Interferon-free Anti-hepatitis C Virus Treatment for Long-term Liver Transplantation Recipients with Failed Interferon Therapy

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Background : Recurrent hepatitis and cirrhosis due to hepatitis C virus (HCV) infection is a major cause of graft loss in liver transplant (LT) patients. Although interferon (IFN)-based therapy has been used in patients with recurrent hepatitis C after LT, the safety and efficacy of treatment remains unclear. IFN-free regimens with direct-acting antiviral agents (DAAs) against HCV showed excellent results in terms of sustained virological response (SVR) in non-LT patients. Recently, the efficacy of DAAs for LT patients has been reported. However, drug-drug interactions, the increasing risk of hepatocellular carcinoma (HCC), and the existence of drug-resistant gene variants require investigation in LT patients.

Method : This study included patients with recurrent hepatitis C after LT who failed IFN therapy and received IFN-free therapy. Medical records were reviewed retrospectively.

Results : Seven recipients were included. The median duration from LT to DAA treatment was 124 (34-181) months. HCV genotype was 1b in 6 patients and 2a in 1 patient. The Child-Pugh classification at IFN-free therapy was A in 6 patients and B in 1 patient. DAAs were used as follows : daclatasvir and asunaprevir in 3 patients, ledipasvir and sofosbuvir in 3, and sofosbuvir and ribavirin in 1. In all patients, sustained virologic response at week 24 was achieved without significant adverse events. No evidence of HCC has been observed.

Conclusion : HCV can be eradicated with interferon-free therapy in LT recipients with failed IFN therapy.
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Key words : direct-acting antiviral agents, interferon, liver transplantation, hepatitis C virus

I Introduction

Liver transplant (LT) recipients with hepatitis C virus (HCV) have a risk of recurrent hepatitis C. Liver cirrhosis (LC) due to the recurrence of HCV is a major cause of graft loss after LT. Interferon (IFN)-based therapy (IFN or peg-IFN with/without ribavirin [RBV]) has been administered for recurrent hepatitis C after LT, and a response rate of 30-40 % was reported[1)2)]. LT recipients frequently discontinued these treatments due to the relatively high incidence of complications and an increased risk of rejection.

Some direct-acting antiviral agents (DAAs) have been approved and high sustained virological response (SVR) rates in non-LT HCV patients treated with DAAs have been reported[3)-7)]. Historically, DAAs have been used with IFN, (peg-IFN + RBV + telaprevir [TVR]/ simeprevir [SMV]). These regimens have been used in LT patients, and improved SVR rates have been observed. However, the frequency of adverse events with these regimens remains high[8)-10)]. Recent IFN-free DAA regimens, including combinations of daclatasvir (DCV) and asunaprevir (ASV)[3)4)], sofosbuvir (SOF) and ledipasvir (LDV)[5)6)], and SOF and RBV[7)] reportedly have greater safety and efficacy. The regimens resulted in high rates of SVR in LT patients[11)], and even remained high in patients with failed IFN therapy. Meanwhile, DAA

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resistant HCV, drug interactions, and higher rates of HCC have also been reported[12].

Herein, we report our long-term experience with 7 cases of IFN-free treatment after failed IFN therapy in LT recipients.

Patients and methods:

Among 46 patients who received LT for HCV disease in our institute, recipients who failed IFN therapy and received IFN-free therapy were selected and included in this study. The medical records were retrospectively analyzed. This study protocol was approved by the Shinshu University Hospital Ethics Committee.

Ⅱ Results

Seven LT recipients with failed IFN therapy treated with DAAs were included in this study. The median age at LT was 53 years old (range: 43-65 years old). All of them underwent living donor transplantation, including one case of re-transplantation. HCV genotype was 1b in 6 patients and 2a in 1 patient. Drug resistance-associated variants (NS3 D168 or NS5A L31 or Y93 variants) were detected in 4 patients. In all cases, liver biopsy specimens were taken at the time of IFN therapy, and recurrent hepatitis was diagnosed. All patients were previously treated with IFN, IFN with RBV, or peg-IFN with RBV after LT. The median duration of IFN-based therapy was 69 weeks (range: 1-274 weeks). IFN-based therapy discontinuation was due to depression, heart failure, retinopathy, rejection, or non-responder status. All patients remained positive for serum HCV-RNA regardless of therapy.

Patients started treatment with IFN-free regimens at 2 to 15 years after LT (median: 12 years). The median age at initiation of IFN-free therapy was 64 years old (range: 55-70 years). Three were treated with DCV and ASV, 3 with LDV and SOF, and 1 with SOF and RBV. Child-Pugh classification at the beginning of the therapy was class A in 6, and class B in 1. Since the use of DAAs for patients with Child-Pugh B was considered an off-label indication in Japan, institutional review board approval and informed consent from the patients were obtained prior to treatment. Calcineurin inhibitors were administered in all patients, with tacrolimus in 5, and cyclosporine in 2. Mycophenolate mofetil was used in combination with a calcineurin inhibitor in 4. Corticosteroids were not administrated to any patients. During the course of DAA treatment, the levels of serum AST and ALT decreased or remained within normal limits in all cases. The serum HCV-RNA levels were 1.2-7.0 logIU/ml (median: 5.2 logIU/ml) before the treatment, and decreased to undetectable levels within 2-9 weeks (median: 3 weeks), and sustained virologic response at week 24 (SVR24) was achieved in all cases. Occurrence of HCC was not observed during this study period. The details of each clinical course are shown in **Table 1-3**. The clinical course of IFN-free therapy in one representative case (Case 1) is shown in **Fig. 1**.

Ⅲ Discussion

After LT for HCV-related cirrhosis, most patients experience recurrence of hepatitis[13]. In our institution, 46 patients received LT due to HCV infection. Forty-five of the 46 experienced recurrence of hepatitis. Among these, 36 were previously treated with IFN-based therapy. SVR was achieved in only 12 with IFN-based therapy. Two were treated with DAAs with IFN and achieved SVR. Four were not able to start DAAs due to their physical condition, and 11 had died. Seven recipients were treated with IFN-free DAA therapy, and were reviewed in this study. A recipient in whom HCV was eradicated with IFN-based therapy before LT had no episodes of recurrent hepatitis. It is known that insufficient HCV therapy will lead to much earlier development of cirrhosis in LT patients, and is associated with a poor prognosis. Liver cirrhosis accounts for above 50 % of graft loss or death in HCV LT recipients[14][15]. Because of the clinical course, LC recipients with HCV had a worse prognosis than LC recipients with other etiologies. Only 2.5 % of patients achieved SVR with IFN monotherapy[1], and 24-45 % of those achieved SVR with peg-IFN and RBV.[2] Not only antiviral effects but also multiple side effects, such as heart failure, retinopathy, depression, cytopenia, and graft

Table 1 The details of patients' characteristics treated with daclatasvir and asunaprevir.

	Case 1	Case 2	Case 3
IFN† -free therapy	DCV¶ + ASV#	DCV + ASV	DCV + ASV
Child-Pugh classification at start of IFN-free therapy	A	A	A
HCV genotype	1b	1b	1b
Age at IFN-free therapy	59	66	60
Time from LT‡ to IFN-free therapy	8y5m	13y11m	15y1m
Immunosuppressive agent at start of IFN-free therapy	Tac†† + MMF‡‡	Tac	Tac
AST pre/post IFN-free therapy (IU/mL)	43/14	24/26	49/27
ALT pre/post IFN-free therapy (IU/mL)	82/10	22/23	43/23
Age at LT (years)	51	53	45
LT modality	LDLT§§	LDLT	LDLT
Time from LT to liver biopsy (weeks)	3	72	5
New Inuyama Classification	A1/F0	A1/F1	A2/F2
Previous therapy	Peg-IFN‖ + RBV¶¶	Peg-IFN + RBV	IFN
Duration of IFN-based therapy (weeks)	20	182	1
Cause of discontinuation of IFN therapy	retinopathy	heart failure	depression
Drug resistance-associated variants	no	NS3 D168T NS5A Y93H	NS5A Y93H
Serum HCV-RNA levels before the treatment (log_{10} IU/ml)	7.0	6.3	6.1
Duration from institution of DAAs§ to undetected HCV RNA (weeks)	6	9	3
Duration from attainment of SVR‖ (months)	30	30	11
Occurrence of HCC	no	no	no

† : interferon ‡ : liver transplantation § : direct-acting antiviral agents ‖ : sustained virological response
¶ : daclatasvir # : asunaprevir †† : tacrolimus ‡‡ : mycophenolate mofetil
§§ : living donor liver transplantation ‖‖ : pegylated interferon ¶¶ : ribavirin

rejection have been reported[16]. Some patients had to discontinue IFN therapy because of adverse effects. Therefore, a safe and effective strategy for HCV therapy after LT has been needed.

DAAs have been introduced in recent years. Regimens have included TVR or SMV, which are NS3/4A protease inhibitors, in combination with IFN. Compared with peg-IFN-only regimens, the response rates were much improved in non-LT patients with use of DAAs. In LT patients, the reported SVR rates with TVR regimens were 67 % [7], and the rate with SMV was 80 %[10]. There were significant improvements in viral response rates using DAAs with IFN. However, the adverse events caused by IFN were still significant. Recently, combination DAA therapy without IFN was reported to have a>90 % SVR rate in non-LT patients[3)4)]. These regimens were also used in LT patients. The SVR rate in LT patients was 93.1 % with DCV + ASV and 100 % with SOF + LDV[11]. Mutation in HCV genes is known to decrease SVR. NS3 D168 variants in a SMV/ASV regimen and NS5A L31 or Y93 in a DCV/ASV regimen have been of concern. In a DCV/ASV regimen, these variants were associated with poor response rates,

Table 2　The details of patients' characteristics treated with sofosbuvir and ledipasvir.

	Case 4	Case 5	Case 6
IFN-free therapy	SOF† + LDV‡	SOF + LDV	SOF + LDV
Child-Pugh classification at start of IFN-free therapy	A	B	A
HCV genotype	1b	1b	1b
Age at IFN-free therapy	64	70	55
Time from LT to IFN-free therapy	6y5m	12y8m	12y9m
Immunosuppressive agent at start of IFN-free therapy	Tac + MMF	CyA§ + MMF	CyA + MMF
AST pre/post IFN-free therapy (IU/mL)	21/18	54/50	32/23
ALT pre/post IFN-free therapy (IU/mL)	9/9	39/36	24/14
Age at LT (years)	58	58	43
LT modality	LDLT	LDLT	① LDLT ② DDLT‖
Time from LT to liver biopsy (weeks)	10	26	21
New Inuyama Classification	A1/F0	A2/F4	A2/F0
Previous therapy	Peg-IFN + RBV	IFN + RBV	Peg-IFN + RBV
Duration of IFN-based therapy (weeks)	160	9	274
Cause of discontinuation of IFN therapy	retinopathy	rejection	depression, infection
Drug resistance-associated variants	undetectable	NS5A L31M NS5A Y93H	NS3 Q80L NS5A Y93H
Serum HCV-RNA levels before the treatment (log_{10} IU/ml)	3.1	3.9	5.1
Duration from institution of DAAs to undetected HCV RNA (weeks)	2	2	2
Duration from attainment of SVR (months)	18	13	25
Occurrence of HCC	no	no	no

† : sofosbuvir　‡ : ledipasvir　§ : cyclosporine　‖ : deceased donor liver transplantation

and only 40 % of patients with these variants could achieve SVR[3]. The SOF/LDV regimen can even attain a high rate of SVR in these patients[17]. In our institution, anti-HCV therapy has been initiated in recipients with recurrent HCV hepatitis diagnosed pathologically. The anti-HCV therapy regimen consisted of IFN with or without RBV and DAAs until 2014, and IFN-free regimens with DAAs were started in 2015. SOF and LDV were used in recent cases. Prior to the approval of SOF/LDV regimen in Japan, patients without L31 or Y93 variants were treated with DCV/ASV, and with those variants were followed closely without DAAs. In genotype 2 cases, an SOF + RBV regimen was used. SVR was achieved in all patients in this study, and levels of serum HCV have remained undetectable. Occult HCV cases in HCV LT recipients treated with DAAs have been reported. In LT patients, the serum levels of HCV and liver functions should be carefully monitored, even in cases that achieved SVR[18].

DAAs are metabolized by CYP3A, and cause drug interactions between DAAs and immunosuppressive agents, such as tacrolimus and cyclosporine. The patients in this study were long-term recipients of LT, and used less immunosuppressive medication ; no

Table 3 The details of patients' characteristics treated with sofosbuvir and ribavirin.

	Case 7
IFN-free therapy	SOF + RBV
Child-Pugh classification at start of IFN-free therapy	A
HCV genotype	2a
Age at IFN-free therapy	68
Time from LT to IFN-free therapy	2y10m
Immunosuppressive agent at start of IFN-free therapy	Tac
AST pre/post IFN-free therapy (IU/mL)	80/35
ALT pre/post IFN-free therapy (IU/mL)	34/33
Age at LT (years)	65
LT modality	LDLT
Time from LT to liver biopsy (weeks)	69
New Inuyama Classification	A2/F1
Previous therapy	Peg-IFN + RBV
Duration of IFN-based therapy (weeks)	69
Cause of discontinuation of IFN therapy	non-responder status
Drug resistance-associated variants	undetectable
Serum HCV-RNA levels before the treatment (log_{10} IU/ml)	1.2
Duration from institution of DAAs to undetected HCV RNA (weeks)	8
Duration from attainment of SVR (months)	26
Occurrence of HCC	no

patients had difficulty controlling blood levels of calcineurin inhibitors. In addition, DAA treatment was completed without severe adverse events except in 1 of the 7 cases with slight elevation of liver enzymes and serum bilirubin level in this study.

Recently, the risk of HCC recurrence after DAA treatment has been reported[12]. IFN-based therapy was thought to have a positive effect on the anti-cancer immune system. However, Li et al. reported that DAA treatment was not associated with a higher incidence of HCC[19]. They also noted that regardless of DAA or IFN use, the incidence of HCC was lower in SVR patients. In the present study, at least in the short term (10 to 30 months after SVR), there was no evidence of HCC recurrence.

Ⅳ Conclusion

All HCV recipients achieved SVR24 with IFN-free DAA treatment. DAA treatment for LT recipients was used safely with monitoring of liver function tests. HCV can be eradicated with interferon-free DAA therapy without significant adverse events in long-term LT patients following failure of IFN therapy.

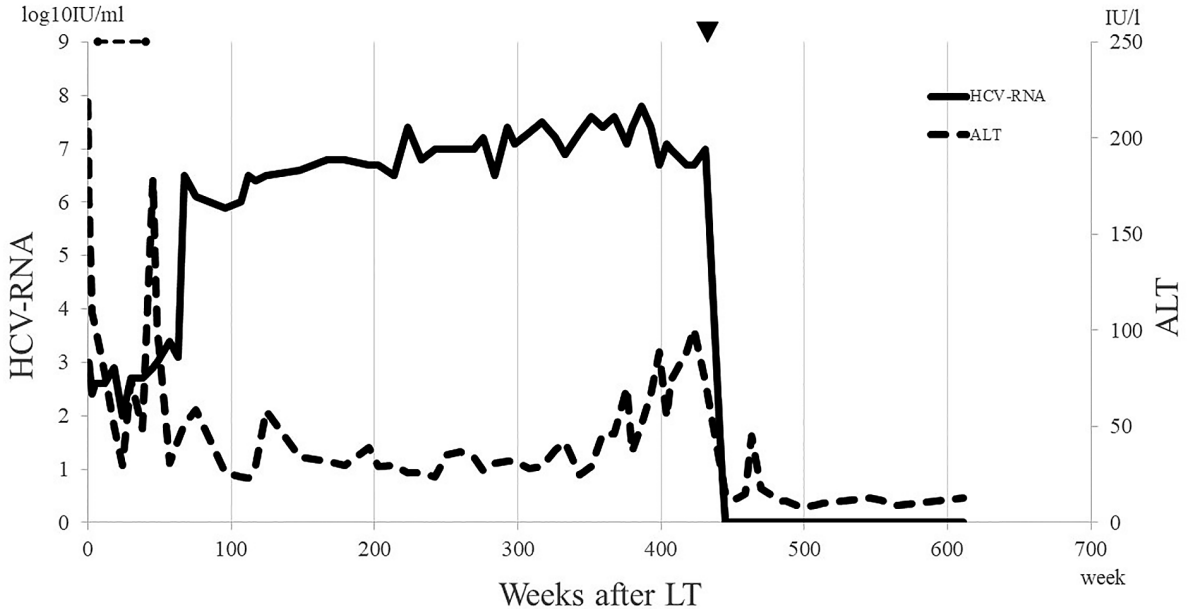

Fig. 1 Clinical course of IFN-free therapy in one representative case (Case 1)
Interrupted line at upper left of figure represents period of IFN-based therapy, and inverted triangle denotes start of IFN-free therapy.

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