Sofosbuvir-based antiviral therapy provided highly treatment efficacy, safety, and good tolerability for Taiwanese chronic hepatitis C patients with decompensated cirrhosis

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Abstract

Background: For patients with hepatitis C virus (HCV)-related decompensated cirrhosis, poor prognosis was documented due to the development of portal hypertension-related complications and hepatocellular carcinoma. Sofosbuvir-based direct-acting antiviral agents (DAAs) has revolutionized the treatment landscape of HCV, particularly in this subpopulation. To date, real-world efficacy, tolerability, and safety profiles for Taiwanese HCV-related decompensated cirrhosis treated by DAAs have not been reported.

Methods: Between December 2015 and June 2020, 50 consecutive HCV-related Child-Turcotte-Pugh (CTP) classes B or C cirrhotics treated by sofosbuvir-based DAAs (with daclatasvir: 7, with ledipasvir: 32, with velpatasvir: 10, with ledipasvir then shifted to velpatasvir: 1) were enrolled. Forty-seven (94%) patients used DAAs in combination with low-dose ribavirin. SVR_{12} was defined by undetectable HCV RNA (<15 IU/mL) at treatment end and 12 weeks after the completion of therapy.

Results: The mean age of the enrolled patients was 68.1 ± 11.2 years, 18% of the patients were CTP class C, and the baseline HCV RNA level was 5.42 ± 1.2 $\log_{10}$ IU/mL. The genotype distribution was as follows: 1a: 3; 1b: 34; 2: 9; 6: 3; and one patient with an unclassified HCV genotype. After DAAs treatment, the rates of undetectable HCV RNA at week 4 and at the end of the treatment were 88.9% and 98.0%, respectively. Subjective adverse events were reported by 42.0% of the patients, but they were generally mild and could be relieved by medications. One patient did not finish therapy due to sepsis with multiple organ dysfunction. The overall SVR_{12} rate was 96.0% (CTP class B: 97.6%, CTP class C: 88.9%). A significant improvement in hepatic functional reserve was noted after successful antiviral therapy.

Conclusion: For patients with HCV-related decompensated cirrhosis, which has been considered a contraindication for interferon-based therapy, sofosbuvir-based all-oral DAAs provided high treatment efficacy, acceptable safety, and good tolerability.

Keywords: Chronic hepatitis C; Decompensated cirrhosis; Direct-acting antivirals; Sofosbuvir; Sustained virological response

1. INTRODUCTION

It is estimated that approximately 71 million people worldwide (~1% of the population) were infected by hepatitis C virus (HCV) in 2015, with varying prevalence in different regions.[1] In Taiwan, the reported seroprevalence of anti-HCV antibody was 4.4% between 1996 and 2005.[2] Chronic HCV infection causes persistent hepatic inflammation and leads to progressive liver disease. It has been estimated that liver cirrhosis developed approximately 10%–20% of patients over 20–30 years after HCV infection with a 3%–6% annual risk of hepatic decompensation and a 1%–5% annual risk of hepatocellular carcinoma (HCC).[3] Once decompensated cirrhosis [Child–Turcotte–Pugh (CTP) class B or C] is established, the prognosis and quality of life of patients are extremely poor due to portal hypertension-related complications such as jaundice, refractory ascites, variceal bleeding, and hepatic encephalopathy, resulting in a considerable burden on the healthcare system.[3,4] According to the results of a meta-analysis, the 2-year survival rates of patients with CTP classes B and C were 70% and 40%, respectively.[5]

Until recently, liver transplantation (LT) had been the only curative and life-saving treatment modality for cirrhotic patients with severe decompensation. However, organ shortage remains a major obstacle. In the past, pegylated interferon (IFN)-based therapy was contraindicated in these patients. Fortunately, the

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therapeutic landscape of chronic hepatitis C (CHC) has changed dramatically after the invention of IFN-free oral direct-acting antiviral agents (DAAs). Growing evidence suggests that for CHC patients with decompensated cirrhosis, therapy with IFN-free oral DAAs offers high sustained virologic response (SVR) rates with good tolerability and short duration of treatment.[6–9]

In Taiwan, all oral DAAs have been conditionally reimbursed by the National Health Insurance Administration of the Ministry of Health and Welfare (NHIA) since January 24, 2017. Sofosbuvir, the cornerstone of DAA regimens for decompensated cirrhosis, has been reimbursed by the NHIA since January 1, 2018. To date, the real-world treatment efficacy, tolerability, and safety profiles of DAAs among Taiwanese CHC patients with decompensated cirrhosis have not been reported. Therefore, we conducted the present study to address these issues.

2. METHODS

2.1. Patients

Between December 2015 and June 2020, 50 consecutive patients with HCV-related decompensated cirrhosis treated with oral DAAs at Taipei Veterans General Hospital were enrolled. The enrollment criteria included adults (≥20 years) with CHC infection, which was defined as detectable HCV antibody (anti-HCV) (Abbott HCV EIA 2.0, Abbott Laboratories, Abbott Park, IL) and quantifiable serum HCV RNA (Cobas TaqMan HCV Test version 2.0; Roche Diagnostics GmbH, Mannheim, Germany; lower limit of quantification: 15 IU/mL) for ≥6 months. Liver cirrhosis was diagnosed by the presence of typical clinical and radiological manifestations.[10] Decompensated liver cirrhosis (CTP class B or C) was defined as a CTP score ≥7 at the time of enrollment in this study.[11] Patients enrolled in this study were required to undergo liver imaging within 3 months of baseline to exclude active HCC. Exclusion criteria were patients who had HCV and human immunodeficiency virus coinfection, history of organ (liver, kidney, or heart) transplantation, prior treatment with DAAs, active HCC, active infection, or unwillingness to provide informed consent. This study was approved by the Institutional Review Board of Taipei Veterans General Hospital and was conducted in accordance with the principles of the Declaration of Helsinki and the International Conference on Harmonization for Good Clinical Practice. Written informed consent was obtained from all the patients before recruitment.

2.2. Study design

This was a retrospective, single-center study. After obtaining informed consent, baseline demographic, imaging, and clinical data including virological response to previous therapy with pegylated IFN/ribavirin (RBV), hemogram, international normalized ratio (INR), serum biochemical profiles (albumin, total bilirubin, direct bilirubin, alanine aminotransferase [ALT], aspartate aminotransferase [AST], creatinine, estimated glomerular filtration rate [eGFR]), anti-HCV antibody, HCV RNA, and HCV genotype were collected from all patients. HCV genotype was determined using a commercially available assay (Cobas HCV GT; Roche Diagnostics GmbH).

The model for end-stage liver disease (MELD) score is calculated using the following formula: 3.78 × ln [serum bilirubin (mg/dL)] + 11.2 × ln [INR] + 9.57 × ln [serum creatinine (mg/dL)] + 6.43. The MELD score was initially formulated to predict survival following elective placement of transjugular intrahepatic portosystemic shunts.[12] Several studies have demonstrated that it can be used to predict the short-term mortality risk in patients with a wide variety of liver diseases and to determine whether the patient is likely to require liver transplantation.[13,14] The Fibrosis-4 (FIB-4) score is a noninvasive scoring system that uses laboratory tests to estimate the degree of hepatic fibrosis. The FIB-4 index ≥2.67 had an 80% positive predictive value for advanced (F3–F4) fibrosis and the FIB-4 index ≤1.30 had a 90% negative predictive value.[15]

2.3. Selection of DAA regimens and strategies to avoid significant drug–drug interactions

In the present study, the DAA regimen was selected by clinical physicians according to the HCV genotype/subtype, viral load, patient characteristics, drug–drug interaction (DDI) profiles, and evolving NHIA reimbursement criteria. Considering the evidence of hepatotoxicity associated with some NS3/4A protease inhibitors, the academic guidelines recommend combining a nucleotide NS5B polymerase inhibitor with an NS5A inhibitor as the standard regimen for patients with decompensated cirrhosis.[16,17] Before the initiation of DAA therapy, an extensive survey of regular medications taken by the enrolled patients was performed to evaluate possible DDIs. Medications that could exhibit potential DDIs were discontinued, switched to alternative drugs, or started at the lowest dose with frequent monitoring by the physicians.[18,19] After assessment by clinical physicians, RBV (200 mg capsule of Robatrol; Genovate Biotechnology Co., Ltd., Taiwan) was added to the regimen of selected patients to enhance their virological response. The dosage of RBV was as follows: 600 mg/d for patients with eGFR ≥ 60 mL/min/1.73 m^2, 400 mg/d for patients with eGFR between 30 and 59 mL/min/1.73 m^2, and 200 mg/d for patients with eGFR < 30 mL/min/1.73 m^2. The dose was reduced after week 4 by 200 mg/d if the hemoglobin level decreased by >2.0 g/dL compared to the baseline level and if serum HCV RNA was undetectable in real-time polymerase chain reaction (PCR).

2.4. Definition of treatment response

The serum quantitative HCV RNA levels were measured before starting the DAA treatment, at week 4 (optional), at the end of the treatment, and at posttreatment week 12 to define the virological response. SVR_{12} was defined as undetectable HCV RNA level on real-time PCR (≤15 IU/mL) at the end of the DAA treatment and at 12 weeks after the completion of the therapy. Patients who lacked the SVR_{12} data were considered to have failed to achieve SVR_{12}.

2.5. Safety and adverse events

During the treatment period, patients were assessed by physicians at weeks 1 and 2 and then every 2 weeks (or more frequently in cases exhibiting adverse events [AEs]) until the end of the therapy. Subjective patient-reported outcomes, physical examination findings, and laboratory data including biochemistry, hematology, and coagulation profiles were recorded in the datasheet. Patients also underwent regular follow-up imaging examinations during the study period to evaluate the complications of liver cirrhosis and the occurrence of HCC. The subjective and laboratory AEs were graded according to the Common Terminology Criteria for Adverse Events version 4.0.

Serious AEs (SAEs) were defined as death, life-threatening events, or hospital admission during the study period. Causes of SAEs, clinical course, and patient outcomes were recorded for the analyses.

2.6. Primary and secondary objectives

The primary objectives of this study were to assess the efficacy, safety, and tolerability among Taiwanese CHC patients with decompensated cirrhosis treated by a nucleotide NS5B polymerase inhibitor (sofosbuvir)-based all oral DAAs. The secondary objectives were to investigate the dynamic changes of laboratory data and liver function tests before and after DAA therapy. Previous study demonstrated that BE3A score, the integrative

index calculated by baseline factors, can identify the subset of patients with decompensation who are likely to derive benefit from treatment.[20] The predictive value of BE3A score was validated by our study cohort.

2.7. Statistical analysis

All analyses were performed using SPSS Statistics version 23.0 (SPSS Inc., Chicago, IL). The baseline patient characteristics were presented as means and standard deviations or as percentages when appropriate. Statistical analyses were performed using the chi-squared test or Fisher's exact test for categorical variables. Independent *t*-tests were used for the continuous variables. Paired *t*-tests were used to compare the sequential changes in the laboratory data and liver function tests before and after DAA therapy. Quantitative HCV RNA levels (IU/mL) were logarithmically transformed for the analysis. Logistic regression analyses were applied to identify the independent factors associate with resolving hepatic decompensation after successful DAA therapy. All statistical tests were two-sided. Statistical significance was set at $p < 0.05$.

3. RESULTS

3.1. Baseline characteristics of the enrolled patients

Fifty patients were included in the analyses. The mean age of the enrolled patients was 68.1 ± 11.2 years, 16 (32%) patients were male, and 9 (18%) patients had experienced failure of previous pegylated IFN therapy. Among the patients who experienced failure of pegylated IFN treatment, 3 (33.3%) patients were relapsers, 3 (33.3%) were partial or null responders, and 3 (33.3%) were intolerant and underwent early treatment termination. All patients included in the study presented with typical clinical or radiological manifestations of liver cirrhosis. Forty-one (82%) patients were diagnosed with CTP class B cirrhosis and 9 (18%) patients were diagnosed with CTP class C cirrhosis. Nine (18%) patients had a history of HCC, but no active disease before the initiation of DAA therapy (Tables 1 and 2).

Table 2 shows the laboratory characteristics of the enrolled patients. The mean baseline HCV RNA level was 5.42 ± 1.2 $\log_{10}$ IU/mL. The HCV genotypes were summarized as follows: 6% with genotype 1a, 68% with genotype 1b, 18% with genotype 2, 6% with genotype 6, and 2% with unclassified genotype. The baseline HCV RNA levels were distributed as follows: ≤ 800 000 IU/mL: 64%; 800 000–2 000 000 IU/mL: 8%; 2 000 000–6 000 000 IU/mL: 18%; and ≥6 000 000 IU/mL: 10%.

Table 1

Baseline clinical characteristics of enrolled 50 patients

Characteristics	Patients (n = 50)
Mean age (y)	68.1 ± 11.2 (37–89)
Age ≥ 65 y	31 (62%)
Male gender	16 (32%)
Antiviral, naive/previous PEG-IFN failure	41 (82%)/9 (18%)
Previous PEG-IFN/RBV response	
Relapser	3 (6%)
Partial or null responder	3 (6%)
Intolerant and early terminated	3 (6%)
HBV coinfection	2 (4%)
History of ascites	29 (58%)
History of hepatic encephalopathy	8 (16%)
History of HCC (stable disease)	9 (18%)

Data are expressed as n (%) or means ± SD (range).
DAAs = directly acting anti-viral drugs; HCC = hepatocellular carcinoma.; PEG-IFN = pegylated-interferon; RBV = ribavirin

Table 2

Baseline laboratory characteristics of enrolled 50 patients

Characteristics	Patients (n = 50)
Genotype, 1a/1b/2/6/unclassified	3 (6%)/34 (68%)/9 (18%)/3 (6%)/1 (2%)
Mean baseline HCV RNA ($\log_{10}$ IU/mL)	5.42 ± 1.2
Baseline HCV RNA	
≤800 000 IU/mL	32 (64%)
800 000–2 000 000 IU/mL	4 (8%)
2 000 000–6 000 000 IU/mL	9 (18%)
≥6 000 000 IU/mL	5 (10%)
Mean hemoglobin (g/dL)	11.3 ± 2.2
Mean white cell count ($\times 10^9$/L)	3.9 ± 1.3
Mean platelet count ($\times 10^9$/L)	82.1 ± 45.5
Prothrombin time (s)	14.4 ± 3.5
INR	1.3 ± 0.3
Mean albumin (g/dL)	3.2 ± 0.5
Alanine aminotransferase (IU/L)	70.0 ± 60.0
Aspartate aminotransferase (IU/L)	90.1 ± 76.3
Mean total bilirubin (mg/dL)	2.1 ± 1.3
Mean creatinine (mg/dL)	0.9 ± 0.3
eGFR, ≥60/59–30/<30 (mL/min/1.73 m^2)	44 (88%)/3 (6%)/3 (6%)
CTP score	
B (7/8/9)	21 (42%)/18 (36%)/2 (4%)
C (10/11/12)	8 (16%)/0 (0%)/1 (2%)
Median MELD score	12 (6–21)
MELD score	
<10	9 (18%)
10–15	33 (66%)
>15	8 (16%)
Median FIB-4 index	17.22 (range: 1.92–29.19)

Data are expressed as n (%) or means ± SD (range).
CTP score = Child-Turcotte-Pugh score; eGFR = estimated glomerular filtration rate; FIB-4 index = Fibrosis-4 index; HCV RNA = hepatitis C virus RNA; HD = hemodialysis; INR = international normalized ratio; MELD score = Model for End-Stage Liver Disease score.

The mean pretreatment ALT and AST levels were 70.0 ± 60.0 and 90.1 ± 76.3 IU/L, respectively. Mean baseline albumin, total bilirubin, and INR were 3.2 ± 0.5 g/dL, 2.1 ± 1.3 mg/dL, and 1.3 ± 0.3, respectively. The MELD scores at the beginning of DAA therapy were distributed as follows: <10: 18%, 10–15: 66%, and >15: 16%.

3.2. Virological response during and after DAA therapy

Detailed DAA regimens for each HCV genotype and subtype are summarized in Table 3. All patients were treated with sofosbuvir (HCV nucleotide NS5B polymerase inhibitor) in combination with an HCV NS5A inhibitor. Seven (14%) patients were treated with daclatasvir, 32 (64%) with ledipasvir, and 10 (20%) with velpatasvir. One (2%) patient was treated with ledipasvir with subsequent shift to velpatasvir. Based on the clinical physician's judgment, 47 (94%) patients used DAAs in combination with RBV. The treatment duration was extended from 12 to 24 weeks in 4 patients due to anemia associated with RBV intolerance (n = 3) and slow viral kinetics (n = 1).

After the commencement of DAA therapy, 36 patients with HCV RNA data available at weeks 4 and 32 (88.9%) had undetectable HCV RNA levels (<15 IU/mL). Four (11.1%) patients had detectable serum HCV RNA after 4 weeks of treatment and three of them had low levels of viremia (HCV RNA levels: 15–50 IU/mL). Only one patient did not finish the therapy due to severe sepsis and multiple organ failure. All patients who completed the antiviral therapy achieved viral clearance (HCV RNA < 15 IU/mL) and the virological response rate at the end of the treatment was 98.0%. After post-treatment follow-up, one patient had virologic relapse (HCV RNA level: 4547 IU/mL)

Table 3

DAAs regimen used for each HCV genotype/subtypes in the current study

HCV genotype/ subtypes	DAAs regimen used
1a (n = 3)	12 wks sofosbuvir 400 mg/d + ledipasvir 90 mg/d + RBV (n = 3)
1b (n = 34)	12 wks sofosbuvir 400 mg/d + daclatasvir 60 mg/d + RBV (n = 1)
	24 wks sofosbuvir 400 mg/d + daclatasvir 60 mg/d + RBV (n = 1)[a]
	12 wks sofosbuvir 400 mg/d + ledipasvir 90 mg/d ± RBV (n = 24)
	12 wks sofosbuvir 400 mg/d + velpatasvir 100 mg/d + RBV (n = 5)
	24 wks sofosbuvir 400 mg/d + velpatasvir 100 mg/d + short-course RBV (n = 2)[a]
	12 wks sofosbuvir 400 mg/d + ledipasvir 90 mg/d + short course RBV then 12 wks sofosbuvir 400 mg/d + velpatasvir 100 mg/d (n = 1)[a]
2 (n = 9)	12 wks sofosbuvir 400 mg/d + daclatasvir 60 mg/d ± RBV (n = 5)
	12 wks sofosbuvir 400 mg/d + ledipasvir 90 mg/d + RBV (n = 1)
	12 wks sofosbuvir 400 mg/d + velpatasvir 100 mg/d + RBV (n = 3)
6 (n = 3)	12 wks sofosbuvir 400 mg/d + ledipasvir 90 mg/d + RBV (n = 3)
Unclassified (n = 1)	12 wks sofosbuvir 400 mg/d + ledipasvir 90 mg/d + RBV (n = 1)

Ninety-four percent (47/50) patients using DAAs in combination with ribavirin (RBV).
DAA = direct-acting antiviral agent; HCV = hepatitis C virus; RBV = ribavirin.
[a]Four patients were treated with a 24-week course of sofosbuvir-based DAAs due to RBV intolerance with anemia (n = 3) and slow viral kinetics (n = 1)

at 12 weeks after the completion of the therapy. This patient was infected by genotype 1b HCV with baseline HCV RNA 70 700 IU/mL, treated by a 12-week combination therapy of sofosbuvir/daclatasvir with RBV. The intent-to-treat analysis revealed that the SVR_{12} rate was 96.0% among the enrolled patients. The SVR_{12} rates for CTP B and CTP class C were 97.6% and 88.9%, respectively ($p = 0.331$).

Using MELD score = 18 as a cutoff value, the SVR_{12} rate for patients with MELD score ≥18 (n = 6) and MELD score <18 (n = 44) was 100% and 95%, respectively ($p = 1$). The SVR_{12} rate for patients with previous HCC (n = 9) and without HCC history (n = 41) was 100% and 95%, respectively ($p = 1$). The SVR_{12} rate for patients received with sofosbuvir + daclatasvir (n = 7) and other sofosbuvir-based regimens (n = 43) was 86% and 98%, respectively ($p = 0.263$). In our current study, a total of 10 patients were treated by sofosbuvir/velpatasvir and only one patient did not combine with RBV. The SVR_{12} rate of patients treated by sofosbuvir/velpatasvir with or without RBV was 100% and 100%, respectively.

3.3. Subjective and laboratory AEs

During the DAA therapy, 21 patients (42.0%) experienced at least one subjective AE. Altogether, 29.3% of the CTP class B and 100% of the CTP class C patients reported subjective AEs ($p < 0.001$). Subjective AEs was reported in 83% of MELD score ≥18 patients and 36% of MELD score <18 patients ($p = 0.07$). Fatigue (24%) was the most common subjective AE reported by all enrolled patients, followed by edema, pruritus, insomnia, asthenia, diarrhea, headache, nausea, and rash (Table 4). The aforementioned AEs were generally mild and could be alleviated symptomatically using medications.

During the study period, >2 g/dL drop in the hemoglobin level was observed in 32% (16/50) of the patients and all of them had been treated with the RBV-containing DAA regimen. Nine patients had grade 3 anemia (hemoglobin level < 8.0) (Table 5). The percentages to have on-treatment Hgb decline > 2.0 g/dL was 0% for MELD score ≥18 and 36% for MELD score <18 patients, respectively ($p = 0.159$). Altogether, 14.9% (7/47) of the patients treated with RBV-containing DAAs required RBV dose reduction or discontinuation of RBV to maintain hemoglobin levels. None of the patients experienced grade 2

Table 4

Subjective adverse events

All patients (n = 50)	n (%)
Fatigue	12 (24%)
Edema	9 (18%)
Pruritus	7 (14%)
Insomnia	6 (12%)
Asthenia	5 (10%)
Diarrhea	3 (6%)
Headache	1 (2%)
Nausea	1(2%)
Dyspnea	1 (2%)
Rash	1 (2%)
Irritability	0 (0.0%)

RBV = ribavirin.

Table 5

Laboratory adverse events

All patients (n = 50)	n (%)
Hemoglobin level	
Grade 2	10 (20%)
Grade 3	9 (18%)
On treatment Hgb decline > 2.0 g/dL	16 (32%)
Total bilirubin	
Grade 2	29 (58%)
Unconjugated hyperbilirubinemia	19
Conjugated hyperbilirubinemia	10
Grade 3	0 (0.0%)
ALT	
Grade 2	0 (0.0%)
Grade 3	0 (0.0%)

Hemoglobin level: Grade 2 (8.0–10.0 g/dL), Grade 3 (<8.0g/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).
ALT = alanine aminotransferase; ULN = upper limit of normal.

(3–5 × the upper limit of normal [ULN]) or grade 3 (5–20 × ULN) ALT elevation after DAA therapy during the study period (Table 5).

Among the 47 patients who received DAA therapy containing RBV, 19 (40.4%) had unconjugated hyperbilirubinemia. However, no patients experienced grade 3 hyperbilirubinemia (>3 × ULN) or evidence of hepatic failure during the study period (Table 5). With continuous DAA therapy, all instances of unconjugated hyperbilirubinemia gradually resolved.

3.4. SAEs during the study period

Altogether, 13 SAEs (death, life-threatening events, or hospital admission) were reported during the study period. The incidence of SAEs was 19.5% in CTP class B patients and 55.6% in CTP class C patients ($p = 0.04$). The incidence to experience SAEs during whole study period was 50% for MELD score ≥18 and 23% for MELD score <18 patients, respectively ($p = 0.173$). All patients required hospitalization for care and the reasons for hospitalization were as follows. Four patients were admitted for ascites control with/without acute kidney injury, one patient was admitted for aggravated ascites and treatment of hepatic encephalopathy, two patients had recurrent HCC and were admitted for therapy, and two patients were admitted for upper gastrointestinal bleeding related to cirrhosis. Four patients were admitted for infection and one of them died due to intraabdominal infection with severe sepsis and multiple organ failure (Table 6). None of the aforementioned SAEs were related to the DAA therapy.

Table 6

Detailed information of SAEs during study period

Case	Age	Gender	HCV genotypes	HCV RNA level, log_{10} IU/mL	Baseline CTP class (score)	Hospitalization	SAEs
1	79	Female	Ib	4.85	B (7)	Yes	Control of ascites and acute kidney injury
2	81	Female	Ib	5.54	B (8)	Yes	Control of ascites and acute kidney injury
3	64	Male	Ib	4.38	C (10)	Yes	Pneumonia
4	65	Female	Ib	6.54	B (9)	Yes	Urinary tract infection and bacteremia
5	83	Female	Ib	6.29	B (8)	Yes	Recurrent HCC for PEIT
6	59	Female	Ib	4.44	C (12)	Yes	Portal hypertensive gastropathy with bleeding
7	74	Male	2	3.99	B (7)	Yes	Recurrent HCC for TACE
8	89	Female	Ib	5.87	B (8)	Yes	Control of ascites
9	67	Female	Ia	5.82	C (10)	Yes	Intra-abdominal infection with severe sepsis and multiple organ failure
10	59	Female	Ib	6.90	C (10)	Yes	Acute cholecystitis
11	65	Male	unclassified	1.70	C (10)	Yes	Aggravated ascites and hepatic encephalopathy
12	79	Male	Ib	6.25	B (8)	Yes	Control of ascites
13	37	Female	Ib	3.65	B (8)	Yes	Esophageal varices bleeding

CTP class = Child-Turcotte-Pugh classes; HCV = hepatitis C virus; HCC = hepatocellular carcinoma; PEIT = percutaneous ethanol injection therapy; RBV = ribavirin; SAEs = serious adverse events; TAE = transcatheter arterial chemoembolization.

3.5. Changes in the laboratory data over time after DAA therapy

Changes in the laboratory data from baseline to 12 weeks after treatment were analyzed in 48 patients who achieved SVR_{12} (Table 7). Significant improvements in albumin (from 3.2 ± 0.5 to 3.5 ± 0.5 g/dL, $p < 0.001$), ALT (from 71.5 ± 60.5 to 25.5 ± 11.6 IU/L, $p < 0.001$), AST (from 92.6 ± 76.9 to 41.9 ± 18.3 IU/L, $p < 0.001$), total bilirubin (from 2.2 ± 1.2 to 1.8 ± 1.0 mg/dL, $p = 0.015$), INR (from 1.35 ± 0.3 to 1.25 ± 0.2, $p = 0.02$), and improvement in PT (from 14.5 ± 3.5 to 13.7 ± 1.9 s, trend toward significance, p = 0.052) were observed after successful DAA therapy. Serum creatinine (from 0.84 ± 0.2 to 0.88 ± 0.3 mg/dL, $p = 0.153$), eGFR (from 100.9 ± 30.6 to 97.4 ± 31.9 mL/min/1.73 m^2, $p = 0.252$), and platelet count (from 82.0 ± 46.4 to 84.2 ± 46.9 × 10^9/L, $p = 0.617$) did not change significantly after DAA therapy. Thirty patients had elevated ALT levels at baseline and 28 (93%) patients accomplished ALT levels normalization after successful DAA therapy.

3.6. Dynamic changes of MELD, CTP, and FIB-4 scores after DAA therapy

Changing in MELD, CTP, and FIB-4 scores after DAA therapy were assessed in 48 patients who achieved SVR_{12}. Markedly decrease of FIB-4 index (11.2 ± 6.9 vs 8.1 ± 4.0, $p < 0.001$), CTP score (8.0 ± 1.2 vs 6.8 ± 1.4, $p < 0.001$), and MELD score (12.7 ± 3.6 vs 11.6 ± 3.0, $p < 0.03$) were found after successful DAA therapy by using paired t-tests (Table 7). Overall, 25 (52%) patients showed improvement in MELD score, 10 (21%) patients had no change and 13 (27%) patients worsened (Fig. 1A). Thirty-five (73%) patients had advancement in CTP score, and 22 (46%) patients had resolved of hepatic decompensation (improved to CTP score A 12 weeks after the completion of therapy) (Fig. 1B). Thirty (62%) patients had improved in FIB-4 score, 10 (21%) patients had no change and 8 patients worsened (Fig. 1C). Phenomenon of resolved hepatic decompensation (ie, liver function improvement to CTP class A) was found in 22 (46%) patients but all of them originally categorized as CTP class B.

Regarding the probability of delisting from liver transplantation waiting list, in our current study, only six patients had baseline more advanced cirrhosis (MELD score ≥ 18–20) and three of them had placed on the waiting list for liver transplantation before starting DAA therapy. After DAA treatment, one patient had delisting from liver transplant list according to medical record. A total of five patients did not continue to follow at our hospital after successful DAA therapy. For the remaining 43 patients who achieved SVR_{12}, the 1-year survival rate was 100% in patients with CTP class B and 90% in CTP class C, respectively.

3.7. Risk factors associated with no liver function improvement after SVR and the predicative value of BE3A score

Demographics, clinical and laboratory data between 35 patients who achieved CTP score improvement and 13 patients who were stable or increased CTP score after successful DAA therapy were compared. In addition, the predictive value of BE3A score to differentiate these two groups was validated using our study cohort. After statistical analyses, no single demographic, clinical or laboratory factor can accurately differentiate these two groups. Significantly higher BE3A score was found for patients had resolved hepatic decompensation as compared to those had persisted hepatic decompensation (2.9 ± 1.0 vs 2.0 ± 0.9, $p = 0.003$). Logistic regression analyses showed BE3A score ≥2 at the beginning of DAA therapy was independently associated with resolving hepatic decompensation (hazard ratio = 11.12; 95% confidence interval: 1.3–96.7; $p = 0.029$).

4. DISCUSSION

Reportedly, patients with HCV-associated decompensated cirrhosis have exhibited poor prognosis due to portal hypertension-related complication such as ascites, variceal bleeding, jaundice, and hepatic encephalopathy.[3,21] The most commonly reported cause of death among this population was liver failure (including hepatorenal syndrome and sepsis), followed by variceal hemorrhage and HCC.[5] A previous cohort study reported that the mean survival of patients with decompensated cirrhosis was 4.1 years.[22] Unfortunately, these patients were left untreated during the pegylated IFN era due to contraindications for the use of pegylated IFN in these patients. Therefore, highly effective antiviral therapy is urgently desired to improve the poor prognosis of patients with decompensated cirrhosis.

Recently, the approval of safe and effective oral DAAs has dramatically changed the care of patients with HCV infection, particularly that of patients with decompensated cirrhosis. Since NS3/4 protease inhibitors have been associated with

Table 7

The dynamic changes of the laboratory data and liver function tests before and after successful DAA therapy (n = 48)

Parameters	Baseline		SVR_{12}		*p* by paired t-test
	Mean ± SD	Median	Mean ± SD	Median	
Albumin (g/dL)	3.2 ± 0.5	3.2	3.5 ± 0.5	3.5	<0.001
Alanine aminotransferase (IU/L)	71.5 ± 60.5	54.0	25.5 ± 11.6	24.0	<0.001
Aspartate aminotransferase (IU/L)	92.6 ± 76.9	70.5	41.9 ± 18.3	42.0	<0.001
Total bilirubin (mg/dL)	2.2 ± 1.2	2.1	1.8 ± 1.0	1.8	0.015
Creatinine (mg/dL)	0.8 ± 0.2	0.8	0.9 ± 0.3	0.8	0.153
Platelet ($\times 10^9$/L)	82.0 ± 46.4	72.5	84.2 ± 46.9	76.0	0.617
PT (s)	14.5 ± 3.5	13.3	13.7 ± 1.9	13.2	0.052
INR	1.3 ± 0.3	1.2	1.3 ± 0.2	1.2	0.02
MELD score	12.7 ± 3.6	12	11.6 ± 3.0	11	0.03
CTP score	8.0 ± 1.2	8.0	6.8 ± 1.4	7.0	<0.001
FIB-4 index	11.2 ± 6.9	10.3	8.1 ± 4.0	7.4	<0.001

CTP score = Child-Turcotte-Pugh score; DAA = direct-acting antiviral agent; FIB-4 index = Fibrosis-4 index; INR = international normalized ratio; MELD score = Model for End-Stage Liver Disease score delete.

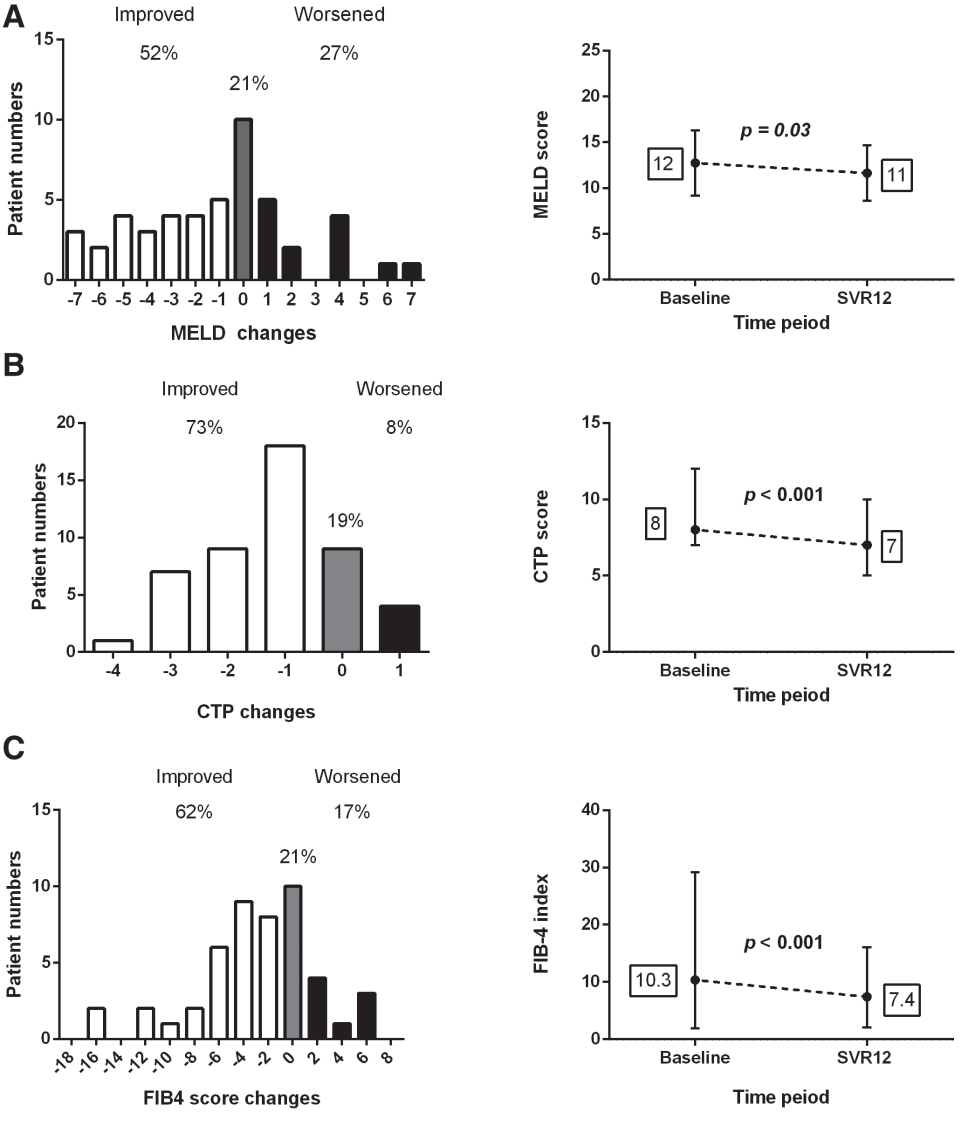

Fig. 1 Changes in MELD score (A), CTP score (B), and FIB-4 index (C) from baseline to post-treatment week 12 in 48 patients with decompensated cirrhosis who achieved SVR_{12}. CTP score = Child-Turcotte-Pugh score; FIB-4 index = Fibrosis-4 index; MELD score = Model for End-Stage Liver Disease score

hepatotoxicity and hepatic decompensation in patients with advanced cirrhosis, the recommended regimen for this subpopulation is combination therapy with NS5B nucleotide polymerase inhibitor sofosbuvir and an NS5A inhibitor. Clinical trial data mainly from the Western countries have demonstrated that the SVR_{12} rates were approximately 83%–96% in patients with decompensated CTP class B cirrhosis and 56%–87% in patients with decompensated CTP class C cirrhosis after using this combination regimen.[6–9,23]

To the best of our knowledge, the present study is the first to report real-world data from Taiwan to investigate the efficacy and safety profiles of genotype-specific or pan-genotypic DAAs for HCV patients with decompensated liver cirrhosis. As clinical trials usually have strict inclusion and exclusion criteria and are managed in rigorously controlled settings, real-life cohorts are valuable in reflecting the efficacy and safety of a new treatment regimen for patients in daily clinical practice. Our real-world data showed that a highly effective antiviral response can be achieved by sofosbuvir-based oral DAAs, even in this difficult-to-treat population. The SVR_{12} rate was 97.6% in CTP class B population and 88.9% in CTP class C population, respectively. Similar to our previously published reports,[24,25] an equivalent or even better treatment response was observed in Taiwanese CHC patients when compared with real-world data from other geographic regions.[26–32] After successful antiviral therapy, a significant improvement in hepatic functional reserve could be achieved. Based on current study results, the percentages to have improved MELD score, CTP score and FIB-4 index after successful DAA therapy were 52%, 73%, and 62%, respectively. Phenomenon of resolved hepatic decompensation (ie, liver function improvement to CTP class A) was found in 22 (46%) patients but all of them originally categorized as CTP class B. More importantly, only one patient did not finish therapy due to sepsis or multiple organ failure. Subjective AEs were generally mild and could be alleviated symptomatically using medications.

An important issue worthy of discussion is the optimal timing to initiate DAAs in patients with decompensated cirrhosis, especially when the patient is a possible LT candidate. Results from clinical trials and real-world data have shown that the SVR_{12} rate after sofosbuvir-based DAA therapy was significantly lower in CTP class C patients when compared with CTP class B patients.[6–9,26–33] The detailed mechanisms responsible for this finding are yet to be clarified. Impaired drug uptake and metabolism, the presence of a portosystemic shunt affecting drug delivery, and impaired immune response have been proposed as possible reasons.[34] In addition, in patients with more advanced cirrhosis (MELD score ≥ 18–20), response to DAAs did not modify the clinical course of the disease and the risk of disease progression and residual HCC still remained.[35–37] In concordance with previous published report,[20] our results showed BE3A score ≥ 2 (ie, less advanced decompensated cirrhosis) at the beginning of DAA therapy was independently associated with resolving hepatic decompensation posttreatment. Thus, current treatment guidelines suggest that in patients with decompensated cirrhosis with a MELD score < 18–20 who are awaiting LT, DAAs could be initiated before LT. In patients with a MELD score ≥ 18–20, LT should be considered first and HCV infection should be treated after LT unless the waiting time on the transplant list exceeds 6 months.[38] The median baseline MELD score in our study population was 12, and only six patients had baseline MELD score ≥ 18–20 with the highest value was 21. Indeed, the high success rate observed in the present study reflected this patient composition.

During the pegylated IFN era, combination therapy with RBV was indispensable to enhance the virological response and to prevent disease relapse. In the era of oral DAAs, RBV remains a useful tool to fine-tune anti-HCV treatment regimens and to optimize their results, especially in patients with genotype 3, decompensated cirrhosis, or previous DAA treatment failure.[39,40] For patients with decompensated cirrhosis, the international guidelines recommend adding low-dose RBV (600 mg/d) to a 12-week sofosbuvir-based regimen to enhance the treatment response. In RBV-ineligible patients, extending the treatment duration to 24 weeks is suggested.[16,17,38] The most bothersome adverse effect related to RBV use is hemolytic anemia. Notably, the incidence and severity of RBV-induced anemia tended to be higher in patients with advanced cirrhosis.[37] In the present study, a drop of more than 2 g/dL in the hemoglobin level was observed in 32% (16/50) of the patients and all of them had been treated with the RBV-containing DAA regimen. In addition, 14.9% of the patients treated with RBV-containing DAAs required RBV dose reduction or discontinuation of RBV to maintain hemoglobin levels. Recent studies from Japan have demonstrated high treatment success rates of a 12-week more potent sofosbuvir-velpatasvir (pan-genotypic) regimen without RBV among patients with decompensated cirrhosis. In addition, addition of RBV did not improve the efficacy, but increased the incidence of AEs.[23,31,32] As the DAA therapy continues to evolve, a highly effective RBV-free regimen is the ideal future goal. However, more studies are needed to define the optimal regimen and duration.

Patients with advanced decompensated cirrhosis were more susceptible to acute infections due to immune dysfunction. In our real-world cohort, 13 SAE-related hospitalizations were noted during the study period and 31% of them were attributed to infection. One patient did not finish the DAA therapy and died due to intraabdominal infection with severe sepsis and multiple organ failure. Therefore, physicians and patients must pay scrupulous attention to possible infectious states. Ascites and hepatic encephalopathy should be carefully managed during the entire treatment course. Advanced endoscopic treatment is needed before the initiation of DAAs in patients with a high risk of rupture of esophageal varices. More importantly, surveillance of recurrent or newly developed HCC should be considered. Fortunately, restoration of liver functional reserve after DAAs might provide more treatment options.

In conclusion, our real-world cohort study demonstrated that high treatment efficacy, acceptable safety, and good tolerability can be achieved using sofosbuvir-based oral DAAs in Taiwanese CHC patients with decompensated cirrhosis. Our results provide valuable information regarding the clinical care of this population. Future large-scale studies are needed to clarify the long-term hepatic beneficial effects of successful HCV clearance on disease prognosis.

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