Well tolerability and highly effective treatment response for hepatitis C virus-human immunodeficiency virus–coinfected patients treated by all-oral direct-acting antivirals

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Abstract

Background: Hepatitis C virus (HCV) and human immunodeficiency virus (HIV) coinfection is common because the two pathogens share their transmission route. Studies have suggested that coinfection is associated with accelerated hepatic fibrosis, increased hepatic decompensation, and hepatocellular carcinoma development. Historically, the sustained virological response (SVR) rates for patients undergoing pegylated interferon (PEG-IFN)-based therapy are poor owing to advanced liver disease, immune dysfunction, and poor medical adherence. This study aimed to investigate the efficacy and safety of oral direct-acting antivirals (DAAs) in HCV-HIV–coinfected patients.

Methods: Between January 2017 and February 2020, 52 consecutive HCV-HIV–coinfected patients treated with oral DAAs (paritaprevir/ritonavir, ombitasvir, and dasabuvir: 7; daclatasvir and asunaprevir: 1; glecaprevir and pibrentasvir: 15; and sofosbuvir-based drugs: 29) were enrolled. The DAA regimen was selected based on the genotype/subtypes, patient characteristics, potential drug-drug interaction profiles, and health insurance reimbursement criteria. SVR_{12} was defined as undetectable HCV RNA (<15 IU/mL) at the end of therapy and 12 weeks after therapy completion.

Results: The mean age of the enrolled patients was 42 ± 10.2 years; 92.3% of the patients were male and 32.7% had advanced fibrosis or cirrhosis. Nine (17.3%) patients had failed previous IFN therapy. The genotype distribution was as follows: 1a: 8; 1b: 23; 2: 14; 3: 1; and 6: 6. The baseline HCV RNA level before DAA administration was 6.56 ± 0.9 $\log_{10}$ IU/mL, and 67.3% of patients had baseline HCV RNA >2 000 000 IU/mL. After posttreatment follow-up, all 52 patients (100%) achieved SVR_{12}. Subjective and laboratory adverse events during therapy were generally mild, and none of the patients terminated therapy early.

Conclusion: A highly effective treatment response and good tolerability were achieved using the oral DAAs for the HCV-HIV–coinfected patient population, which has been considered difficult to treat using IFN-based therapy in the past with urgent unmet medical needs.

Keywords: Chronic hepatitis C; Direct-acting antivirals; Drug-drug interactions; Genotype; Human immunodeficiency virus; Interferon; Sustained virological response

1. INTRODUCTION

Chronic hepatitis C (CHC) virus infection is one of the leading causes of liver cirrhosis, hepatic decompensation, and hepatocellular carcinoma (HCC) worldwide, including in Taiwan.[1,2] As the two pathogens share their transmission route, hepatitis C virus (HCV) and human immunodeficiency virus (HIV) coinfection is common. Studies performed on western populations showed that HIV-infected individuals have six times higher HCV infection rates than the general population. Subgroup analyses revealed that the prevalence of coinfection is higher among injection drug users (IDUs) and men engaging in sexual intercourse with men, ranging from 6.4% to 30% and 80% to 90%, respectively.[3,4] Epidemiological data from different studies suggest that the seroprevalence of HCV in HIV-infected Taiwanese

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patients ranged from 18.6% to 43.4%.[5–7] The reported incidence of HCV-HIV coinfection among HIV-infected subpopulations is as follows: 13% in HIV-infected adolescents, 5.3% to 10.9% among adults with sexually transmitted HIV infection, and 65.5% to 100% among IDUs.[8]

Several studies have demonstrated that HCV-HIV coinfection exerts a strong negative effect on the natural course of HCV infection, which include increase in HCV viral load and alanine aminotransferase (ALT) level, rapid liver fibrosis, and increased risk of hepatic decompensation and HCC development.[9–11] In the context of antiretroviral therapy (ART), liver disease has emerged as a major cause of morbidity and mortality in HIV-infected individuals.[12] However, the treatment of HCV-HIV coinfection using a pegylated interferon (PEG-IFN)-based regimen was hindered owing to lower sustained virological response (SVR) rates (27%-50%), poor adherence, and ongoing substance abuse.[13–17] Therefore, highly effective therapies for HCV-HIV coinfection are urgently required to improve patient outcomes.

The therapeutic landscape of CHC changed rapidly after the invention of IFN-free oral direct-acting antivirals (DAAs). Compared with PEG-IFN–based regimens, oral DAAs offer advantages such as shorter treatment duration, superior efficacy, broader candidacy, and excellent safety profiles.[18] In Taiwan, the costs of all-oral DAAs were conditionally reimbursed by the National Health Insurance Administration, Ministry of Health and Welfare (NHIA) after January 24, 2017. To date, there has been no reported real-world data of the treatment of Taiwanese patients with HCV-HIV coinfection, the population that was considered difficult to treat in the PEG-IFN era, using brand-name DAAs. Here, we investigate the antiviral efficacy and safety of DAAs in the same population.

2. METHODS

2.1. Patients

Between January 2017 and February 2020, 52 consecutive HCV-HIV–coinfected patients treated with all-oral DAAs at Taipei Veterans General Hospital were enrolled. The enrollment criterion was adult (age ≥20 years) with 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, 15 IU/mL) for ≥6 months. Patients were required to undergo a stable ART regimen for HIV before the administration of all-oral DAAs. Patients were excluded from the analyses if they had a history of decompensated liver cirrhosis, received organ (liver, kidney, or heart) transplantation, prior DAA treatment, 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 patients before their recruitment in the study.

2.2. Study design

This was a retrospective cohort single-center study. After signing the patient consent form, baseline demographic and clinical data, HIV treatment status (ART regimen, HIV RNA, and CD4 T-cell count levels), virological response to previous therapy with PEG-IFN/ribavirin (RBV), hemogram, international normalized ratio (INR), serum biochemical profiles (albumin, total bilirubin, direct bilirubin, ALT, aspartate aminotransferase [AST], creatinine, and estimated glomerular filtration rate [eGFR]), and anti-HCV, HCV RNA, and HCV genotype data were collected for all patients. The HCV genotype was determined using a commercially available assay (Cobas HCV GT; Roche Diagnostics GmbH). Two methods were used to determine the degree of hepatic fibrosis. The Fibrosis-4 (FIB-4) score is a non-invasive scoring system that uses laboratory tests to estimate the degree of hepatic fibrosis. A FIB-4 index ≥2.67 has an 80% positive predictive value for advanced (F3-F4) fibrosis, whereas a FIB-4 index ≤1.30 has a 90% negative predictive value.[19] Some patients agreed to undergo self-financed transient elastography (FibroScan®; Echosens, Paris, France) for liver stiffness measurement. 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), and F4 (≥12.5 kPa).[20] Cirrhosis of the liver was defined either by a liver stiffness value ≥12.5 kPa or the presence of typical clinical or radiological manifestations. Hepatic decompensation was defined by a Child-Pugh score ≥7.

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

In the current study, the DAA regimen selection was assessed by clinical physicians based on the HCV genotype/viral load, patient characteristics, drug-drug interaction (DDI) profiles, and evolving NHIA reimbursement criteria. Clinically complex DDIs between DAAs and ART medications are well documented, as several of these medications can act as substrates, inducers, or inhibitors of the cytochrome P450 system or other transporter systems, which might reduce or increase the therapeutic blood level of coexisting medications.[21–23] Before the initiation of DAA therapy, regular medications, including ART medications, administered to the enrolled patients were extensively surveyed for detecting possible DDIs. Medications that could have potential DDIs were discontinued, exchanged with alternative drugs, or administered at the lowest dose with frequent monitoring, as assessed by physicians. For example, the coadministration of DAAs and ART regimens comprising protease inhibitors (PIs) is not currently recommended. HCV-HIV–coinfected patients are often administered ART regimens containing non-nucleoside reverse transcriptase inhibitors (NNRTIs), such as efavirenz or etravirine, which might significantly reduce the concentration of sofosbuvir/velpatasvir and lead to virological treatment failure. Based on these findings, to avoid clinically significant DDIs, other ART regimens were adopted after comprehensive discussion with HIV-treating physicians. Table 1 summarizes the detailed information of the eight patients for whom the ART regimen was switched before DAA administration was initiated.

Ribavirin (Robatrol®, 200 mg capsule; Genovate Biotechnology Co., Ltd., Taipei, Taiwan) was administered as a body weight–based drug, if necessary. The dosage of RBV was as follows: 1200 mg/d for body weight ≥75 kg, 1000 mg/d for body weight 50-75 kg, 800 mg/d for body weight <50 kg, and 200-400 mg/d for eGFR ≤30 mL/min/1.73 m^2. The dose could be reduced after week 4 if the hemoglobin content decreased >2.0 g/dL compared with baseline levels if serum HCV RNA was undetectable using real-time polymerase chain reaction (PCR).

2.4. Definition of treatment response

The serum HCV RNA levels were quantified before treatment commencement, at week 4 (optional), at the end of the treatment period, and at posttreatment week 12 to define the virological response. SVR_{12} was defined as undetectable HCV RNA levels (≤15 IU/mL) at the end of DAA therapy and 12 weeks after therapy completion. Patients for whom the SVR_{12} data were lacking were considered to have failed to achieve SVR_{12}.

Table 1

Information on HCV-HIV–coinfected patients who changed ART regimen for drug-drug interaction concerns before DAA therapy

Case	Age	Gender	HCV genotypes	HCV RNA level in $\log_{10}$ IU/mL	Selected DAA regimen	Original ART regimen	Reasons for changing ART regimen	New ART regimen during DAA therapy
1	51	Male	Ib	6.7	Paritaprevir/ritonavir/ ombitasvir/dasabuvir	NNRTI-based	Prolong QT interval	INSTI-based
2	51	Male	Ib	4.6	Paritaprevir/ritonavir/ ombitasvir/dasabuvir	PI-based	Increase level of paritaprevir	INSTI-based
3	34	Male	Ia	6.3	Paritaprevir/ritonavir/ ombitasvir/dasabuvir/RBV	NNRTI-based	Decrease level of paritaprevir/ ritonavir/ombitasvir/dasabuvir	INSTI-based
4	62	Male	Ib	6.3	Paritaprevir/ritonavir/ ombitasvir/dasabuvir	NNRTI-based	Prolong QT interval	INSTI-based
5	41	Male	6	6.7	Sofosbuvir/ledipasvir	NNRTI-based	Increase level of tenofovir	INSTI-based
6	47	Male	6	7.7	Sofosbuvir/ledipasvir/RBV	NNRTI-based	Increase level of tenofovir	INSTI-based
7	29	Male	2	6.6	Glecaprevir/pibrentasvir	NNRTI-based	Decrease level of glecaprevir/ pibrentasvir	INSTI-based
8	39	Male	Ia	6.4	Glecaprevir/pibrentasvir	NNRTI-based	Decrease level of glecaprevir/ pibrentasvir	INSTI-based

ART = antiretroviral therapy; DAAs = direct-acting antivirals; INSTI = integrase strand transfer inhibitor; NNRTI = non-nucleoside reverse transcriptase inhibitor; PI = protease inhibitor; RBV = ribavirin.

2.5. Safety and adverse events

During the treatment period, patients were assessed by physicians at weeks 1 and 2 and then after every 2 weeks (or more frequently in cases exhibiting adverse effects) until the end of therapy. Subjective patient-reported outcomes, physical examination findings, and laboratory data including biochemistry, CD4 cell count, viral load (HIV RNA) count, and hematology and coagulation profiles were recorded in the datasheet. Adverse events (AEs) were graded according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0. During the study period, changes to the antiretroviral regimens and dose adjustments were recorded.

2.6. Statistical analysis

Data analyses were performed using the Statistical Program for Social Sciences (SPSS Statistics Version 18.0; IBM Corp., Armonk, NY, USA). Baseline patient characteristics are expressed in terms of mean with SD and percentages as appropriate. Statistical analyses were performed using the chi-squared or Fisher's exact tests for categorical variables. Independent *t*-tests were used for the continuous variables. Paired *t*-tests were used to compare the sequential changes in the FIB-4 index before and after DAA therapy. The quantitative HCV RNA levels (IU/mL) were logarithmically transformed for analysis. All statistical tests were two-sided. Differences between groups were considered statistically significant at $p < 0.05$.

3. RESULTS

3.1. Baseline characteristics of enrolled patients

Fifty-two patients were included in the analyses. The mean age of the enrolled population was 42 ± 10.2 years; 48 (92.3%) patients were male, and 9 (17.3%) of them failed in previous PEG-IFN therapy. Among the patients who failed PEG-IFN treatment, 5 (55.6%) were relapsers, 3 (33.3%) were partial or null responders, and 1 (11.1%) were intolerant and underwent early treatment termination. Based on transient elastography or the FIB-4 index, the degree of hepatic fibrosis was as follows: F1-F2 fibrosis, 67.3%; F3-F4 fibrosis, 32.7%. All patients considered to be afflicted by liver cirrhosis were compensated cirrhosis (Child-Pugh A). Before the administration of all-oral DAAs, the ART regimens were categorized as follows: integrase strand transfer inhibitor (INSTI)-based, 50%; PI-based, 3.9%; NNRTI-based, 34.6%; nucleoside reverse transcriptase inhibitors (NRTIs) combination: 9.6%; without treatment: 1.9% (Table 2).

Table 3 summarizes the laboratory characteristics of the enrolled patients. Mean pretreatment ALT and AST values were 99.4 ± 112.2 and 55.3 ± 42.9 IU/L, respectively. The mean baseline HCV RNA level was 6.56 ± 0.9 $\log_{10}$ IU/mL. The infected HCV genotypes are summarized as follows: 1a: 15.4%; 1b: 44.2%; 2: 26.9%; 3:1.9%; 6: 11.6%. The baseline HCV RNA levels were distributed as follows: ≤800 000 IU/mL: 15.4%; 800 000 to 2 000 000 IU/mL: 17.3%; 2 000 000 to 6 000 000 IU/mL: 17.3%; ≥6 000 000 IU/mL: 50%.

3.2. Virological response during and after DAA therapy

The detailed DAA regimens for each HCV genotype/subtype are summarized in Table 4. In brief, 29 (55.8%) patients were treated using a sofosbuvir-based regimen; 7 (13.5%) using a paritaprevir/ritonavir, ombitasvir, and dasabuvir (PrOD)-based regimen; 15 (28.8%) using glecaprevir plus pibrentasvir; and 1 (1.9%) using daclatasvir plus asunaprevir. Nine patients (17.3%) were treated with DAAs in combination with RBV.

Table 2

Baseline clinical characteristics of enrolled patients

Characteristics	Patients (n = 52)
Mean age, y	42.0 ± 10.2
Age ≥65 y, %	1 (1.9%)
Male, %	48 (92.3%)
Antiviral naïve/previous PEG-IFN failure, %	43 (82.7%)/9 (17.3%)
Previous PEG-IFN/RBV response, %	
Relapser	5 (55.6%)
Partial or null responder	3 (33.3%)
Intolerant and early terminated	1 (11.1%)
Severity of liver disease, %	
≤F2 fibrosis	35 (67.3%)
Advance fibrosis or liver cirrhosis	17 (32.7%)
ART regimen before DAAs, %	
INSTI-based	26 (50%)
Boosted PI-based	2 (3.9%)
NNRTI-based	18 (34.6%)
NRTI combination	5 (9.6%)
Untreated	1 (1.9%)

ART = antiretroviral therapy; DAAs = direct-acting antivirals; INSTI = integrase strand transfer inhibitor; NNRTI = non-nucleoside reverse transcriptase inhibitor; NRTI = nucleoside reverse transcriptase inhibitor; PEG-IFN = pegylated interferon; PI = protease inhibitor; RBV = ribavirin.

Table 3

Baseline laboratory characteristics of enrolled patients

Characteristics	Patients (n = 52)
Genotype, 1a/1b/2/3/6	8(15.4%)/23(44.2%)/14(26.9%)/1(1.9%)/6(11.6%)
Mean baseline HCV RNA (log_{10} IU/mL)	6.56 ± 0.9
Baseline HCV RNA	
≤800 000 IU/mL	8 (15.4%)
800 000-2 000 000 IU/mL	9 (17.3%)
2 000 000-6 000 000 IU/mL	9 (17.3%)
≥6 000 000 IU/mL	26 (50%)
HIV RNA level[a]	
<50 copies/mL	47 (94%)
50-400 copies/mL	3 (6%)
Mean CD4, cells/μL	560 (56-1135)
Mean hemoglobin, g/dL	14.5 ± 1.7
Mean white cell count ($\times 10^9$/L)	5.8 ± 1.5
Mean platelet count ($\times 10^9$/L)	217.3 ± 66.8
Prothrombin time, s	11.1 ± 0.8
INR	1.0 ± 0.1
Mean albumin, g/dL	4.3 ± 0.3
Alanine aminotransferase, IU/L	99.4 ± 112.2
Aspartate aminotransferase, IU/L	55.3 ± 42.9
Mean total bilirubin, mg/dL	0.8 ± 0.4
Mean creatinine, mg/dL	1.1± 0.9
eGFR, ≥60/59-30/<30 and HD (mL/min/1.73 m^2)	51(98.1%)/0(0%)/1(1.9%)

eGFR = estimated glomerular filtration rate; HCV RNA = hepatitis C virus RNA; HD = hemodialysis; HIV RNA = human immunodeficiency virus RNA; INR = international normalized ratio.
[a]Two HCV-HIV–coinfected patients without HIV RNA data.

After the commencement of DAA treatment, 20 patients with HCV RNA data available at weeks 4 and 18 (90%) had undetectable HCV RNA, as shown by real-time PCR (<15 IU/mL). The two (10%) patients with detectable serum HCV RNA after 4 weeks of treatment exhibited low levels of viremia (HCV RNA levels 15-50 IU/mL). All patients completed the all-oral DAA therapy without interruption and completed the posttreatment follow-up. The SVR_{12} rate was 100% for the enrolled population.

Table 4

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

HCV genotype/subtypes	DAA regimen used
1a (n = 8)	12 wk paritaprevir/ritonavir/ombitasvir 75 mg/50 mg/12.5 mg/d + dasabuvir 250 mg bid + RBV (n = 1)
	12 wk sofosbuvir 400 mg/d + ledipasvir 90 mg/d ± RBV (n = 5)
	12 wk glecaprevir 100 mg/d + pibrentasvir 40 mg/d (n = 1)
	12 wk sofosbuvir 400 mg/d + velpatasvir 100 mg/d + RBV (n = 1)
1b (n = 23)	12 wk paritaprevir/ritonavir/ombitasvir 75 mg/50 mg/12.5 mg/d + dasabuvir 250 mg bid (n = 6)
	12 wk sofosbuvir 400 mg/d + ledipasvir 90 mg/d ± RBV (n = 14)
	24 wk daclatasvir 60 mg/d + asunaprevir 100 mg bid (n = 1)
	8 wk glecaprevir 100 mg/d + pibrentasvir 40 mg/d (n = 1)
	12 wk sofosbuvir 400 mg/d + velpatasvir 100 mg/d + RBV (n = 1)
2 (n = 14)	12 wk sofosbuvir 400 mg/d + ledipasvir 90 mg/d (n = 3)
	12 wk glecaprevir 100 mg/d + pibrentasvir 40 mg/d (n = 1)
	8 wk glecaprevir 100 mg/d + pibrentasvir 40 mg/d (n = 10)
3 (n = 1)	12 wk glecaprevir 100 mg/d + pibrentasvir 40 mg/d (n = 1)
6 (n = 6)	12 wk sofosbuvir 400 mg/d + ledipasvir 90 mg/d ± RBV (n = 5)
	8 wk glecaprevir 100 mg/d + pibrentasvir 40 mg/d (n = 1)

DAAs = direct-acting antivirals; HCV = hepatitis C virus; RBV = ribavirin.
[a]17.3% (9/52) patients using DAAs in combination with RBV.

3.3. ALT normalization and changes in FIB-4 index after DAA treatment

In the current study, baseline serum ALT levels of >40 IU/L were observed in 38 (73.1%) members of the study population. For patients with abnormal ALT values at baseline, ALT normalization was observed in 84.2% of patients at week 4, 86.8% at the end of the treatment period, and 89.5% at posttreatment week 12. All patients with normal ALT values at baseline showed normal ALT values at the above-mentioned time points.

For patients with F1-F2 fibrosis, the FIB4-index did not change significantly before and after DAAs therapy (mean value from 0.96 to 0.95, $p = 0.94$). For patient with advanced (F3-F4) fibrosis, the FIB4-index decreased after completing DAAs therapy (mean value from 2.49 to 1.93, $p = 0.095$), nearly reaching statistically significant level.

3.4. Subjective and laboratory AEs

During DAA administration, 10 patients (19.2%) experienced at least one subjective AE. Pruritus (9.6%) was the most common subjective AE reported by all enrolled patients, followed by fatigue, rash, insomnia, and headache (Table 5). The percentages of patients reporting fatigue and headache were significantly higher among patients receiving DAAs with ribavirin than in those in the DAA-only group ($p < 0.05$). Grades of the above-mentioned subjective AEs were generally mild, and the AEs were symptomatic and could be relieved by medications.

With respect to laboratory AEs, grade 2 ALT elevation (3-5 × ULN) was detected in 2.3% patients (1/52), and grade 3 ALT elevation (5-20 × ULN) was detected in 2.3% (1/52) of the enrolled patients during the study period. None of the patients with on-treatment grade 2 or 3 ALT elevation exhibited hyperbilirubinemia. Grade 2 (1.5-3.0 × ULN) hyperbilirubinemia was detected in 9.6% (5/52) of the enrolled patients during the study period, and four of them (80%) exhibited unconjugated hyperbilirubinemia (Table 6). No patients with grade 2 hyperbilirubinemia showed significant (>2 × ULN) ALT elevation or evidences of hepatic decompensation. With continuous DAA therapy, the incidents of unconjugated hyperbilirubinemia were gradually resolved. There were no significant changes in the eGFR during the course of DAA therapy among the enrolled patients.

During the study period, no patient showed grade 2 (8.0-10.0 g/dL) anemia. However, one patient with Child-Pugh A cirrhosis and renal failure under regular hemodialysis, who was treated with PrOD alone, showed grade 3 anemia (< 8.0 g/dL), as noted from baseline values and during the treatment course.

Table 5

Subjective adverse events

All patients (n = 52), n (%)		With RBV (n = 9), (17.3%)	Without RBV (n = 43), (82.7%)	p
Fatigue	4 (7.7%)	4 (44.4%)	0 (0.0%)	<0.001
Headache	2 (3.8%)	2 (11.1%)	0 (0.0%)	0.027
Nausea	0 (0.0%)	0 (0.0%)	0 (0.0%)	...
Insomnia	2 (3.8%)	0 (0.0%)	2 (4.7%)	>0.99
Pruritus	5(9.6%)	1(11.1%)	4 (9.3%)	>0.99
Diarrhea	1 (1.9%)	1 (11.1%)	0 (0.0%)	0.173
Asthenia	0 (0.0%)	0 (0.0%)	0 (0.0%)	...
Rash	3 (5.8%)	1 (11.1%)	2 (4.7%)	0.442
Irritability	0 (0.0%)	0 (0.0%)	0 (0.0%)	...
Dizziness	0 (0.0%)	0 (0.0%)	0 (0.0%)	...
Dyspnea	0 (0.0%)	0 (0.0%)	0 (0.0%)	...
Edema	0 (0.0%)	0 (0.0%)	0 (0.0%)	...

RBV = ribavirin.

Table 6

Laboratory adverse events

All patients (n = 52), n (%)		With RBV (n = 9), (17.3%)	No RBV (n = 43), (82.7%)	*p*
Hemoglobin level				
Grade 2	0 (0%)	0 (0.0%)	0 (0.0%)	
Grade 3	1 (1.9%)	0 (0.0%)	1 (2.3%)	>0.99
On-treatment Hgb decline >2.0 g/dL	3 (5.8%)	3 (33.3%)	0 (0.0%)	0.004
Total bilirubin				
Grade 2	5 (9.6%)	2 (22.2%)	3 (7.0%)	0.202
Grade 3	0 (0%)	0 (0.0%)	0 (0.0%)	
ALT				
Grade 2	1 (1.9%)	0 (0.0%)	1 (2.3%)	>0.99
Grade 3	1 (1.9%)	0 (0.0%)	1 (2.3%)	>0.99

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

Blood transfusion was arranged to relieve the anemia symptoms of the patient; however, we believe that the anemia was not affected by DAA treatment. More than 2 g/dL drop of hemoglobin during the treatment course was observed in 5.8% (3/52) of patients, and all of them were treated with RBV-containing DAAs. Two (66.7%) patients required RBV dose reduction to maintain hemoglobin levels. None of the patients discontinued DAA therapy owing to the subjective or laboratory AEs discussed above.

4. DISCUSSION

HCV-HIV coinfection has been associated with several unique characteristics, including higher HCV viral load, rapid liver fibrosis, increased risk of hepatic decompensation, chances of earlier HCC development, and increased mortality.[11] According to the findings from a meta-analysis, the relative risk of liver cirrhosis and hepatic decompensation in HCV-HIV–coinfected patients was 2.92 (95% CI, 1.70-5.01) and 6.14 (95% CI, 2.86-13.20), respectively, compared with that in HCV mono-infected subjects.[24] Another meta-analysis demonstrated that in the highly active ART era, the risk ratio for overall mortality was 1.35 (95% CI, 1.11-1.63) among coinfected patients, compared with that among patients with HIV monoinfection.[25] Therefore, owing to poor long-term prognosis, antiviral therapy should be a high priority for treating this particular population.

Over the past two decades, IFN/PEG-IFN-based therapy has been used to treat chronic HCV infections in patients with HIV coinfection. Data from studies on western populations showed that the SVR rates in HIV-infected patients with chronic HCV infection treated by 24 to 48 weeks of PEG-IFN plus RBV combination therapy were only 27% to 50%.[13–17] Meanwhile, patients with HCV genotype 1 or 4 infection tend to show lower SVR rates than those with genotype 2 or 3 infection (14%-38% vs. 44%-73%). The possible reasons for lower SVR rates in HCV-HIV–coinfected patients compared with that in HCV mono-infected subjects might include higher viral load, advanced liver disease, immune dysfunction, multiple comorbidities, and poor medical adherence. A prospective cohort study conducted in Taiwan showed that among patients undergoing response-guided therapy with PEG-IFN plus RBV (12-72 weeks for HCV genotypes 1 or 6 and 24-48 weeks for genotypes 2 or 3), the SVR rates were 68% for patients with chronic HCV genotype 1 or 6 and 72% for chronic HCV genotype 2 or 3 infection.[26] Similarly, among patients with CHC monoinfection, the SVR rates after PEG-IFN plus RBV tended to be higher in Asian individuals owing to racial differences in human interleukin 28B gene polymorphism.[27–29] However, the SVR rates obtained are still far from ideal. In addition, the side effects of PEG-IFN plus RBV and the ineligibility of patients remain the major obstacles to the initiation of antiviral therapy.

The treatment paradigm of CHC infection evolved significantly after the invention of all-oral DAAs. In the DAA era, multiple phase III clinical trials have demonstrated that the SVR_{12} rates (>93%) in patients with HCV-HIV coinfection are comparable with the rates in patients with HCV monoinfection.[30–40] For example, the phase III ION-4 trial enrolled 335 patients with HCV-HIV coinfection (GT1, 4) who received 12 weeks of sofosbuvir/ledipasvir. Of them, 322 patients (96%) achieved SVR_{12}. Neither liver cirrhosis nor the previous treatment status affected the SVR_{12} rates.[33] In a pan-genotypic regimen, glecaprevir/pibrentasvir yielded 100% SVR_{12} rates (136/136) in patients with HCV-HIV coinfection without cirrhosis (8-week regimen) and 93% (14/15) in patients with cirrhosis (12-week regimen) during the phase III EXPEDITION-2 study.[40] In the phase III ASTRAL-5 study, SVR_{12} was achieved after a 12-week regimen with sofosbuvir/velpatasvir in 95% (101/106) of HCV-HIV–coinfected patients (GT1-4).[35] Moreover, several studies have demonstrated significant improvement in health-related quality parameters of life and patient-reported outcomes in coinfected patients after treatment with DAAs.[41,42]

To our knowledge, this is the first study to provide real-world data on the efficacy and safety profiles of brand-name DAAs (genotype-specific or pan-genotypic) in patients with HCV-HIV coinfection in Taiwan. As clinical trials usually follow strict inclusion and exclusion criteria, real-life cohorts are valuable in reflecting the efficacy and safety of new treatment regimens for patients in regular clinical practice. In the real-world cohort of the Taiwanese population used in this study, which included 50% individuals with baseline HCV RNA ≥6 million IU/mL, 17.3% showed failure with previous PEG-IFN plus RBV therapy, and 32.7% patients had advanced fibrosis or liver cirrhosis. With a wide variety of HCV genotypes detected, a highly effective antiviral response was achieved using all-oral DAAs in the current study, even for the deemed difficult-to-treat population. No patient terminated DAA therapy early, and the overall SVR_{12} rate was 100%. Similar to the findings in the PEG-IFN era,[29] an equivalent or even better treatment response was observed in Taiwanese patients with CHC infection than in western populations.

The selection of a DAA regimen in the setting of HCV-HIV coinfection is complicated but crucial. A number of DAA regimens adopted in the current study were selected based on diverse patient characteristics, different HCV genotypes/subtypes, and evolving NHIA reimbursement criteria. Because the potential DDIs between HCV and HIV medication are well documented, a thorough DDI risk assessment is necessary before the initiation of HCV treatment and administration of other medications during treatment.[43] Apart from the DDIs in the ART regimen, numerous complex DDIs can develop between DAAs and comedications. Medications that could exhibit potential DDIs were discontinued, exchanged with alternative drugs, or administered at the lowest dose with frequent monitoring. As mentioned in Table 1, eight patients (15.4%) in this study required a change in their ART regimen before DAA treatment. For seven patients, an NNRTI-based ART regimen was switched to an INSTI-based regimen, and for one patient, a PI-based regimen was switched to an INSTI-based regimen, to avoid contradictory DDIs. From the viewpoint of DDIs, the INSTI-based ART regimen seemed to be the rational choice for treating HCV-HIV–coinfected patients. After carefully handling, DDIs should not be a barrier for HCV-HIV–coinfected patients to initiate DAAs.

The common subjective AEs in our current study were pruritus, fatigue, rash, insomnia, and headache. In combination, the use of ribavirin was significantly associated with fatigue and headache. Fortunately, the grades of the subjective AEs were generally low and could be relieved symptomatically by medication. With respect to laboratory AEs, the factors responsible for unconjugated hyperbilirubinemia were possibly related to the inhibition of the bilirubin transporters OATP1B1 and OATP1B3 by PIs alongside RBV-induced hemolysis.[43–45] On-treatment hemoglobin decline was significantly associated with the use of RBV, and careful monitoring was required for the same. As DAA therapy continues to evolve, a highly effective RBV-free regimen is the ideal future goal; however, further studies are required for clarification.

HCV reinfection after SVR is a critical issue in HCV-HIV–coinfected patients, especially in those exhibiting persistent risk behaviors such as intravenous drug use or unprotected sexual activity. The literature based on meta-analyses revealed that the cumulative 5-year incidence of HCV reinfection in HCV-HIV–coinfected patients post SVR was 15.02%.[46] High-frequency injection drug use and high-risk sexual activity are reported to be the major risk factors.[47] Notably, there were two patients in our study population diagnosed with HCV reinfection within a year after they achieved SVR_{12}; these patients required a second course of self-financed DAA therapy that was not reimbursed by NHIA. Therefore, patient education, targeted counseling, and measures to reduce risk behaviors are important for treating HCV-HIV–coinfected patients, particularly after SVR achievement.

This study had several limitations. First, the sample size was relatively small, and data were collected from a single tertiary medical center. Moreover, the patient population was predominantly male. The above reasons might limit the generalizability of our results to the female population or primary care institutes. Second, to make our study population more homogenous, we excluded HIV-infected people with acute HCV infection or coinfected patients with hepatic decompensation. Recently published results indicate that owing to the high potency and excellent safety profiles of DAAs, they remained highly effective even in these clinical situations.[48–51]

In conclusion, the study presented a real-world cohort of HCV-HIV–coinfected patients in which multiple HCV genotypes/subtypes were included; 17.3% of the patients had failed previous PEG-IFN/RBV, 67.3% had baseline HCV RNA >2 000 000 IU/mL, and 32.7% exhibited advanced fibrosis. Treatment with all-oral DAAs yielded an outstanding success rate, good tolerability, and excellent safety profiles for this subpopulation, which usually exhibits poor long-term prognosis.

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