

[ORIGINAL ARTICLE]

The Real-world Efficacy and Safety of Ombitasvir/Paritaprevir/Ritonavir for Hepatitis C Genotype 1

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Abstract:

Objective There are few reports on the outcomes of 12-week paritaprevir, ombitasvir, and ritonavir (PTV/OBV/r) treatment in real-world clinical settings. We aimed to evaluate the efficacy and safety of 12-week treatment with ritonavir-boosted paritaprevir and ombitasvir in patients with hepatitis C virus (HCV) genotype 1 infection in a real-world setting.

Methods Fifty-eight patients with chronic hepatitis or compensated hepatic cirrhosis and genotype-1 HCV infection were treated with PTV/OBV/r and followed for 24 weeks after the completion of treatment in 10 centers in northern Tohoku. The efficacy and safety of this 12-week treatment regimen was analyzed.

Results Among the 58 treated patients, 18 (31%) had compensated liver cirrhosis, while 11 (19%) patients had experienced treatment failure with another treatment regimen. NS5A resistance-associated variants (RAVs) were detected at baseline in 3 patients (5.2%), including Y93H in two patients and L31M in two patients. One patient had NS5A RAVs at both positions 93 and 31. The overall sustained virological response (SVR) 24 rate was 96.6%. Three patients with NS5A RAVs also achieved an SVR24. The SVR24 rate was not significantly affected by age, sex, prior treatment, prior history of HCC, or liver stiffness. The mean alanine aminotransferase (ALT) levels decreased significantly during this treatment. Adverse events occurred in 15 patients (26%), 26% of which were grade 1 or 2. No severe adverse events occurred.

Conclusion In this real-world study, 12-week PTV/OBV/r treatment was effective and safe for treating patients with HCV-1 infection who had chronic hepatitis or compensated hepatic cirrhosis.

Key words: hepatitis C virus, direct acting antivirals, paritaprevir/ombitasvir/ritonavir, real-world setting

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Introduction

Hepatitis C virus (HCV) is a leading cause of hepatic cirrhosis and hepatocellular carcinoma (HCC) (1, 2). HCV clearance by interferon (IFN)-based treatment suppresses the progression of chronic liver disease (3, 4). Genotype 1b HCV accounts for 67% of HCV infections in Japan (5).

Thus, until recently, NS3/4A protease inhibitors, in combination with pegylated interferon alpha (PEG-IFN α) and ribavirin for 24 weeks, have been the standard treatment for Japanese patients with HCV genotype 1 (HCV-1). The development of direct acting antiviral agents (DAAs) has led to the establishment of IFN-free treatment protocols. All oral DAAs have been widely utilized for the treatment of chronic HCV-1 since 2014 and have been shown to be both highly

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effective and safe. Several other oral antiviral combinations are now available to treat HCV-1.

A phase II clinical trial reported on the efficacy and safety of DAAs combined with paritaprevir (PTV, an NS3/4A protease inhibitor), ombitasvir (OBV, an NS5A inhibitor) and ritonavir (r) (PTV/OBV/r) in the treatment of HCV-1 infection in Japanese patients (6). The feature of this regimen is that low-dose ritonavir increases the peak and trough levels of PTV, thereby increasing the overall drug exposure (7). In a phase III clinical trial, treatment with ritonavir-boosted PTV and OBV was shown to achieve a high sustained virological response (SVR) rate of 95% in patients with HCV-1 infection, including those with compensation cirrhosis; furthermore, it was safe and well-tolerated (8). Based on the data from that clinical trial, PTV/OBV/r was approved in Japan in November 2015. Since its commercial release, this medicine has been administered to patients with HCV-1. However, there are few reports on the outcomes of 12-week PTV/OBV/r treatment in real-world clinical settings.

The aims of this study were to evaluate the efficacy and safety of PTV/OBV/r treatment in chronic HCV-1 patients in a real-world setting, and to characterize the laboratory abnormalities that occur during PTV/OBV/r treatment.

Materials and Methods

Study design

Between October 2014 and December 2016, a total of 58 consecutive patients with chronic HCV-1 infection underwent 12-week treatment with PTV/OBV/r at Iwate Medical University Hospital and 9 viral treatment centers. This study was a retrospective cohort study. The enrollment criteria included age ≥ 18 years and the confirmation of chronic HCV-1 infection before treatment. The presence of cirrhosis was investigated at screening by local physicians based on various combinations of liver biopsy findings [*e.g.*, a METAVIR score of 4 (9)], a Fibro Index of ≥ 4 (10), an aspartate aminotransferase (AST) to platelet ratio index (APRI) of > 2 (11), a Fib-4 index of > 3.25 (12), serum markers of fibrosis [*e.g.* M2BPGi (13)], transient elastography [*e.g.* Shear wave elastography (14)] and a liver imaging examination (ultrasonography, computed tomography or MR imaging) that revealed signs of cirrhosis (*e.g.* enlargement of the left lobe of the liver, atrophy of the right lobe of the liver, irregularity of the hepatic surface, and splenomegaly) in combination with the clinical state. Patients with an HCV genotype other than 1, decompensated liver disease (Child-Pugh grade B or C), other causes of liver disease, hepatitis B infection, human immunodeficiency virus infection, stage 4-5 chronic kidney disease, and patients undergoing hemodialysis were excluded from the present study.

This study was performed in accordance with the Declaration of Helsinki and was also approved by the ethics committee of Iwate Medical University and each the respective

committees at treatment site. Informed consent was obtained from all of the patients before treatment.

Patients were treated for 12 weeks with PTV (150 mg, once daily), OBV (100 mg, once daily) and ritonavir (25 mg, once daily) (Viekirax[®], AbbVie, North Chicago, USA). The final decision to reduce the dose, or discontinue the treatment was made by the local physician.

Peripheral blood samples were obtained before treatment, at 1, 2 and 4 weeks after the first administration of PTV/OBV/r, and every 4 weeks thereafter until 36 weeks. The serum HCV RNA levels were measured by the COBAS TaqMan HCV test (Roche Diagnostics, Tokyo, Japan). The detection range of this quantitation assay ranges from 15 to 6.9×10^7 IU/mL (1.2-7.8 Log IU/mL) and an undetectable level of HCV RNA is defined as negative. The HCV genotypes were determined by a polymerase chain reaction (PCR) according to the method of Okamoto et al. (15).

To assess the effect of baseline NS5A resistance-associated variants (RAVs), NS5A amino acid position 31 and 93 were checked by direct sequencing and NS5A Y93 mutations were evaluated at baseline by a Cycleave PCR (16) (SRL Laboratory, Tokyo, Japan) or the PCR-Invader method (17) (BML, Tokyo, Japan).

The evaluation of the treatment efficacy

An SVR was defined as undetectable HCV RNA at 24 weeks after the completion of treatment. A non-SVR was defined as a detectable level of HCV RNA at the end of treatment, or an undetectable level of HCV RNA at the end of treatment but a detectable level of HCV RNA at 24 weeks after treatment. The primary efficacy endpoint was the percentage of patients who achieved an SVR 24 in the intention-to-treat analysis.

Safety assessment

Treatment-associated adverse events (AEs), including clinical, biochemical and hematological abnormalities occurring during this study were reported and collected. The frequency of PTV/OBV/r-associated AEs was calculated. The grades of AEs were classified in accordance with the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0. The primary safety endpoint was the frequency of AEs.

Statistical analyses

All of the statistical analyses were performed using the SPSS software program (SPSS Statistics for Windows, SPSS, Chicago, USA). The treatment outcomes were analyzed on an intention-to-treat basis, which was defined by all patients who received at least one dose of the study drug (including cases of nonvirological failure; *e.g.* lost to follow-up or early discontinuation). The 95% confidence interval (CI) was calculated for the SVR24 rate. The clinical parameters were compared between the groups using the Mann-Whitney U-test or chi-squared test. Two-tailed p values of < 0.05 were considered to indicate statistical signifi-

Table 1. The Baseline Characteristics of the Patients.

characteristics	OBV/PTV/r (n=58)
Gender (male/female)	29/29
Age (years old) ^a	68±12
Body mass index ^a	22.8±3.7
Aspartate transferase (IU/L) ^a	45±26
Alanine transferase (IU/L) ^a	44±28
White blood cell count (/mL) ^a	4,760±1,495
Hemoglobin (g/dL) ^a	13.6±1.7
Platelet count (×10 ⁴ /mL) ^a	15.9±1.7
Chronic hepatitis/compensated liver cirrhosis	40/18
Past history of HCC (yes/no)	5/53
HCV-RNA (LogIU/mL) ^a	5.8±0.8
Y93H (yes/no) ^b	2/56
L31L/I (yes/no) ^b	2/56
Previous antiviral treatment (yes/no/unknown)	11/45/2
estimated Glomerular Filtration Rate (mL/min/1.73m ²) ^a	69.5±16.1
Taking calcium channel blockers	4

^aData are expressed as the mean±standard deviation

^bdirect sequence

cance.

Results

Patients' characteristics

Table 1 summarizes the baseline clinical features of the 58 patients, (male, n=29; female, n=29). The mean age was 68 years (range: 30-84 years). The mean serum alanine aminotransferase (ALT) level at baseline was 44 IU/L (range: 12-122). The mean serum HCV RNA level before treatment was 5.8 Log IU/mL (range: 2.2-7.0). NS5A RAVs were detected at baseline in 3 of the 58 patients (5.2%), including Y93H in two patients and L31M in two patients. One patient had NS5A RAVs at both positions 93 and 31. Eighteen patients (31.0%) had compensated cirrhosis. Previous antiviral treatment had failed in 11 of the 58 (19.0%) patients. One of those patients had previous exposure to treatment with a combination of NS5A and NS5B inhibitors (Ledipasvir and Sofosbuvir, Harvoni[®], Gilead Sciences, Foster City, USA). This patient had NS5A RAVs at both positions 93 and 31.

Five (8.6%) patients had a prior history of HCC. Hypertension was present in 17 (29.3%) patients. Calcium channel blockers were changed to angiotensin II receptor blockers in four of the patients with hypertension.

Responses to treatment (virologic analysis)

The HCV-RNA disappearance rates according to time are shown in Fig. 1A.

Two patients were considered to show nonvirological failure. One patient discontinued treatment prematurely because of AEs; the other was lost to follow-up.

Serum samples of 53 of the 58 (91.4%) patients were negative for serum HCV RNA at 4-weeks after the initial

administration of PTV/OBV/r. At 8 weeks after the initial administration, serum HCV RNA disappeared in 56 of the 57 (98.2%) patients, and the seronegativity persisted until the end of treatment. The overall SVR24 rate was 96.6% (56 of 58, 95%CI 88.1-99.6). The baseline features of the patients were analyzed to determine if any features were associated with an SVR (Fig. 1B). The age, sex, prior treatment and liver stiffness did not differ to a statistically significant extent between the patients with and without an SVR24.

Fifty-four of the 56 (96.4%) patients without NS5A RAVs at amino acid 93 achieved an SVR24: as did the 2 (100%) patients with NS5A RAVs at the same position. Similarly, 54 of 56 (96.4%) patients without NS5A RAVs at amino acid 31 and both of the patients (100%) with NS5A RAVs at the same position achieved an SVR24. Meanwhile, one patient who had previously been treated with a combination of NS5A and NS5B inhibitors achieved an SVR24.

Safety and treatment discontinuation

Two patients discontinued treatment. One patient stopped due to ALT elevation. The other patient, who ceased treatment after 4 weeks (based on the patient's wishes) went on to achieve an SVR24. All of the other patients completed the 12-week course of treatment. No deaths were reported within the study period.

Fifteen (25.9%) patients reported AEs, which were mostly mild in severity (Table 2). The most common AEs were headache (n=3, 5.1%) and gastrointestinal disorder (n=3, 5.1%). No edema-related AEs occurred. The AEs were predominantly grade 1 or 2; no severe adverse events occurred.

Biochemistry (laboratory) abnormalities

Hyperbilirubinemia was defined as a total bilirubin level of >1.2 mg/dL. Fig. 2A depicts the change in the mean total

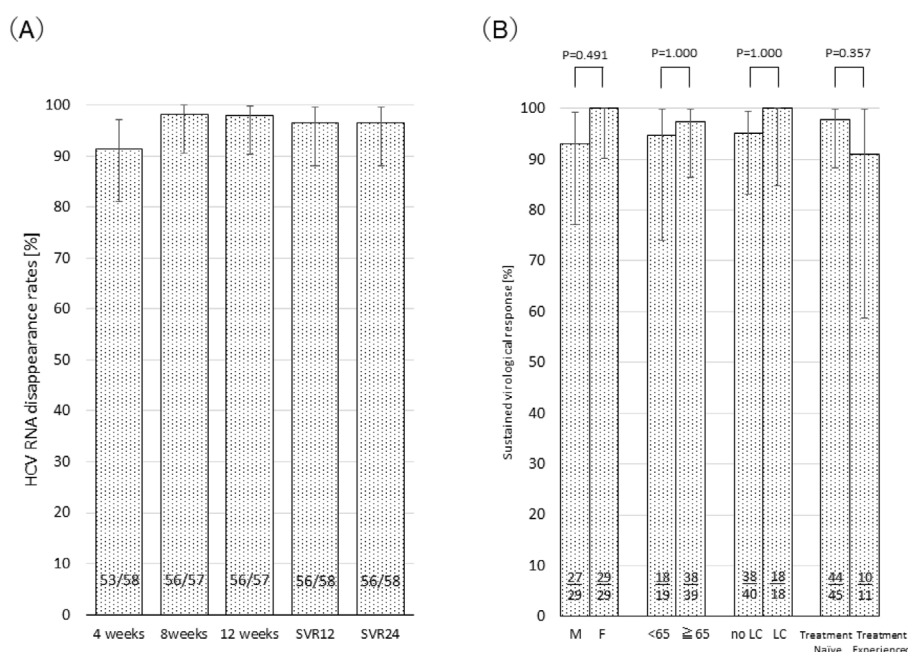


Figure 1. The virological responses to PTV/OBV/r treatment. (A) The percentages of patients in whom HCV RNA was undetectable during and after treatment. (B) The SVR rate according to the patient characteristics.

Table 2. Adverse Events (AEs).

	n (%)
Treatment discontinuation due to AEs	1
Death	0
Treatment-related serious AEs	0
Treatment-related common AEs	
Fever	2 (3.4)
Headache	3 (5.1)
Rash	1 (1.7)
Pruritus	2 (3.4)
Dizziness	2 (3.4)
Rhinorrhea	1 (1.7)
Cough	1 (1.7)
Gastroesophageal reflux disease	1 (1.7)
Gastrointestinal disorders	3 (5.1)
Duodenal ulcer	1 (1.7)
Constipation	1 (1.7)
Diarrhea	2 (3.4)
Laboratory abnormalities	
ALT, >5×ULN	0
AST, >5×ULN	0
Total Bilirubin, >3×ULN	0
Hemoglobin, <8g/dL	0
eGFR, <30 mL/min/1.73m ²	0

bilirubin concentration. Hyperbilirubinemia was present at baseline in 4 (6.9%) patients and occurred in 11 (19.0%) patients, with most only experiencing a mild (Grade ≤ 2) elevation. The mean total bilirubin concentration was the highest at 1 week after the initial treatment. No patients showed Grade ≥3 total bilirubin elevation.

The normalization of ALT was defined as an ALT level of

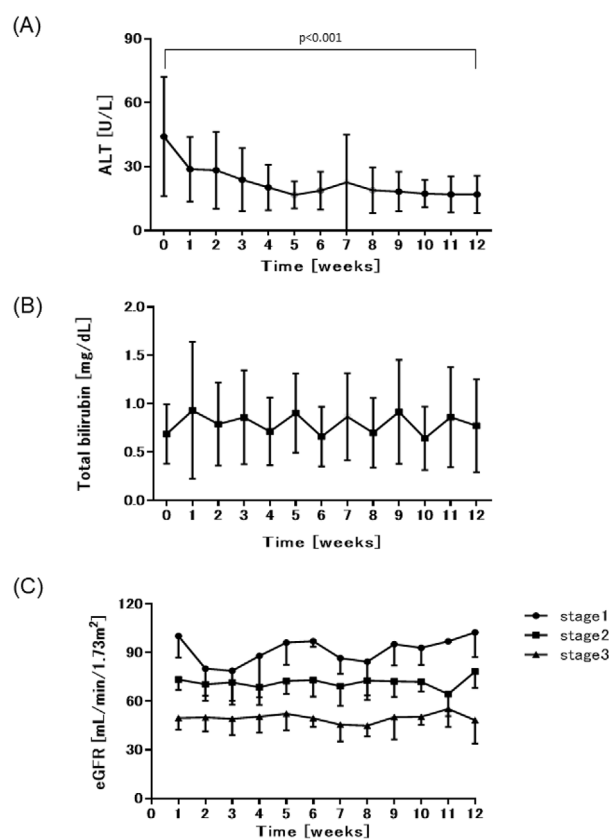


Figure 2. Changes from baseline to the end of treatment. (A) ALT. (B) Total bilirubin. (C) eGFR. The ALT level significantly decreased during PTV/OBV/r treatment.

<30 U/L. Fig. 2B shows the changes in the mean ALT levels. Twenty-five patients showed an ALT level of >30 U/L at

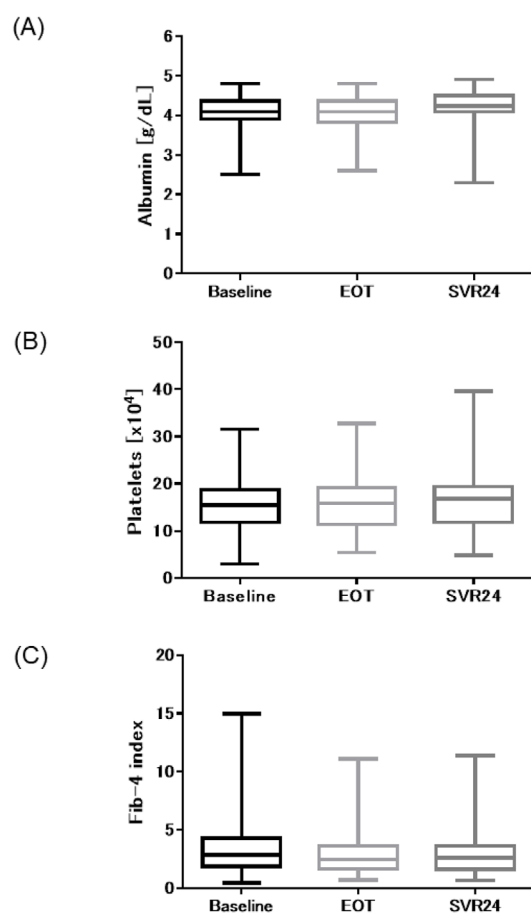


Figure 3. Changes from baseline to posttreatment week 24. (A) Albumin. (B) Platelet count. (C) Fib-4 index. There were no statistically significant improvements in the albumin level, platelet count, or Fib-4 index from baseline to post-treatment week 24.

baseline; the ALT levels then decreased with PTV/OBV/r treatment and normalized in all of these patients at the end of treatment. Finally, 55 patients (91.5%) had normal ALT levels at the end of treatment. At the end of treatment, the mean ALT level decreased from 44 U/L to 17 U/L ($p < 0.001$). However, 2 patients developed grade 2 ALT elevation during treatment with PTV/OBV/r. The dosage of PTV/OBV/r was reduced in one patient with ALT elevation at 7 weeks after the initiation of treatment, after which the patient's ALT levels normalized. One patient discontinued PTV/OBV/r treatment at 6 weeks after its initial administration due to ALT elevation. This patient did not achieve an SVR.

Chronic kidney disease stages 1, 2 and 3 are defined by estimated glomerular filtration rates (eGFRs) (mL/min/1.73 m²) of >90, 60-89 and 30-59, respectively. Fig. 2C illustrates change in the mean eGFR according to the stage. There were no significant changes in the eGFR (according to stage) from baseline to the end of treatment.

The albumin level, platelet count, and Fib-4 index did not show any statistically significant improvements from baseline to post-treatment week 24 in the overall study popula-

tion (Fig. 3).

Discussion

This study investigated the treatment efficacy and safety of PTV/OBV/r in daily clinical practice. The study population was a cohort of real-world patients treated with PTV/OBV/r. We analyzed 58 HCV-1 patients. Our main finding was that in daily clinical practice PTV/OBV/r therapy resulted in a high SVR24 rate of 96.6% in patients with HCV-1 infection (with chronic hepatitis or compensated hepatic cirrhosis). This high SVR24 rate was comparable to the rates reported for other interferon-free PTV/OBV/r regimens (8, 18). Moreover, a low rate of virological failure was observed in this study.

In Japan, NS5A variants Y93H and L31M are reported to be present in 8.2-25% and 2.2-4.6% of HCV-1b-infected patients, respectively (19, 20). In a phase III clinical trial, 14% of the patients had preexisting Y93H, and 83% of the patients with Y93H achieved an SVR24 (8). In the present study, few patients had NS5A RAVs and 3 patients with NS5A RAVs at amino acids 31 and/or 93 achieved an SVR24. Based on the outcomes of phase III clinical trials, patients with NS5A Y93 or L31 mutations may be strictly excluded, and those patients might have received other DAAs instead.

In the present study, all of the 18 (100%) patients with compensated cirrhosis achieved an SVR24. This was in line with other studies that reported high SVR rates (8, 18). It is noteworthy that the SVR rates of patients with compensated cirrhosis were similar to those of patients without cirrhosis.

The rate of discontinuation due to AEs was low in the present study. The overall incidence of AEs was 25.9% ($n = 15$). These AEs were mostly mild in severity. The most common AEs were headache and gastrointestinal disorder, which occurred in 3 patients each (5.1%). A phase III clinical trial demonstrated that the concomitant administration of PTV/OBV/r and calcium channel blockers increased the frequency of edema-related AEs; based on this finding, it was suggested that a different class of drug should be considered for the treatment of hypertension during PTV/OBV/r treatment (8, 21). Thus, in the present study, calcium channel blockers were exchanged for angiotensin II receptor blocker prior to treatment and no edema-related AEs occurred.

Hyperbilirubinemia and ALT elevation were observed during PTV/OBV/r treatment in clinical trials; however, the severity was predominantly grade 1 or 2 (8, 18). Such laboratory abnormalities are thought to be related to PTV (a protease inhibitor), which is primarily metabolized and eliminated by the liver (22). In the present study, no cases of ALT elevation to greater than five times the upper limit of normal or total bilirubin elevation to greater than three times the upper limit of normal were seen. PTV/OBV/r treatment was generally well tolerated.

Most real-world studies have limitations. This study was conducted in multiple centers. Consequently, the methods of data collection and the methods that were applied to the as-

assessment of cirrhosis were heterogeneous. Furthermore, the characteristics of the enrolled patients tended to be heterogeneous. However, this reflects the actual characteristics of patients treated in daily clinical practice. Alternatively, because the physician had a good understanding of the efficacy and safety of this treatment, it is likely that only those patients who satisfied the strict criteria received this treatment. The administration of PTV/OBV/r to patients with renal failure and patients on hemodialysis has been reported (23, 24). The present study did not include patients with stage 4-5 chronic kidney disease or patients on hemodialysis.

In conclusion, in this real-world study, 12-weeks of treatment with PTV/OBV/r achieved an SVR24 rate of 96.6% in HCV-1 infected patients with chronic hepatitis or compensated hepatic cirrhosis. This PTV/OBV/r treatment was well tolerated and the rate of discontinuation due to AEs was low. These results suggest that in daily clinical practice IFN- and ribavirin-free PTV/OBV/r treatment is a promising therapeutic option for HCV-1 infected patients with chronic hepatitis or compensated hepatic cirrhosis.

The authors state that they have no Conflict of Interest (COI).

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