Internal Medicine
The Japanese Society of Internal Medicine
doi: 10.2169/internalmedicine.0621-17
Intern Med 57: 2843-2845, 2018
http://internmed.jp

【 CASE REPORT 】

Successful Ombitasvir/Paritaprevir/Ritonavir Plus Ribavirin Retreatment for a Chronic Hepatitis C Genotype 2a Patient Who Relapsed after Sofosbuvir Plus Ribavirin Treatment

Toru Ishikawa, Michitaka Imai, Takashi Owaki, Hiroki Sato, Yujiro Nozawa, Tomoe Sano, Akito Iwanaga, Keiichi Seki, Terasu Honma and Toshiaki Yoshida

Abstract:
The optimum retreatment strategy for chronic hepatitis C virus (HCV) patients who failed directly-acting antiviral agents (DAA)-based therapy is unknown. We herein report the outcomes of an HCV genotype (GT) 2a-infected patient with virologic failure following treatment with sofosbuvir plus ribavirin (SOF+RBV) who was successfully retreated with ombitasvir/paritaprevir/ritonavir plus ribavirin (OBV/PTV/r+RBV).

Key words: HCV genotype 2a, retreatment, sofosbuvir plus ribavirin, ombitasvir/paritaprevir/ritonavir plus ribavirin

(Intern Med 57: 2843-2845, 2018)
(DOI: 10.2169/internalmedicine.0621-17)

Introduction

Recently, interferon (IFN)-free DAA-based combination therapy has become mainstream in the treatment of chronic hepatitis C (CHC) (1). Thus, the effectiveness and safety of several DAA regimens have been reported in detail since such agents become available.

However, DAA therapies are unfortunately unsuccessful in some cases. Few clinical experiences have been reported regarding retreatment options for patients who fail their first DAA regimen (2). Therefore, selecting retreatment options is an important matter to consider for the future.

We herein report the successful outcomes of retreatment with OBV/PTV/r+RBV in an HCV GT2a-infected patient with virologic failure following treatment with sofosbuvir plus ribavirin (SOF+RBV).

Case Report

A 75-year-old woman with a history of small intestine bleeding had been diagnosed with HCV GT2a infection at 70 years of age in 2012. Her single-nucleotide polymorphism (SNP) of the interleukin 28B (IL28) polymorphism was TT genotype (rs8099917). A histological diagnosis of chronic hepatitis C was established, with Grade 2 inflammatory activity (grading), and Grade 3 fibrosis (staging). She was treated with peginterferon plus ribavirin (PEGIFN+RBV) in 2013 after partial splenic arterial embolization (PSE) for thrombocytopenia. However, she was a non-responder to PEGIFN+RBV.

In July 2016, she began treatment with an all-oral regimen of sofosbuvir (SOF) at 400 mg daily and ribavirin (RBV) at 600 mg daily. At the time of starting the treatment, her height and weight were 155.2 cm and 48.35 kg, respectively. Her viral load was 4.9 Log IU/mL at baseline, and it became undetectable at week 4 of treatment, remaining undetectable throughout the 12 weeks of treatment. Treatment adherence was maintained because there were no serious adverse events during the SOF+RBV treatment. However, at 4 weeks after treatment had ended, the viral load increased to 5.9 Log IU/mL, indicating relapse.

At that time, the newest and particularly potent DAA regimen, glecaprevir (nonstructural protein 3/4A protease inhibitor) and pibrentasvir (nonstructural protein 5A inhibitor), had not yet been approved in Japan. Therefore, we chose OBV/PTV/r at 25/150/100 mg daily and RBV at 600 mg daily for retreatment of this patient in January 2017. This

Department of Gastroenterology and Hepatology, Saiseikai Niigata Daini Hospital, Japan
Received: December 1, 2017; Accepted: February 12, 2018; Advance Publication by J-STAGE: May 18, 2018
Correspondence to Dr. Toru Ishikawa, toruishi@ngt.saiseikai.or.jp

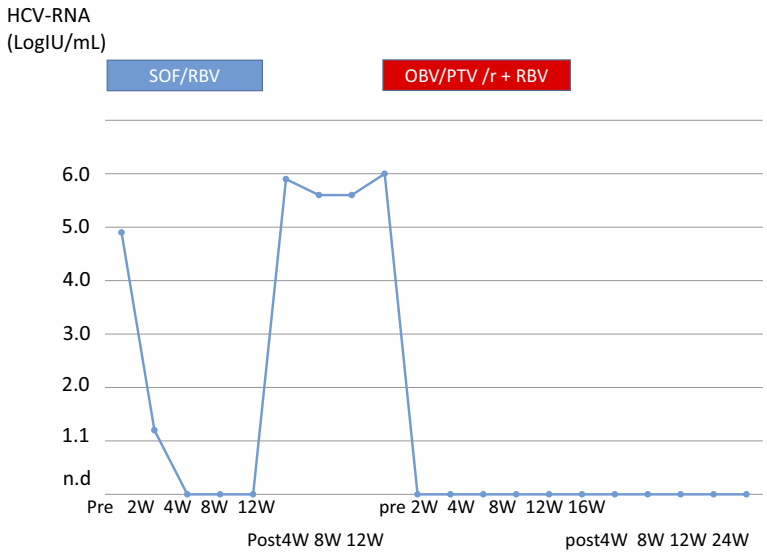

Figure. **The clinical course of the patient. SOF+RBV: sofosbuvir plus ribavirin, OBV/PTV/r+RBV: ombitasvir/paritaprevir/ritonavir plus ribavirin, n.d: not detected, Pre: pretreatment**

was due to the fact that the OBV/PTV/r+RBV regimen showed high sustained virologic response (SVR) rates in GT 2a CHC patients in Japanese phase 3 studies. After 2 weeks of OBV/PTV/r+RBV treatment, the viral load decreased from 5.9 Log IU/mL to undetectable, ultimately achieving SVR24 (Figure). Furthermore, there were no serious adverse effects of the OBV/PTV/r+RBV treatment.

Discussion

In Japan, an estimated 1.4-1.6 million people are infected with HCV (3, 4). An estimated 67% of HCV-infected patients in Japan are infected with HCV GT1b, while approximately 22% are infected with HCV GT2a and 10% with HCV GT2b (5). With the introduction of all-oral, IFN-free DAAs, new treatment options are becoming available for patients with HCV GT2 infection. Combination therapy of the nucleic acid type NS5B polymerase inhibitor SOF+RBV is recommended according to the treatment guidelines of the Japanese Society of Hepatology as a first-line therapy for treatment-naïve patients with HCV GT2 infections, except for those severe renal dysfunction or renal failure needing dialysis (6).

In accordance with these guidelines, we have introduced SOF+RBV therapy in several HCV GT2 patients; unfortunately, however, this approach failed in the present patient. A large, multicenter study of SOF+RBV for patients with HCV GT2 infections showed that non-cirrhosis was independently associated with SVR12 (7). Therefore, this patient might have failed to achieve SVR with SOF+RBV due to progression of hepatic fibrosis. Combination therapy with the NS5A inhibitor ombitasvir (OBV) and the NS3/4A protease inhibitor paritaprevir (PTV) has shown potent antiviral activity against multiple HCV types, including 1a, 1b, 2a, 2b, 3a, 4a, and 6a, *in vitro* (8, 9).

In a clinical trial conducted in Japan, the SVR12 rates were consistently higher in patients with HCV GT2a infection compared with HCV GT2b infection. In the week 16 treatment arm, the SVR rates for HCV GT2a and GT2b were 93.9% and 85.7%, respectively, in treatment-naïve patients and 93.8% and 56.3%, respectively, in treatment-experienced patients (10). The factors that were identified as associated with higher odds of SVR12 based on a stepwise logistic regression analysis were HCV GT2a infection and no treatment experience (10).

Based on these findings, even if the treatment failed with SOF+RBV combination therapy, there may be a possibility of retreatment with OBV/PTV/r+RBV combination therapy with different mechanism of action being successful. In addition, since the present patient had a GT2a, SVR was achieved by introducing retreatment with OBV/PTV/r+RBV combination therapy.

Recently, the safety and efficacy of combination therapy of glecaprevir (nonstructural protein 3/4A protease inhibitor) and pibrentasvir (nonstructural protein 5A inhibitor) (G/P), which is a RBV free DAA regimen, was evaluated in Japanese patients infected with HCV GT2 (11). Research is needed to clarify the underlying causes of DAA-based treatment failure and to identify the best salvage regimens for patients who have failed certain drug combinations.

In summary, this case study shows that HCV GT2a infected patients experiencing virologic failure with SOF+RBV therapy can be re-treated with other therapies, such as OBV/PTV/r+RBV regimens, containing components with a different mechanism of action from the initial treatment.

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

References

1. Sarrazin C, Hézode C, Zeuzem S, Pawlotsky JM. Antiviral strategies in hepatitis C virus infection. J Hepatol **56**: S88-S100, 2012.

2. Premoli C, Aghemo A. Directly acting antivirals against hepatitis C virus: mechanisms of action and impact of resistant associated variants. Minerva Gastroenterol Dietol **62**: 76-87, 2016.
3. Messina JP, Humphreys I, Flaxman A, et al. Global distribution and prevalence of hepatitis C virus genotypes. Hepatology **61**: 77-87, 2015.
4. Gower E, Estes C, Blach S, Razavi-Shearer K, Razavi H. Global epidemiology and genotype distribution of the hepatitis C virus infection. J Hepatol **61**: S45-S57, 2014.
5. Matsuo J, Mizui M, Okita H, et al. Follow up of the 987 blood donors found with hepatitis C virus infection over 9-18 years. Hepatol Res **42**: 637-647, 2012.
6. Japan Society of Hepatology. JSH guidelines for the management of hepatitis C virus infection, version 5.4 (in Japanese) [Internet]. [cited 2017 Apr. 30]. Available from: http://www.jsh.or.jp/
7. Ogawa E, Furusyo N, Nomura H, et al. Effectiveness and safety of sofosbuvir plus ribavirin for HCV genotype 2 patients 65 and over with or without cirrhosis. Antiviral Res **136**: 37-44, 2016.
8. Krishnan P, Beyer J, Mistry N, et al. In vitro and in vivo antiviral activity and resistance profile of ombitasvir, an inhibitor of hepatitis C virus NS5A. Antimicrob Agents Chemother **59**: 979-987, 2015.
9. Pilot-Matias T, Tripathi R, Cohen D, et al. In vitro and in vivo antiviral activity and resistance profile of the hepatitis C virus NS3/4 A protease inhibitor ABT-450. Antimicrob Agents Chemother **59**: 988-997, 2015.
10. Sato K, Chayama K, Alves K, et al. Randomized phase 3 trial of ombitasvir/paritaprevir/ritonavir and ribavirin for hepatitis C virus genotype 2-infected Japanese patients. Adv Ther **34**: 1449-1465, 2017.
11. Toyoda H, Chayama K, Suzuki F, et al. Efficacy and safety of glecaprevir/pibrentasvir in Japanese patients with chronic genotype 2 hepatitis C virus infection. Hepatolgy **67**: 505-513, 2018.