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CASE REPORT Open Access

Successful treatment of chronic hepatitis C virus genotype 1b infection of a patient with compensated cirrhosis after renal transplantation using daclatasvir-asunaprevir combination therapy: a case report and literature review

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Abstract

Background: Hepatitis C virus (HCV) infection a major disorder that is not only a liver-related disease but also a cardiovascular complication in renal transplant recipient. Interferon-based therapy is a contraindication after transplantation because interferon is possibly induced to graft rejection. Only limited anecdotal evidence exists on the antiviral efficacy and tolerability of HCV direct acting antivirals (DAAs) in patients with chronic kidney disease (CKD), including renal transplant recipients. Then, we report a successful treatment case of chronic hepatitis C virus genotype 1b infection in a patient with compensated cirrhosis after renal transplantation using daclatasvir-asunaprevir combination therapy and reviewed the literature.

Case presentation: A 64-year-old female renal transplantation (RT) recipient complicated with compensated cirrhosis due to hepatitis C virus (HCV) genotype 1b infection was treated with interferon (INF)–ribavirin-free combinations of DAAs such as daclatasvir plus asunaprevir. She was medicated with daclatasvir 60 mg once a day and asunaprevir 100 mg twice a day for 24 weeks. Her initial HCV RNA was log10 6.2 IU/ml, and HCV RNA was not detected from 10 weeks. She achieved a sustained virological response at 24 weeks (SVR24). During this therapy, her serum creatinine and tacrolimus trough level were slightly elevated, but those abnormalities were returned to the basal level by decreasing the dose of extended-release tacrolimus. No other adverse event requiring discontinuation of the treatment occurred.

Conclusions: Almost all DAA treatments of HCV infection in renal transplant recipients have been sofosbuvir-based antiviral treatment, but we considered that daclatasvir-asunaprevir combination therapy is suitable to renal-impaired recipient because sofosbuvir is contraindicated in patients whose estimated GFR is <30 ml/min/1.73 m^2, and both of daclatasvir and asunaprevir are mainly primarily metabolized by the liver. We showed excellent effect daclatasvir-asunaprevir combination therapy to a renal transplant recipient with chronic HCV infection and reviewed the literature.

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Background

Chronic hepatitis C virus (HCV) infection progresses to hepatic dysfunction, cirrhosis, and hepatocellular carcinoma, and the target of the therapy is elimination of the virus [1]. Since Omata et al. [2] reported the effectiveness of interferon (IFN) in 1991, it has been the standard therapy for chronic HCV infection until the appearance of direct acting antivirals (DAAs) [3]. However, the use of IFN is prohibited in renal transplantation (RT) patients because IFN could induce acute rejection. Kidney Disease Improving Global Outcomes (KDIGO) recommends IFN therapy for recipients with HCV infection before RT [4]. Therefore, there has been no choice of treatment in post-transplant patients with chronic HCV infection. Here, we report the successful treatment of a patient with oral IFN- and ribavirin-free DAAs (daclatasvir plus asunaprevir) for compensated cirrhosis due to HCV genotype 1b infection after RT. These new DAAs may change the natural history of HCV infection after RT. However, there is as yet no evidence to support the use of DAAs in the RT setting because the understanding of DAA metabolism and drug–drug interaction is insufficient. In addition, there have been no large studies of DAA treatment in this patient group [5].

Case presentation

A 64-year-old female was diagnosed with chronic glomerulonephritis in March 1976 and soon started hemodialysis. She showed intermittent elevation of transaminase and thrombocytopenia at the start of hemodialysis. We considered that these abnormalities were caused by chronic non-A and non-B hepatitis, which is now called type C hepatitis, because she did not show abnormal neurological signs, jaundice, or ascites. She had never received a transfusion and was not a drug addict. Therefore, the infection route of hepatitis C virus (HCV) was unknown. She underwent hemodialysis three times a week for about 26 years, and she then received a cadaveric RT in April 2003. Before transplantation, she underwent an examination by upper gastrointestinal endoscopy, which revealed no esophageal varices or other abnormalities. After transplantation, her clinical course was very good except for mild liver injury and thrombocytopenia. HCV antibody positivity was first detected on screening for infections in April 1991, when this examination became commercially available in Japan. For the first time, we checked HCV RNA, which was positive in April 2008. Upper gastrointestinal endoscopy to screen for malignancy, which was carried out in June 2014, revealed esophageal varices at the upper esophagus. At that time, her height was 141.1 cm, body weight 39.2 kg, body temperature 36.5 °C, and blood pressure 125/60 mmHg. Her consciousness was clear, and neurological examination was normal. Her palpebral conjunctiva was not anemic, and bulbar conjunctiva was not icteric. Her abdomen was not distended, and hepatomegaly was not present. Her spleen was palpable about 6 cm below the left hypochondrium. Lower abdominal wall vein dilatation (so called Caput medusae) was present. There were no vascular spiders, palmar erythema, digital clubbing, or asterixis. Urinalysis revealed 1+ proteinuria, but occult blood was negative. The amount of proteinuria over 24 h was 0.25–0.35 g. Other laboratory findings were as follows: leukocytes 5400/μl, erythrocytes 423×10^4/μl, hemoglobin 11.7 g/dl, hematocrit 35.7 %, platelets 6.7×10^4/μl, blood urea nitrogen 36.9 mg/dl, serum creatinine 1.30 mg/dl, e-GFR 32.6 ml/min/1.73 m^2, uric acid 5.2 mg/dl, total protein 6.5 g/dl, albumin 3.9 g/dl, AST 64 IU/l (normal value 8–38 IU/l), ALT 65 IU/l (normal value 40–40 IU/l), γ~GTP 47 IU/l (normal value <70 IU/l), total bilirubin 0.78 mg/dl, ALP 430 IU/l (normal value 100–335 IU/l l), i-PTH 222 pg/ml (normal value 10–65 pg/ml), hepaplastin test 101.3 % (normal value 70–130 %), PT 85.6 % (normal value 70–140 %), type IV collagen·7S 7.6 ng/ml (normal value <6.0), procollagen III peptide 1.9 U/ml (normal value <1.0 U/ml), HCV RNA 6.2 $\log_{10}$ IU/ml, and HCV genotype 1b. We examined the patient for pretreatment resistance-associated variants. There were no variants in the L31M and Y93H regions. A computed tomography (CT) scan revealed splenomegaly and a tiny quantity of ascites (Fig. 1). There were no findings of liver atrophy or tumor (Fig. 2). We diagnosed well-compensated liver cirrhosis (Child–Pugh grade A; score 6 points). After the local ethics committee approval and written informed consent, we decided to treat her HCV chronic infection with the interferon (IFN)-free DAAs daclatasvir plus asunaprevir because of the risk of acute renal rejection after IFN treatment. We prescribed daclatasvir 60 mg once daily plus asunaprevir 100 mg twice daily for 24 weeks. Her other prescription medications were extended-release tacrolimus 2 mg/day,

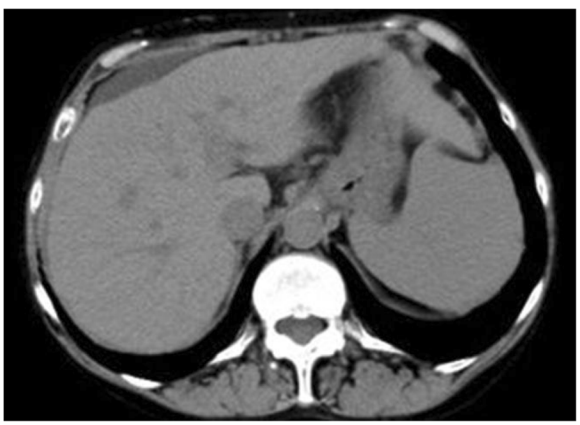

Fig. 1 Abdominal CT findings. Marked splenomegaly was observed, and a small amount of ascites were present on the surface of the liver. No liver atrophy or tumors were found

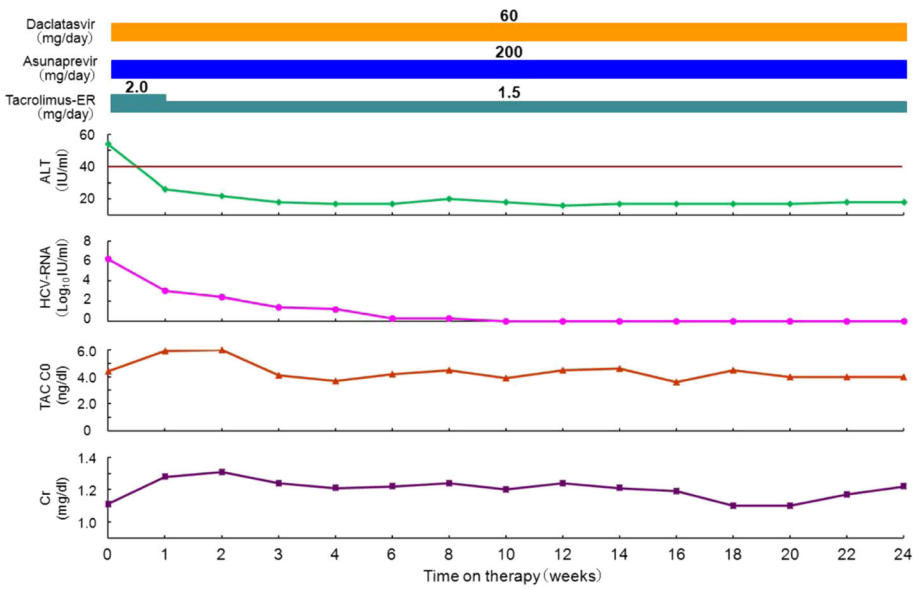

Fig. 2 HCV RNA, ALT, serum creatinine (Cr), and trough level of tacrolimus (TAC C0) during treatment with daclatasvir and asunaprevir in the present case

mycophenolate mofetil 500 mg/day, prednisolone 2 mg/day, valsartan 40 mg/day, alfacalcidol 0.25 μg/day, cinacalcet 25 mg/day, febuxostat 40 mg/day, ursodeoxycholic acid 600 mg/day, menatetrenone 15 mg/day, and acetaminophen 800 mg/day. Her HCV RNA level decreased rapidly and was undetectable from 10 weeks after the start of treatment, and she achieved a sustained virologic response (SVR) at 24 weeks (SVR_{24}). Her slightly elevated transaminase level was normalized quickly. Slightly elevated serum creatinine and trough level of tacrolimus were decreased after dose adjustment of extended-release tacrolimus from 2 to 1.5 mg/day (Fig. 2). There were no other adverse events. A follow-up CT scan was performed after 24 weeks' treatment with daclatasvir and asunaprevir and showed persistent splenomegaly, but no more ascites.

Discussion

About 170–180 million people are chronically infected with HCV worldwide [6]. The prevalence of infection in kidney transplant recipients is significantly higher than in the general population [7], and it is associated with increased morbidity and mortality [8]. RT recipients have an HCV infection rate of 5–15 % in developed countries, with substantially higher rates reported in the developing world. After RT, HCV-RNA-positive recipients have an increased risk of cirrhosis, hepatocellular carcinoma, and death. Infection with HCV is also an independent risk factor for graft loss and is associated with proteinuria, chronic rejection, transplant glomerulopathy, posttransplant diabetes, and HCVassociated glomerulonephritis. Therefore, prevention and management of HCV infection is a critical factor in RT therapy [5].

HCV is a positive, single-stranded RNA virus, and it is divided into seven genotypes [9]. Genotype 1 is the most prevalent worldwide, accounting for approximately 60 % of infections [10]. Type lb infection is more closely associated with the development of liver cirrhosis and hepatocellular carcinoma than type 2a or 2b through its role in the progression of chronic liver inflammation to a cirrhotic stage [11]. IFN-based antiviral therapies are the standard approach to control HCV infection. However, KDIGO recommends that HCV-infected kidney transplant candidates are considered for treatment with standard IFN before transplantation because IFN has been associated with higher renal allograft rejection rates [4]. In 2014, a meta-analysis performed by Wei et al. demonstrated that IFN-based therapy for HCV infection post-RT has poor efficacy and limited safety. They identified 12 clinical trials (140 patients in total). The summary estimates for the SVR rate, dropout rate, and graft rejection rate were 26.6, 21.1, and 4 %, respectively. The most frequent side-effect requiring discontinuation of treatment was graft dysfunction (45.1 %) [12]. As described above, the use of IFN-based therapy is avoided in the treatment of chronic HCV-infected patients after RT, but IFN-free regimens are a great hope as a new treatment for RT recipients. DAAs show potential for greater efficacy in the eradication of HCV, and their reduced toxicity makes them an attractive therapeutic option after RT [5]. However, there are very few reports on DAA therapy in RT recipients. All existing reports involved sofosbuvir-based antiviral therapy (Table 1) [13–15]. Kamar et al. [13] reported the efficacy and safety of sofosbuvir-based antiviral therapy for treating HCV infection after RT. They

Table 1 DAAs after renal transplantation

Number of case	Sex Male/female	Platelets count, ×103/mm^3, median (range)	CNI	HCV genotype	DAA regimen	Rate of SVR12	Reference
35	15:10	160 (180–290)	Tac:9 CyA:1	1a: 4 1b:15 2: 2 3:1 4:3	SOF/LDV:9 SOF/SMV:6 SOF/DCV:4 SOF/RBV:3 SOF:LDV/RBV:1 SOF/SMV/RBV:1 PEG-IFN/RBV/SOF:1	35/35	[13]
20	16:4	180 (59–284)	Tac:19 CyA:1	1:4 1a:6 1a/1b:1 1b:6 2b:2 2a/2c:1	SOF/LDV:7 SOF/SMV:9 SOF/DCV:1 SOF/RBV:3	20/20	[14]
4	2:1	201 (158–269)	Tac:3	4:3	SOF/RBV:3	3/3	[15]

CNI calcineurin inhibitor, *CyA* cyclosporin A, *DAA* direct-acting antivirals, *DCV* daclatasvir, *HCV* hepatitis C virus, *LDV* ledipasvir, *PEG-IFN* pegylated interferon, *RBV* ribavirin, *SMV* simeprevir, *SOF* sofosbuvir, *SVR12* sustained a virologic response at 24 weeks, *Tac* tacrolimus

treated 25 RT recipients with chronic HCV infection. At 4 and 12 weeks after completing DAA therapy, all had a SVR. The tolerance of anti-HCV therapy was excellent, and no adverse events were observed. Sawinski et al. [14] showed 20 consecutive RT recipients treated with IFN-free sofosbuvir-based antiviral treatment regimens for HCV. All patients cleared the virus while on therapy, and 100 % achieved a SVR at 12 weeks after completion of therapy. These DAAs were well tolerated, and less than half of the patients required calcineurin inhibitor dose adjustment during treatment. Hussein et al. [15] also demonstrated successful treatment of HCV genotype 4 in RT recipients with sofosbuvir and ribavirin. They treated three patients and achieved SVR12 without major adverse events. Sofosbuvir is mainly eliminated by the kidney; therefore, its use is contraindicated in patients with severe renal impairment (glomerular filtration rate <30 mL/min/1.73 m^2) or chronic renal failure undergoing dialysis [16].

Daclatasvir plus asunaprevir has received its first global approval in this indication in Japan, which is the first all-oral, IFN-, and ribavirin-free regimen for HCV genotype 1b [17]. Kumada H. et al. demonstrated that 24-week treatment with daclatasvir and asunaprevir provides a highly effective option for non-transplantation patients who currently have no effective treatment options (ineligible for or intolerant of IFN-based therapy) and for those patients who did not achieve SVR with prior treatment. In addition, they described that 22 patients with virologic failure had NS5A polymorphisms L31 and/or Y93 prior to treatment. The present case showed no variants in the L31M and Y93H region. The patients had a complication with compensated cirrhosis, and Kumada H. et al. also

Table 2 Characteristics of DAA and dose adjustments for renal or hepatic impairment

Drug	Inhibition	Induction	Substrate	Renal impairment	Hepatic impairment
Asunaprevir	Moderate inhibitor of CYP2D6	Weak inhibitor of CYP3A4 and P-gp	Substrate of CYP3A4, P-gp, and OATP1B1	No adjustment needed	Should likely be avoided in patients with CTP class B or C disease
Daclatasvir	Moderate inhibitor of P-gp and OATP	NA	Substrate of CYP3A and P-gp	No adjustment needed	No adjustment needed
Ledipasvir	Mild inhibitor of P-gp, BCRP	NA	Substrate of P-gp	No adjustment needed	No adjustment needed
Paritaprevir, ritonavir, and ombitasvir plus dasabuvir	Inhibitor of CYP3A4, CYP2D6, P-gp, OATP, and BCRP	Inhibitor of CYP1A2, CYP2C8, CYP2C9, and CYP2C19 (based on ritonavir pharmacokinetics)	Substrate of CYP3A4, CYP2C8, and CYP2D6	Likely no adjustment needed	Not recommended in patients with CTP class B disease and contraindicated in patients with CTP class C disease
Simeprevir	Mild inhibitor of intestinal CYP3A and CYP1A2; mild inhibitor of OATP and P-gp	NA	Substrate of CYP3A	No adjustment needed	Should be used with caution in patients with CTP class B or C disease
Sofosbuvir	NA	NA	Substrate of P-gp	Not recommended if GFR <30 mL/min/1.73 m^2	No adjustment needed

BCRP breast cancer resistance protein, *CTP* Child-Turcotte-Pugh, *CYP* cytochrome P450, *DAA* direct-acting antiviral drugs, *GFR* glomerular filtration rate, *NA* not available, *OATP* organic anion-transporting polypeptide, *P-gp* P-glycoprotein. Adapted from Hill et al. [20]

reported that their patients with cirrhosis also achieved high rates of SVR_{24} (20/22, 90.9 %) [18]. Most RT recipients showed chronic kidney disease stage 3 or more [19]. Hence, it is very important to recognize DAA metabolism and drug–drug interactions, and we showed here effectiveness of DAA and the use of dose adjustments for renal or hepatic impairment (Table 2) [20]. Daclatasvir and asunaprevir are primarily metabolized by the liver. Therefore, it is suggested that there is no need to adjust the doses of these drugs according to renal function. Daclatasvir and asunaprevir are suitable drugs to renal transplant recipients with impaired real function. Asunaprevir is a substrate of CYP3A, P-gp, and OATP 1B1 and 2B1. It inhibits OATP 1B1, 1B3, and 2B1 and P-gp and CYP2D6 and induces CYP3A4. Daclatasvir and asunaprevir are both contraindicated in patients taking strong CYP3A4 inducers, such as rifampicin, rifabutin, phenytoin, carbamazepine, phenobarbital, systemic dexamethasone, and products including foods containing *Hypericum perforatum* (St. John's wort) [21]. Asunaprevir is also contraindicated in patients taking cyclosporin [22].

Our patient had moderate renal and hepatic impairment (Child–Pugh grade A) and treatment with daclatasvir plus asunaprevir was highly effective in the elimination of HCV without any adverse reactions other than a slight increase in serum creatinine and the trough level of tacrolimus.

Conclusions

To the best of our knowledge, we report herein the first case of successful daclatasvir plus asunaprevir treatment for a patient who received a cadaveric RT complicated with compensated cirrhosis caused by HCV genotype 1b infection without any adverse effects. This new treatment may be considered for chronic HCV infection after RT.

Abbreviations

DAAs: Direct acting antivirals; HCV: Hepatitis C virus; IFN: Interferon; KDIGO: Kidney Disease Improving Global Outcomes; RT: Renal transplantation; SVR24: Sustained virological response at 24 weeks

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Availability of data and materials

We wish to share our data.

Authors' contributions

RM and KM took care of patients and participated in the decision of treatment. RM prepared the manuscript. Both authors read and approved the final manuscript.

Competing interests

Miyazaki has received lecture fees from Bristol-Myers Squibb. Miyagi has no conflicts to report.

Consent for publication

We gained written informed consent for publication from this patient.

Ethics approval and consent to participate

After the local ethics committee approval, we obtained written informed consent from this patient.

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