Case Reports in Gastroenterology

Case Rep Gastroenterol 2016;10:248–256

DOI: 10.1159/000445374
Published online: May 27, 2016

Case Report

Successful Eradication of Hepatitis C Virus by Interferon-Free Regimens in Two Patients with Advanced Liver Fibrosis following Kidney Transplantation

Reina Sasaki[a] Tatsuo Kanda[a] Shin Yasui[a] Yuki Haga[a]
Masato Nakamura[a] Mutsumi Yamato[a] Shuang Wu[a]
Shingo Nakamoto[a, b] Makoto Arai[a] Shigeru Mikami[c]
Hideaki Miyauchi[d] Hisahiro Matsubara[d] Osamu Yokosuka[a]

[a]Department of Gastroenterology and Nephrology, Chiba University, Graduate School of Medicine, Chiba, Japan; [b]Department of Molecular Virology, Chiba University, Graduate School of Medicine, Chiba, Japan; [c]Department of Internal Medicine, Kikkoman General Hospital, Noda, Japan; [d]Department of Frontier Surgery, Chiba University, Graduate School of Medicine, Chiba, Japan

Keywords
Direct-acting antivirals · Hepatitis C virus · Kidney transplantation · Sustained virological response

Abstract
Hepatitis C virus (HCV) infection leads to acute and chronic hepatitis, cirrhosis, and hepatocellular carcinoma. Following kidney transplantation, HCV increases the risk of graft loss and patient mortality compared with uninfected patients. The achievement of a sustained virological response with antiviral therapy improves survival and diminishes the risk of hepatic decompensation in HCV patients after a kidney transplant. It has been reported that direct-acting antivirals (DAAs) are relatively safe and highly effective for the eradication of HCV in patients who are liver transplant recipients. In the present study, we investigated HCV eradication via interferon-free therapies with DAAs in two HCV patients with advanced liver fibro-

KARGER

Assist. Prof. Reina Sasaki, MD, or Assoc. Prof. Tatsuo Kanda, MD, PhD
Department of Gastroenterology and Nephrology
Chiba University, Graduate School of Medicine
1-8-1 Inohana, Chuo-ku, Chiba 260-8677 (Japan)
E-Mail reina_sasaki_0925@yahoo.co.jp or kandat-cib@umin.ac.jp

sis following renal transplantation. In both cases, the interferon-free regimens with DAAs were effective in eradicating HCV in the patients after kidney transplantation. No adverse events caused by interferon were identified with the exception of anemia. Interferon-free regimens with DAAs for recurrent HCV in patients following kidney transplantation are relatively safe and effective. However, attention should be focused on anemia during these treatments.

Introduction

Hepatitis C virus (HCV) infection causes acute and chronic hepatitis, cirrhosis, and hepatocellular carcinoma [1]. In kidney transplantation, HCV infection also leads to an increased risk of graft loss and patient mortality compared with uninfected patients [2]. The transplantation of HCV-positive kidneys as opposed to HCV-negative kidneys into HCV-positive recipients resulted in similar graft survival; however, it compromised patient survival in the long term [2]. Approximately 40% of biopsies indicate a progression of liver fibrosis; however, the natural course of HCV-related liver disease following kidney transplantation remains poorly understood [3].

The achievement of a sustained virological response (SVR) with antiviral therapy improves survival and diminishes the risk of hepatic decompensation in patients with chronic hepatitis C. Without an immunosuppression status, peginterferon and ribavirin for 48 weeks resulted in only ~50% SVR in patients with HCV genotype 1; however, for 24 weeks, it led to 80% SVR in patients with HCV genotype 2/3 [4].

Interferon-based therapy in HCV-infected renal transplant recipients has been associated with a high risk of acute allograft rejection and poor efficacy [5, 6], although contradictory findings exist [7].

The HCV RNA genome encodes at least 10 proteins, including structural (core, E1, E2, and p7) and nonstructural (NS2, NS3, NS4A, NS4B, NS5A, and NS5B) proteins [4]. A direct-acting antiviral (DAA) against HCV comprises a small molecule inhibitor of HCV proteins, such as NS3/4A, NS5A, or NS5B [4]. Technological progress in DAAs has completely transformed the treatment of HCV. Combination therapy with the HCV NS3/4A inhibitor asunaprevir and the HCV NS5A inhibitor daclatasvir is currently available and effective for HCV genotype 1b patients in Japan; however, NS5A and/or NS3/4A resistance-associated variants may attenuate its efficacy [8]. Combination therapy with the HCV NS5B inhibitor sofosbuvir and ribavirin is currently available and highly effective for HCV genotype 2 patients; however, sofosbuvir may only be used in patients with an estimated glomerular filtration rate (eGFR) ≥30 ml/min/1.73 m^2, and ribavirin may induce anemia as an adverse event [9].

DAAs are relatively safe and highly effective for the eradication of HCV in liver transplant recipients [10, 11]. However, there has been a limited number of reports of DAA use after kidney transplantation [10–14]. In the present study, we investigated HCV eradication via interferon-free therapy with DAAs in two HCV-infected patients with advanced liver fibrosis following renal transplantation.

Case Reports

Case 1

A 57-year-old Japanese man was infected with HCV genotype 1b (7.1 log IU/ml of serum HCV RNA and TT of IL28B rs8099917). He had been treated with hemodialysis for 32 years (from 1974 to 2005) for end-stage renal disease caused by Alport syndrome. In 2005, he received a renal allograft from a deceased donor. He had a history of blood transfusion 31 years before kidney transplantation. In 2013, the HCV RNA was positive, and the aspartate aminotransferase (AST), alanine transaminase (ALT), total bilirubin, and platelet count were 82 IU/l, 114 IU/l, 1.0 mg/dl, and 8.2×10^4/μl, respectively. A 21.3-kPa liver stiffness was observed with transient elastography (Fibroscan); thus, we diagnosed him with cirrhosis of the liver as a result of HCV infection without liver biopsy. He is an interferon treatment-naïve patient.

In January 2015, daily treatment with a combination of 200 mg of asunaprevir and 60 mg of daclatasvir was initiated after we had confirmed no resistance-associated variants at the positions L31 and Y93 of HCV NS5A using a direct sequencing method. This regimen was selected as a result of his renal dysfunction [8]. His height, body weight, and body mass index were 1.59 m, 50 kg, and 19.8 kg/m^2, respectively. He did not drink alcohol. His laboratory data prior to treatment are shown in table 1. One month after treatment initiation, his serum HCV RNA was undetectable (fig. 1a). Although he received surgery for purulent gonitis with pseudogout at 20 weeks, he completed this treatment for 24 weeks. He achieved an SVR at 12 weeks (SVR12) following treatment termination. At this time, the AST, ALT, total bilirubin, and platelet count were 15 IU/l, 10 IU/l, 0.6 mg/dl, and 11.6×10^4/μl, respectively.

Prior to initiating this treatment, his eGFR had been 22.9 ml/min/1.73 m^2. Two months after treatment initiation, his eGFR worsened to 17.5 ml/min/1.73 m^2. The dose of asunaprevir was decreased (100 mg daily) 3 months after treatment initiation, and his eGFR immediately improved to 26.9 ml/min/1.73 m^2. His eGFR was 23.7 ml/min/1.73 m^2 12 weeks after the termination of his therapy. During the treatment, erythropoietin and blood transfusion were implemented depending on the situation.

Three months prior to the initiation of this interferon-free treatment, we had changed the medication from 200 mg daily of cyclosporine to 1,000 mg daily of mycophenolate mofetil, because it had been reported that asunaprevir significantly interacts with cyclosporine [15]. During the antiviral treatment, he was also taking 2 mg daily of tacrolimus, 1,000 mg daily of mycophenolate mofetil, and 5 mg of prednisolone as immunosuppressants. We monitored the trough level of tacrolimus, and it was within the normal range during the treatment.

Case 2

A 62-year-old Japanese man was infected with HCV genotype 2b (7.0 log IU/ml of serum HCV RNA and TT of IL28B rs8099917). He had been treated with hemodialysis for 30 years (from 1981 to 2010) for end-stage renal disease caused by glomerulonephritis with nephrotic syndrome. He had undergone surgery for intestinal obstruction and posttransfusion hepatitis in 1982. In 2010, he received a renal allograft from a deceased donor. In 2013, the AST, ALT, total bilirubin, and platelet count were 52 IU/l, 81 IU/l, 0.8 mg/dl, and 4.2×10^4/μl, respectively. An 18.6-kPa liver stiffness was observed with transient elastography (Fibroscan); thus, we diagnosed him with cirrhosis of the liver as a result of HCV infection without liver biopsy. In May 2014, he was subsequently treated with peginterferon-α-2b and ribavirin [4] for his liver dysfunction. His HCV RNA levels were 6.4 log IU/ml and <1.2 IU/ml

before treatment and 2 months after treatment initiation, respectively. However, his treatment with peginterferon-α-2b and ribavirin was terminated 3 months after the initiation of treatment because of severe pancytopenia. Instead, he was treated with intermittent natural interferon-β [16, 17] 1–3 times per week for 11 months, and his ALT levels were within the normal range with HCV RNA levels of 7.0 log IU/ml in June 2015.

In July 2015, treatment with a daily combination of 400 mg of sofosbuvir and 200 mg of ribavirin was initiated. His height, body weight, and body mass index were 1.58 m, 57 kg, and 22.8 kg/m^2, respectively. He was a social drinker. His laboratory data prior to treatment are shown in table 2. He was also taking 1.5 mg daily of tacrolimus, 1,000 mg daily of mycophenolate mofetil, and 5 mg of prednisolone as immunosuppressants. Four and 8 weeks after the initiation of treatment, his HCV RNA levels were <1.2 RNA IU/ml and undetectable, respectively (fig. 1b). He maintained this treatment for 12 weeks and achieved SVR12. At this time, the AST, ALT, total bilirubin, and platelet count were 16 IU/l, 10 IU/l, 1.0 mg/dl, and 5.5 × 10^4/μl, respectively. During the treatment, an injection of 30 μg erythropoietin once in 2 weeks was also performed for his anemia without a change in his immunosuppressants. We did not identify any other serious adverse events.

Discussion

We presented two patients with chronic HCV infection and advanced liver fibrosis following kidney transplantation who had a long past history of ~30 years of hemodialysis and were treated via interferon-free regimens. In case 1, the patient was infected with HCV genotype 1b, his eGFR was <30 ml/min/1.73 m^2, and he was treated with a combination of asunaprevir and daclatasvir for 24 weeks because it is estimated to be safe for patients with renal dysfunction [8, 18].

Suda et al. [8] reported that asunaprevir and daclatasvir combination therapy for chronic hemodialysis patients with HCV genotype 1 is highly effective and well tolerated. They also indicated that the median hemodialysis duration for their patients was 7 years; the anemia in their patients was mild and was speculated to result, in part, from renal anemia [8]. In the present study, case 1, the patient with profound anemia, had a long history of hemodialysis, and he required blood transfusion. It is possible that the adverse events of this combination therapy after kidney transplantation may be different from the adverse events in chronic hemodialysis patients.

Case 2, the patient infected with HCV genotype 2b, could not achieve a virological response with interferon-including therapy. He was treated with a combination of sofosbuvir and ribavirin for 12 weeks. He did not achieve a rapid virological response, which was defined by undetectable viremia 4 weeks after the initiation of DAA therapy [4, 12]. The need for erythropoietin support also remained unchanged during this treatment, which supports the previous finding [12].

Both patients achieved SVR12; however, they had advanced liver fibrosis. They had anemia as adverse events, and erythropoietin was used with or without blood transfusion. These cases suggest that interferon-free treatment with DAAs is well tolerated and effective for the eradication of HCV from patients after kidney transplantation. Without ribavirin, careful attention should be paid to anemia during DAA treatment.

Treatment of HCV infection after kidney transplantation remains challenging. The use of peginterferon and ribavirin is restricted by severe adverse events and inadequate efficacy [3]. Because of pancytopenia as a result of cirrhosis and renal dysfunction, it is impossible to

use full doses of peginterferon and ribavirin [3]. Some patients require a dose reduction of the medication and/or termination of this therapy because of severe adverse events.

In addition, there exists immune-mediated allograft dysfunction as a result of peginterferon [3]. However, interferon-free therapy does not always result in severe adverse events or exert the immune reactions demonstrated with the use of interferon, and it improves the efficacy of HCV eradication [8, 9]. Fortunately, an immune reaction was not identified during the interferon-free regimens in the present cases.

In general, patients use several immunosuppressants after kidney transplantation. A drug-drug interaction between DAAs and immunosuppressants does exist. Some patients treated with DAAs, such as case 1, require a change in immunosuppressants; however, interferon-including regimens do not always modify them. The adequacy of the selection of an interferon-free regimen and the management of adverse events may increase the efficacy of HCV eradication from HCV-infected patients after kidney transplantation. Recently, more effective regimens for HCV eradication have been reported [19, 20]. These regimens may make it possible to shorten the duration of treatment and easily achieve an SVR.

In conclusion, interferon-free regimens make it easy to eradicate HCV RNA in post-kidney transplant patients with advanced liver fibrosis. Anemia should be monitored in interferon-free regimens with or without ribavirin.

Acknowledgements

This study was partially supported by KAKEN grants (24590955).

Statement of Ethics

There are no ethical conflicts to declare.

Disclosure Statement

T.K. and O.Y. received lecture fees from Gilead Sciences. The other authors have no conflicts of interest to disclose.

References

1 Di Bisceglie AM: Hepatitis C and hepatocellular carcinoma. Hepatology 1997;26(suppl 1):34S–38S.
2 Singh N, Neidlinger N, Djamali A, Leverson G, Voss B, Sollinger HW, Pirsch JD: The impact of hepatitis C virus donor and recipient status on long-term kidney transplant outcomes: University of Wisconsin experience. Clin Transplant 2012;26:684–693.
3 Baid-Agrawal S, Pascual M, Moradpour D, Frei U, Tolkoff-Rubin N: Hepatitis C virus infection in haemodialysis and kidney transplant patients. Rev Med Virol 2008;18:97–115.
4 Kanda T, Imazeki F, Yokosuka O: New antiviral therapies for chronic hepatitis C. Hepatol Int 2010;4:548–561.
5 Wei F, Liu J, Liu F, Hu H, Ren H, Hu P: Interferon-based anti-viral therapy for hepatitis C virus infection after renal transplantation: an updated meta-analysis. PLoS One 2014;9:e90611.
6 Fabrizi F, D'Ambrosio R, Pallotti F, Berardinelli L, Messa P, Martin P, Aghemo A: Acute allograft rejection following interferon therapy for hepatitis C in recipients who have returned to dialysis after kidney transplant failure: case study. Int J Artif Organs 2014;37:803–808.

7 Sanai FM, Mousa D, Al-Mdani A, Al-Shoail G, Al-Ashgar H, Al Meshari K, Al-Qahtani A, Saadeh M, Bzeizi KI, Aleid H: Safety and efficacy of peginterferon-α2a plus ribavirin treatment in renal transplant recipients with chronic hepatitis C. J Hepatol 2013;58:1096–1103.

8 Suda G, Kudo M, Nagasaka A, Furuya K, Yamamoto Y, Kobayashi T, Shinada K, Tateyama M, Konno J, Tsukuda Y, Yamasaki K, Kimura M, Umemura M, Izumi T, Tsunematsu S, Sato F, Terashita K, Nakai M, Horimoto H, Sho T, Natsuizaka M, Morikawa K, Ogawa K, Sakamoto N: Efficacy and safety of daclatasvir and asunaprevir combination therapy in chronic hemodialysis patients with chronic hepatitis C. J Gastroenterol 2016, Epub ahead of print.

9 Zeuzem S, Dusheiko GM, Salupere R, Mangia A, Flisiak R, Hyland RH, Illeperuma A, Svarovskaia E, Brainard DM, Symonds WT, Subramanian GM, McHutchison JG, Weiland O, Reesink HW, Ferenci P, Hézode C, Esteban R; VALENCE Investigators: Sofosbuvir and ribavirin in HCV genotypes 2 and 3. N Engl J Med 2014;370:1993–2001.

10 Brown RS Jr, O'Leary JG, Reddy KR, Kuo A, Morelli GJ, Burton JR Jr, Stravitz RT, Durand C, Di Bisceglie AM, Kwo P, Frenette CT, Stewart TG, Nelson DR, Fried MW, Terrault NA; Hepatitis C Therapeutic Registry Research Network Study Group: Interferon-free therapy for genotype 1 hepatitis C in liver transplant recipients: real-world experience from the Hepatitis C Therapeutic Registry and Research Network. Liver Transpl 2016;22:24–33.

11 Poordad F, Schiff ER, Vierling JM, Landis C, Fontana RJ, Yang R, McPhee F, Hughes EA, Noviello S, Swenson ES: Daclatasvir with sofosbuvir and ribavirin for HCV infection with advanced cirrhosis or post-liver transplant recurrence. Hepatology 2016;63:1493–1505.

12 Kamar N, Marion O, Rostaing L, Cointault O, Ribes D, Lavayssière L, Esposito L, Del Bello A, Métivier S, Barange K, Izopet J, Alric L: Efficacy and safety of sofosbuvir-based antiviral therapy to treat hepatitis C virus infection after kidney transplantation. Am J Transplant 2016;16:1474–1479.

13 Sawinski D, Kaur N, Ajeti A, Trofe-Clark J, Lim M, Bleicher M, Goral S, Forde KA, Bloom RD: Successful treatment of hepatitis C in renal transplant recipients with direct-acting antiviral agents. Am J Transplant 2016;16:1588–1595.

14 Bonacci M, Londoño MC, Esforzado N, Forns X, Sotoca JM, Campistol JM: Antiviral treatment with sofosbuvir and simeprevir in a kidney transplant recipient with HCV-decompensated cirrhosis: viral eradication and removal from the liver transplant waiting list. Transpl Int 2015;28:1345–1349.

15 European Association for Study of Liver: EASL Recommendations on Treatment of Hepatitis C 2015. J Hepatol 2015;63:199–236.

16 Kanda T, Nakamoto S, Arai M, Miyamura T, Wu S, Fujiwara K, Yokosuka O: Natural interferon-beta plus ribavirin therapy led to sustained virological response after seven unsuccessful courses of anti-viral treatment in a chronic hepatitis C patient. Clin J Gastroenterol 2013;6:160–163.

17 Sasaki R, Kanda T, Nakamoto S, Haga Y, Nakamura M, Yasui S, Jiang X, Wu S, Arai M, Yokosuka O: Natural interferon-beta treatment for patients with chronic hepatitis C in Japan. World J Hepatol 2015;7:1125–1132.

18 Hill L: Hepatitis C virus direct-acting antiviral drug interactions and use in renal and hepatic impairment. Top Antivir Med 2015;23:92–96.

19 Roth D, Nelson DR, Bruchfeld A, Liapakis A, Silva M, Monsour H Jr, Martin P, Pol S, Londoño MC, Hassanein T, Zamor PJ, Zuckerman E, Wan S, Jackson B, Nguyen BY, Robertson M, Barr E, Wahl J, Greaves W: Grazoprevir plus elbasvir in treatment-naive and treatment-experienced patients with hepatitis C virus genotype 1 infection and stage 4–5 chronic kidney disease (the C-SURFER study): a combination phase 3 study. Lancet 2015;386:1537–1545.

20 Feld JJ, Jacobson IM, Hézode C, Asselah T, Ruane PJ, Gruener N, Abergel A, Mangia A, Lai CL, Chan HL, Mazzotta F, Moreno C, Yoshida E, Shafran SD, Towner WJ, Tran TT, McNally J, Osinusi A, Svarovskaia E, Zhu Y, Brainard DM, McHutchison JG, Agarwal K, Zeuzem S; ASTRAL-1 Investigators: Sofosbuvir and velpatasvir for HCV genotype 1, 2, 4, 5, and 6 infection. N Engl J Med 2015;373:2599–2607.

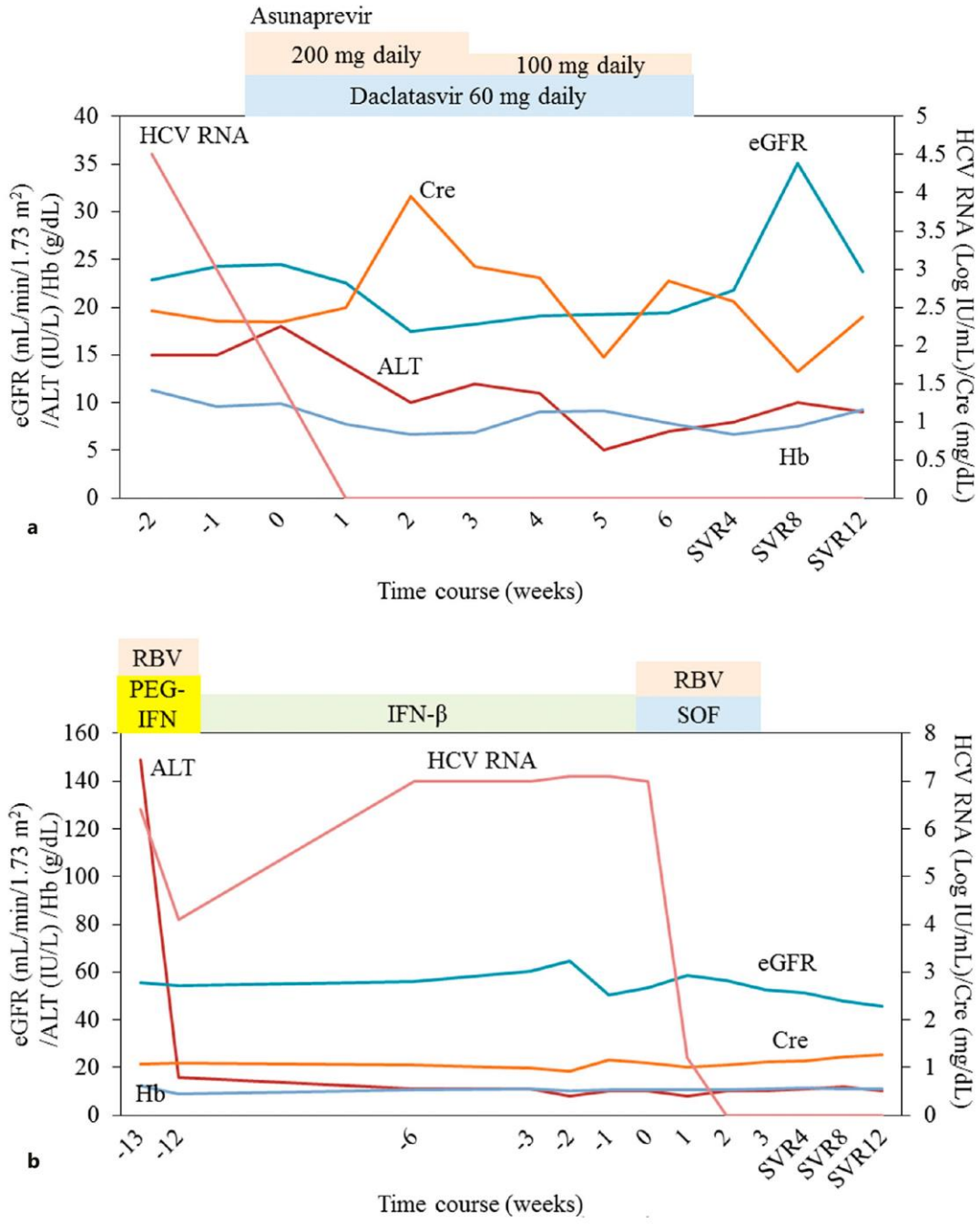

Fig. 1. Clinical course of the patients in the present study. **a** Case 1. **b** Case 2. SVR4, SVR8, and SVR12 indicate an SVR at 4, 8, and 12 weeks, respectively. Cre = Creatinine; Hb = hemoglobin; RBV = ribavirin; PEG-IFN = peginterferon; SOF = sofosbuvir.

Table 1. Laboratory findings prior to the initiation of the combination treatment with asunaprevir and daclatasvir in case 1

Item	Value	Item	Value	Item	Value
AST	15 IU/l	WBC	4,500/μl	AFP	4.6 ng/ml
ALT	18 IU/l	RBC	368 × 10^4/μl	PIVKA-2	14 mAU/ml
LDH	191 IU/l	hemoglobin	11.3 g/dl	ferritin	426.1 ng/ml
ALP	459 IU/l	hematocrit	34.7%	TSH	0.665 μIU/ml
γ-GTP	67 IU/l	platelets	10.9 × 10^4/μl	fT_3	2.48 pg/ml
T.BIL	0.5 mg/dl	PT	120%	fT_4	1.12 ng/dl
D.BIL	0.1 mg/dl	PT-INR	1.00	blood sugar	100 mg/dl
TP	6.7 g/dl	anti-HCV	positive	HbA_{1c}	5.3%
Alb	4 g/dl	HCV RNA	4.5 log IU/ml	CRP	0 mg/dl
T.CHO	169 mg/dl	HCV genotype	1b		
UA	7 mg/dl	HBsAg	negative		
UN	57 mg/dl	anti-HBs	negative		
Cre	2.45 mg/dl	anti-HBc	negative		
eGFR	22.9 ml/min/1.73 m^2	anti-HIV	negative		

LDH = Lactate dehydrogenase; ALP = alkaline phosphatase; γ-GTP = γ-glutamyltransferase; T.BIL = total bilirubin; D.BIL = direct bilirubin; TP = total protein; Alb = albumin; T.CHO = total cholesterol; UA = uric acid; UN = urea nitrogen; Cre = creatinine; WBC = white blood cell count; RBC = red blood cell count; PT = prothrombin time; PT-INR = PT international normalized ratio; anti-HCV = anti-HCV antibody; HBsAg = hepatitis B virus surface antigen; anti-HBs = anti-hepatitis B virus surface antibody; anti-HBc = anti-hepatitis B virus core antibody; anti-HIV = anti-human immunodeficiency virus antibody; AFP = α-fetoprotein; PIVKA-2 = protein induced by vitamin K absence-2; TSH = thyroid-stimulating hormone; fT_3 = free triiodothyronine; fT_4 = free thyroxine; HbA_{1c} = hemoglobin A_{1c}; CRP = C-reactive protein.

Table 2. Laboratory findings prior to the initiation of the combination treatment with sofosbuvir and ribavirin in case 2

Item	Value	Item	Value
AST	10 IU/l	WBC	2,900/μl
ALT	17 IU/l	RBC	372 × 10^4/μl
LDH	164 IU/l	hemoglobin	10.8 g/dl
ALP	265 IU/l	hematocrit	33.4%
γ-GTP	53 IU/l	platelets	4.7 × 10^4/μl
T.BIL	0.7 mg/dl	PT	100%
D.BIL	0.1 mg/dl	PT-INR	1.03
TP	6.6 g/dl	anti-HCV	positive
Alb	3.7 g/dl	HCV RNA	7.0 log IU/ml
T.CHO	152 mg/dl	HCV genotype	2b
UA	6.9 mg/dl	HBsAg	negative
UN	26 mg/dl	anti-HBs	negative
Cre	1.10 mg/dl	HBV DNA	negative
eGFR	53.5 ml/min/1.73 m^2	anti-HIV	negative

LDH = Lactate dehydrogenase; ALP = alkaline phosphatase; γ-GTP = γ-glutamyltransferase; T.BIL = total bilirubin; D.BIL = direct bilirubin; TP = total protein; Alb = albumin; T.CHO = total cholesterol; UA = uric acid; UN = urea nitrogen; Cre = creatinine; WBC = white blood cell count; RBC = red blood cell count; PT = prothrombin time; PT-INR = PT international normalized ratio; anti-HCV = anti-HCV antibody; HBsAg = hepatitis B virus surface antigen; anti-HBs = anti-hepatitis B virus surface antibody; anti-HIV = anti-human immunodeficiency virus antibody.