A 12-week rescue therapy by PrOD-based regimen for advanced fibrotic genotype-1 CHC patients who failed to pegylated interferon plus ribavirin

Sih-Hsien Wu[a], Chi-Jen Chu[a,b,*], Chung-Chi Lin[b,c], Chien-Wei Su[a,b], 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]

[a]Division of Gastroenterology and Hepatology, Department of Medicine, Taipei Veterans General Hospital, Taipei, Taiwan, ROC; [b]Faculty of Medicine, School of Medicine, National Yang-Ming University, Taipei, Taiwan, ROC; [c]Healthcare and Services Center, Taipei Veterans General Hospital, Taipei, Taiwan, ROC; [d]Division of Gastroenterology, Department of Medicine, Cheng Hsin General Hospital, Taipei, Taiwan, ROC

Abstract

Background: Treatment of chronic hepatitis C (CHC) evolved rapidly due to the invention of interferon-free direct antiviral agents. Previous clinical trials showed combination therapy with paritaprevir/ritonavir, ombitasvir, and dasabuvir (PrOD) with or without ribavirin (RBV) can cure over 95% of genotype 1 CHC patients, regardless with cirrhosis or not. However, real-world data regarding the efficacy and safety of PrOD-based therapy in Asian HCV genotype 1 CHC patients are limited, especially for advanced-fibrotic patients who failed previous therapy with pegylated interferon (PEG-IFN) plus RBV.

Methods: Between January and October 2017, 60 advanced fibrotic (≥F3) genotype 1 CHC patients who failed previous therapy with PEG-IFN and received PrOD-based therapy for 12 weeks were retrospectively enrolled. Weight-based RBV 800 to 1200 mg/d was added for genotype 1b patients with cirrhosis and all genotype 1a patients. Sustained virological response (SVR) was defined by undetectable HCV RNA at the end and 12 weeks after the completion of therapy.

Results: The mean age was 63.2 ± 9.3 years, 26 (43.3%) of them were males and 20 (33.3%) were diagnosed to have liver cirrhosis. The mean baseline HCV RNA level was 6.19 ± 0.88 $\log_{10}$ IU/mL and 86.7% (52/60) of patients were infected by HCV genotype 1b. After PrOD-based therapy, the rates undetectable HCV RNA (<15 IU/mL) at week 2, 4, and 12 were 61.7%, 90.0%, and 100%, respectively; 69.6% (16/23) of patients with detectable HCV RNA at week 2 were < 100 IU/mL. Pruritus, fatigue, headache, insomnia, and dizziness were the most common patient-reported adverse events. Grade 2 hyperbilirubinemia were found in 21.6% (13/60) of patients during study period and all belonged to unconjugated hyperbilirubinemia. After posttherapy follow up, all 60 patients (100%) achieved SVR.

Conclusion: Our real-world data in Taiwan revealed that PrOD-based rescue therapy is well-tolerated and highly effective for genotype 1 CHC patients with advanced fibrosis failing previous therapy with PEG-IFN plus RBV.

Keywords: Chronic hepatitis C; Direct acting antiviral agent; Genotype; Pegylated interferon; Rescue therapy; Sustained virological response

1. INTRODUCTION

Chronic hepatitis C virus (HCV) infection is one of the leading causes of liver cirrhosis, hepatic decompensation, hepatocellular carcinoma (HCC), and liver transplantation candidacies.[1–3] The worldwide prevalence of HCV infection is estimated to be 3% and results in approximately 350 000 deaths annually.[4,5] Therefore, early intervention of chronic hepatitis C (CHC) infection is urgently needed to reduce or halt the consequences of liver-related morbidity and mortality. Genotype 1 accounts for approximately 70% of all HCV infections and subgenotype 1b is most predominant in Europe and Eastern Asia, including Taiwan.[6,7]

Before January 2017, the standard therapy for CHC in Taiwan was pegylated interferon (PEG-IFN) plus ribavirin (RBV). Data from Western countries showed the overall sustained virological response (SVR) rate for CHC was 54% to 63%. Although studies demonstrating SVR rates after PEG-IFN plus RBV tend to be higher in Asian CHC populations due to racial differences of human interleukin-28B (IL-28B) gene polymorphism, the SVR rates still far from ideal.[8–10] In addition, PEG-IFN plus RBV related side effects and ineligibility remained the major obstacles to initiate antiviral therapy for elderly population and those with various comorbidities.

Treatment options of CHC evolved rapidly in recent years due to the invention of IFN-free all oral direct antiviral agents (DAAs). When compared with IFN-based antiviral therapies, all oral DAAs were equipped with better efficacy, shorter treatment duration, and less adverse events (AEs).[11] Paritaprevir/ritonavir co-dosed with ombitasvir and dasabuvir (PrOD), an IFN-free all oral DAA regimen containing inhibitors of HCV nonstructural regions 3/4, 5A and 5B products was reimbursed by the Bureau

*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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of National Health Insurance (BNHI) of Taiwan after January 2017 for advanced fibrotic genotype 1 CHC patients. According to previous large-scaled registration trials, 12 or 24 weeks PrOD with or without RBV can achieve > 95% SVR rates for naive or treatment-experienced genotype 1 CHC patients with or without liver cirrhosis.[12–17] To date, the real-world experience of efficacy and safety of PrOD-based therapy in East Asian HCV genotype 1 patients are limited. More importantly, no published data focus on PrOD to treat advanced fibrotic patients having failed previous therapy with PEG-IFN plus RBV being more likely to have higher overall or liver-related mortality rates. Therefore, we conducted this study to address these important issues.

2. METHODS

2.1. Patients

Between January and October 2017, a total of 60 adult (≥20-years-old) advanced fibrotic (≥ METAVIR fibrosis stage 3) genotype 1 CHC patients who had failed previous therapy with PEG-IFN/RBV and received PrOD-based therapy for 12 weeks at Taipei Veterans General Hospital were retrospectively enrolled for analyses. Patients were excluded for analyses if they had history of decompensated liver cirrhosis, other than genotype 1 or mixed type HCV infection, chronic kidney disease stage 5, coinfected with hepatitis B or human immunodeficiency virus, and status post organ (liver, kidney, or heart) transplantation. 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 (albumin, total bilirubin, direct bilirubin, alanine aminotransferase [ALT], aspartate aminotransferase, creatinine, estimated glomerular filtration rate [eGFR]), anti-HCV, HCV RNA, HCV genotype were collected for all patients. Anti-HCV was detected by commercially available assay (anti-HCV; Abbott HCV EIA 2.0, Abbott Laboratories, Abbott Park, Illinois, USA) and serum quantitative HCV RNA level was determined by real-time PCR (Cobas Taqman HCV Test v2.0, Roche Diagnostics, Mannheim, Germany) with lower detection limit of 15 IU/mL. Stage of fibrosis was measured by liver stiffness using transient elastography (FirboScan, Echosens, Paris, France). The reference range of hepatic fibrosis by transient elastography was as follows: F0-F1 (≤7.0 kPa), F2 (7.1 to 9.4 kPa), F3 (9.5 to 12.4 kPa), F4 (≥12.5 kPa).[18]

All patients received paritaprevir/ritonavir and ombitasvir (Viekirax, 75 mg/50 mg/12.5 mg film-coated tablet, Abbvie Deutschland GmbH & Co, KG, Germany) two tablets daily, and dasabuvir (Exviera, 250 mg film-coated tablet, Abbvie Deutschland GmbH & Co, KG, Germany) one tablet twice daily (PrOD) for 12 weeks. Weight-based RBV (Robatrol, 200 mg capsule, Genovate Biotechnology Co., Ltd. Taiwan) was added for genotype 1b patients with cirrhosis and all HCV genotype 1a patients. 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.

Before the initiation of PrOD, extensive survey of regular medications taken by enrolled patients for possible drug-to-drug interaction (DDI) was performed. Medications that could have potential DDI were discontinued, shifted to alternative drugs, or started at the lowest dose as judged by physicians. The dose of RBV can be reduced by 200 mg/day after Week 4 if hemoglobin decreases > 2.0 g/dL compared to 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 posttreatment week 12 to define virological response. SVR_{12} was defined by undetectable HCV RNA level (<15 IU/mL) at the end of PrOD and 12 weeks after completion of therapy. Patients who lacked SVR_{12} data were considered failure to achieve SVR_{12}.

2.4. Safety and adverse events

During treatment period, patients were assessed by physicians at Weeks 1 and 2 and then every two weeks or more often in case of having 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 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 statistical significant at $p < 0.05$.

3. RESULTS

3.1. Baseline characteristics of enrolled patients

A total of 60 patients were recruited in this study for analyses. The mean age of enrolled population was 63.2 ± 9.3 years, 26 (43.3%) of them were males and 20 (33.3%) diagnosed to have liver cirrhosis. The mean baseline HCV RNA level was 6.19 ± 0.88 $\log_{10}$ IU/mL and 70% (42/60) of them were with baseline HCV RNA ≥ 800 000 IU/mL; 86.7% (52/60) of them were infected by HCV genotype 1b and the others were infected by subtype 1a (Table 1). Previous treatment response to PEG-IFN plus RBV was as follows: relapser 63.3% (38/60), partial or null responder 23.3% (14/60), intolerant and early terminated 13.3% (8/60). Regarding treatment regimen, 32 patients (53.3%) received PrOD without RBV and the remaining 28 patients (46.7%) received PrOD plus weight-based RBV for 12 weeks.

3.2. Virological response during and after PrOD

After PrOD-based therapy, the rates undetectable HCV RNA by real-time PCR assay at week 2, 4, and 12 were 61.7%, 90.0%, and 100%, respectively. Detailed virological responses to PrOD among different subgenotypes and with or without RBV were summarized in Table 2. For the 23 (38.3%) patients with detectable serum HCV RNA after 2 weeks of PrOD, 11 of them had lower level HCV RNA between 15 and 50 IU/mL and only seven patients had HCV RNA higher than 100 IU/mL (Table 3). All 60 patients finished 12 weeks of PrOD-based therapy without interruption and completed posttreatment follow-up, and the SVR_{12} rate was 100% for enrolled population (Table 2).

3.3. ALT normalization

In our cohort of patients, baseline serum ALT ≥ 40 IU/L was found in 76.7% (46/60) and 23.3% (14/60) had baseline serum ALT < 40 IU/L. ALT normalization was found as early as treatment Week 2 from 23.3% to 86.9% followed by 91.3%, 92.8%, and 93.3% at Week 4, Week 12, and posttreatment Week 12, respectively. Median time to ALT normalization was 3.4 ± 4.1 weeks.

Table 1

Baseline characteristics of enrolled 60 patients

Characteristics	Patients (n = 60)
Mean age, y	63.2 ± 9.3
Age ≥ 65 y, %	28 (46.7%)
Male gender, %	26 (43.3%)
F3 fibrosis/liver cirrhosis, %	40 (66.7%)/20 (33.3%)
History of HCC, %	6 (10.0%)
Previous PEG-IFN/RBV response, %	
Relapser	38 (63.3%)
Partial or null responder	14 (23.3%)
Intolerant and early terminated	8 (13.3%)
Genotype, 1a/1b	8 (13.3%)/52 (86.7%)
PrOD regimen, %	
PrOD for 12 wks	32 (53.3%)
PrOD with RBV for 12 wks	28 (46.7%)
Mean baseline HCV RNA, log IU/mL	6.19 ± 0.88
Baseline HCV RNA > 800 000 IU/mL, %	42 (70%)
Mean haemoglobin, g/dL	13.4 ± 1.6
Mean white cell count, $\times 10^9$/L	6.3 ± 2.0
Mean platelet count, $\times 10^9$/L	162.5 ± 72.2
Mean albumin, g/dL	4.05 ± 0.36
Alanine aminotransferase, IU/L	89.2 ± 77.8
Mean total bilirubin, mg/dL	0.84 ± 0.41
eGFR, mL/min/1.73 m^2	71.2 ± 24.8
≥60	49 (81.7%)
30-59	7 (11.7%)
<30	4 (6.6%)
Mean creatinine, mg/dL	0.82 ± 0.2

HCC = Hepatocellular carcinoma; HCV RNA = Hepatitis C virus RNA; Peg-IFN = pegylated-interferon; PrOD = paritaprevir/ritonavir, ombitasvir, and dasabuvir; RBV = ribavirin.

3.4. Safety and adverse events

Forty patients (66.7%) had at least one AE. Pruritus, fatigue, headache, dizziness, insomnia, and skin rashes were the most common subjective AEs that all enrolled patients reported (Table 4). For patients who received PrOD therapy only, the most common AEs experienced were fatigue, pruritus, insomnia, and headache. Among these AEs, PrOD group was more likely to have fatigue, insomnia, and constipation ($p < 0.05$). For patients who received PrOD plus RBV, the most common AEs reported were pruritus, headache, dizziness, and fatigue. Among these AEs, PrOD plus RBV group was more likely to have headache, pruritus, diarrhea, asthenia, dizziness, dyspnea, and edema ($p < 0.05$). Grades of the above subjective AEs were generally mild and could be symptomatically relieved by medications.

Regarding the laboratory AEs, the mean decline of hemoglobin (Hgb) during treatment for patients with PrOD alone or in combination with RBV were 0.134 ± 0.09 g/dL and 1.48 ± 1.29 g/dL, respectively ($p < 0.0001$). We also found that PrOD plus RBV group was more likely to have hyperbilirubinemia and ALT elevation ($p < 0.05$). Only 5% (3/60) of patients had grade 2 (Hgb: 8.0 to 10.0 g/dL) anemia during whole treatment course, and no grade 3 anemia (Hgb < 8.0 g/dL) was found (Table 5). Grade 2 ALT elevation (3 to 5 × ULN) was detected in 3.3% of enrolled patients and no patients reached grade 3 (5 to 20 × ULN) ALT elevation. Grade 2 (1.5 to 3.0 × ULN) hyperbilirubinemia was found in 21.6% (13/60) of enrolled patients during study period and all of them belonged to unconjugated hyperbilirubinemia. With continuous PrOD-based 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 5).

Table 3

Distribution of HCV RNA levels after 2 weeks of PrOD

Week 2 HCV RNA level	Number	Percentage (%)
<15 IU/mL	37	61.7%
15-50 IU/mL	11	18.3%
50-100 IU/mL	5	8.4%
>100 IU/ mL	7	11.6%

HCV RNA = Hepatitis C virus RNA; PrOD = paritaprevir/ritonavir, ombitasvir, and dasabuvir.

4. DISCUSSION

Successful antiviral treatment response brings huge beneficial effect on long-term outcome for patients with CHC. 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.[19] Moreover, the all-cause mortality can further be reduced to about 74% for CHC patients with cirrhosis. Metaanalyses results also demonstrated CHC patients with SVR have improved hepatic and extrahepatic outcomes, including the reduction of HCC risk and better renal/circulatory consequences.[20] On the contrary, according to longitudinal follow-up study, advanced fibrotic CHC patients failing previous IFN-based therapy had significantly higher rate of all-cause mortality, liver-related mortality, liver failure, and HCC compared to CHC patients who achieved SVR.[21] Therefore, effective rescue therapies for CHC patients who failed previous IFN-based treatment are in urgent need to improve these patients' outcome.

The therapeutic landscape of CHC changed rapidly after the invention of DAAs. Early data from Western countries revealed that SVR rates with adding telaprevir or boceprevir, the first available DAAs, to PEG-IFN/RBV are generally lower in previous IFN failure than treatment of naive patients, and are noticeably lower among prior IFN null responders.[22–26] Fortunately, the above therapeutic drawback was overcome by more potent second generation all oral DAAs. For example, registration trials showed 12 or 24 weeks PrOD with or without RBV can achieve >95% SVR rates for genotype 1 CHC patients with or without liver cirrhosis.[12–17] Previous major determinants of SVR during PEG-IFN era, including age, ethnicity, baseline HCV RNA level, stages of fibrosis, and previous treatment response, did not strongly influence the ultimate treatment outcome during treatment of CHC with novel DAAs. The efficacy of PrOD with or without RBV was validated recently in several real-life cohorts in Europe and the United States. Consistent with previous trial reports, real-world data in Western HCV genotype 1 patients receiving PrOD with or without RBV for 12 weeks showed that SVR_{12} rates ranges from 87.6 to 98.9%.[27–32]

Table 2

Virological responses to PrOD among different subgenotypes

	Undetectable HCV RNA (%)			
Time	Overall (n = 60)	Subtype 1a (n = 8)	Subtype 1b with cirrhosis (n = 20)	Subtype 1b with F3 fibrosis (n = 32)
Week 2	37 (61.7%)	4 (50.0%)	11 (55.0%)	22 (68.8%)
Week 4	54 (90.0%)	5 (62.5%)	18 (90.0%)	31 (96.9%)
Week 12	60 (100%)	8 (100%)	20 (100%)	32 (100%)
Posttreatment week 12	60 (100%)	8 (100%)	20 (100%)	32 (100%)

HCV RNA = Hepatitis C virus RNA; PrOD = paritaprevir/ritonavir, ombitasvir, and dasabuvir.

Table 4

Subjective adverse events during PrOD therapy

All patients (n = 60), n, %		PrOD (n = 32), n, %	PrOD + RBV (n = 28), n, %	*p*
Fatigue	17 (28.3%)	11 (34.4%)	6 (21.4%)	<0.001
Headache	14 (23.3%)	6 (18.8%)	8 (28.5%)	<0.001
Nausea	2 (3.3%)	1 (3.1%)	1 (3.6%)	0.20
Insomnia	10 (16.6%)	6 (18.8%)	4 (14.3%)	0.02
Pruritus	18 (30.0%)	7 (21.9%)	11 (39.3%)	<0.001
Diarrhoea	6 (10.0%)	2 (6.3%)	4 (14.3%)	0.001
Asthenia	4 (6.6%)	1 (3.1%)	3 (10.7%)	0.006
Rash	9 (15.0%)	5 (15.6%)	4 (14.3%)	0.06
Irritability	1 (1.7%)	1 (3.1%)	0 (0.0%)	0.05
Dizziness	10 (16.6%)	3 (9.4%)	7 (25.0%)	<0.001
Dyspnea	3 (5.0%)	1 (3.1%)	2 (7.1%)	0.04
Edema	3 (5.0%)	1 (3.1%)	2 (7.1%)	0.04
Constipation	2 (3.3%)	2 (6.3%)	0 (0.0%)	0.01

PrOD = paritaprevir/ritonavir, ombitasvir, and dasabuvir; RBV = ribavirin.

Table 5

Laboratory adverse events during PrOD therapy

All patients (n = 60), n, %		PrOD (n = 32), n, %	PrOD + RBV (n =28), n, %	*p*
Hemoglobin level				
Grade 2	3 (5.0%)	1 (3.1%)	2 (7.1%)	0.04
Grade 3	0 (0.0%)	0 (0.0%)	0 (0.0%)	
Total bilirubin				
Grade 2	13 (21.6%)	6 (18.8%)	7 (25%)	0.001
Grade 3	0 (0.0%)	0 (0.0%)	0 (0.0%)	
ALT				
Grade 2	2 (3.3%)	0 (0.0%)	2 (7.1%)	0.01
Grade 3	0 (0.0%)	0 (0.0%)	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).
PrOD = paritaprevir/ritonavir, ombitasvir, and dasabuvir.

To date, this is the first real world Asian study focusing on the efficacy of PrOD for advanced fibrotic genotype 1 CHC patients who failed previous therapy with PEG-IFN plus RBV, the high risk group to develop complications of liver cirrhosis and HCC. 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. Highly effective antiviral response by PrOD was demonstrated in the current study, even in this difficult-to-treat population. Our study showed HCV RNA undetectable (<15 IU/mL) rate after 2 and 4 weeks of PrOD therapy were 61.7% and 90.0%, respectively. In addition, 47.8% (11/23) of patients with detectable HCV RNA at Week 2 belonged to low-level viremia (HCV RNA < 50 IU/mL). No patient early terminated PrOD therapy and the overall SVR_{12} rate was 100%. Like data in the PEG-IFN era, equivalent or even better treatment response was found in Taiwanese CHC patients when compared with Western populations.[10] Besides, our study showed concordant results with two recently published real-world studies from Hong Kong and Taiwan,[33,34] in which the SVR_{12} rates after PrOD therapy were 94.3% and 98.1%, respectively, and all kinds of CHC subpopulations were taken into analyses.

Elevated total bilirubin level was in the most frequent laboratory abnormality during treatment with PrOD. In the current study, 13 patients (21.6%) had grade 2 hyperbilirubinemia during the first two weeks of therapy. All of them belonged to unconjugated type hyperbilirubinemia and gradually resolved with continuous treatment with PrOD. Factors responsible for unconjugated hyperbilirubinemia were probably related to the inhibition of bilirubin transporters OATP1B1 and OATP1B3 by paritaprevir alongside RBV-induced hemolysis.[12–14] Previous reports showed hepatic decompensation can occur during PrOD therapy, especially for the patients with advanced liver disease or history of hepatic decompensation. Although no hepatic decompensation was found in our study, clinical physicians should closely monitor the total and direct type bilirubin levels during PrOD-based therapy to secure patient's safety, particularly in patients with compensated liver cirrhosis as these patients tend to have higher serum concentration of PrOD due to poor liver reservation than the noncirrhotic patients.[28,30–32] In addition, prior to the initiation of PrOD, detailed regular medication survey to avoid potential DDI was very important. In summary, the subjective and laboratory AEs of our enrolled patients are generally mild and tolerable; therefore, no one need to stop PrOD prematurely.

In conclusion, our real world data in Taiwan demonstrated for genotype 1 CHC patients with advanced fibrosis who failed previous therapy with PEG-IFN plus RBV, the subpopulation with high likelihood to develop complications of cirrhosis and HCC, a 12-week PrOD-based rescue therapy is well-tolerated and highly effective.

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