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CASE REPORT

Three renal failure cases successfully treated with ombitasvir/paritaprevir/ritonavir for genotype 1b hepatitis C virus reinfection after liver transplantation

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Abstract

We report three cases of genotype 1b hepatitis C virus (HCV) reinfection after liver transplantation. When antiviral treatment was considered, all three patients had renal dysfunction and had been treated with immunosuppressive agents for a long time; one with tacrolimus (TAC) and the others with cyclosporine A (CyA). Therefore, the possible antiviral regimens among direct-acting antivirals (DAA) were limited and so we treated all three patients with ombitasvir/paritaprevir/ritonavir (OBV/PTV/r). Because ritonavir is known to markedly increase the blood concentration of TAC and CyA through drug–drug interactions, close monitoring of blood concentrations of TAC or CyA and dose adjustments of immunosuppressive agents were needed. Sustained virus response was achieved in all the patients treated, and there were no adverse effects or transplant rejection. OBV/PTV/r might be a useful DAA regimen for patients with genotype 1 HCV reinfection in the setting of renal dysfunction.

Keywords Ombitasvir/paritaprevir/ritonavir · Hepatitis C virus · Liver transplantation · Reinfection · Direct-acting antiviral

Introduction

Liver transplantation (LT) is one of several treatment options for liver cirrhosis and/or hepatocellular carcinoma (HCC) due to hepatitis C virus (HCV) infection. Reinfection of a liver graft with HCV may cause dysfunction of the graft and result in poor prognosis [1]. Reinfection with HCV occurs in almost 100% of LT cases and, in the presence of immunosuppressive therapy, causes rapid progression of liver fibrosis [2, 3]. In HCV-infected patients not receiving immunosuppressive therapy, liver fibrosis is reported to progress by 0.1–0.2 liver fibrosis stages every year, advancing to cirrhosis after about 30 years. On the other hand, in HCV-infected patients receiving immunosuppressive therapy after LT, liver fibrosis is reported to progress by 0.3–0.6 liver fibrosis stage per year, and advances to cirrhosis in 9.5 years [2, 3]. Therefore, HCV should be eradicated by antiviral treatment as soon as possible after reinfection with HCV. The survival rate among patients who achieved permanent eradication of HCV following antiviral treatment, which is by definition a sustained viral response (SVR), is reported to be significantly higher than among patients who do not achieve SVR [1].

Pegylated interferon and ribavirin were the standard of care for HCV infection for a long time. The SVR rate for this combined therapy was around 50% for genotype 1 HCV, and it was accompanied by many adverse effects [4]. Pegylated interferon and ribavirin were also frequently used to treat HCV infection after LT, however, SVR rates in these cases were lower than in cases unrelated to LT [1, 5–7]. Due to clinical complications after LT, such as renal dysfunction and pancytopenia, it was sometimes difficult to use adequate pegylated interferon and ribavirin or even to start pegylated interferon and ribavirin treatment after LT. Moreover, it is reported that the use of pegylated interferon itself is a potential risk for immune-mediated graft dysfunction due to its immune modulatory effects [8]. Recently, many direct-acting

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antivirals (DAA) against HCV have been developed and the current antiviral treatment for HCV has primarily been the combination of DAAs without interferon, referred to as interferon-free DAA treatment [9, 10]. The latest interferon-free DAA treatments have been reported to eliminate HCV in more than 95% patients with much fewer adverse effects than interferon-based treatment and have a shorter treatment period.

Interferon-free DAA treatment is expected to dramatically increase the probability of SVR in patients with HCV reinfection after LT compared with interferon-based treatment. However, it is sometimes difficult to treat the patients after LT with DAAs because of accompanied renal dysfunction or drug–drug interactions with immunosuppressive agents [11–13]. For example, an NS5B inhibitor, sofosbuvir, which is one of most frequently used DAAs, cannot be administered to the patients with renal dysfunction [14, 15]. A combination treatment with the NS5A inhibitor ombitasvir, the NS3/4A protease inhibitor paritaprevir, and the HIV protease inhibitor ritonavir (OBV/PTV/r) is helpful in treating HCV-infected patients after LT who have renal dysfunction, because OBV/PTV/r is metabolized in the liver. However, ritonavir inhibits cytochrome P450 3A (CYP3A) that metabolizes calcineurin inhibitors, such as tacrolimus (TAC) and cyclosporine A (CyA), both of which are generally used as immunosuppressive agents after LT, therefore, the use of OBV/PTV/r with TAC or CyA could prominently increase the blood concentrations of TAC or CyA and dose adjustment of TAC or CyA is needed [11–13].

We used OBV/PTV/r to treat three cases of HCV reinfection after LT in patients with renal failure. Although close monitoring of blood concentrations of TAC or CyA and dose adjustment of immunosuppressive agents was required, SVR was achieved in all three patients, without any serious adverse effect or graft rejection. This report clearly shows that OBV/PTV/r may be a treatment option for HCV reinfection in patients with renal dysfunction after LT.

Case report

Case 1

A male patient presented to us at 71 years of age. He had been diagnosed with HCV infection when he was 46 years old. At the age of 51 years, he was diagnosed with primary hepatocellular carcinoma (HCC) for the first time and treated with radiofrequency ablation and transcatheter arterial chemoembolization. However, the HCC recurred repeatedly and liver function gradually worsened. At age of 60 years, he developed liver failure with advanced HCC and underwent living-related LT, following which HCV reinfection of the liver graft occurred. After LT, an immunosuppressive agent, TAC, was immediately administered. At the age of 61 years, liver enzymes were found to be elevated due to HCV infection; he initially received pegylated interferon and ribavirin therapy, but this was interrupted due to pancytopenia, and SVR was not achieved. At 65 years old, he developed renal dysfunction with a gradually increasing serum creatinine (Cr) level. The reasons for this renal dysfunction were assumed to be immunosuppressive agent-related nephropathy, HCV-related membranous proliferative glomerulonephritis, or cryoglobulinemia-related nephropathy. Because he declined a renal biopsy, the etiology of the renal dysfunction remained undetermined. At the age of 69 years, he started to undergo hemodialysis due to progression of chronic renal failure.

At the age of 71 years, in May 2016, he started antiviral treatment with Obv (25 mg/day)/Ptv (150 mg/day)/R (100 mg/day). He was admitted to hospital for initiation of therapy, because of the expected need for frequent measurement of the trough blood concentration and subsequent adjustment of TAC. At the beginning of the antiviral treatment, platelet count (Plt) was 20.1×10^4/μL, alanine aminotransferase (ALT) 15 IU/L, Cr 9.42 mg/dL, estimated glomerular filtration rate (eGFR) was calculated as 4.91 mL/min/1.73 m^2. HCV genotype was 1b, and HCV-RNA was 6.0 logIU/mL. NS5A resistance-associated variants at L31 and Y93 were not observed (Tables 1, 2). Before starting antiviral treatment with OBV/PTV/r, he took the medicines shown in Table 3, including nifedipine, a calcium channel

Table 1 Laboratory data for the three patients at the initiation of antiviral therapy

Case	1	2	3
WBC (/μL)	6210	3160	6060
Hb (g/L)	9.6	8.3	11.2
Plt (/μL)	201,000	132,000	263,000
PT (%)	88	89	80
UN (mg/dL)	62	37	39
Cr (mg/dL)	9.42	1.36	1.56
eGFR (mL/min/1.73 m^2)	4.91	30.64	35.81
Na (mEq/L)	140	142	144
K (mEq/L)	4.9	5.1	4.8
Cl (mEq/L)	102	111	111
ALP (IU/L)	307	386	223
γGTP (IU/L)	80	46	42
AST (IU/L)	6	19	26
ALT (IU/L)	15	21	27
T-Bi l(mg/dL)	0.5	0.5	0.3
D-Bil (mg/dL)	0.2	0.1	0.1
Alb (g/L)	3.6	4.0	3.4
AFP (ng/mL)	13	12	20
HCV-RNA (LogIU/mL)	6.0	7.0	5.3

Table 2 Clinical data for the three patients at the initiation of antiviral therapy

Case	Sex	Age	Time after LT (months)	Immunosuppressive agent	Previous antiviral treatment after LT	Liver histology	Histology timing	FIB4 score	HCV genotype	NS5A RAV	IL28B SNPs rs8099917
1	M	71	130	TAC	PegIFN + RBV relapse	CH	6 years before	0.55	1b	None	Non-major
2	F	67	117	CyA	PegIFN + RBV NR	CH	At the therapy	2.1	1b	None	Non-major
3	M	63	47	CyA	None	CH	3 years before	1.2	1b	None	Major

blocker. The use of nifedipine was stopped before starting OBV/PTV/r because concomitant use of calcium channel blockers with OBV/PTV/r is reported to possibly cause serious adverse events of edema [16]. He had been treated with 0.5 mg/day of TAC before antiviral therapy, but from the start of antiviral treatment (day 1), the TAC dose was reduced to 0.2 mg/3 days. Trough blood concentration of TAC was 2.2 ng/mL before starting antiviral treatment and was 2.0 and 3.2 ng/mL at day 2 and day 6, respectively.

Thereafter, he was discharged from the hospital at day 7 without any adverse effects. At the first follow-up clinic visit, on day 10, trough blood concentration of TAC increased to 7.1 ng/mL. By day 21, it had risen to 12.1 ng/mL; therefore, the TAC dose was further reduced to 0.2 mg/5 days. Subsequently, trough blood concentration of TAC remained relatively high at 9.6, 8.5, and 10.7 ng/mL on days 35, 42, and 56, respectively. On day 56, he underwent esophagogastroduodenoscopy to determine the reason for upper abdominal pain. Although an esophagogastroduodenoscopy examination revealed esophageal candidiasis, he was not treated with antifungal medicines because his disease was mild and his abdominal pain disappeared within a week after examination. Finally, on week 12 (day 84), the course of OBV/PTV/r therapy was completed as scheduled without any dose reduction. HCV RNA was undetectable at the end of treatment (Fig. 1a). TAC dose was increased to 0.2 mg/day on the day after cessation of the antiviral treatment, then to 0.5 mg/day on the third day after cessation, the same as the dose before antiviral treatment. Trough blood concentration of TAC was 2.0, 2.0, and 2.8 ng/mL at weeks 4, 8, and 12 after antiviral treatment, respectively (Fig. 1b). Finally, he achieved SVR12. During and after antiviral treatment, no dialysis setting change was required and no blood pressure change was observed that would require additional medications. Additionally, no liver injury, which would have suggested rejection, was observed.

Case 2

A female patient presented to us at 67 years of age. She had been diagnosed with HCV infection at age of 45 years. At the age of 56 years, a diagnosis of HCC was made for the first time and she was treated with radiofrequency ablation and transcatheter arterial chemoembolization. The HCC recurred repeatedly and liver function gradually worsened. At 57 years, she developed liver failure with advanced HCC, and underwent living-related LT. After LT, the immunosuppressive agent, CyA, was immediately administered. At the age of 58 years, she was found to have elevated liver enzymes due to HCV infection, and underwent pegylated interferon and ribavirin therapy, but SVR was not achieved. At the age of 59 years, she developed renal dysfunction with a gradually increasing serum

Table 3 Medicines for the three patients before and during antiviral therapy

Case 1		Case 2		Case 3	
Name of medicines	Dose/day	Name of medicines	Dose/day	Name of medicines	Dose/day
Ursodeoxycholic acid	600 mg	Ursodeoxycholic acid	900 mg	Ursodeoxycholic acid	600 mg
Esomeprazole	20 mg	Rabeprazole	10 mg	Doxazosin mesilate	1 mg
Nifedipine[a]	40 mg	Warfarin potassium	2 mg	Amlodipine[a]	5 mg
		Telmisartan	80 mg	Frusemide	20 m
		Sodium hydrogen carbonate	1.5 g	Febuxostat	20 mg
		Calcium polystyrene sulfonate	75 g	Prednisolone	5 mg
		Levothyroxine sodium hydrate	50 μg	Carvedilol	20 mg
				Mycophenolte mofetil	1000 m
				Calcium polystyrene sulfonate	50 g
				Spironolactone	50 mg

[a]Stopped before starting OBV/PTV/r

Cr level, but the reason for renal dysfunction remained undetermined. At age of 67 years, in May 2016, she started OBV/PTV/r therapy and was admitted to the hospital because of the need for frequent measurement of trough blood concentration and adjustment of CyA. At the beginning of the therapy, Plt was 12.9×20^4/μL, ALT 15 IU/L, Cr 1.39 mg/dL, and eGFR 29.9 4.91 mL/min/1.73 m^2. HCV genotype was 1b and HCV-RNA, 7.0 logIU/mL. NS5A resistance-associated variants at L31 and Y93 were not seen (Tables 1, 2). The medications for her are shown in Table 3.

She had earlier been treated with 100 mg/day of CyA, but from the first day of antiviral therapy (day 1), the CyA dose was reduced to 40 mg/day. Trough blood concentration of CyA was 164 ng/mL before starting antiviral therapy, and was 175 ng/mL on day 2, so the CyA dose was further reduced to 20 mg/day on day 3. Trough concentration was 175, 156, 167, 182, and 167 ng/mL on days 3, 4, 5, 6, and 7, respectively. Then, the CyA dose was reduced to 10 mg/day on day 8, and the trough concentration was 187, 117, and 111 ng/mL on days 8, 9, and 10, respectively. She was discharged from hospital on day 11. At the first clinic visit, day 18, trough blood concentration of CyA was 54 ng/mL, and it remained stable until the end of antiviral treatment. Finally, at week 12 (day 84), OBV/PTV/r therapy was completed as scheduled without any dose reduction (Fig. 2a). HCV RNA was undetectable at the end of treatment. The CyA dose was increased to 100 mg/day on the day after cessation of antiviral treatment, which was the same dose before antiviral treatment. Trough blood concentration of CyA was 109, 76, and 63 ng/mL on days 1, 3, and 7 after antiviral treatment, respectively (Fig. 2b). Finally, she achieved SVR12. During and after antiviral treatment, no renal function change and no blood pressure change was observed that would require additional medications. Additionally, no liver injury, which would have suggested rejection, was observed.

Case 3

A male patient presented to us at 63 years of age. He had undergone LT at age 59 due to liver failure and HCC; and immunosuppressive treatment with CyA was started immediately. Renal function gradually declined, possibly due to CyA. At age of 63 years, in May 2016, 47 months after LT, he began OBV/PTV/r therapy for HCV reinfection. He was hospitalized for the treatment. At the time Cr was 1.56 mg/dL and eGFR was calculated as 35.81 mL/min/1.73 m^2. HCV genotype was 1b and HCV-RNA, 7.0 logIU/mL. NS5A resistance-associated variants at L31 and Y93 were not observed. Clinical background and laboratory data are shown in Tables 1 and 2. Before starting antiviral treatment with OBV/PTV/r, he took the medicines shown in Table 3, including the calcium channel blocker, amlodipine. The use of amlodipine was also stopped before starting of OBV/PTV/r similar to case 1. He had been treated with 60 mg/day of CyA, but from the first day of antiviral therapy (day 1), the CyA dose was reduced to 20 mg/day. Finally, the CyA dose was reduced to 10 mg/day and the trough concentration was around 180 ng/mL during antiviral treatment. OBV/PTV/r therapy was completed as scheduled without any dose reduction. HCV RNA quickly became undetectable during antiviral treatment, and finally, SVR12 was achieved. During and after antiviral treatment, no renal function change and no blood pressure change was observed that would require additional medications. Additionally, no liver injury, which would have suggested rejection, was observed.

Discussion

Most of the guidelines for treatment of HCV reinfection after LT recommend interferon-free DAA as a first choice rather than interferon-based treatment, due to lower SVR rates

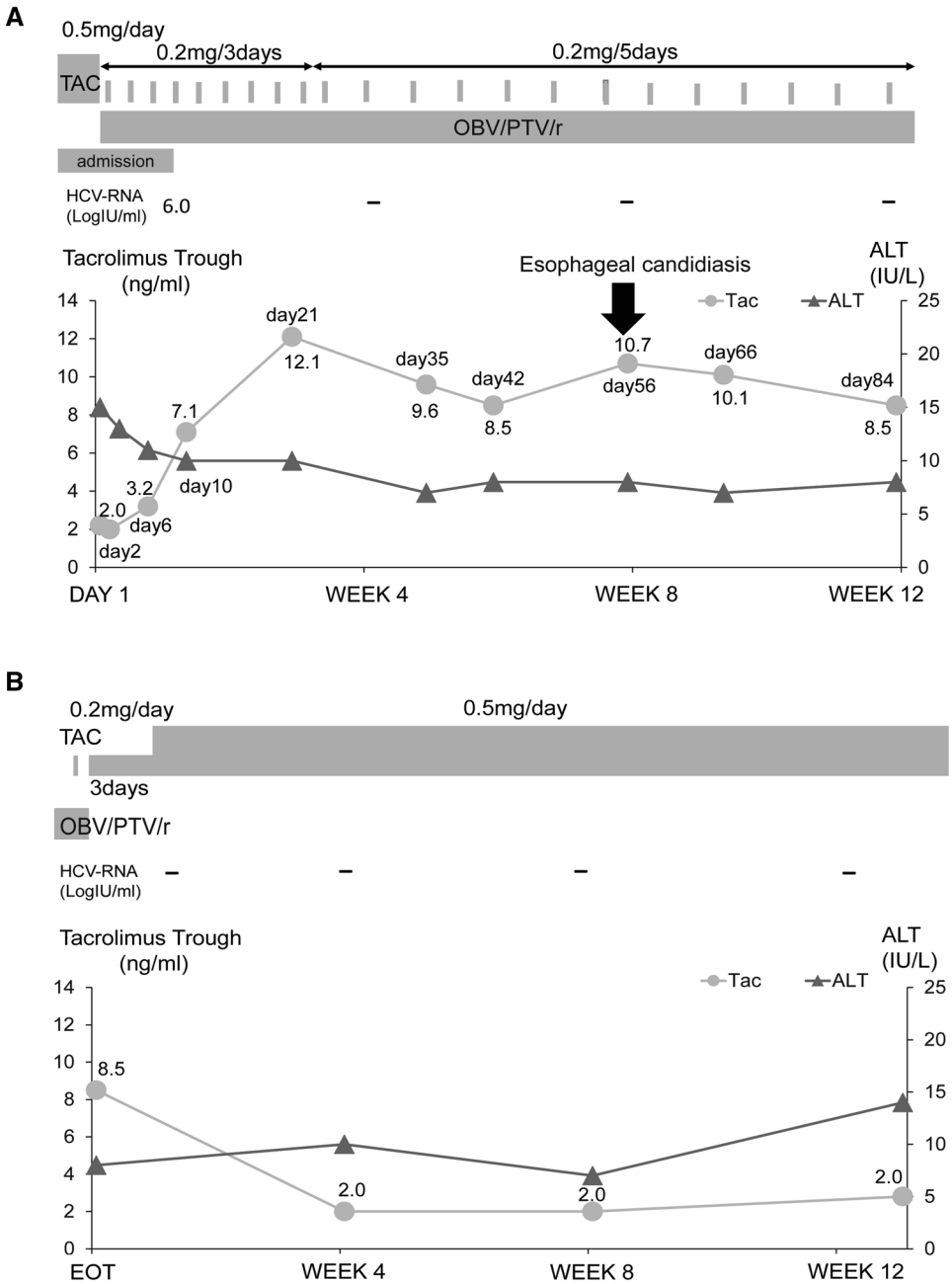

Fig. 1 **a** Clinical course of case 1 (TAC case) on antiviral therapy. **b** Clinical course of case 1 (TAC case) after antiviral therapy. *EOT* end of treatment

and the risk of immune-mediated graft dysfunction with interferon-based treatment. The latest guidelines from The Japan Society of Hepatology (JSH) recommend daclatasvir plus asunaprevir (DCV plus ASV), ledipasvir/sofosbuvir (LDV/SOF), or elbasvir/grazoprevir (EBR plus GZR) for the treatment of reinfection with genotype 1 HCV after LT. The guidelines do not recommend OBV/PTV/r, because ritonavir inhibits CYP3A, which metabolizes calcineurin inhibitors such as TAC and CyA, and the concentration of TAC or CyA could increase [17]. However, the guidelines from the American Association for the Study of Liver Diseases (AASLD) and from the European Association for the Study of the Liver (EASL) recommend LDV/SOF as the first-line treatment choice for reinfection with genotype 1 HCV after LT [18, 19]. The ASSLD and EASL guidelines also recommend OBV/PTV/r plus an NS5B inhibitor, dasabuvir (which is not available in Japan) as an alternative therapy for reinfection. We treated three patients with HCV reinfection after LT using OBV/PTV/r and achieved SVR in all patients, suggesting that OBV/PTV/r is also a good alternative therapy for genotype 1 HCV infection after LT.

Selecting available DAA regimens for the treatment of HCV reinfection after LT is sometimes complicated for the following reasons: (1) After LT, patients often develop renal

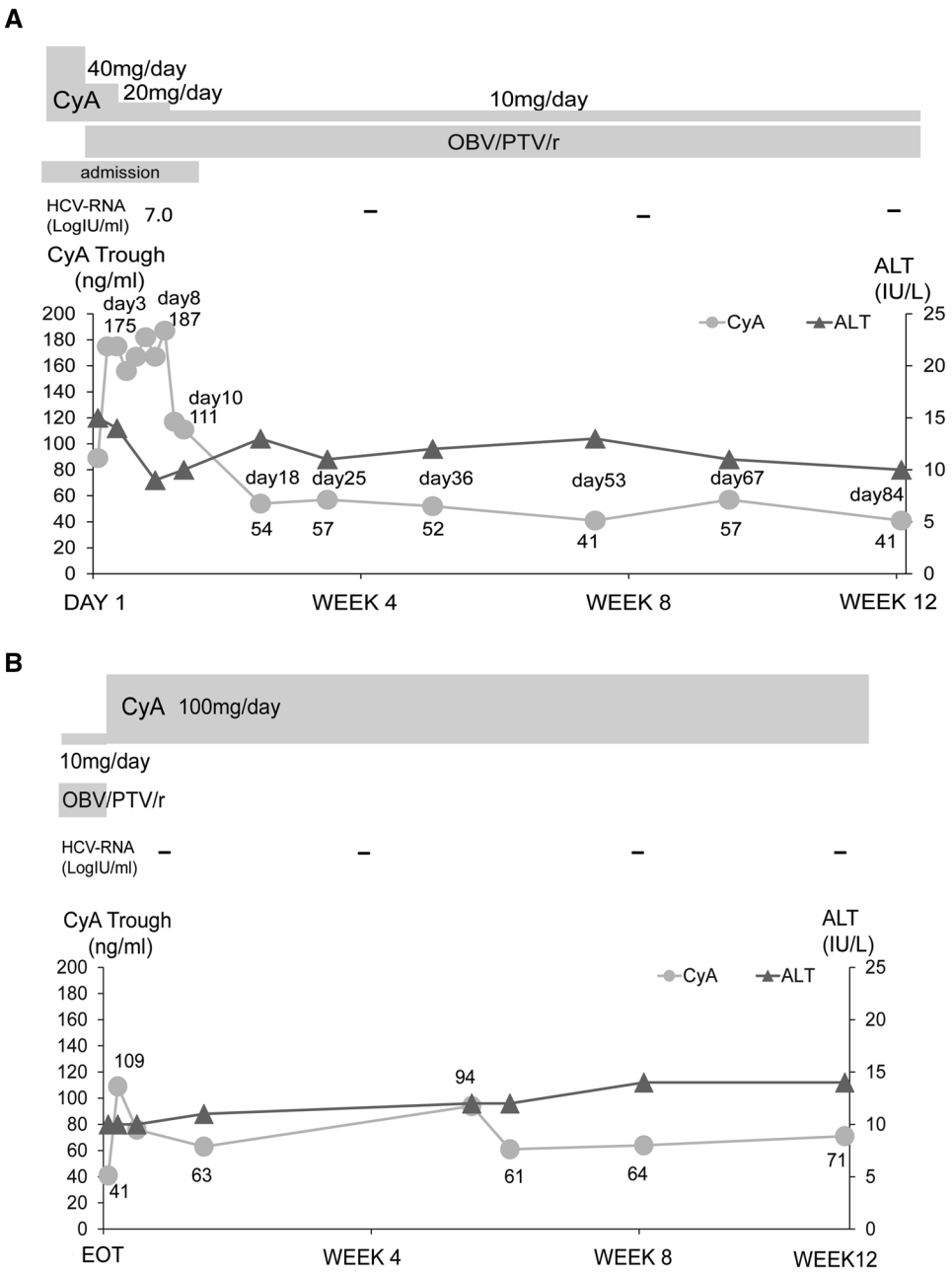

Fig. 2 **a** Clinical course of case 2 (CyA case) on antiviral therapy. **b** Clinical course of case 2 (CyA case) after antiviral therapy. *EOT* end of treatment

dysfunction and one of the major DAAs, sofosbuvir, cannot be used in patients with advanced renal dysfunction. (2) Enzymes that metabolize calcineurin inhibitors and DAAs sometimes compete, which can affect the concentrations of calcineurin inhibitors and DAAs. Tables 4, 5 and 6, respectively, show the impact of CyA on DAA concentration, the

Table 4 Effect of CyA on DAAs area under the curve (AUC)

	OBV/PTV/r	ASV + DSV	SOF/LDV	EBR + GZR	OBV/PTV/r + dasabuvir	GLE/PIB
AUC	OBV:1.096 PTV:1.455	DSV:1.4 ASV: reduced	SOF:4.53	EBR:1.98 GZR:15.21	OBV:1.08 PTV:1.72 r :1.11 dasabuvir:0.7	GLE:1.37 PIB:1.22

OBV ombitasvir, *PTV* paritaprevir, *r* ritonavir, *ASV* asunaprevir, *DSV* daclatasvir, *SOF* sofosbuvir, *LDV* ledipasvir, *EBR* elbasvir, *GZR* grazoprevir, *PIB* pibrentasvir, *GLE* glecaprevir

Table 5 Effect of TAC on DAAs area under the curve (AUC)

	OBV/PTV/r	ASV + DSV	SOF/LDV	EBR + GZR	OBV/PTV/r + dasabuvir	GLE/PIB
AUC	OBV:0.954 PTV:0.794 r:0.840	DSV:1.05	SOF:1.13	EBR:0.97 GZR:1.12	OBV:0.94 PTV:0.66 r :0.87 dasabuvir:0.9	GLE:1.01 PIB:1.01

OBV ombitasvir, *PTV* paritaprevir, *r* ritonavir, *ASV* asunaprevir, *DSV* daclatasvir, *OF* sofosbuvir, *LDV* ledipasvir, *EBR* elbasvir, *GZR* grazoprevir, *PIB* pibrentasvir, *GLE* glecaprevir

Table 6 Effect of DAAs on CyA and TAC area under the curve (AUC)

	OBV/PTV/r	ASV + DSV	SOF/LDV	EBR + GZR	OBV/PTV/r + dasabuvir	GLE/PIB
CyA	4.28	1.03	0.98	0.96	5.82	1.01
TAC	57–85.81	1.00	1.09	1.43	57.13	1.45

OBV ombitasvir, *PTV* paritaprevir, *r* ritonavir, *ASV* asunaprevir, *DSV* daclatasvir, *SOF* sofosbuvir, *LDV* ledipasvir, *EBR* elbasvir, *GZR* grazoprevir, *PIB* pibrentasvir, *GLE* glecaprevir

impact of TAC on DAA concentration, and the impact of DAA on concentration of CyA and TAC.

In the three cases presented here, all the patients had renal dysfunction. Therefore, we could not treat them with SOF/LDV. Possible DAA regimens were: ASV plus DCV, EBV plus GZR, pibrentasvir/glecaprevir (GLE/PIB), or OBV/PTV/r because these DAAs are metabolized by the liver. In fact, safety and effectiveness of ASV plus DCV and OBV/PTV/r for patients during dialysis were reported [20, 21]. GLE/PIB and EBV plus GZR regimens were not yet available in Japan at the time of treatment, which left ASV plus DCV or OBV/PTV/r as possible options.

In the case of the first-generation DAA regimen ASV plus DCV, ASV cannot be used concomitantly with CyA because both are metabolized by the same enzyme, organic anion transporting polypeptide 1B1 (OATP1B1), and the blood concentration of ASV is markedly reduced in cotreatment [10]. In addition, the duration of ASV plus DCV treatment is 24 weeks, which is longer than others, and is sometimes associated with adverse effects such as high fever and liver injury and is not effective especially for patients with NS5A resistance-associated variants [7]. Therefore, the use of ASV plus DCV is very limited, and so we decided to treat these three patients with OBV/PTV/r.

Furthermore, OBV/PTV/r is useful in treating HCV reinfection after LT because neither TAC nor CyA significantly alter the concentrations of OBV, PTV, or ritonavir. However, the concomitant use of OBV/PTV/r with TAC or CyA prominently increases the blood concentration of TAC and CyA because ritonavir inhibits CYP3A, which metabolizes calcineurin inhibitors. The area under the curve (AUC) for TAC and CyA is increased with OBV/PTV/r by 4.28-fold and 57- to 85.81-fold, respectively, compared with the concentration without calcineurin inhibitors [22, 23]. Therefore, close monitoring of blood concentrations and dose adjustments of calcineurin inhibitors are necessary when OBV/PTV/r is administered concomitantly.

In the present cases, we adjusted the dose and dosing interval of immunosuppressive agents according to available pharmacokinetic data. Reports on the interactions between OBV/PTV/r and immunosuppressive agents showed that OBV/PTV/r prolongs the half-life (T1/2) of TAC to 232 h (a 7.25-fold increase), and the T1/2 of CyA to 25 h (a 3.5-fold increase) [22, 23]. Based on these data, we reduced the dose of TAC to 0.2–0.5 mg and extended the dosing interval from twice a day to once every 3–7 days. Similarly, we reduced the dose of CyA by one-fifth and increased the dosing interval from twice a day to once a day. The target trough level was set between 5 and 10 ng/mL for TAC and between 100 and 150 ng/mL for CyA, based on AASLD guidelines [24]. During and after antiviral treatment, we closely monitored the trough concentrations of the immunosuppressive agents and adjusted their doses as needed. During antiviral treatment, esophageal candidiasis was observed in case 1. The trough concentration of TAC was not extremely high at that time; therefore, it is unlikely that the esophageal candidiasis was caused by high concentrations of TAC. After cessation of OBV/PTV/r, the recovery dose and interval of the immunosuppressive agents is very important because lower concentrations of immunosuppressive agents could cause graft rejection. Because the T1/2 of OBV/PTV/r is about 24 h, the blood concentration should be almost zero within 3–4 days after cessation of OBV/PTV/r. Therefore, we reverted the dose and dose interval of TAC to baseline 3–4 days after the discontinuation of OBV/PTV/r. In the case of CyA-treated patients, the dose and dose interval of CyA was returned to the same as before starting OBV/PTV/r the day after discontinuing OBV/PTV/r.

Since the treatment of the patients described here, two additional regimens have become available in Japan for the

treatment of genotype 1 HCV: GLE/PIB and EBV plus GZR; all these DAAs are metabolized by the liver [25, 26], so both regimens are feasible in patients with renal dysfunction. Regarding EBV plus GZR, GZR cannot be used concomitantly with CyA because, as mentioned above, GZR and CyA are metabolized by the same enzyme, OATP1B1, and the blood concentration of GZR will markedly increase. However, EBR plus GZR is an alternative for patients treated with TAC because neither DAAs nor TAC markedly alter the blood concentrations of the other. PIB/GLE can be used with CyA or TAC because neither of these drugs alter the blood concentrations of the other. Although the opportunity to use OBV/PTV/r is currently limited, OBV/PTV/r could be a treatment option for patients who show drug allergies to PIB/CLE or EBV plus GZR. Furthermore, in countries where PIB/CLE or EBV plus GZR are not yet available and OBV/PTV/r is available, OBV/PTV/r could be a treatment option.

In summary, OBV/PTV/r is a useful DAA regimen for patients with reinfection of genotype 1 HCV and renal dysfunction, however, frequent measurement of the trough blood concentration and adjustment of the immunosuppressive agents are necessary.

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