; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; RNA, ribonucleic acid; HBV, hepatitis B virus; HIV, human immunodeficiency virus; CKD, chronic kidney disease; PR, peginterferon plus ribavirin.												

Safety

A total of 1,065 (56.6%) patients were reported to have at least one AE. Among the 44 (2.3%) patients with serious AE, including 20 deaths, none were judged related to SOF/VEL. Four (0.2%) patients discontinued SOF/VEL because of treatment-emergent AEs (fatigue in 2, diarrhea in 1, and increase of total bilirubin from 1.9 mg/dL to 2.4 mg/dL in 1). The common AEs with the reported rates $\geq 10\%$ included headache (316 patients, 16.8%), fatigue (304 patients, 16.2%), nausea (221 patients, 11.8%) and insomnia (208 patients, 11.1%). Fifty-seven (3.0%) and 9 (0.5%) patients had on-treatment grade 2 and grade 3 total bilirubin elevations. Fourteen (0.7%) and 2 (0.1%) patients had on-treatment grade 2 and 3 ALT level elevations (Table 4). Among the 78 patients who had ablated HCC before SOF/VEL and who underwent hepatic imaging surveillance after SOF/VEL, 4 (5.1%) had tumor recurrence during a 24-week study period. Among the 1,782 patients who did not have HCC before SOF/VEL and who underwent hepatic imaging surveillance after SOF/VEL, 3 (1.7%) had tumor occurrence during a 24-week study period. Seven of the 13 patients with BCLC stage C active HCC died and 6 of the 7 deaths were attributed to HCC. One of the 7 patients with BCLC stage B active HCC died of progressive HCC. In patients with HBV coinfection, one (0.7%) patient had on-treatment grade 2 ALT elevation, but the serum HBV DNA level was undetectable at the time of ALT elevation. With regard to eGFR evolution, patients with baseline CKD stage 3a (55 versus 58 mL/min/1.73m², $p = 0.02$), 3b (40 versus 44 mL/min/1.73m², $p = 0.02$), 4 (27 versus 36 mL/min/1.73m², $p < 0.001$), and 5 (12 versus 13 mL/min/1.73m², $p = 0.04$) had significant eGFR improvement after treatment. The eGFR remained stable in patients with baseline CKD stage 2 (78 versus 78 mL/min/1.73m², $p = 0.58$) and decreased in patients with CKD stage 1 (103 versus 100 mL/min/1.73m², $p < 0.001$) after treatment (Supplementary Fig. 1).

Table 4
Safety summary

Event, n (%)	Patients (N = 1,880)
Any AE	1,065 (56.6)
Discontinuation due to treatment-emergent AE	4 (0.2)
Serious AE †	44 (2.3)
Death	20 (1.1)
DAA-related serious AE or death	0 (0)
AE occurring in ≥ 10% of patients	
Headache	316 (16.8)
Fatigue	304 (16.2)
Nausea	221 (11.8)
Insomnia	208 (11.1)
Laboratory abnormalities	
Total bilirubin	
Grade 2 (1.5-3.0 x ULN)	57 (3.0)
Grade 3 (> 3.0 x ULN) ‡	9 (0.5)
ALT	
Grade 2 (3.0–5.0 x ULN) §	14 (0.7)
Grade 3 (> 5.0 x ULN) ¶	2 (0.1)
AE, adverse event; DAA, direct acting antiviral; ULN; upper limit of normal; ALT, alanine aminotransferase.	
† Twenty deaths, including lung cancer (n = 2), pneumonia (n = 2), traumatic subdural hemorrhage (n = 1), urinary tract infection with septic shock (n = 2), pancreatic cancer (n = 1), intra-abdominal infection with septic shock (n = 1), unknown reason (n = 4), cardiac arrest (n = 1) and hepatocellular carcinoma (n = 6). Twenty-four events with in-patient hospitalization, including recurrence of hepatocellular carcinoma (n = 4), occurrence of hepatocellular carcinoma (n = 2), active hepatocellular carcinoma (n = 3), pneumonia (n = 1), urinary tract infection (n = 1), colorectal cancer (n = 2), lung cancer (n = 1), schizophrenia (n = 1), ischemic stroke (n = 1), peptic ulcer bleeding (n = 2), traffic accident (n = 1), chronic obstructive pulmonary disease (n = 1), esophageal variceal bleeding (n = 1), near syncope (n = 1), thalassemia with symptomatic anemia (n = 1), and rheumatoid arthritis (n = 1).	
‡ Four patients had unconjugated hyperbilirubinemia. Three of them had on-treatment ALT levels of < ULN, and one had on-treatment ALT levels of 1.0–2.0 x ULN. No patients developed hepatic decompensation. The other 5 patients, all of whom had active hepatocellular carcinoma, had conjugated hyperbilirubinemia. Two of the 5 patients had on-treatment ALT levels of 3.0–5.0 x ULN.	
§ One patient had HBV coinfection, and the serum HBV DNA level was undetectable at the time of ALT elevation. No patients developed grade 3 total bilirubin elevation or hepatic decompensation. Two patients had active hepatocellular carcinoma and developed grade 3 total bilirubin elevation. Both patients died of hepatocellular carcinoma at on-treatment weeks 6 and 10, respectively. All except the two patients with active hepatocellular carcinoma had undetectable HCV RNA level at on-treatment week 12 and off-treatment weeks 12.	
¶ One patient had persistently ALT levels of 5.3 x ULN and 6.8 x ULN at on-treatment weeks 4 and 12, and the ALT level was 3.8 x ULN at off-treatment week 12. The other one patient had ALT levels of 5.9 x ULN and 2.7 x ULN at on-treatment weeks 4 and 12, and the ALT levels was 1.5 x ULN at off-treatment week 12. Both patients did not have total bilirubin elevation or hepatic decompensation. Both patients had undetectable HCV RNA levels at on-treatment week 12 and off-treatment weeks 12.	

Discussion

In addition to the pangenotypic, panfibrotic, PI-free and ribavirin (RBV)-free advantages for chronic HCV-infected patients with compensated liver disease, the high efficacy and tolerability of SOF/VEL demonstrated in global and regional clinical trials confirm the excellent performance of SOF/VEL against HCV which may facilitate the HCV elimination [11–13]. To our knowledge, this study is the first large-scale real-world study in East Asia to evaluate the effectiveness and safety of SOF/VEL for 12 weeks in chronic HCV-infected patients with compensated liver disease. In line with a recently published meta-analysis which showed that the overall SVR₁₂ rate was 92.6%, we demonstrated the SVR₁₂ rate were 95.6% by EP analysis [14]. By excluding patients who failed to achieve SVR₁₂ due to non-virologic failures, the proportion of virologic failures in our study was only 0.7%, which was similar to the phase 3 trials and the real-world pooled meta-analysis [11–14]. Furthermore, the subgroup analyses demonstrated that the SVR₁₂ rates were comparably high regardless of age, sex, prior treatment experience, prior HCC history, HBV or HIV coinfection, renal function, HCV viral load, HCV genotype and stage of hepatic fibrosis.

Compared to the SVR₁₂ rate of 95% for HCV GT 3a or other GT 3 unconfirmed subgenotypes, the Asian phase 3 trial indicated that the SVR₁₂ rate was only 76% for HCV GT 3b by SOF/VEL for 12 weeks [13]. Because most HCV GT 3 patients in Taiwan were infected with HCV GT 3a, the SVR₁₂ rate in our HCV GT 3 patients was 97.2%, which was similar to the SVR₁₂ rate of 97.5% in HCV GT 3a patients in a pooled analysis of phase 3 SOF/VEL trials [20, 23]. While we did not find any clinical parameter to predict 13 patients with virologic failures, HCV GT3 patients with NS5A resistance associated substitution (RAS) at locus Y93H significantly compromised the SVR₁₂ rate by SOF/VEL which was tested in our patients [23]. Furthermore, we also showed that the SVR₁₂ rate in patients with Child-Pugh A6 cirrhosis remained excellent, compared to patients without cirrhosis or with Child-Pugh A5 cirrhosis (100% versus 97.9%-99.3%). It is clinically relevant to practitioners because of the safety concerns for Child-Pugh A6 cirrhotic patients receiving PI-based DAAs [24].

Interestingly, 2 patients who had low levels of serum HCV RNA (28 IU/mL and 51 IU/mL) at on-treatment week 12 achieved SVR₁₂ after stopping SOF/VEL, whereas 3 who had relatively high levels of serum HCV RNA (1,600 IU/mL, 1,500,000 IU/mL and 3,710,000 IU/mL) failed to achieve SVR₁₂. The presence of low-level HCV viremia at the end of treatment in our patients with SVR₁₂ could be reasoned by the persistent augmentation of host immune system which might clear low-level viremia after stopping DAAs, and by the detection of noninfectious or fragmented viral particles [25]. Therefore, the patients and practitioners should not worry too much about the presence of low-level viremia at the end of DAA treatment because it may not necessarily suggest treatment failure.

Our real-world study included 20 patients with BCLC stage B or C active HCC and 5 with virologic failures to prior NS5A-containing DAAs, who were conventionally excluded from the clinical trials. Seven of our 20 patients with active HCC died during the study period, although all the remaining 13 patients who completed follow-up achieved SVR₁₂. The physicians should judiciously optimize DAA treatment because the benefit of achieving SVR₁₂ would be minimal in patients with limited life expectancy [5–7]. All 5 patients with HCV GT1 or GT2 infection who relapsed from prior course of GLE/PIB, SOF/LDV or SOF plus DCV in our study achieved SVR₁₂. Currently, SOF/VEL has not been labeled for retreating patients who fail prior NS5A-containing DAAs, although a recent study revealed that the SVR₁₂ rate of SOF/VEL plus RBV for 24 weeks can reach 97% for retreating HCV GT1 or GT2 patients [26]. Therefore, the physicians should be cautious about the routine use of SOF/VEL alone for 12 weeks to retreat patients not responsive to prior NS5A-containing DAAs to avoid treatment failures. This is of particular importance because the SVR₁₂ rates would be even lower in the presence of NS5A L31 or Y93 RAS [26].

Regarding drug adherence, 98.9% of our patients consumed > 95% of the dispensed pills. Because that SOF/VEL has the advantages of easy dosing without food effects, low pill burden, short treatment duration, low risk of treatment-emergent AEs, the excellent drug adherence may contribute to the high SVR₁₂ rate in our patients [27].

Although 56.6% of our patients were reported to have at least one AE, only 4 (0.2%) patients discontinued treatment due to treatment-emergent AE. Moreover, all serious AEs and deaths were considered not related to the use of SOF/VEL. The proportions of patients with common AEs in our study were also in line with those reported in clinical trials [11–13]. With regard to laboratory abnormalities, only a limited number of patients had $\geq$ grade 2 total bilirubin or ALT elevation, implying that treatment with SOF/VEL has a high degree of liver safety. The proportions of HCC occurrence and recurrence in our study were 1.7% and 5.1%, respectively, during a 24-week study interval, which were comparable to the annual HCC risks of occurrence and recurrence of 3.0% and 12.2% in a meta-analysis study [28]. In addition to achieving comparably high SVR₁₂ rates, the eGFR tended to improve in patients with baseline CKD stages 3a-5, implying that the HCV-related renal damages tended to be mitigated following successful viral eradication. Taken together, the tolerance of SOF/VEL for 12 weeks was excellent in our HCV-infected patients with compensated liver disease. In addition to the distinguishing performance of SOF/VEL in terms of efficacy and safety, SOF/VEL for HCV has also been shown to improve patients' quality of life and to be cost-effective which warrants consideration in implementing programs for HCV elimination [29].

Our study had several limitations. First, the numbers of patients with HCV GT4 and GT5 infection were limited, making the effectiveness and safety of SOF/VEL for patients with HCV GT4 and GT5 infection in Taiwan uncertain. Second, we did not have stored blood samples to assess the profiles of RASs in patients with virologic failures due to the retrospective nature of our study. Third, information regarding to the HCV GT3 subtypes was not available because we used commercially-based HCV genotyping in this study. Fourth, all patients were included at academic centers, and the effectiveness and safety of SOF/VEL at community hospitals or local clinics need to be validated. Fifth, our study was retrospective in nature which lacked the standardized report forms for AEs, and therefore the reporting biases might exist. Finally, the proportion of HBV reactivation following SOF/VEL was unknown. However, none developed HBV-associated hepatitis, defined as the presence of $\geq$ grade 2 ALT elevation and $\geq 1 \log_{10}$ increase of serum HBV DNA level, which led to hepatic decompensation in our HBV-coinfected patients [30].

In summary, our large-scale real-world study shows that SOF/VEL for 12 weeks is efficacious and well-tolerated for chronic HCV-infected patients without cirrhosis and with compensated cirrhosis in Taiwan.

Abbreviations

HCV, hepatitis C virus; HCC, hepatocellular carcinoma; IFN, interferon; DAA, direct acting antiviral; SOF, sofosbuvir; VEL, velpatasvir; SVR, sustained virologic response; HBV, hepatitis B virus; HIV

human immunodeficiency virus; FDC, fixed-dose combination; GT, genotype; DDI, drug-drug interaction; PI, protease inhibitor; LLOQ, lower limit of quantification; ULN, upper limit of normal; eGFR, estimated glomerular filtration rate; RNA:ribonucleic acid, DNA:deoxyribonucleic acid; AST, aspartate aminotransferase; ALT, alanine aminotransferase; FIB-4, fibrosis index based on 4 parameters; APRI, aspartate aminotransferase to platelet ratio index; AE, adverse event; IQR, interquartile range; CI:confidence interval; RBV, ribavirin; RAS, resistance associated substitution

Declarations

Ethical approval

The study was approved by the Research Ethics Committee of each participating center (ID: 202007043RIND) and was conducted in accordance with the principles of Declaration of Helsinki in 1975.

Financial

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Data availability

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

Animal research

This was not an animal research.

Consent to participate

This was a retrospective study with clinical data collection, and the Research Ethics Committee of each participating center approved to waive the patient consent.

Consent to publish

All the authors consented the publish the work.

Clinical trials registration

The was a retrospective observation study and was not a drug trial. There was no need for clinical trial registration.

Author contributions:

Conception and design: CH Liu, JH Kao.

Analysis and interpretation of data: CH Liu.

Drafting of the article: CH Liu, JH Kao.

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Conflicts of interest

Chen-Hua Liu: advisory board for Abbvie, Gilead Sciences, Merck Sharp & Dohme; speaker's bureau for Abbott, Abbvie, Gilead Sciences, Merck Sharp & Dohme; research grant from Abbvie, Gilead Science, Merck Sharp & Dohme. Sheng-Shun Yang: advisory board for Abbvie, Roche, Ipsen; speaker's bureau for Abbvie, Bristol-Myers Squibb, Gilead Sciences, Ipsen, Merck Sharp & Dohme. Chien-Ching Hung: advisory board for Abbvie, Gilead Sciences, ViiV Healthcare; speaker's bureau for Gilead Sciences; research grant from Gilead Sciences, ViiV Healthcare, Merck Sharp & Dohme. Jia- Horng Kao: advisory board for Abbott, Abbvie, Bristol-Myers Squibb, Gilead Sciences, GlaxoSmithKline, Merck Sharp & Dohme, Novartis, Roche; speaker's bureau for Abbott, Abbvie, Bayer, Bristol-Myers Squibb, Gilead Sciences, GlaxoSmithKline, Merck Sharp & Dohme, Novartis, Roche. All other authors declare no competing interests.

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Figures

Figure 1

Study flow.

Figure 2

Sustained virologic response rates by per-protocol (PP) analysis according to subgroup. The position of the square indicates the sustained virologic response rate at off-treatment week 12 week (SVR₁₂) in each subgroup; the horizontal lines indicate 95% confidence intervals (CIs). The dotted vertical line represents the overall SVR₁₂ rate. The A5 and A6 indicate compensated cirrhotic patients with Child-Pugh score of 5 and 6, respectively. SOF, sofosbuvir; VEL, velpatasvir; PR, peginterferon plus ribavirin; DAA, direct acting antiviral; HCC, hepatocellular carcinoma; HBV, hepatitis B virus; HIV, human immunodeficiency virus; HCV, hepatitis C virus; RNA, ribonucleic acid; CKD, chronic kidney disease.

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