Efficacy and safety of sofosbuvir-based pangenotypic direct-acting antiviral agents for chronic hepatitis C patients without genotype determination

Real-world experience of a retrospective study

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Abstract

Several new, pangenotypic direct-acting antiviral agents (DAAs) have been approved, may reduce the need for genotyping to guide therapy decisions for patients with chronic hepatitis C (CHC).

This study aimed to investigate the efficacy and safety of Sofosbuvir (SOF)-based pangenotypic DAAs therapy for CHC patients without genotype (GT determination in the real-world practice.

This retrospective cohort study included treatment-naïve CHC patients without GT determination, who received SOF-based DAAs therapy, including 400 mg SOF plus 60 mg daclatasvir (DCV) daily or 400 mg SOF plus 100 mg velpatasvir (VEL) daily for 12 or 24 weeks. Clinical and laboratory data, including sustained virologic response (SVR), were obtained at baseline, end of treatment (EOT), 12 weeks after EOT, and 48 weeks after EOT.

A total of 95 CHC patients, including 30 (31.58%) had liver cirrhosis were enrolled. SVR rates after 12 weeks of treatment (SVR12) was 96.84% (92/95), including 96.20% (76/79) of patients receiving SOF plus DCV and 100% (16/16) of patients receiving SOF plus VEL. For 92 patients achieving an SVR12, no virological relapse was observed at 48 weeks after EOT. Furthermore, serum evaluation of liver fibrosis aspartate aminotransferase-to-platelet ratio index and Fibrosis-4 score were decreased significantly at EOT and 12 weeks after EOT, compared to pre-treatment values (both $P < .05$). Treatment was well-tolerated by our patients.

SOF-based pangenotypic DAAs including SOF plus DCV and SOF plus VEL, were effective and safe for CHC patients without GT determination in this study. This may provide a potential simple strategy for CHC treatment without GT determination.

Abbreviations: AEs = adverse events, APRI = aspartate aminotransferase to platelet ratio index, AST = aspartate aminotransferase, DAAs = direct-acting antiviral agents, DCV = daclatasvir, EOT = end of therapy, FIB-4 = fibrosis-4, GLE = glecaprevir, GT = genotype, HCC = hepatocellular carcinoma, HCV = hepatitis C virus, IFN = interferon, LLOQ = lower limit of quantification, PIB = pibrentasvir, PLT = platelet, py = per year, SAEs = serious adverse events, SOF = sofosbuvir, SVR = sustained virologic response, SVR12 = SVR rates after 12 weeks of treatment, VEL = velpatasvir.

Keywords: chronic hepatitis C, direct-acting antiviral agents, genotype, sofosbuvir

1. Introduction

Hepatitis C virus (HCV), a small, positive-stranded RNA-enveloped virus of genus *Hepacivirus*, family *Flaviviridae*, was first isolated in 1989.[1,2] HCV infection is a major cause of chronic liver disease, causing liver injury ranging from minimal hepatic injury to liver fibrosis, cirrhosis and hepatocellular carcinoma (HCC).[3,4] Globally, approximately 71 million people have chronic hepatitis C (CHC), and that 399,000 patients had died from cirrhosis or HCC in 2015.[5] Although direct-acting antiviral agents (DAAs) are used clinically for CHC treatment, with the sustained virological response (SVR) achieved in more than 90% of CHC patients. There were 14 million patients (20%) had been diagnosed, only 1.1 million (7%) had been started on therapy, and approximately 71 million untreated individuals with HCV.[5,6] HCV infection is still a major public health concern; hence, HCV eradication, although challenging, must be attempted.

DAAs therapy has revolutionized hepatitis C management and has provided the therapeutic tools to potentially eradicate the disease. For CHC patients with interferon based therapy, the SVR rate is achieved 40% to 82%, and HCV genotype (GT), genetic polymorphisms located in chromosome 19 and stage of liver fibrosis are the strongest baseline predictors of SVR.[7] Together with the increased SVR rate and decreased rate of serious adverse events (SAEs) when compared with interferon based therapy, the DAAs treatment for CHC has shown satisfactory efficacy and safety in patients with CHC, and achieved a better SVR rate of more than 90%.[3,4,8]

The recommendations for DAA treatment for CHC per the HCV guidelines for the initial treatment of HCV infection included the following: sofosbuvir (SOF), SOF plus ledipasvir, SOF plus velpatasvir (VEL), paritaprevir/ombitasvir/ritonavir, dasabuvir, daclatasvir (DCV), glecaprevir (GLE)/pibrentasvir (PIB), grazoprevirplus elbasvir, and simeprevir.[3,5,8] Based on the HCV GT, liver disease severity, and/or prior therapy history, the indications for treatment should be interpreted in a personalized manner.[3] The licensed DAA treatments are significantly more effective on certain GT; thus, it may be important to know the HCV GT before initiating treatment. However, in many low-income and middle-income countries, the cost of genotyping can be prohibitively high, and the GT distribution remains unknown.[9] Moreover, due to the high sequence heterogeneity among the different types and subtypes and the low agreement between different detection methods, the HCV GT determination is still a challenge in clinical practice.[10–12]

Several new, pangenotypic DAAs therapies have been approved by the United States Food and Drug Administration and the European Medicines Agency.[3,5,8] Pangenotypic DAAs therapies can achieve high treatment efficacy across all 6 major HCV GTs, thereby enabling the treatment of CHC patients without HCV GT and subtype determination.[3,5] Pangenotypic DAAs therapies was also cost-effectiveness versus GT-dependent DAA treatments in a previously-validated microsimulation model in India.[13] This may be useful in the regions wherein HCV GT tests are not easily available or costly to simplify therapy in the resource-limited area.[3,5,13] To our knowledge, data regarding the simple strategy of treating CHC patients and the safety and efficacy of pangenotypic DAAs for CHC therapy without HCV GT determination are still limited. The present retrospective study aimed to evaluate the efficacy and safety of pangenotypic DAAs (SOF plus DCV and SOF plus VEL) therapy in CHC patients without HCV GT determination in Southwest China.

2. Patients and methods

2.1. Study design and participants

This retrospective clinical study involved CHC patients without detection of HCV GT, from West China Hospital of Sichuan University in the Southwest China (Registration number: ChiCTR1800014889). This study was approved by the Ethics Committee of West China Hospital of Sichuan University, and was allowed exception to the requirement of informed consent for this study. Patients aged 18 years or older, with positive titers of antibodies against HCV for more than 6 months, and consulted and inquired for liver disease, who had received pangenotypic DAAs regimens (SOF plus DCV or SOF plus VEL) during HCV treatment between January 2016 and May 2017 were enrolled. The clinical data, laboratory data, and follow-up information regarding treatment outcome were collected. Safety profiles were reported by the CHC patients themselves.

In our CHC patient cohort, the DAAs drugs were purchased from overseas pharmacies or hospitals by patients themselves. All patients had completed 12 or 24 weeks of pangenotypic DAAs treatment regimens (SOF plus DCV or SOF plus VEL) therapy and were followed-up for at least 48 weeks after the end of therapy (EOT). The therapeutic cycle were chosen based on the status of liver fibrosis and cirrhosis according to the EASL HCV guidelines.[4,14] Pangenotypic DAA regimens for CHC patients included either of the following strategies: 400 mg SOF plus 60 mg DCV daily for 12 or 24 weeks; or 400 mg SOF plus 100 mg VEL daily for 12 or 24 weeks.

2.2. Evaluation of virological response, and safety

The clinical and virological characteristics for example, age, sex, past medical history, and clinical findings, for example, routine blood tests, biochemical parameters. HCV RNA quantification was performed using a COBAS AmpliPrep TaqMan kit (Roche Diagnostics, Branchburg, NJ, USA), the lower limit of quantification (LLOQ) is 15 IU/mL. Imaging findings was using ultrasonography. Liver cirrhosis was reported by our patients using the ultrasonography. These clinical data were collected at baseline, at EOT (week 12 or 24), 12 weeks after EOT.

The primary endpoint in this study was an SVR12, which was defined as HCV RNA undetectable (<15 IU/mL) at 12 weeks after EOT. The secondary endpoints were the evaluation of liver fibrosis using noninvasive measurements and treatment-related adverse events (AEs). The noninvasive measurement of liver fibrosis used fibrosis-4 (FIB-4) index (FIB-4 = age [years] $\times$ aspartate aminotransferase [AST] [U/L]/(platelet [PLT] [10^9/L] $\times$ (AST [U/L])$^{1/2}$) and AST to PLT ratio index (APRI) (APRI = AST (/ULN)/PLT (10^9/L) $\times$ 100).[15] Safety profiles were reported by patients themselves and obtained at baseline, EOT and 12 weeks after EOT. Adverse event was defined as any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medical treatment or procedure that may or may not be considered related to the therapy or procedure according to the Common Terminology Criteria for Adverse Events (CTCAE) v5.0 (https://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm). SAEs was defined as events (laboratory or clinical) that interfered with the therapy or procedure, including immediately life-threatening, hospitalization or prolongation of hospitalization indicated, disabling, or death.

2.3. Statistical analysis

Baseline patients' clinical characteristics and EOT and the follow-up outcomes were reported. Categorical data are presented as numbers (percentages); continuous variables as median (range, minimum-maximum). Serum HCV RNA levels are expressed as log transformations. The demographic, clinical and laboratory characteristics of CHC patients were compared in each treatment group. For continuous variables, the F-test was performed for overall within-group comparisons and the paired t test or Mann–Whitney U test was performed for between-group comparisons. For categorical data, Chi-squared test was used for group comparisons. All statistical analysis was conducted using SPSS version 20.0 (IBM Corp., Armonk, NY). All P values reported
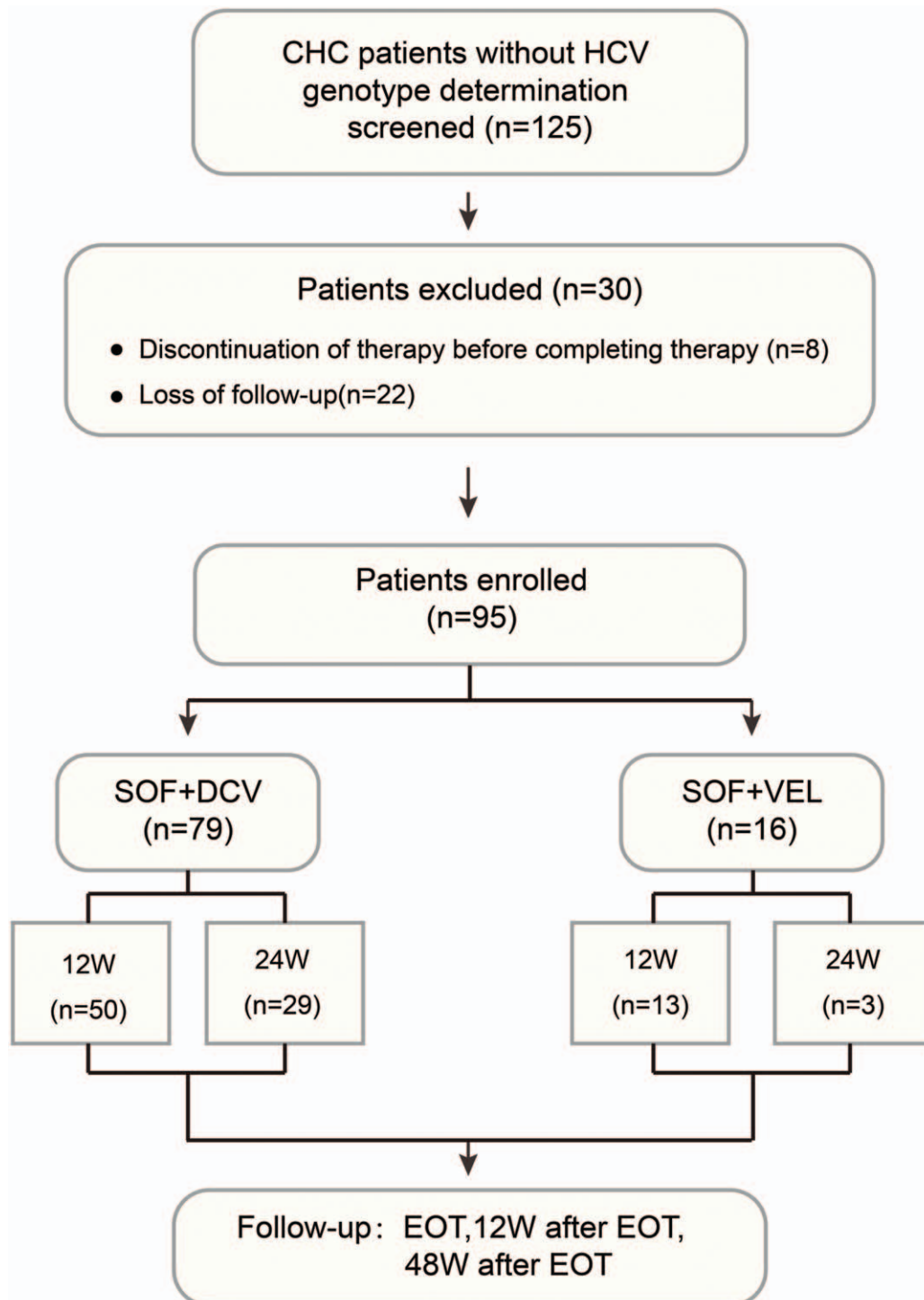

Figure 1. Flow chart of patients screening in the present study. CHC = chronic hepatitis C, DCV = daclatasvir, EOT = end of therapy, HCV = hepatitis C virus, SOF = sofosbuvir, VEL = velpatasvir.

were 2-tailed and a *P* value < .05 was considered statistically significant.

3. Results

3.1. Demographic and clinical characteristics of the study population

In total, 125 CHC treatment-naïve patients without HCV GT determination were screened. Thirty patients were excluded owing to discontinuation of therapy before completing therapy (n=8), loss of follow-up (n=22) (Fig. 1). Finally, 95 CHC patients were included (Table 1). In the present cohort, 79 (83.16%) patients received with SOF plus DCV therapy, and 16 (16.85%) received with SOF plus VEL therapy. Demographic and clinical characteristics of the study population are presented in Table 1. The median age was 50 years (range, 24–79 years), and 45 (47.40%) were male. Thirty (31.58%) patients had liver cirrhosis, 25 (26.32%) and 23 (24.21%) patients suffered from hypertension and diabetes. The percentages of patients with history of drinking and smoking were 22.11% (21/95) and 31.58% (30/95), respectively. The median HCV RNA level was 6.37 $\log_{10}$ IU/mL (range, 3.03–7.98 $\log_{10}$ IU/mL); the alanine aminotransferase level was 47.00 IU/L (range, 8.00–356.00 IU/L); the AST level was 47.00 IU/L (range, 6.00–258.00 IU/L); the PLT count was 119.00 × 10^9/L (range, 29.00–408.00 × 10^9/L).

Forty-eight (50.53%) patients were infected through blood transfusions, 15 (15.79%) through intravenous drug use and 32 (33.68%) patients' route of infection is other or unknown.

The number of patients used SOF plus DCV therapy for 12 and 24 weeks was 50 (52.63%) and 29 (30.53%), respectively; and the number of patients used SOF plus VEL therapy for 12 and 24 weeks was 13 (13.68%) and 3 (3.16%), respectively (Table 2). Of 29 patients used SOF plus DCV therapy for 24 weeks, 93.10% (27/29) patients had liver cirrhosis and 6.90% (2/29) patients have advanced liver fibrosis. Three (3/16, 18.75%) patients with liver cirrhosis received SOF plus VEL therapy for 24 weeks.

3.2. Virological response

During and after treatment, HCV RNA was detected at baseline, EOT, and 12 weeks after EOT, and 48 weeks after EOT. The HCV RNA levels under the LLOQ were found in 98.95% (94/95) of patients at EOT, 96.84% (92/95) of patients at 12 weeks after EOT. The LLOQ rates for CHC patients receiving SOF plus DCV therapy and for those receiving SOF plus VEL therapy at EOT and at 12 weeks after EOT were 98.73%, 96.20%, and 100%, 100%, respectively (Table 3).

The overall percentage of patients with SVR12 was 96.84% (Fig. 2A); and the SVR rate of DAAs therapy differed significantly at 12 and 24 weeks after EOT (100% and 90.63%, respectively; *P* = .008; Fig. 2B). Based on the statistics, the cohort was divided

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Table 1

Demographic and clinical characteristics of the study population.

Characteristic	Total	SOF+DCV	SOF+VEL
Total subjects (n,%)	95 (100)	79 (83.16)	16 (16.85)
Age, median (range), y	50, (24–79)	50, (24–79)	51, (27–68)
Sex (n, %)			
Male	45 (47.40)	39 (41.05)	6 (6.32)
Female	50 (52.60)	40 (42.11)	10 (10.53)
Complication (n, %)			
Hypertension	25 (26.32)	20 (25.32)	5 (31.25)
Diabetes	23 (24.21)	19 (24.05)	4 (25.00)
Liver cirrhosis	30 (31.58)	28 (35.44)	2 (12.50)
Drinking	21 (22.11)	17 (21.52)	4 (25.00)
Smoking	30 (31.58)	24 (30.38)	6 (37.50)
Laboratory data, median (range)			
ALT, IU/L	47.00, (8.00–356.00)	48.00, (8.00–356.00)	45.50, (18.00–275.00)
AST, IU/L	47.00, (6.00–258.00)	46.00, (6.00–258.00)	49.00, (6.00–191.00)
PLT, 10^12/L	119.00, (29.00–408.00)	119.00, (29.00–408.00)	159.00, (59.00–315.00)
HCV RNA, $\log_{10}$ IU/mL	6.37, (3.03–7.98)	6.47, (3.03–7.98)	6.21, (3.18–7.18)
Route of infection (n, %)			
Other or unclear	32 (33.68)	26 (32.91)	6 (37.50)
Drug injection	15 (15.79)	13 (16.46)	2 (12.50)
Transfusion	48 (50.53)	40 (50.63)	8 (50)

ALT = alanine aminotransferase, AST = aminotransferase, DCV = daclatasvir, HCV = hepatitis C virus, PLT = platelets, SD = standard deviation, SOF = sofosbuvir, VEL = velpatasvir.

Table 2

Treatment regimen and therapeutic cycle.

Therapeutic cycle	Treatment regimen		Total
	SOF plus DCV	SOF plus VEL	
12 wk	50 (52.63)	13 (13.68)	63 (66.32)
24 wk	29 (30.53)	3 (3.16)	32 (33.68)
total	79 (83.16)	16 (16.84)	95 (100)

DCV = daclatasvir, VEL = velpatasvir, SOF = sofosbuvir.

Table 3

Virological response of chronic hepatitis C patients during and after treatment.

Variable	Total (n = 95)	SOF+DCV (n = 79)	SOF+VEL (n = 16)
HCV RNA <LLOQ			
EOT	94 (98.95)	78 (98.73)	16 (100)
SVR12	92 (96.84)	76 (96.20)	16 (100)

DCV = daclatasvir, HCV = hepatitis C virus, LLOQ = lower limit of quantification (15 IU/mL), SOF = sofosbuvir, SVR12 = sustained virologic response 12 weeks after treatment, VEL = velpatasvir.

into several subgroups based on the statistics, and SVR12 rates were calculated overall and in each group. The SVR12 rate differed slightly but not significantly among CHC patients receiving SOF plus DCV and those receiving SOF plus VEL (96.20% and 100%, respectively; $P = .475$; Fig. 2A). The SVR12 rate differed significantly between CHC patients with and those without liver cirrhosis (90.00% and 100%, respectively; $P = .004$; Fig. 1C). The SVR12 rate was slightly but not significantly different between CHC patients with and those without hypertension (96.00% and 97.14%, respectively; $P = .931$; Fig. 2D) and between CHC patients with and those without diabetes (100% and 95.83%, respectively; $P = .271$; Fig. 2E). For 92 patients achieving an SVR12, the virological response was confirmed in our patients at 48 weeks after EOT and no virological relapse occurred.

3.3. Non-Invasive evaluation of liver fibrosis

Improvements in liver fibrosis were evaluated using the APRI and FIB-4 scores before and after treatment in different subgroups. APRI and FIB-4 scores were decreased significantly in CHC patients at EOT (mean 0.54, range, 0.12–2.21; mean, 1.79, range, 0.39–6.05, respectively) and 12 weeks after EOT (mean 0.51, range, 0.07–2.92; mean 1.58, range, 0.29–7.69, respectively) after DAAs treatment compared to baseline values (mean,

1.18, range, 0.09–7.97; mean, 2.41, range, 0.28–9.7) ($P < .05$) (Fig. 3A, D). In different subgroups of patients with and without liver cirrhosis, patients receiving SOF plus DCV or SOF plus VEL, the APRI and FIB4 scores were decreased significantly at EOT and 12 weeks after EOT compared to baseline values (all $P < .001$) (Fig. 3 B-C, E-F).

3.4. Adverse events during and after therapy

Safety profiles were reported by CHC patients themselves during this study. Out of 95 patients in this study, treatment was well-tolerated by our patients. A total of 46 (48.42%) AEs was reported and fatigue, headache, nausea, and cough were the most reported common AEs, which was occurred in 34 (32.30%), 6 (6.32%), 5 (5.26%), and 1 (1.05%) patients, respectively (Table 4). No SAEs were reported in our patients.

4. Discussion

The present study aimed to assess the efficacy of SOF-based pangenotypic DAAs for CHC patients without GT determination in Southwest China, and the efficacy of therapy was satisfactory. The CHC patients receiving SOF plus DCV or SOF plus VEL therapy achieved high SVR12 rate, while only 3 patients with cirrhosis did not achieve SVR12. Moreover, liver fibrosis was
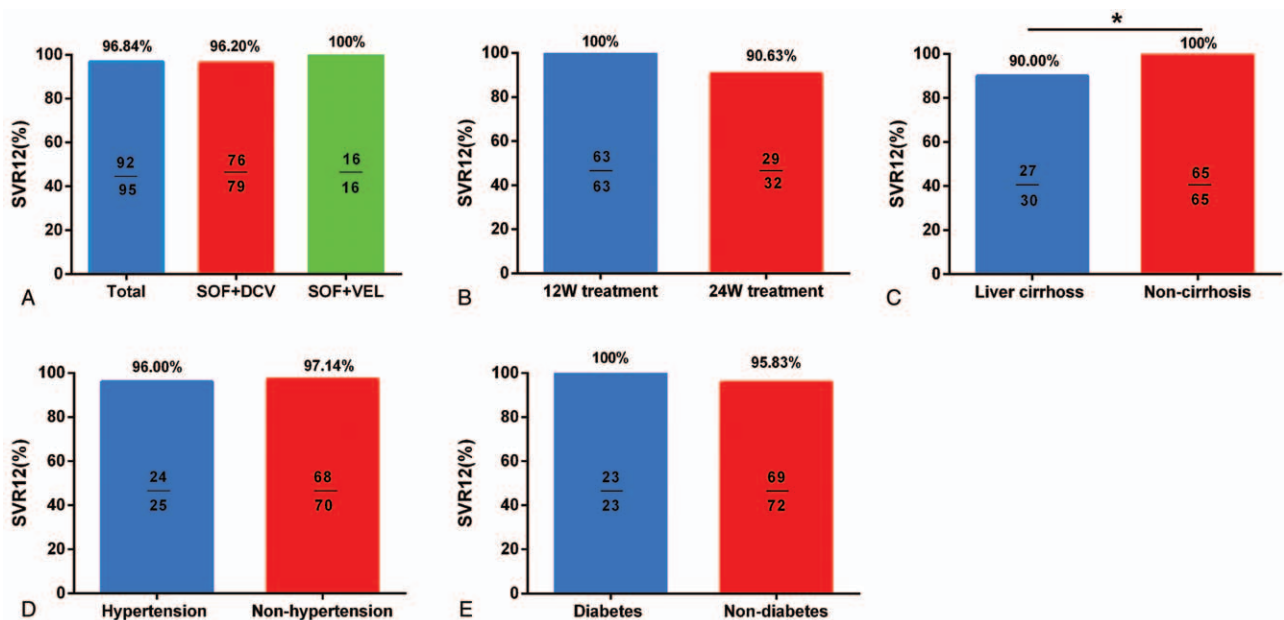

Figure 2. Sustained virologic response after treatment of chronic hepatitis C (CHC) patients with sofosbuvir (SOF)-based pangenotypic direct-acting antiviral agents without genotype determination. (A) CHC patients with treatment cycle of 12 and 24 weeks; (B) CHC patients receiving SOF plus daclatasvir or SOF plus velpatasvir and CHC patients with or without cirrhosis; (C) CHC patients with or with hypertension and patients with or without diabetes. CHC = chronic hepatitis C, DCV = daclatasvir, SOF = sofosbuvir, VEL = velpatasvir. $P < .05$ indicates statistical significance.
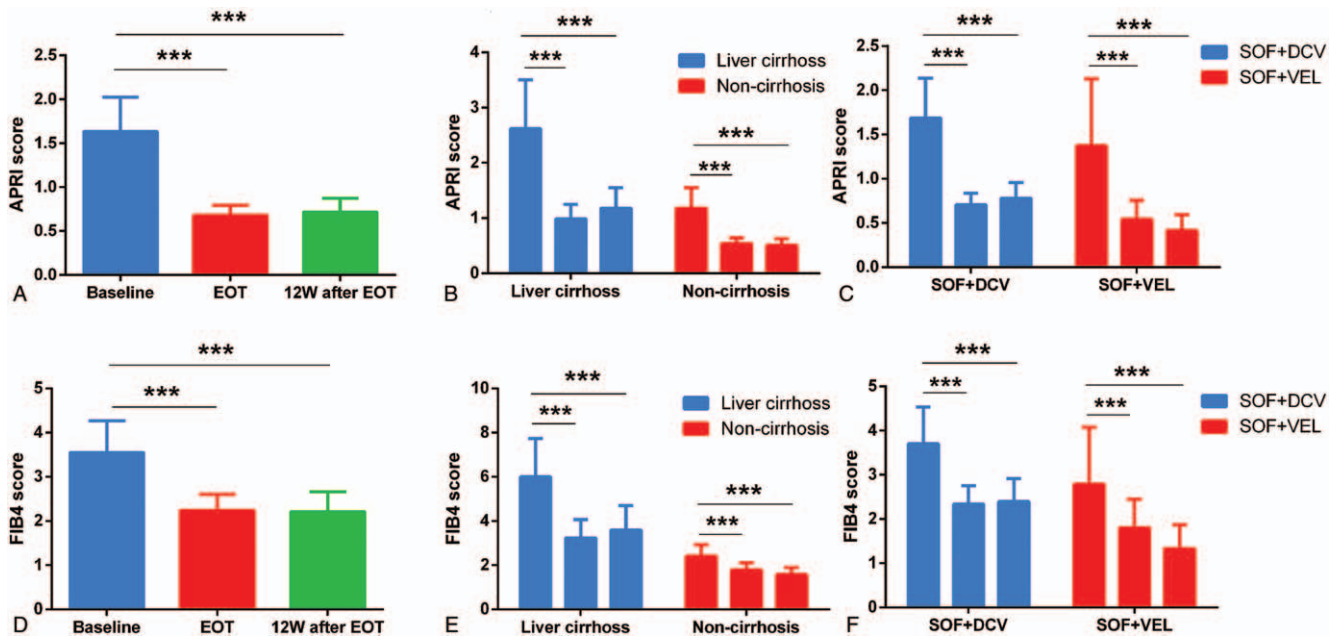
Figure 3. Non-invasive evaluation of liver fibrosis during and after antiviral therapy. (A) Evaluation of aspartate aminotransferase to platelet ratio index (APRI) score in chronic hepatitis C (CHC) patients; (B) Evaluation of APRI score in CHC patients with or with cirrhosis; (C) Evaluation of APRI score in CHC patients receiving sofosbuvir (SOF) plus daclatasvir or SOF plus velpatasvir therapy; (D) Evaluation of fibrosis-4 (FIB-4) score in CHC patients; (E) Evaluation of FIB-4 score in CHC patients with or with cirrhosis; (F) Evaluation of FIB-4 score in CHC patients receiving SOF plus daclatasvir or SOF plus velpatasvir therapy. APRI = aspartate transaminase-to-platelet ration index, CHC = chronic hepatitis C, DCV = daclatasvir, EOT = end of treatment, FIB-4 = fibrosis-4, SOF = sofosbuvir, VEL = velpatasvir. $P < .05$ indicates statistical significance.

improved upon non-invasive measurement of liver fibrosis and that the APRI and FIB-4 scores were decreased significantly in CHC patients at EOT and 12 weeks after EOT, compared to the baseline values. Furthermore, treatment achieved high efficacy and was well-tolerated by our CHC patients.

The reported SVR12 rate in CHC patients receiving DAAs therapy exceed 90%, compared to the low HCV cure rates in patients treated with PEGylated interferon plus ribavirin treatment regimens.[3,5] As of May 2018, the Food and Drug Administration or the European Medicines Agency had approved 13 DAAs from 4 classes, including NS3/4A (protease) inhibitors, NS5A inhibitors, NS5B polymerase inhibitors (nucleotide analogue) and NS5B polymerase inhibitors (non-nucleotide analogue).[5] CHC management with DAAs should be administered after considering of liver disease severity, baseline virological parameters, especially the HCV GT, which must be assessed prior to treatment to determine the choice of DAA regiments and therapy duration.[3] There are several techniques

used to HCV GT determination in the clinical practice, including real-time PCR, line-probe assay, heteroduplex mobility analysis, restriction fragment length polymorphism.[10,11,16] The currently available commercial techniques for HCV GT 1 failed in 2% to 16% patients.[16,17] In a large CHC cohort of 8,945 patients from phase II/III DAAs clinical trials, Tania Welzel[10] et al compared HCV GT and subtypes with INNO-LiPA 2.0 vs amplicon sequencing. The study showed that 8904/8945 (99.5%) GT determinations were concordant between INNO-LiPA and amplicon sequencing, and INNO-LiPA incorrectly determined 29 GT 1 patients as GT 2. INNO-LiPA was insufficient for subtype determination for HCV GT 2, 3, 4, and 6 when compared with amplicon sequencing.[10] Hence, the sequence analysis is still the golden standard method for HCV determination, but due to the longer time and higher cost for test, and required professional equipment, the widespread application for this technology was limited.[10,11] Currently, pangenotypic DAAs are available in numerous countries, the use of which should be

Table 4

Adverse events during treatment.

	Total (n = 95)	SOF+DCV (n = 79)	SOF+VEL (n = 16)
AEs, n (%)	46 (48.42)	38 (48.10)	8 (50.00)
Fatigue	34 (32.30)	29 (36.71)	5 (31.25)
Headache	6 (6.32)	4 (5.06)	2 (12.50)
Nausea	5 (5.26)	4 (5.06)	1 (6.25)
Cough	1 (1.05)	1 (1.27)	0 (0)
Serious AEs, n (%)	0 (0)	0 (0)	0 (0)

AEs = adverse events, DCV = daclatasvir, SOF = sofosbuvir, VEL = velpatasvir.

prioritised because they achieve high treatment efficacy across all 6 major HCV GTs. Treatment with pangenotypic DAAs can be initiated without determination of the GT and subtype in the regions where GT test is not available and/or not affordable, or to simplify therapy.[3,5,8]

According to the 2018 World Health Organization HCV guidelines, the use of pangenotypic DAA regimens such as SOF plus VEL, SOF plus DCV, and GLE/PIB are recommended to treat patients aged ≥ 18 years, with chronic HCV infection.[5] Thus far, SOF-based pangenotypic DAA therapy has achieved high HCV cure rates in CHC patients. SOF plus VEL is effective in a broad range of patients with a chronic HCV infection, with reported SVR12 rates of 98% to 99%, 96% to 100%, 91% to 100%, 100%, 95%, and 100% in patients harbouring the HCV GTs 1, 2, 3, 4, 5, and 6, respectively.[18–22] DCV is a selective NS5A inhibitor owing to its high antiviral activity in vitro, and it is also used in the clinical practice.[4] According to the 2018 World Health Organization HCV guidelines, SOF plus DCV constitutes a pangenotypic DAA therapy, achieving high efficacy in patients with HCV GTs 1 to 4 in the clinical trails.[5] The SVR12 rates of SOF plus DCV therapy were achieved 98%, 92% to 100%, 89% to 98%, and 90.4% to 100% in patients with GT 1, 2, 3, and 4, respectively.[23–28] In our previous study, a satisfactory virological response was obtained after SOF plus DCV and SOF plus VEL treatment in Chinese CHC patients with HCV GT 3, and the total SVR24 rate was 90.20% (92/102), with 85.96% in patients with SOF plus DCV therapy, 91.67% in SOF plus DCV plus RBV therapy and 100.00% in SOF plus VEL therapy.[22] Concurrent with previous reports, SOF-based pangenotypic DAAs therapy yielded a high SVR12 rate of 96.84% in CHC patients without GT determination in the present study. The achieved high HCV cure rates in our patients receiving SOF plus DCV and SOF plus VEL therapy yielded a SVR12 rate of 96.20% and 100%, respectively. Only 3 CHC patients with cirrhosis receiving SOF plus DCV therapy for 24 weeks did not achieve SVR12. Liver fibrosis or cirrhosis may responsible for the failure of virological response. Advanced liver fibrosis or cirrhosis or baseline NS5A resistance-associated substitution Y93H may responsible for the failure of the virologic response, owing to its interference with responses to DAA therapy affect virological response to DAAs therapy.[29,30] Furthermore, SOF based pangenotypic DAAs therapy also achieved high SVR12 rate in CHC patients with hypertension or diabetes of our cohort. Another pangenotypic DAA, GLE/PIB also yield high SVR12 rates in CHC patients with HCV GT 1 to 6 with or without cirrhosis, ranging from 91% to 100%.[31–33]

Successful management of CHC with DAAs has revolutionised the treatment of patients with an HCV infection; however, improvements in long-term outcomes should be documented in future clinical practice. In a previous study involving a cohort of 392 CHC patients with SVR after DAA therapy, transient elastography, FIB-4, and APRI scores decreased significantly.[34] Furthermore, liver fibrosis after DAA treatment improved in patients harbouring HCV GT 4 and in CHC patients with or without an HIV coinfection.[35,36] Concurrently, the present results indicate that non-invasive measurements of liver fibrosis, APRI index, and FIB-4 score were gradually reduced when patients achieved SVR12 after DAA therapy, suggesting that eradication of HCV may be responsible for decreased APRI and FIB-4 score. These scores were improved significantly upon laboratory investigation owing to normalization of liver enzymes after treatment. We found that the serum level of alanine aminotransferase and AST were lowed at EOT and 12 weeks after EOT than bassline, but PLT count did not changed significantly (Fig. 4). Thus, long-term follow-up evaluation of liver fibrosis is still needed. Furthermore, selectively using 4 questionnaires (Short Form36, Chronic Liver Disease Questionnaire-HCV, Work Productivity, and Activity Index, Functional Assessment of Chronic Illness Therapy-Fatigue) to evaluate patient-reported outcomes before, during, and after DAAs treatment, short form36, Chronic Liver Disease Questionnaire, and FACIT-F scores improved significantly in CHC patients during and post-treatment.[37]

Furthermore, whether DAA therapy can reduce the risk of HCC is still an ongoing concern and controversy. Recently, a meta-analysis reported that the DAA therapy is associated with a significantly lower risk of HCC compared to no treatment patients, both overall and beyond 1 year of treatment.[38] Another prospective cohort study of 4234 CHC patients without a history or presence of HCC receiving DAA treatment in Italy was explored to evaluate the incidence of newly diagnosed HCC and associated risk factors in CHC patients treated with DAAs.[39] With a mean follow-up of 536.2 ± 197.6 days, HCC was newly diagnosed de novo in 55 patients, and HCC incidence was 0.46% in patients with liver fibrosis F3, 1.49% in those with Child-Pugh-A and 3.61% in those with Child-Pugh-B patients with cirrhosis upon 1-year follow-up evaluation, thereby indicating that the risk of developing HCC during the first year after DAAs therapy is similar to that without antiviral treatment or even reduced.[39] SVR to DAA treatment decreased the incidence of HCC, and failure to achieve SVR was strongly associated with HCC pathogenesis during and after treat-
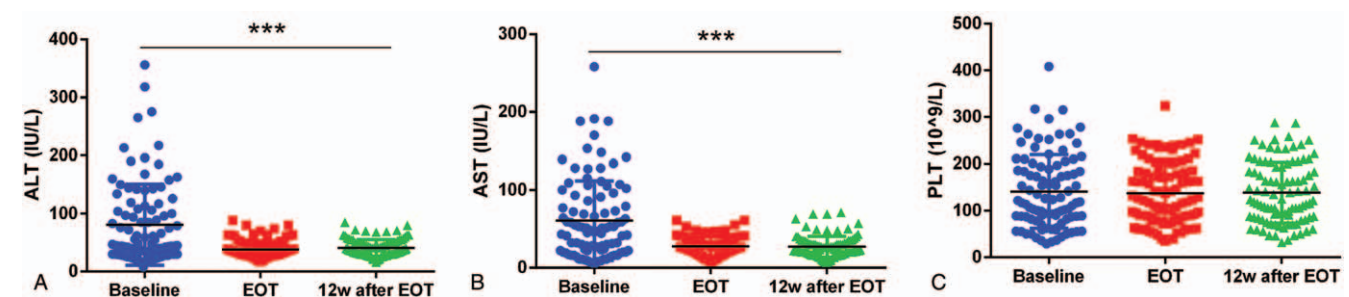

Figure 4. Serum levels of alanine aminotransferase, aminotransferase, and platelet during and after antiviral therapy. (A) Serum level of alanine aminotransferase in chronic hepatitis C (CHC) patients; (B) Serum level of aminotransferase, in CHC patients; (C) Serum level of platelet in CHC patients. ALT = alanine aminotransferase, AST = aminotransferase, PLT = platelet. *P* < .05 indicates statistical significance.

ment.[39–41] History of HCV-related cirrhosis, advanced liver fibrosis (APRI score > 2.5), HBV coinfection, older age, and type 2 diabetes are the primary risk factors for HCC in CHC patients.[39,42] Interferon (IFN)-based therapy reportedly reduces the risk of HCC in cirrhosis patients with HCV infection.[43] In a meta-analyses, Reem Waziry[43] et al analysed 41 studies (including 13,875 patients in total) to compare the HCC occurrence and recurrence rates in CHC patients after DAA or IFN-based curative therapy. They reported that HCC occurrence and recurrence was 1.14/100 per year (py) and 9.21/100 py after IFN therapy, and 2.96/100 py and 12.16/100 py during DAA studies, respectively; however, there is no evidence for differential HCC occurrence or recurrence risk following SVR to DAA and IFN-based therapy.[43] Moreover, HCV eradication reduced the risk of cardiovascular events, bacterial infections, liver decompensation, and death from liver-related and non-liver-related causes in patients with HCV-associated cirrhosis achieving a SVR to DAAs therapy.[44,45] More well-designed studies are needed to determine the effect of DAA on the risk of HCC recurrence in future.

While this study represents a real-world cohort of CHC patients receiving SOF based pangenotypic DAAs therapy without HCV GT determination, it has underlying limitations. The study design and small sample size may limit the interpretation of the study results. Owing to the retrospective nature of the study, a selection bias may have occurred. To overcome the heterogeneity in the study cohort, subjects were restricted to CHC patients from Southwest China. Moreover, patients presenting poor SVRs were easily lost to follow-up, thereby potentially influencing the results of SVR analysis. Moreover, the SOF plus VEL therapy was approved in June 2016, so this was the reason why there were less patients in our study cohort receiving SOF plus VEL therapy during HCV treatment between January 2016 and May 2017. A larger cohort study should be designed to validate the present results, and we intend to update the data in the further study.

5. Conclusion

In summary, SOF-based pangenotypic DAA therapy for CHC patient without GT determination in Southwest China was effective and safe in this study. SOF plus DCV or SOF plus VEL therapy yielded high SVR12 rates in CHC patients without GT determination, including those with liver cirrhosis. Moreover, liver fibrosis was improved after DAA treatment in CHC patients achieving SVR12 after DAAs treatment. The present results suggest that SOF-based pangenotypic DAA treatment regimens including SOF plus DCV and SOF plus VEL may be potentially recommendable treatment strategies for CHC patients without GT determination to simplify therapy.

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Author contributions

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Juan Li, Dongbo Wu, Wei Jiang, Xuebin Chen, Guibao Xiao, Yonghong Wang, Menglan Wang, Yachao Tao, Enqiang Chen performed the research; Juan LI, Dongbo Wu, Wei Jiang and Enqiang Chen collected and analyzed the data; Juan LI,

Dongbo Wu and Enqiang Chen wrote the paper; Xuebin Chen, Guibao Xiao, Yonghong Wang, Yachao Tao and Menglan Wang contributed to the design of the study.
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