

Daclatasvir plus sofosbuvir, with or without ribavirin, is highly effective for all kinds of genotype-2 chronic hepatitis-C infection in Taiwan

Sih-Hsien Wu^a, Chi-Jen Chu^{a,b,*}, Chien-Wei Su^{a,b}, Chung-Chi Lin^{b,c}, Shou-Dong Lee^{b,d}, Yuan-Jen Wang^{b,c}, Fa-Yauh Lee^{a,b}, Yi-Hsiang Huang^{a,b}, Ming-Chih Hou^{a,b}

^aDivision of Gastroenterology and Hepatology, Department of Medicine, Taipei Veterans General Hospital, Taipei, Taiwan, ROC; ^bFaculty of Medicine, National Yang-Ming University, Taipei, Taiwan, ROC; ^cHealthcare and Services Center, Taipei Veterans General Hospital, Taipei, Taiwan, ROC; ^dDivision of Gastroenterology, Department of Medicine, Cheng Hsin General Hospital, Taipei, Taiwan, ROC

Abstract

Background: Based on the previously published results, 12 weeks of sofosbuvir (SOF) 400mg/day plus ribavirin (RBV), the current direct antiviral agent regimen reimbursed by Bureau-of National-Health-Insurance (BNHI) of Taiwan for genotype-2 chronic hepatitis C (CHC), is suboptimal in efficacy, especially for difficult-to-treat subpopulations such as liver cirrhosis, previous interferon (IFN) treatment failure, and high viral-load. This study aimed to evaluate the efficacy and safety of SOF plus daclatasvir (DCV) for Taiwanese genotype-2 CHC patients.

Methods: Between March 2017 and December 2018, a total of 50 consecutive genotype-2 CHC patients who completed 12 weeks combination of SOF (400mg/day) plus DCV (60mg/day) with or without RBV by investigators were enrolled for analyses. When RBV was added, weight-based (800-1200mg/day) approach was applied. Sustained virological response (SVR₁₂) was defined by undetectable HCV RNA (<15 IU/mL) at the end and 12 weeks after completion of therapy.

Results: The mean age was 62.0 ± 11.4 years, 16 (32.0%) of them were males and 20 (40.0%) of them failed to previous IFN. Severity of liver diseases was as follows: ≤F2 fibrosis: 24.0%; F3 fibrosis: 40.0%, Child-Pugh A cirrhosis: 30.0%; and Child-Pugh B-C cirrhosis: 6.0%. The mean baseline HCV RNA level was 6.19 ± 0.91 log₁₀ IU/mL and 30 (60.0%) had baseline HCV RNA ≥ 2 million IU/mL. The rates of undetectable HCV RNA (<15 IU/mL) at weeks 2, 4, and end-of-treatment were 40%, 94%, and 100%, respectively. Majority (66.7%) of patients with detectable HCV RNA at week 2 belonged to low-level viremia (<50 IU/mL). Subjective adverse events (AEs) and laboratory abnormalities were more common for patients combining RBV. Grades of AEs were generally mild and all patients finished therapy without interruption. After post-treatment follow-up, all 50 patients (100%) achieved SVR₁₂.

Conclusion: Our real-world cohort of Taiwan showed that a 12-week SOF/DCV-based treatment was well-tolerated and highly effective for genotype-2 CHC patients with or without liver cirrhosis.

Keywords: Chronic hepatitis C; Daclatasvir; Genotype-2; Pegylated interferon; Sofosbuvir; Sustained virological response

1. INTRODUCTION

Hepatitis C virus (HCV) infection is a major global health issue. Chronic hepatitis C (CHC) infection affects approximately 71.1 million people worldwide and causes 700 000 deaths per year.¹ As disease progresses, CHC can result in the development of liver cirrhosis, hepatocellular carcinoma (HCC), and complications of liver diseases.^{2,3} Epidemiological studies suggested the

prevalence of CHC in Taiwan was between 3and 4.4% but varied in different geographic regions.⁴⁻⁷ Following genotype-1b, genotype-2 is the second most common genotype, accounts for 31% to 65% of overall CHC infection, and is more prevalent in southern part of Taiwan.^{8,9}

Successful antiviral treatment response brings huge beneficial effect on long-term outcome for patients with CHC, reflected by significantly reduced liver-related and all-cause mortality rates.^{10,11} Although the sustained virological response (SVR) rates for genotype-2 CHC by pegylated interferon (PEG-IFN) plus ribavirin (RBV) for 16–24 weeks are around 80% to 94%; however, IFN-based therapy is side effects prone.¹²⁻¹⁵ In addition, a significant proportion of patients are unwilling or ineligible to receive IFN-based therapy. Fortunately, treatment options of CHC evolved rapidly in recent years because of the invention of IFN-free all oral direct antiviral agents (DAAs). When compared with IFN-based therapies, all oral DAAs were equipped with superior efficacy, short treatment duration, and less adverse events (AEs).¹⁶

Sofosbuvir (SOF) is a pan-genotypic DAA to inhibit HCV RNA-dependent RNA polymerase, first approved by the USA in

*Address correspondence. Dr. Chi-Jen Chu, Division of Gastroenterology and Hepatology, Department of Medicine, Taipei Veterans General Hospital, 201, Section 2, Shi-Pai Road, Taipei 112, Taiwan, ROC. E-mail address: cjchu@vghtpe.gov.tw (C.-J. Chu).

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2013 then worldwide to treat CHC. For genotype-2 CHC, the efficacy and safety by SOF in combination with weight-based RBV for 12 weeks was investigated in several large-scaled phase III pivotal trials.¹⁷⁻²⁰ According to these trials, the SVR rates for treatment-naïve and previous IFN failure genotype-2 CHC without liver cirrhosis were 97% and 90% to 92%, respectively. However, SVR rates were generally lower for patients presenting with liver cirrhosis. One study reported that SVR rate was only 60% by 12 weeks of SOF plus RBV for genotype-2 cirrhotic patients who failed previous IFN-based therapy.¹⁸ Extended treatment duration to 16 or 24 weeks could increase the SVR rates to 78% to 87% and 100%, respectively.^{18,20} Therefore, academic guidelines suggested the regimen of 12 weeks SOF plus RBV should be suboptimal for all kinds of genotype-2 CHC.^{21,22}

Daclatasvir (DCV) is a potent pan-genotypic inhibitor of the HCV NS5A protein. DCV in combination with SOF for genotype-2 CHC has been evaluated in clinical trials. In 26 treatment-naïve patients, SOF/DCV with or without RBV for 24 weeks is well-tolerated and achieved 92% SVR rates.²³ Later, Mangia et al reported that for genotype-2 CHC patients who cannot tolerate RBV, a 12-week combination of DCV and SOF for 8 noncirrhotics and 24-week course for 11 cirrhotics resulted in 100% SVR rates.²⁴ Based on these results, SOF/DCV was recommended by academic societies as one of the standard regimens for genotype-2 CHC.^{21,22}

In Taiwan, a 12-week course of SOF plus RBV was reimbursed by the Bureau of National Health Insurance (BNHI) as the standard treatment option for genotype-2 CHC after January, 2018. However, as stated previously, the potency of this regimen might not be sufficient in real world population, especially for those featuring unfavorable response characteristics such as liver cirrhosis, previous IFN treatment failure, and higher baseline HCV RNA level. Therefore, we conducted this study to investigate the efficacy and safety of SOF/DCV, with or without RBV for Taiwanese patients with genotype-2 CHC.

2. METHODS

2.1. Patients

Between March 2017 and December 2018, a total of 50 consecutive genotype-2 CHC patients having completed 12 weeks treatment of SOF (400 mg/day) plus DCV (60 mg/day) with or without RBV at Taipei Veterans General Hospital by the investigators were enrolled for analyses. Enrollment criteria were adult (≥ 20 years) genotype-2 CHC infection, defined as 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 were excluded from the analysis if they had had mixed genotypes, coinfecting with hepatitis B or human immunodeficiency virus (HIV), estimated glomerular filtration rate (eGFR) < 30 mL/min/1.73 m² prior DAA exposure, active HCC, status post organ transplantation, or being unwilling to provide informed consent form. This study was approved by the Institutional Review Board of Taipei Veterans General Hospital and was conducted in accordance with the principles of Declaration of Helsinki and the International Conference on Harmonization for Good Clinical Practice. Written informed consent forms were provided by all patients before participating in this study.

2.2. Study design

This is a retrospective cohort single center study. Baseline demographic data, virological response of previous therapy with PEG-IFN/RBV, hemogram, international normalized ratio

(INR), serum biochemical profiles such as albumin, total bilirubin, direct bilirubin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), creatinine, eGFR, anti-HCV, HCV RNA, HCV genotype were collected for all patients. HCV genotype was determined by commercially available assay (Cobas HCV GT, Roche Diagnostics GmbH, Mannheim, Germany). The fibrosis-4 (FIB-4) index is calculated using the following formula: $FIB-4 = \text{age (years)} \times \text{AST (U/L)} / [\text{PLT} (10^9/\text{L}) \times \text{ALT} (1/2 \text{ U/L})]$. Stage of fibrosis was measured by liver stiffness using transient elastography (FibroScan, Echosens, Paris, France). The reference range of hepatic fibrosis by transient elastography was as follows: F0-F1 (≤ 7.0 kPa), F2 (7.1-9.4 kPa), F3 (9.5-12.4 kPa), F4 (≥ 12.5 kPa).²⁵ Cirrhosis of liver was determined either by fibroscan (≥ 12.5 kPa) or typically clinical or radiological evidence. Presence of decompensation was defined as Child-Pugh score ≥ 7 .

All patients received SOF (Sovaldi, 400 mg film-coated tablet, Gilead Sciences, Ireland UC) one tablet daily, and DCV (Daklinza, 60 mg film-coated tablet, Bristol-Myers Squibb Company, USA) one tablet daily for 12 weeks. Before January 1, 2018, study subjects were treated with self-pay SOF/DCV without RBV. After January 1, 2018, enrolled patients were treated with SOF/self-pay DCV in combination with RBV because the cost of SOF and RBV was reimbursed by BNHI. RBV (Robatrol, 200 mg capsule, Genovate Biotechnology Co., Ltd. Taiwan) was prescribed by weight-based approach. The dose of RBV was as follows: 1200 mg/day for body weight ≥ 75 kg, 1000 mg/day for body weight between 50 and 75 kg, 800 mg/day for body weight < 50 kg, and fine-tuned according to eGFR value. The dose of RBV should be reduced to 200 to 400 mg/day in case if patient's eGFR declined to less than or equal to 30 mL/min/1.73 m² during treatment course.

Before the initiation of SOF/DCV therapy, extensive survey of regular medications taken by enrolled patients for possible drug-to-drug interaction (DDI) was performed. Medications that could have potential DDI got discontinued, shifted to alternative drugs, or started at lowest dose as judged by physicians. The dose of RBV can be reduced by 200 mg/day after week 4 if hemoglobin (Hgb) decreases to > 2.0 g/dL when compared with baseline in condition of serum HCV RNA undetectable by real-time PCR.

2.3. Definition of treatment response

Serum quantitative HCV RNA levels were measured at week 2, 4, 8, 12 and post-treatment week 12 to define virological response. SVR₁₂ was defined by undetectable HCV RNA level (< 15 IU/mL) at the end of treatment and 12 weeks after completion of therapy. Patients who lacked SVR₁₂ data were considered failure to achieve SVR₁₂.

2.4. Safety and AEs

During treatment period, patients were assessed by physicians at weeks 1 and 2 and then every two weeks or more often in case there were adverse effects until the end of therapy. Subjective patient reported outcome, physical examination findings, and laboratory data including biochemistries, hematology, and coagulation profiles were recorded into datasheet. The AEs were graded according to the definition of Common Terminology Criteria for Adverse Events (CTCAE) version 4.0.

2.5. Statistical analysis

All analyses were performed using Statistical Program for Social Sciences (SPSS statistics Version 18.0, IBM Corp., Armonk, New York, USA). The baseline patient characteristics were shown in mean with SD and percentages when appropriate. Statistical analyses were performed using χ^2 or Fisher's exact tests for categorical

variables. Independent *t* tests were used for continuous variables. Quantitative HCV RNA level (IU/mL) was logarithmic transformed for analysis. All statistical tests were two-sided. Results were considered statistically significant at $p < 0.05$.

3. RESULTS

3.1. Baseline characteristics of enrolled patients

In this study, a total of 50 patients were recruited for analyses. The mean age of enrolled population was 62.0 ± 11.4 years, 16 (32.0%) of them were male, 18 (36.0%) diagnosed to have liver cirrhosis, and three (6%) patients had decompensated liver cirrhosis. The mean baseline HCV RNA level was $6.19 \pm 0.91 \log_{10}$ IU/mL and the distribution of baseline HCV RNA levels were as follows: $\leq 800\,000$ IU/mL: 32.0%; 800 000 to 2 000 000 IU/mL: 8.0%; 2 000 000 to 6 000 000 IU/mL: 30.0%; $\geq 6\,000\,000$ IU/mL: 30.0% (Table 1). For 20 PEG-IFN plus RBV treatment failure patients, previous response was summarized as follows: relapser 55.0% (11/20), partial or null responder 40.0% (8/20), intolerant and early terminated 5.0% (1/20). Regarding treatment regimen, 13 patients (26.0%) received SOF/DCV without RBV and the remaining 37 patients (74.0%) received SOF/DCV plus weight-based RBV for 12 weeks. The majority (14 patients, 77.8%) of cirrhotic patients and (23 patients, 71.8%) of noncirrhotic patients received SOF/DCV plus RBV treatment.

Table 1
Baseline characteristics of 50 patients

Characteristics	Patients (n = 50)
Mean age, years	62.0 ± 11.4
Age ≥ 65 y/o	20 (40%)
Male gender	16 (32%)
Body mass index, kg/m ²	24.9 ± 4.1
Baseline HCV RNA (\log_{10} IU/mL)	6.19 ± 0.91
Baseline HCV RNA	
$\leq 800\,000$ IU/mL	16 (32.0%)
800 000-2 000 000, IU/mL	4 (8.0%)
2 000 000-6 000 000, IU/mL	15 (30.0%)
$\geq 6\,000\,000$, IU/mL	15 (30.0%)
Hemoglobin	13.5 ± 1.8
White cell count ($\times 10^9/L$)	5.2 ± 1.9
Platelet count ($\times 10^9/L$)	157.3 ± 69.3
Prothrombin time, INR	1.07 ± 0.1
Creatinine, mg/dL	0.84 ± 0.2
eGFR: $\geq 90/60-89/30-59$ (mL/min/1.73 m ²)	18 (36.0%)/28 (56.0%)/4 (8.0%)
Albumin, g/dL	4.0 ± 0.38
Total bilirubin, mg/dL	0.89 ± 0.59
ALT, IU/L	106.6 ± 125
AST, IU/L	83.0 ± 93.8
Severity of liver disease	
$\leq F2$ fibrosis/F3 fibrosis	12 (24.0%)/20 (40.0%)
Liver cirrhosis Child-Pugh A	15 (30.0%)
Liver cirrhosis Child-Pugh B-C	3 (6.0%)
Antiviral-naïve/IFN failure	30 (60.0%)/20 (40.0%)
Previous PEG-IFN/RBV response	
Relapser	11 (55.0%)
Partial or null responder	8 (40.0%)
Intolerant and early terminated	1 (5.0%)
History of HCC	3 (6.0%)
Regimen	
Sofosbuvir/daclatasvir	13 (26.0%)
Sofosbuvir/daclatasvir/ribavirin	37 (74.0%)

ALT = alanine aminotransferase; AST = aspartate aminotransferase; CKD = chronic kidney disease; HCC = hepatocellular carcinoma; HCV RNA = hepatitis C virus RNA; IFN = interferon; PEG-IFN = pegylated interferon.

3.2. Severity of liver disease

By FibroScan data and clinical parameters, severity of liver diseases of enrolled patients was as follows: $\leq F2$ fibrosis: 24.0%; F3 fibrosis: 40.0%, Child-Pugh A cirrhosis: 30.0%; and Child-Pugh B-C cirrhosis: 6.0%. Mean FIB-4 score of enrolled patients was 4.23 ± 3.53 . We found that there was a significant positive correlation between FibroScan (kPa) and FIB-4 results for liver fibrosis ($\gamma = 0.34$; $p = 0.012$).

3.3. Virological response during and after SOF/DCV

After SOF/DCV-based therapy, the rates undetectable HCV RNA (< 15 IU/mL) by real-time PCR assay at week 2, 4, and 12 were 40.0%, 94.0%, and 100%, respectively. Detailed viral kinetics for patients with or without liver cirrhosis were depicted in Fig. 1. Out of 30 (60.0%) patients with detectable serum HCV RNA after 2 weeks of SOF/DCV, 20 of them had low-level HCV RNA between 15 and 50 IU/mL and only seven patients had HCV RNA higher than 100 IU/mL (Table 2). The percentages to have undetectable HCV RNA at weeks 2 and 4 were comparable between patients combined with or without RBV. All 50 patients finished 12 weeks of SOF/DCV-based therapy without interruption and completed post-treatment follow up with the SVR₁₂ rate 100% for enrolled population (Fig).

3.4. Safety and AEs

Thirty-one patients (62.0%) had at least one AE. Fatigue, pruritus, dizziness, skin rashes, and insomnia were the most common subjective AEs that all enrolled patients reported (Table 3). For patients who received SOF/DCV therapy only, the most common AEs were fatigue, insomnia, pruritus, and skin rashes. For patients receiving SOF/DCV plus RBV, the most common AEs reported were fatigue, pruritus, dizziness, and skin rashes. Among these AEs, SOF/DCV plus RBV group was more likely to have fatigue, pruritus, asthenia, and dizziness when compared with SOF/DCV therapy only ($p < 0.05$). Grades of the above subjective AEs were generally mild and could be symptomatically relieved by medications.

Regarding the laboratory AEs, the mean decline of Hgb during treatment for patients with SOF/DCV alone or in combination with RBV was 0.24 ± 0.12 g/dL and 1.62 ± 1.34 g/dL, respectively ($p < 0.0001$). During the whole treatment course, 14.0% (7/50) of patients had grade 2 (Hgb: 8.0-10.0 g/dL) anemia and 4.0% (2/50) of patients had grade 3 anemia (Hgb < 8.0 g/dL) (Table 4). All patients with grade 3 anemia belonged to the group of SOF/DCV plus RBV. Phenomenon of hyperbilirubinemia during treatment course was found in patients treated with SOF/DCV plus RBV only. Grade 2 ($1.5-3.0 \times$ ULN) hyperbilirubinemia, all unconjugated, was found in 13.5% (5/37) of patients in combination use of RBV. With continuous SOF/DCV plus RBV therapy, all phenomenon of unconjugated hyperbilirubinemia gradually resolved. No patients had grade 3 or 4 hyperbilirubinemia or evidence of hepatic decompensation during study period (Table 4). Throughout the whole treatment course, no ALT elevation was found in our study population. Serum creatinine and eGFR value remained stable during study period, and there was no decline in patient's eGFR value to less than or equal to 30 mL/min/1.73 m² during the DAA treatment course.

4. DISCUSSION

CHC infection is one of the most common etiologies of chronic liver diseases worldwide, including Taiwan. More importantly, CHC can be cured by a finite course of antiviral therapy. Successful antiviral treatment response brings huge beneficial effect on long-term outcome for patients with CHC. According to longitudinal follow-up study, advanced fibrotic CHC patients

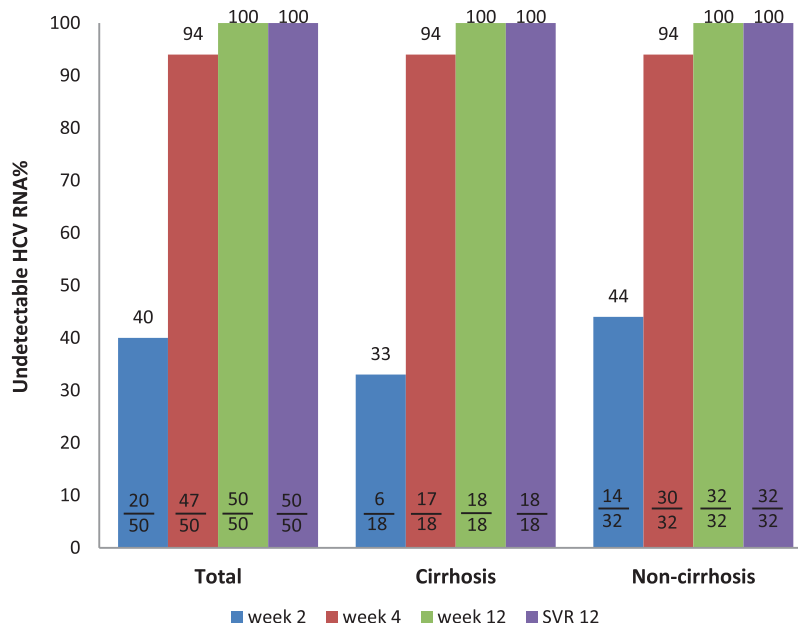


Fig. 1 Virological responses of SOF/DCV-based treatment. DCV, daclatasvir; SOF, sofosbuvir.

Table 2
Distribution of HCV RNA levels after 2 weeks of SOF/DCV

Week 2 HCV RNA level	Number	Percentage (%)
<15 IU/mL	20	40.0%
15-50 IU/mL	20	40.0%
50-100 IU/mL	3	6.0%
>100 IU/mL	7	14.0%

DCV = daclatasvir; HCV RNA = hepatitis C virus RNA; SOF = sofosbuvir.

Table 3
Subjective adverse events during SOF/DCV therapy

All patients (n = 50), n (%)	SOF/DCV (n = 13), (26%)	SOF/DCV + RBV (n = 37), (74%)	p	
Fatigue	20 (40.0%)	4 (30.8%)	16 (43.2%)	<0.001
Headache	4 (8.0%)	1 (7.7%)	3 (8.1%)	0.33
Nausea	0 (0.0%)	0 (0.0%)	0 (0.0%)	
Insomnia	6 (12.0%)	3 (23.1%)	3 (8.1%)	<0.001
Pruritus	13 (26.0%)	2 (15.4%)	11 (29.7%)	0.002
Diarrhea	1 (2.0%)	0 (0.0%)	1 (2.7%)	0.32
Asthenia	2 (4.0%)	0 (0.0%)	2 (5.4%)	0.03
Rash	9 (18.0%)	2 (15.4%)	7 (18.9%)	0.23
Irritability	3 (6.0%)	1 (7.7%)	2 (5.4%)	0.21
Dizziness	10 (20.0%)	0 (0.0%)	10 (27.0%)	<0.001
Dyspnea	0 (0.0%)	0 (0.0%)	0 (0.0%)	
Edema	0 (0.0%)	0 (0.0%)	0 (0.0%)	

DCV = daclatasvir; RBV = ribavirin; SOF = sofosbuvir.

having failed to previous IFN-based therapy had significantly higher rate of all-cause mortality, liver-related mortality, liver failure, and HCC when compared with CHC patients who achieved SVR.¹¹ In addition, previous large-scaled study revealed, when compared with patients without SVR, that the all-cause mortality can be reduced to 50% for general CHC population with SVR. Moreover, the all-cause mortality can further be reduced to about 74% for CHC patients with cirrhosis.¹⁰

Table 4
Laboratory adverse events during SOF/DCV therapy

All patients (n = 50), n (%)	SOF/DCV (n = 13), (26%)	SOF/DCV + RBV (n = 37), (74%)	p	
Hemoglobin level				
Grade 2	7 (14.0%)	2 (15.4%)	5 (13.5%)	0.37
Grade 3	2 (4.0%)	0 (0.0%)	2 (5.4%)	0.03
Total bilirubin				
Grade 2	5 (10.0%)	0 (0.0%)	5 (13.5%)	0.01
Grade 3	0 (0.0%)	0 (0.0%)	0 (0.0%)	
ALT				
Grade 2	0 (0.0%)	0 (0.0%)	0 (0.0%)	
Grade 3	0 (0.0%)	0 (0.0%)	0 (0.0%)	

Hemoglobin level: Grade 2 (8.0–10.0 g/dL), Grade 3 (< 8.0 g/dL).

Total bilirubin: Grade 2 (1.5–3.0 × ULN), Grade 3 (3.0–10.0 × ULN).

ALT: Grade 2 (3–5 × ULN), Grade 3 (5–20 × ULN).

DCV = daclatasvir; RBV = ribavirin; SOF = sofosbuvir.

Similar finding was reported by the investigators during the era of IFN-free all oral DAAs.²⁶ Therefore, by the viewpoint of long-term outcome, effective antiviral therapies are in urgent need for CHC patients with advanced fibrosis or failing to previous IFN-based treatment.

The introduction of IFN-free DAAs has made a rapid paradigm shift for HCV treatment, based on the excellent efficacy and safety profiles. SOF in combination with RBV is the first available IFN-free regimen for treatment of CHC. According to registration clinical trials,^{17–20} this regimen was highly effective for genotype-2 patients without liver cirrhosis. However, the SVR rates were lower for patients with liver cirrhosis, especially for those who failed to previous IFN therapy.^{18,20} In recent years, effectiveness by SOF plus RBV for real world population with genotype-2 CHC has been investigated by several studies. HCV-TARGET,²⁷ a prospectively longitudinal study conducted at 57 centers in North America and four centers in Europe examined the SVR rates of 12 or 16 weeks SOF plus RBV for genotype-2 CHC. Results from this study showed the SVR₁₂ in patients without cirrhosis was 91.0% and 92.9% for 12 or 16 weeks of therapy, respectively. In cirrhotic patients treated with SOF plus

RBV for 12 or 16 weeks, SVR₁₂ was 79.0% and 83%, respectively. Similar findings were reported by real-world investigations and all studies suggested SVR rates in real-life are lower than expected from clinical trials.^{28,29} One study involving 823 genotype-2 U.S. veterans showed the SVR rates for a 12-week course SOF plus RBV were 81.6% for treatment-naïve and 70.9% for treatment-experienced patients.²⁸ Another European study analyzed 236 genotype-2 patients treated with 12 weeks SOF and RBV. As a result, SVR rates for this regimen were only 80% in treatment-experienced patients, 74% in cirrhotics, and 75% in patients with HCV RNA \geq 6 million IU/mL.²⁹

Regarding the real-world effectiveness of SOF plus RBV for CHC genotype-2 in Asia, a meta-analysis was published last year in which a total of 2208 patients from 13 studies were included.³⁰ According to the results, patients with cirrhosis had 8.7% lower SVR₁₂ than noncirrhotic patients, and treatment-experienced patients had 7.2% lower SVR₁₂ than treatment-naïve patients. Cirrhotic treatment-experienced patients had the lowest SVR₁₂ at 84.5%. Therefore, based on the study results from Western countries and Asia and in line with academic guidelines, it can be concluded that potency of SOF plus RBV might be insufficient in real world population especially for those featuring unfavorable response characteristics such as liver cirrhosis, previous IFN treatment failure, and higher baseline HCV RNA level.

As we stated in the introduction section, SOF/DCV combination therapy is highly effective for genotype-2 CHC with or without cirrhosis during clinical trials.^{23,24} Besides, for genotype-1 CHC patients who were treatment-naïve or previous IFN failure, this pangenotypic regimen achieved excellent treatment efficacy with SVR₁₂ rates 98% for HCV subtype 1a and 100% for subtype 1b, respectively.²³ Moreover, several clinical studies validated SOF/DCV was well tolerated and achieved SVR₁₂ rates exceeding 90% in patients who had been challenging to treat effectively, including those with advanced liver disease, hepatic decompensation, HIV/HCV coinfection, HCV genotype-3 infection, and HCV recurrence after liver transplant.³¹⁻³⁶ These findings led to widespread approval of combination of SOF and DCV for the treatment of various CHC infection.^{21,22}

As the DAAs therapy for CHC continue to evolve, till now, the optimal regimen for genotype-2 CHC remains to be defined. Regarding current guidelines for genotype-2 CHC patients, the American Association for the Study of Liver Diseases (AASLD) recommends SOF plus velpatasvir (VEL), or glecaprevir plus pibrentasvir (GLE/PIB) for treatment-naïve or previous IFN-failure patients, and SOF/DCV has been listed as an alternate choice.²² The European Association for the Study of the Liver (EASL) 2016 hepatitis C treatment guideline recommended SOF/DCV or SOF/VEL as treatment choices for naïve or previous IFN-failure patients,²¹ and GLE/PIB was added by the 2018 version of guideline as one of the treatment option.³⁷ The 2016 Asian-Pacific Association for the Study of the Liver (APASL) recommendation for genotype-2 CHC patients was as follows: 12 weeks SOF plus weight-based RBV for treatment naïve patients, therapy can be prolonged to 16 or 24 weeks for previous IFN-failure subjects SOF/DCV, SOF plus ledipasvir, or SOF/VEL was suggested for patients who cannot tolerate RBV.³⁸

To date, real-world experience regarding treatment of all kinds of genotype-2 CHC patients with the combination of SOF and DCV was scanty in Asia. As registration trials usually have strict inclusion and exclusion criteria, real-life cohorts are valuable to reflect the efficacy and safety of a new treatment regimen for patients in daily clinical practice. In our real-world cohort containing 76.0% patients with advanced (\geq F3) fibrosis, 40.0% failed to previous PEG-IFN plus RBV, and 60.0% had baseline HCV RNA \geq 2 million IU/mL, and highly effective antiviral response by SOF/DCV was demonstrated in the current study,

even in difficult-to-treat subpopulations. Our study showed the HCV RNA undetectable ($<$ 15 IU/mL) rate after 2 and 4 weeks of SOF/DCV therapy were 40.0% and 94.0%, respectively. In addition, the majority (66.7%) of patients with detectable HCV RNA at week 2 belonged to low-level viremia (HCV RNA $<$ 50 IU/mL). No patient early terminated SOF/DCV therapy and the overall SVR₁₂ rate after completing post-treatment follow up was 100%. A recently published study from southern Taiwan showed concordant results with our current study findings.³⁹

By our understandings, there were no randomized controlled studies to compare the treatment efficacy of SOF/DCV vs SOF/RBV for patients with genotype-2 CHC. Recently, Belperio et al reported the real-world effectiveness of 255 U.S. Veterans with genotype-2 CHC treated with SOF/DCV, and SVR₁₂ rates were 94.6% in treatment-naïve, 94.3% in treatment-experienced, and 92.0% in cirrhotic patients.⁴⁰ The above results showed improved treatment efficacy when compared with data extracted from the same database in which the SVR₁₂ rates for a 12-week course SOF/RBV were only 81.6% for treatment-naïve and 70.9% for treatment-experienced patients.²⁸ Taken together of our study findings with above studies results, it can be confidently concluded that compared to SOF plus RBV, SOF/DCV is a better treatment option for genotype-2 CHC. Similar to other genotypes, combination therapy with different classes of DAAs seemed to be the future mainstay. Data obtained from our current study hopefully could provide valuable information during future revision of regional treatment guideline.

Our current results showed fatigue, dizziness, pruritus, asthenia, and laboratory abnormalities such as decreased Hgb and hyperbilirubinemia were significantly associated with the use of RBV. Consistent with U.S. Veterans study,⁴⁰ our current results showed that the addition of RBV did not have strong impact on SVR₁₂ rates. Therefore, role of RBV during the era of combination DAAs needs more studies for clarification.

Several limitations of this study need to be addressed here. First, the study design was retrospective and all patients were enrolled from one single medical center. Second, sample size of current study was not large-scaled, especially for patients with decompensated liver diseases. Third, we did not evaluate the efficacy of SOF in combination with VEL, another NS5A inhibitor, for Taiwanese genotype-2 CHC because SOF/VEL was not approved for use by our regulatory authorities. Lastly, we did not investigate the impact of baseline NS5A or NS5B resistance-associated substitutions on treatment response.

In conclusion, in our real-world cohort of Taiwan containing 76.0% patients with advanced (\geq F3) fibrosis, 40.0% failed to previous PEG-IFN plus RBV, and 60.0% had baseline HCV RNA \geq 2 million IU/mL, and a 12-week SOF/DCV-based treatment was well-tolerated and highly effective for genotype-2 CHC with or without liver cirrhosis.

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