Case Reports in Gastroenterology

Case Rep Gastroenterol 2021;15:729–735
DOI: 10.1159/000518306
Received: June 18, 2021
Accepted: July 1, 2021
Published online: August 6, 2021

Single Case

Successful Treatment with Crushed Sofosbuvir/Velpatasvir of a Patient with Decompensated Cirrhosis C and Thrombocytopenia

Aiko Murayama[a] Kazuto Tajiri[a] Chiharu Kanegane[b] Jun Murakami[c] Yuka Hayashi[a] Ichiro Yasuda[a]

[a]The Third Department of Internal Medicine, Faculty of Medicine, University of Toyama, Toyama, Japan; [b]Department of Pediatrics, National Hospital Organization Toyama Hospital, Toyama, Japan; [c]Division of Transfusion Medicine and Cell Therapy, Toyama University Hospital, Toyama, Japan

Keywords
Decompensated cirrhosis C · Thrombocytopenia · Direct-acting antiviral · Intractable epilepsy · Crushed administration

Abstract
A 36-year-old woman with decompensated liver cirrhosis type C was referred to our hospital to receive antiviral treatment for hepatitis C virus (HCV). She had been diagnosed with intractable epilepsy and cerebral palsy at birth and was managed by central venous nutrition and nasal gastric feeding. At age 34 years, she was diagnosed with thrombocytopenia, probably associated with HCV infection. She showed refractory ascites for several months and was therefore administered crushed sofosbuvir/velpatasvir tablets via a nasal gastric tube. Her HCV infection was successfully eradicated, her ascites disappeared, and thrombocytopenia improved with a marked decrease in platelet-associated IgG.

Introduction

Treatment of decompensated cirrhosis C with direct-acting antivirals (DAAs) has been shown to improve hepatic reserve function and reduce mortality and has been recommended by the clinical guidelines of the American Association for the Study of Liver Diseases (AASLD) and the European Association for the Study of the Liver (EASL) [1, 2]. In addition, a phase 3

Correspondence to:
Kazuto Tajiri, tajikazu@med.u-toyama.ac.jp

Case Rep Gastroenterol 2021;15:729–735
DOI: 10.1159/000518306

randomized, controlled trial in Japan in patients with decompensated cirrhosis C found that treatment with sofosbuvir (SOF) and velpatasvir (VEL) had a sustained viral response (SVR) rate of 92.2%, with 30–40% of treated patients showing improvements in hepatic reserve function [3]. Clinical guidelines in Western countries recommend 12 weeks of treatment with SOF/VEL plus ribavirin or 24 weeks of treatment with SOF/VEL, with evidence on the effectiveness of 12 weeks of SOF/VEL being limited. Moreover, few reports have assessed the effectiveness of DAAs in patients who have difficulty swallowing tablets [4–10], and no studies to date have evaluated SOF/VEL in Japanese patients who have difficulty swallowing tablets.

This report describes a patient with decompensated cirrhosis C accompanied by intractable epilepsy and thrombocytopenia due to HCV infection. Treatment with crushed SOF/VEL administered through a nasal feeding tube resulted in SVR, with thrombocytopenia improving following HCV eradication.

Case Presentation

A 36-year-old woman was referred to our hospital for treatment of decompensated cirrhosis C. She had been diagnosed with intractable epilepsy and cerebral palsy at birth. At age 1 year, she was found to have a varicella zoster virus infection followed by thrombotic thrombocytopenic purpura and was treated with red blood cell transfusion, which probably resulted in HCV infection at that time. She had been fed by central venous nutrition and nasal enteral feeding for decades. She had no history of alcohol drinking, and her family had no history of liver diseases. She had a persistent HCV infection, with HCV-RNA viral loads of 4.7 logIU/mL at age 32 years and 4.5 logIU/mL at age 33 years. Treatment for HCV infection was therefore considered at age 34 years, at which time she was being treated with clobazam, zonisamide, and carbamazepine (CBZ) for her intractable epilepsy. Because of harmful drug interactions between CBZ and some DAAs for HCV, her antiepileptic regimen was changed to levetiracetam (LEV). Although LEV was found to control her epilepsy, she developed thrombocytopenia (platelet count: 4–6 × 10^4/μl, Fig. 1). LEV was therefore discontinued, and she was started on valproic acid (VPA).

Her thrombocytopenia was not accompanied by coagulation abnormalities. The activity of a disintegrin and metalloproteinase with thrombospondin type 1 motifs 13 was not decreased, being ≥101% (normal range ≥10%). The concentration of platelet-associated IgG (PA-IgG) was 606.1 ng/10^7 cells, markedly higher than normal (≤30.2 ng/10^7 cells). Moreover, examination of a bone marrow aspirate showed reactive small megakaryocytes without abnormal cells or blast cells, suggesting that thrombocytopenia in this patient was due to reactive secondary immune thrombocytopenia (ITP). Although her platelet count was as low as 2 × 10^4/μl, it generally fluctuated from 4 to 6 × 10^4/μL (Fig. 1).

The patient subsequently developed pneumonia and showed decreased activity. Her VPA dose was reduced, and she was started on clarithromycin, which improved her systemic condition. However, her serum albumin concentration remained below 3.0 g/dL, and she developed leg edema and ascites, which did not improve. Despite her nutrition intake by central venous feeding and a nasal gastric tube being stable and maintained as usual, her pancytopenia, leg edema, and ascites did not improve. Ascites was also not improved by administration of diuretics through a nasal gastric tube, albumin infusion, venous administration of diuretics, or administration of tolvaptan through a nasal gastric tube (Fig. 1). Examination of ascites fluid showed transudation but no evidence of infection. The increase in liver fibrosis markers indicated that the refractory ascites in this patient was due to decompensated cirrhosis C.

Case Rep Gastroenterol 2021;15:729–735
DOI: 10.1159/000518306

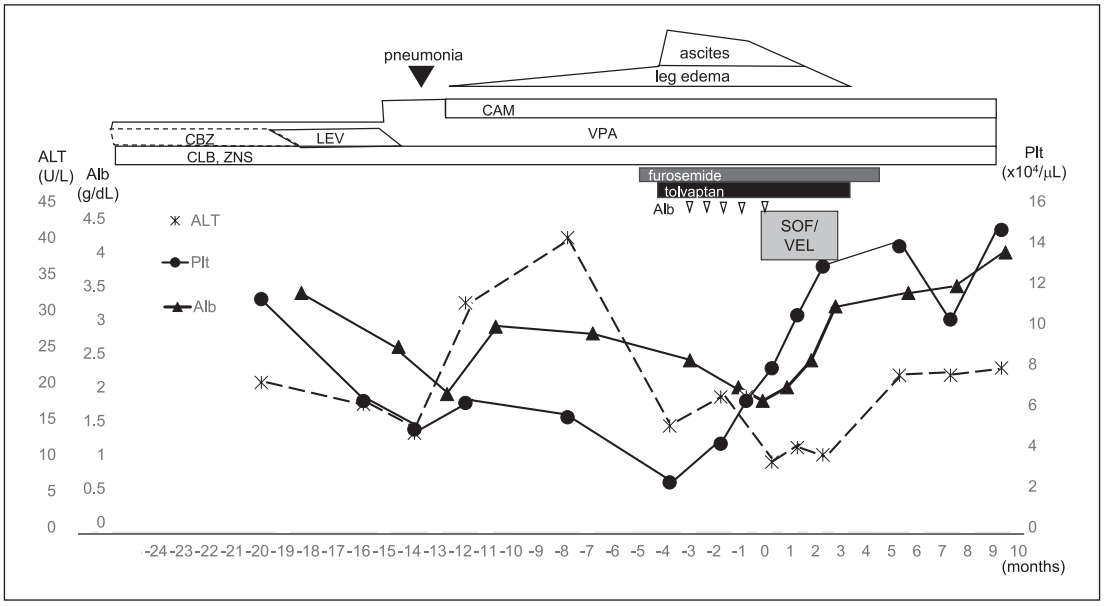

Fig. 1. Clinical course of this patient during DAA treatment. DAA, direct-acting antivirals; ALT, alanine aminotransferase; Alb, albumin; Plt, platelets; CBZ, carbamazepine; CLB, clobazam; ZNS, zonisamide; LEV, levetiracetam; CAM, clarithromycin; VPA, sodium valproate; SOF, sofosbuvir; VEL, velpatasvir.

This patient was transferred to our department for treatment of HCV infection. Physical examination showed that her body weight was 54 kg (47 kg 1 year earlier), and her body temperature was normal. She showed massive ascites and leg edema. Laboratory data examination showed a marked reduction in serum albumin concentration and increase in fibrosis markers (Table 1). CT showed liver deformity, mild splenomegaly, and massive ascites (Fig. 2). Although her viral load was not very high, she was found to have sustained infection with HCV serotype 2 (Table 1).

The indication for HCV eradication was carefully considered. Although she had been bedridden, this patient showed sustained HCV infection, and her ascites, which was caused by HCV-derived cirrhosis, was refractory to conservative treatment including albumin infusion. Her epilepsy was well controlled at that time, and her intake of nutrition via central venous nutrition and nasal gastric tube feeding was stable. After obtaining repeated informed consent from her mother, the patient was started on SOF/VEL for 12 weeks. Because she could not swallow tablets due to dysphagia, she was administered crushed SOF/VEL through the nasal gastric tube. Despite co-administration of antiepilepsy drugs, this patient did not experience any adverse effects of crushed SOF/VEL. HCV-RNA disappeared after 2 weeks of SOF/VEL administration. She completed 12 weeks of SOF/VEL treatment without any adverse events, and her ascites and edema were improved (Fig. 1). At the end of treatment, her liver function and thrombocytopenia were improved, and CT showed no evidence of ascites (Fig. 3). She was confirmed as having achieved SVR at both 12 and 24 weeks after treatment. Twelve weeks after treatment, her platelet count was 13.8 × 10^4/μL, her serum albumin concentration was 3.4 g/dL, her Mac2 binding protein glycan isomer (M2BPGi) concentration was 1.98 cutoff index (COI), and her type IV collagen concentration was 179 ng/mL. At 24 weeks after the end of treatment, her platelet count was 16.6 × 10^4/μL, her serum albumin concentration was 4.0 g/dL, her M2BPGi concentration was 1.84 COI, her type IV collagen concentration was 159 ng/mL, and her PA-IgG concentration was 86.6 ng/10^7 cells, and she was in good condition.

Case Rep Gastroenterol 2021;15:729–735
DOI: 10.1159/000518306

Table 1. Laboratory data before DAA treatment

Hematology		*Blood chemistry*		HBsAg	Negative
WBC	2,550/μL	AST	51 U/L	HBsAb	Negative
Neut	22.4%	ALT	14 U/L	HBcAb	Negative
Eosino	0.0%	LDH	176 U/L	HCVAb	Positive
Lymph	65.1%	ALP	371 U/L	HCV-RNA	2.78 LogIU/mL
Mono	12.5%	γ-GTP	186 U/L	HCV serotype	2
RBC	252 ×104/μL	T-Bil	0.54 mg/dL	ANA	Negative
Hb	8.8 g/dL	TP	4.2 g/dL	AMA (M2)	Negative
Ht	28.5%	ALB	1.4 g/dL	IgG	1,496 mg/dL
Plt	6.1 ×104/μL	BUN	21.6 mg/dL	IgA	367 mg/dL
Coagulation		Cre	0.36 mg/dL	IgM	57 mg/dL
PT	79.1%	T-cho	83 mg/dL	AFP	16.6 ng/mL
PT-INR	1.15	Na	140 mEq/L	DCP	22 mAU/mL
APTT	37.3 s	K	3.6 mEq/L	Type IV collagen	216 ng/mL
Urinalysis		Cl	103 mEq/L	M2BpGi	2+ 7.16 COI
Protein	(-)	Glucose	100 mg/dL	Hyaluronic acid	537 ng/mL
		NH_3	98 μg/dL		

DAA, direct-acting antivirals; WBC, white blood cell; Neut, neutrophil; Eosino, eosinophil; Lymph, lymphocyte; Mono, monocyte; RBC, red blood cell; Hb, hemoglobin; Ht, hematocrit; Plt, platelet; PT, prothrombin time; INR, international ratio; APTT, activated partial thromboplastin time; AST, aspartate aminotransferase; ALT, alanine aminotransferase; LDH, lactate dehydrogenase; ALP, alkaline phosphatase; γ-GTP, γ-glutamyl transpeptidase; T-Bil, total bilirubin; TP, total protein; ALB, albumin; BUN, blood urea nitrogen; Cre, creatinine; T-cho, total cholesterol; HBsAg, hepatitis B surface antigen; HBsAb, hepatitis B surface antibody; HBcAb, hepatitis B core antibody; HCVAb, hepatitis C virus antibody; ANA, anti-nuclear antibody; AMA, anti-mitochondria antibody; IgG, immunoglobrin G; AFP, alpha fetoprotein; DCP, des-γ-carboxy prothrombin; M2BpGi, Mac2-binding protein glucosylation isomer.

Discussion

Although a phase 3 trial in Japan found that SOF/VEL was effective in the treatment of decompensated cirrhosis C [3], treatment with drugs that induce P-glycoprotein, such as rifampicin, CBZ, phenytoin, and phenobarbital, is regarded as contraindications to SOF/VEL therapy. Treatment of patients with epilepsy with both antiepilepsy drugs and DAAs requires careful consideration of the former. Furthermore, the present patient was unable to swallow tablets due to her systemic condition. Although treatment with crushed DAAs, such as SOF/ledipasvir or glecaprevir/pibrentasvir, has been reported for patients who could not swallow tablets [4–10], few patients to date have been treated with crushed SOF/VEL [8–10], with none of these patients being from Japan. Administration of crushed SOF/VEL via a feeding tube was found to result in 13–23% of the SOF/VEL adsorbing to the tube itself [9]. Furthermore, tube feeding with acidic fluid could alter the concentration of SOF/VEL [10]. Thus, the precise metabolism of crushed SOF/VEL is unclear.

Administration of crushed SOF/VEL to the present patient not only improved her liver function but also her thrombocytopenia. The pathogenesis of thrombocytopenia occurring during HCV infection is complicated, involving both the increased destruction and reduced production of platelets [11]. Autoantibodies to platelets and hypersplenism with sequestration are regarded as increasing platelet destruction, whereas HCV-induced bone marrow

Case Rep Gastroenterol 2021;15:729–735
DOI: 10.1159/000518306

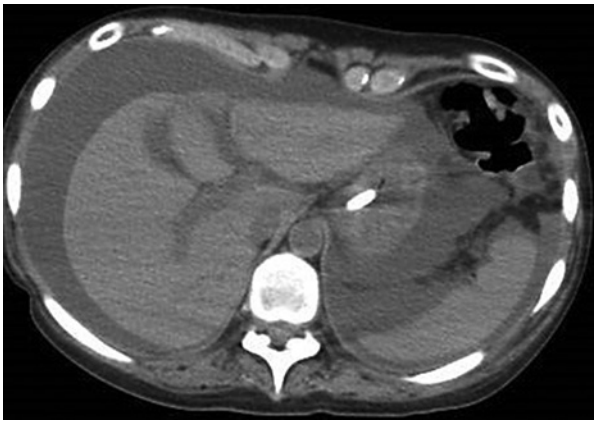

Fig. 2. Abdominal CT prior to SOF/VEL treatment, showing deformity of the liver, mild splenomegaly, and ascites.

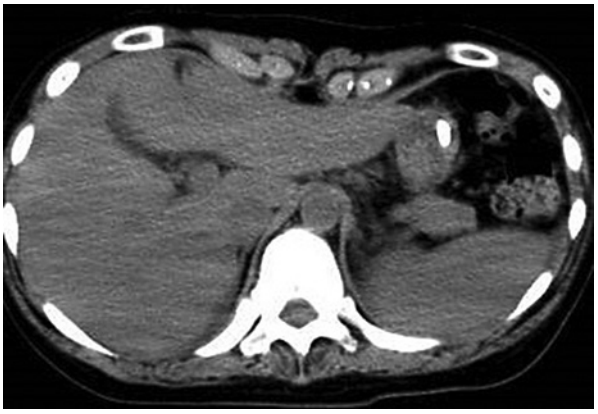

Fig. 3. Abdominal CT following SOF/VEL treatment, showing the disappearance of ascites.

suppression and decreased thrombopoietin are regarded as decreasing platelet production [11]. HCV eradication in the present patient resulted in a significant improvement in thrombocytopenia with a reduction in PA-IgG, confirming that thrombocytopenia in this patient was caused by an immune-related mechanism. Her platelet count increased despite continuous administration of antiepileptic drugs, suggesting that her thrombocytopenia was not drug induced. PA-IgG is frequently elevated in HCV-infected patients due to the presence of various autoantibodies [12, 13]. Because ITP may be induced by HCV infection itself [14–16], HCV eradication with DAA may improve ITP [16]. The etiology of thrombocytopenia accompanying HCV infection is complex, requiring careful examination in individual patients.

SOF/VEL has shown therapeutic benefits in patients with decompensated cirrhosis C, with SVR rates of 95% and improvement of hepatic reserve in real-world settings [17–20]. The degree of liver fibrosis development in the present patient was unclear, as liver biopsy samples were not obtained and liver elasticity not measured before and after SOF/VEL treatment. Although treatment with SOF/VEL for 12 weeks can benefit patients with decompensated cirrhosis C, it may be less beneficial in patients with complicated underlying diseases. Because patients such as the present patient may show alterations in drug metabolism, there are concerns about the risk of eradication failure and the appearance of serious side effects due to inadequate treatment. The efficacy and safety of SOF/VEL treatment may also be complicated by drug-drug interactions, suggesting the need to measure the pharmacological kinetics of these agents in blood.

Case Rep Gastroenterol 2021;15:729–735
DOI: 10.1159/000518306

In conclusion, the present case indicates that crushed SOF/VEL treatment for decompensated cirrhosis C could improve not only hepatic reserve function but also HCV-induced immune thrombocytopenia. This treatment may result in successful HCV eradication in patients with complicated background diseases, such as intractable epilepsy or a swallowing disorder. Although DAA treatment must be carefully considered in each patient, SOF/VEL for 12 weeks can be a useful option for patients with decompensated cirrhosis C.

Acknowledgment

We thank Eriko Murakami, a senior student of Faculty of Medicine, University of Toyama, for summarizing the present case.

Statement of Ethics

Written informed consent for publication was obtained from the patient's mother for publication of this case report and any accompanying images. This study protocol was approved by Institutional Ethics Committee of the University of Toyama (Approval No. R2019131).

Conflict of Interest Statement

The authors declare that they have no conflicts of interest.

Funding Sources

There were no funding sources.

Author Contributions

Aiko Murayama and Kazuto Tajiri wrote this manuscript, and all authors contributed to the patient's medical treatment.

Data Availability Statement

All data generated during this study are included in this article. Further inquiries can be directed to the corresponding author.

References

1 AASLD-IDSA HCV Guidance Panel. Hepatitis C guidance 2018 update: AASLD-IDSA recommendations for testing, managing, and treating hepatitis C virus infection. Clin Infect Dis. 2018;67(10):1477–92.
2 European Association for the Study of the Liver. Electronic address EEE, European Association for the Study of the L. EASL recommendations on treatment of hepatitis C 2018. J Hepatol. 2018;69:461–511.
3 Takehara T, Sakamoto N, Nishiguchi S, Ikeda F, Tatsumi T, Ueno Y, et al. Efficacy and safety of sofosbuvir-velpatasvir with or without ribavirin in HCV-infected Japanese patients with decompensated cirrhosis: an open-label phase 3 trial. J Gastroenterol. 2019;54:87–95.

Case Rep Gastroenterol 2021;15:729–735
DOI: 10.1159/000518306

4 Fulco PP, Sterling RK, Lavoie SR. Administration of crushed ledipasvir-sofosbuvir tablets via gastrostomy button in a patient coinfected with HIV and hepatitis C virus. Am J Health Syst Pharm. 2017;74:1761–2.
5 von Felden J, Scheurich C, Yamamura J, Brainard DM, Mogalian E, Lohse AW, et al. Successful treatment of chronic hepatitis C with ground ledipasvir/sofosbuvir in a patient with Crohn's disease and short bowel syndrome. J Viral Hepat. 2018;25:214–5.
6 Jindracek L, Stark J. Treatment of chronic hepatitis C virus infection with crushed ledipasvir/sofosbuvir administered via a percutaneous endoscopic gastrostomy Tube. J Pharm Pract. 2018;31(5):522–4.
7 Tanaka Y, Tateishi R, Koike K. Successful treatment of chronic hepatitis C virus infection with crushed glecaprevir/pibrentasvir administered via a percutaneous endoscopic gastrostomy tube: case report and review of the literature. Clin J Gastroenterol. 2019;12:588–91.
8 Mogul A, Teixeira E, McAuliffe L, Promrat K, Zullo AR. Effectiveness of crushed sofosbuvir-velpatasvir in a patient with dysphagia. Am J Health Syst Pharm. 2020;77:417–8.
9 van Seyen M, Samson AD, Cullen L, Eastick K, Knol H, Colbers A, et al. Crushed application of sofosbuvir and velpatasvir in a patient with swallowing disorder. Int J Antimicrob Agents. 2020;55:105934.
10 Lalanne S, Jézéquel C, Tron C, Verdier MC, Mercerolle M, Pronier C, et al. Therapeutic drug monitoring-guided crushed sofosbuvir-velpatasvir treatment: a case study. Ther Drug Monit. 2020;42:163–4.
11 Rawi S, Wu GY. Pathogenesis of thrombocytopenia in chronic HCV infection: a review. J Clin Transl Hepatol. 2020;8:184–91.
12 Nagamine T, Ohtuka T, Takehara K, Arai T, Takagi H, Mori M. Thrombocytopenia associated with hepatitis C viral infection. J Hepatol. 1996;24:135–40.
13 Weksler BB. Review article: the pathophysiology of thrombocytopenia in hepatitis C virus infection and chronic liver disease. Aliment Pharmacol Ther. 2007;26 Suppl 1:13–9.
14 Pockros PJ, Duchini A, McMillan R, Nyberg LM, McHutchison J, Viernes E. Immune thrombocytopenic purpura in patients with chronic hepatitis C virus infection. Am J Gastroenterol. 2002;97:2040–5.
15 Chiao EY, Engels EA, Kramer JR, Pietz K, Henderson L, Giordano TP, et al. Risk of immune thrombocytopenic purpura and autoimmune hemolytic anemia among 120 908 US veterans with hepatitis C virus infection. Arch Intern Med. 2009;169:357–63.
16 Honma Y, Shibata M, Hayashi T, Kusanaga M, Ogino N, Minami S, et al. Effect of direct-acting antivirals on platelet-associated immunoglobulin G and thrombocytopenia in hepatitis C virus-related chronic liver disease. Liver Int. 2019;39:1641–51.
17 Atsukawa M, Tsubota A, Kondo C, Toyoda H, Nakamuta M, Takaguchi K, et al. Real-world clinical application of 12-week sofosbuvir/velpatasvir treatment for decompensated cirrhotic patients with genotype 1 and 2: a prospective, multicenter study. Infect Dis Ther. 2020;9(4):851–66.
18 Ohya K, Imamura M, Teraoka Y, Morio K, Fujino H, Nakahara T, et al. Real-world efficacy of sofosbuvir plus velpatasvir therapy for patients with hepatitis C virus-related decompensated cirrhosis. Hepatol Res. 2020;50:1234–43.
19 Tahata Y, Hikita H, Mochida S, Kawada N, Enomoto N, Ido A, et al. Sofosbuvir plus velpatasvir treatment for hepatitis C virus in patients with decompensated cirrhosis: a Japanese real-world multicenter study. J Gastroenterol. 2021;56(1):67–77.
20 Takaoka Y, Miura K, Morimoto N, Ikegami T, Kakizaki S, Sato K, et al. Real-world efficacy and safety of 12-week sofosbuvir/velpatasvir treatment for patients with decompensated liver cirrhosis caused by hepatitis C virus infection. Hepatol Res. 2021;51(1):51–61.