

Single Case

Successful Management of Graft Reinfection of HCV Genotype 2 in Living Donor Liver Transplantation from a Hepatitis B Core Antibody-Positive Donor with Sofosbuvir and Ribavirin

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Keywords

Hepatitis C virus · Direct-acting antivirals · Living donor liver transplantation · Sofosbuvir

Abstract

Direct-acting antivirals (DAAs) are relatively safe and highly effective for the eradication of hepatitis C virus (HCV) in liver transplant recipients. In this case study, we present a female with a graft reinfected with HCV genotype 2 who was treated with a combination of sofosbuvir and ribavirin after living donor liver transplantation (LDLT). Because the graft was from a hepatitis B core antibody-positive donor, passive immunization with hyperimmune hepatitis B immunoglobulin (HBIG) and entecavir were also provided to prevent hepatitis B virus (HBV) reactivation. It became clear that the combination of sofosbuvir and ribavirin promptly led to a sustained virologic response and that this combination was safe to treat graft reinfection with HCV genotype 2 after LDLT. Adverse events caused by DAAs were not observed,

except for slight anemia. HBIG and entecavir were useful in the prevention of HBV reactivation. In conclusion, the present case indicated that DAA treatment for graft reinfection with HCV is safe and effective in LDLT from hepatitis B core antibody-positive donors.

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Introduction

Hepatitis C virus (HCV) infection is a leading cause of end-stage liver disease and hepatocellular carcinoma [1, 2]. HCV-related liver disease is the most common indication for orthotopic liver transplantation in the USA and Northern Europe and for living donor liver transplantation (LDLT) in Japan [3–5]. Unfortunately, liver transplantation is not a cure for HCV infection, and the occurrence of graft reinfection with HCV is universal, leading to progression of liver fibrosis and occasionally to graft loss at rates higher than in transplant patients not infected with HCV [5, 6].

In Japan, because of long-standing legal difficulties associated with cadaveric donation [7], LDLT is the main type of liver transplantation for end-stage liver disease. Infection with HCV is of negative predictive value in LDLT [8]. The sustained virologic response (SVR) rate was ~40% in donors of LDLT treated with pegylated interferon (peginterferon) plus ribavirin [9], although adverse events were commonly observed even in nontransplanted patients receiving this treatment [10]. Akamatsu et al. [9] reported that the dose reduction rate and the discontinuation rate of peginterferon plus ribavirin treatment was 40 and 42%, respectively.

Recent progress in the development of direct-acting antivirals (DAAs) against HCV has made it possible to eradicate HCV effectively and to shorten the treatment duration compared to the previous standard of care, i.e. peginterferon plus ribavirin [10]. Treatment with the HCV NS5B polymerase inhibitor sofosbuvir plus ribavirin for 12 weeks was shown to lead to high rates of SVR (~97%) in Japanese patients infected with chronic HCV genotype 2 [11].

Asian-Pacific countries, including Japan, account for ~50% of all chronic hepatitis B virus (HBV) infection globally [12]. Given the prevalence of HBV, LDLT from hepatitis B core antibody-positive donors to recipients was occasionally performed with passive immunization with hyperimmune hepatitis B immunoglobulin (HBIG) plus nucleos(t)ide analogs [13].

Here, we report on an LDLT recipient who was reinfected with HCV genotype 2a after receiving a graft from a hepatitis B core antibody-positive donor. HCV genotype 2a was eradicated by a 12-week treatment with sofosbuvir plus ribavirin with HBIG plus entecavir, one of the nucleos(t)ide analogs, for the successful prevention of HBV reappearance.

Case Report

A 66-year-old Japanese woman developed liver failure due to cirrhosis and HCV genotype 2a infection. She was a treatment-naïve patient, but her IL28B rs8099917 was a favorable genotype (TT). Two years prior to LDLT, she has been diagnosed with liver cirrhosis due to HCV infection without liver biopsy. She had been infected with HCV after having received a blood transfusion during childbirth at the age of 30 years. At LDLT, she had peripheral edema with a MELD (Model for End-Stage Liver Disease) score of 12. LDLT with a right liver graft from a hepatitis B core antibody-positive donor was performed in February 2015.

Five months after LDLT, the HCV RNA level was 5.8 log IU/ml, and she was diagnosed with graft reinfection with HCV genotype 2a. Combination treatment with 400 mg daily of sofosbuvir and 400 mg daily of ribavirin was commenced. Her height, body weight, and body mass index were 1.56 m, 50 kg, and 20.5, respectively. She abstained from consumption of alcohol. Her laboratory data before treatment are shown in [table 1](#). The HCV RNA level before treatment was 5.8 log IU/ml. After LDLT, she received triple immunosuppressive therapy consisting of tacrolimus (3 mg daily), mycophenolate mofetil, and basiliximab with passive immunization with HBIG and 0.5 mg daily of entecavir.

Four weeks after initiating the combination treatment with sofosbuvir and ribavirin, HCV RNA levels were undetectable. She completed this treatment for 12 weeks and achieved SVR at 24 weeks following the termination of this treatment (SVR24) ([fig. 1](#)). There was no evidence of HBV reactivation.

Because her hemoglobin level was 12.2 g/dl before the commencement of this treatment, an oral iron preparation was also started. After 2 months of treatment, her hemoglobin level fell to 10.8 mg/dl. Then, the dose of ribavirin was decreased to 200 mg daily, and her hemoglobin level improved to 12.8 g/dl ([fig. 1](#)). During this period of treatment, she did not develop evidence of bone marrow suppression, such as observed in peginterferon-plus-ribavirin treatment. No serious adverse events were observed. During treatment, the trough level of tacrolimus remained stable.

Discussion

We presented a female patient with living donor-related graft reinfection with HCV genotype 2a who was treated with a combination of sofosbuvir and ribavirin for 12 weeks. Although several DAAs have drug-drug interactions, no changes in this patient's drug protocol, which included immunosuppressants and combination treatment of sofosbuvir plus ribavirin, were necessary in this case.

Treatment of HCV infection after liver transplantation is a challenge. Peginterferon plus ribavirin with or without DAAs may be attempted, but the use of peginterferon is restricted by severe side effects and inadequate efficacy [5]. In addition, interferon has an immune-mediated cytotoxicity, occasionally causing allograft dysfunction [14]. Interferon-free therapy is a viable treatment option and improves treatment efficacy [15–20]. This case suggests that DAAs are well tolerated and effective for the eradication of HCV from post-liver transplantation patients.

In the present case of LDLT, graft reinfection with HCV genotype 2 was treated with a combination of sofosbuvir plus ribavirin. The patient achieved SVR24, although she had anemia as an adverse event, and anti-HCV treatment was continued without blood transfusion. Curry et al. [17] reported that common adverse events of combination treatment with sofosbuvir and ribavirin were fatigue (in 38% of patients), headache (23%), and anemia (21%) after liver transplantation. Charlton et al. [18] reported that the most common adverse events were fatigue (30%), diarrhea (28%), headache (25%), and anemia (20%) during a 24-week combination treatment course of sofosbuvir plus ribavirin after liver transplantation.

In the present study, the patient received a liver graft from a hepatitis B core antibody-positive donor, and, in general, HBV from these donors is transmitted to recipients at a high rate [13]. Therefore, passive immunization with HBIG plus treatment with entecavir were provided to prevent HBV reactivation. Curing HCV infection with DAAs in HBV/HCV coinfection

tion and monitoring for HBV reactivation should be performed [21], because DAAs against HCV do not have any effect on HBV replication, unlike interferon. In the present case, the patient was treated with HBIG and entecavir, and there was no evidence of HBV reactivation.

Recently, more effective regimens with DAAs against HCV have been reported [22, 23]. These regimens may make it possible to shorten the duration of treatment and to make it easier to achieve SVR. The use of interferon-free regimens is possible for the eradication of HCV in post-LDLT patients with grafts from hepatitis B core antibody-positive donors, as was demonstrated by our patient, who was successfully treated with HBIG and entecavir to prevent HBV reactivation. In conclusion, 12-week treatment with sofosbuvir plus ribavirin is relatively safe and highly effective for the eradication of HCV genotype 2 in LDLT patients.

Acknowledgements

We thank all colleagues at the liver units of their hospitals who cared for the patients described herein.

Statement of Ethics

The authors have no ethical conflicts to disclose.

Disclosure Statement

Tatsuo Kanda and Osamu Yokosuka received lecture fees from Gilead Sciences. The other authors declare that there is no conflict of interest regarding the publication of this manuscript.

References

- 1 Armstrong GL, Alter MJ, McQuillan GM, Margolis HS: The past incidence of hepatitis C virus infection: implications for the future burden of chronic liver disease in the United States. *Hepatology* 2000;31:777–782.
- 2 El-Serag HB: Epidemiology of viral hepatitis and hepatocellular carcinoma. *Gastroenterology* 2012;142:1264–1273.
- 3 Organ Procurement and Transplantation Network: 2012 Annual Data Report. http://srtr.transplant.hrsa.gov/annual_reports/2012/Default.aspx (accessed on February 7, 2016).
- 4 Guillouche P, Féray C: Systematic review: anti-viral therapy of recurrent hepatitis C after liver transplantation. *Aliment Pharmacol Ther* 2011;33:163–174.
- 5 Kaneko J, Sugawara Y, Yamaguchi T, Harada N, Akamatsu N, Ishizawa T, Aoki T, Sakamoto Y, Hasegawa K, Tamura S, Tanaka T, Kokudo N: Telaprevir-based triple therapy for hepatitis C null responders among living donor liver transplant recipients. *Biosci Trends* 2014;8:339–345.
- 6 Berenguer M, Prieto M, Rayón JM, Mora J, Pastor M, Ortiz V, Carrasco D, San Juan F, Burgueño MD, Mir J, Berenguer J: Natural history of clinically compensated hepatitis C virus-related graft cirrhosis after liver transplantation. *Hepatology* 2000;32:852–858.
- 7 Kanda T, Yokosuka O, Ehata T, Maru Y, Imazeki F, Saisho H, Shiratori Y, Omata M: Detection of GBV-C RNA in patients with non-A-E fulminant hepatitis by reverse-transcription polymerase chain reaction. *Hepatology* 1997;25:1261–1265.
- 8 Kawaguchi Y, Sugawara Y, Akamatsu N, Kaneko J, Hamada T, Tanaka T, Ishizawa T, Tamura S, Aoki T, Sakamoto Y, Hasegawa K, Kokudo N: Impact of early reoperation following living-donor liver transplantation on graft survival. *PLoS One* 2014;9:e109731.

- 9 Akamatsu N, Sugawara Y, Kokudo N, Eguchi S, Fujiwara T, Ohdan H, Nagano H, Taketomi A, Kitagawa Y, Shimada M, Ku Y, Yanaga K, Shirabe K, Ikegami T, Mizokami M, Takeuchi M, Maehara Y: Outcomes of living donor liver transplantation for hepatitis C virus-positive recipients in Japan: results of a nationwide survey. *Transpl Int* 2014;27:767–774.
- 10 Kanda T, Imazeki F, Yokosuka O: New antiviral therapies for chronic hepatitis C. *Hepatol Int* 2010;4:548–561.
- 11 Omata M, Nishiguchi S, Ueno Y, Mochizuki H, Izumi N, Ikeda F, Toyoda H, Yokosuka O, Nirei K, Genda T, Umemura T, Takehara T, Sakamoto N, Nishigaki Y, Nakane K, Toda N, Ide T, Yanase M, Hino K, Gao B, Garrison KL, Dvory-Sobol H, Ishizaki A, Omote M, Brainard D, Knox S, Symonds WT, McHutchison JG, Yatsuhashi H, Mizokami M: Sofosbuvir plus ribavirin in Japanese patients with chronic genotype 2 HCV infection: an open-label, phase 3 trial. *J Viral Hepat* 2014;21:762–768.
- 12 Sarin SK, Kumar M, Lau GK, Abbas Z, Chan HL, Chen CJ, Chen DS, Chen HL, Chen PJ, Chien RN, Dokmeci AK, Gane E, Hou JL, Jafri W, Jia J, Kim JH, Lai CL, Lee HC, Lim SG, Liu CJ, Locarnini S, Al Mahtab M, Mohamed R, Omata M, Park J, Piratvisuth T, Sharma BC, Sollano J, Wang FS, Wei L, Yuen MF, Zheng SS, Kao JH: Asian-Pacific clinical practice guidelines on the management of hepatitis B: a 2015 update. *Hepatol Int* 2016;10:1–98.
- 13 Uemoto S, Sugiyama K, Marusawa H, Inomata Y, Asonuma K, Egawa H, Kiuchi T, Miyake Y, Tanaka K, Chiba T: Transmission of hepatitis B virus from hepatitis B core antibody-positive donors in living related liver transplants. *Transplantation* 1998;65:494–499.
- 14 Ikegami T, Yoshizumi T, Yoshida Y, Kurihara T, Harimoto N, Itoh S, Shimokawa M, Fukuhara T, Shirabe K, Maehara Y: Telaprevir versus simeprevir for the treatment of recurrent hepatitis C after living donor liver transplantation. *Hepatol Res* 2016;46:E136–E145.
- 15 Fontana RJ, Hughes EA, Bifano M, Appelman H, Dimitrova D, Hindes R, Symonds WT: Sofosbuvir and daclatasvir combination therapy in a liver transplant recipient with severe recurrent cholestatic hepatitis C. *Am J Transplant* 2013;13:1601–1605.
- 16 Kim B, Trivedi A, Thung SN, Grewal P: Case report of successful treatment of fibrosing cholestatic hepatitis C with sofosbuvir and ribavirin after liver transplantation. *Semin Liver Dis* 2014;34:108–112.
- 17 Curry MP, Forns X, Chung RT, Terrault NA, Brown R Jr, Fenkel JM, Gordon F, O’Leary J, Kuo A, Schiano T, Everson G, Schiff E, Befeler A, Gane E, Saab S, McHutchison JG, Subramanian GM, Symonds WT, Denning J, McNair L, Arterburn S, Svarovskaia E, Moonka D, Afdhal N: Sofosbuvir and ribavirin prevent recurrence of HCV infection after liver transplantation: an open-label study. *Gastroenterology* 2015;148:100–107.
- 18 Charlton M, Gane E, Manns MP, Brown RS Jr, Curry MP, Kwo PY, Fontana RJ, Gilroy R, Teperman L, Muir AJ, McHutchison JG, Symonds WT, Brainard D, Kirby B, Dvory-Sobol H, Denning J, Arterburn S, Samuel D, Forns X, Terrault NA: Sofosbuvir and ribavirin for treatment of compensated recurrent hepatitis C virus infection after liver transplantation. *Gastroenterology* 2015;148:108–117.
- 19 Ueda Y, Kaido T, Hatano E, Ohtsuru S, Uemoto S: Safe and effective treatment with daclatasvir and asunaprevir in a liver transplant recipient with severe cholestatic hepatitis C. *Hepatol Res* 2015;45:1360–1362.
- 20 Kawaoka T, Imamura M, Morio K, Nakamura Y, Tsuge M, Nelson Hayes C, Kawakami Y, Aikata H, Ochi H, Ishiyama K, Ide K, Tashiro H, Ohdan H, Chayama K: Three patients treated with daclatasvir and asunaprevir for recurrent hepatitis C after liver transplantation: case report. *Hepatol Res* 2016;46:707–712.
- 21 Collins JM, Raphael KL, Terry C, Cartwright EJ, Pillai A, Anania FA, Farley MM: Hepatitis B virus reactivation during successful treatment of hepatitis C virus with sofosbuvir and simeprevir. *Clin Infect Dis* 2015;61:1304–1306.
- 22 Curry MP, O’Leary JG, Bzowej N, Muir AJ, Korenblat KM, Fenkel JM, Reddy KR, Lawitz E, Flamm SL, Schiano T, Teperman L, Fontana R, Schiff E, Fried M, Doehle B, An D, McNally J, Osinusi A, Brainard DM, McHutchison JG, Brown RS Jr, Charlton M; ASTRAL-4 Investigators: Sofosbuvir and velpatasvir for HCV in patients with decompensated cirrhosis. *N Engl J Med* 2015;373:2618–2628.
- 23 Foster GR, Afdhal N, Roberts SK, Bräu N, Gane EJ, Pianko S, Lawitz E, Thompson A, Shiffman ML, Cooper C, Towner WJ, Conway B, Ruane P, Bourlière M, Asselah T, Berg T, Zeuzem S, Rosenberg W, Agarwal K, Stedman CA, Mo H, Dvory-Sobol H, Han L, Wang J, McNally J, Osinusi A, Brainard DM, McHutchison JG, Mazzotta F, Tran TT, Gordon SC, Patel K, Reau N, Mangia A, Sulkowski M; ASTRAL-2 Investigators; ASTRAL-3 Investigators: Sofosbuvir and velpatasvir for HCV genotype 2 and 3 infection. *N Engl J Med* 2015;373:2608–2617.

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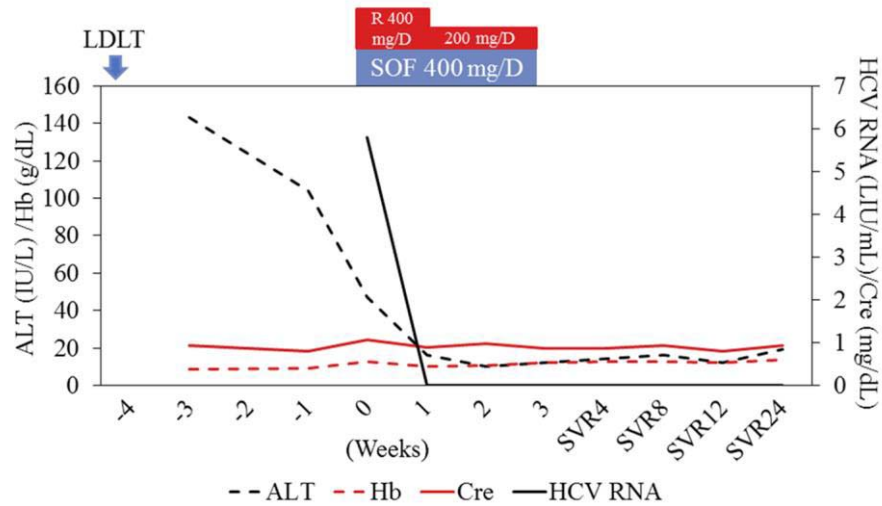


Fig. 1. Clinical course of the patient in the present study. SVR4, SVR8, SVR12, and SVR24 denote SVRs at 4, 8, 12 and 24 weeks, respectively. ALT = Alanine transaminase; Cre = creatinine; Hb = hemoglobin; LDLT = living donor liver transplantation; R = ribavirin; SOF = sofosbuvir.

Table 1. Laboratory findings before the commencement of the combination treatment with sofosbuvir and ribavirin in the present case

Item	Value	Item	Value
AST	74 IU/l	WBC	2,500/ μ l
ALT	61 IU/l	RBC	362×10^4 / μ l
LDH	223 IU/l	Hemoglobin	12.2 g/dl
ALP	525 IU/l	Hematocrit	35.6%
γ -GTP	40 IU/l	Platelets	12.1×10^4 / μ l
T.BIL	0.5 mg/dl	PT	120%
D.BIL	0.1 mg/dl	PT-INR	0.96
TP	6.5 g/dl	Anti-HCV	positive
Alb	4.0 g/dl	HCV RNA	5.8 log IU/ml
T.CHO	156 mg/dl	HCV genotype	2a
UA	6.0 mg/dl	HBsAg	negative
UN	23 mg/dl	Anti-HBs	positive
Cre	1.12 mg/dl	HBV DNA	negative
eGFR	38.1 ml/min/1.73 m ²	Anti-HIV	negative

AST = Aspartate aminotransferase; ALT = alanine transaminase; 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; eGFR = estimated glomerular filtration rate; WBC = white blood cell count; RBC = red blood cell count; PT = prothrombin time; PT-INR = PT international normalized ratio; anti-HCV = anti-hepatitis C virus antibody; HBsAg = hepatitis B virus surface antigen; anti-HBs = anti-hepatitis B virus surface antibody; anti-HIV = anti-human immunodeficiency virus antibody.