Brief Report

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Ledipasvir and sofosbuvir for recurrent hepatitis C after liver transplantation

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Summary **Management of recurrent hepatitis C following liver transplantation still remains a challenge. Here, we report five patients who achieved viral responses following combined treatment with ledipasvir and sofosbuvir. All the patients received tacrolimus for immunosuppression. No dose adjustment was made before the ledipasvir and sofosbuvir therapy. All completed the intended 12-week treatment course with the full dose of ledipasvir and sofosbuvir. There were no significant adverse events greater than grade 2. During the study period, no acute rejection episodes were detected. The trough levels of tacrolimus were maintained stably. Hepatitis C virus RNA was not detected at week 12 in any of the patients. Based on the findings from this pilot study, combined ledipasvir and sofosbuvir therapy for 12 weeks is effective and safe for living - donor liver transplantation recipients with recurrence of hepatitis C virus.**

Keywords: Liver transplantation, living donor, hepatocellular carcinoma

1. Introduction

In the United States, Europe, and Japan, cirrhosis following hepatitis C virus (HCV) infection is the most common indication for liver transplantation (*1*). Liver transplant recipients with HCV infection have a poorer prognosis than those without HCV infection (*2*) when the virological response is not enough (*3*). Up to 30% of HCV-infected living-donor liver transplantation (LDLT) recipients develop cirrhosis within 5 years after transplantation (*4-6*). The interferon-based therapy (pegylated interferon and ribavirin with/without HCV protease inhibitor, such as simeprevir or telaprevir) for recurrent HCV is less effective for inducing an antiviral response in liver transplant recipients.

A sustained virologic response (SVR), indicating HCV eradication following anti-viral therapies, is associated with an improved clinical outcome in LDLT recipients (*5,7*). Treatment for HCV infection has been limited to pegylated interferon and ribavirin, which results in poor SVR rates (< 50%) and is accompanied by frequent adverse events, including flu-like symptoms, pancytopenia, hemolysis, and psychologic disorders (*e.g*., depression) (*8*).

New interferon - free direct-acting antiviral therapies, however, produce high SVR rates in patients after liver transplantation with a lower incidence of side effects and consequent improved tolerability (*9*). Direct-acting antiviral therapies, *e.g*., sofosbuvir (nucleotide NS5B polymerase inhibitor) plus ledipasvir (NS5A replication complex inhibitor) or daclatasvir (NS5A replication complex inhibitor), and ombitasvir (NS5A replication complex inhibitor) plus paritaprevir (NS3/4A protease inhibitor) and ritonavir have demonstrated higher safety and efficacy in patients with recurrent HCV after transplantation (*10-12*).

Here we report five post-transplant patients with recurrent HCV. They achieved an SVR for more than 12 weeks by ledipasvir and sofosbuvir treatment with minimum effect on trough levels of the immunosuppressive agents.

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2. Materials and Methods

2.1. *Antiviral treatment regimen and patients*

Between December 1998 and May 2016, adult-to-adult LDLT was performed in 315 patients at Kumamoto University Hospital. Of these 315 patients, the 93 patients were indicated for HCV cirrhosis. In the patients who underwent LDLT for HCV after the end of 2013 when the ledipasvir and sofosbuvir were available in Japan, the therapy was indicated for the first line therapy (n = 1). In the patients who underwent LDLT for HCV before the end of 2013, 41 patients were non -responders after interferon based therapy. Of these four were alive with sustainably positive HCV-RNA at the time of inclusion in this study. Totally 5 patients were the subjects of the study.

Liver biopsy was performed at 3, 6, 12, 24, and 36 months after transplantation. The combined ledipasvir and sofosbuvir therapy was started when hepatitis recurrence was diagnosed on biopsy, along with the HCV RNA and transaminase levels. Patients received 90 mg of ledipasvir and 400 mg of sofosbuvir as a fixed-dose combination tablet (ledipasvir-sofosbuvir) once a day for 12 weeks. No patients received ribavirtin with ledipasvir and sofosbuvir. Patients with estimated glomerular filtration rate [eGFR] < 30 mL/min/1.73 m^2 were excluded from the treatment.

2.2. *Blood analysis and histological assessment*

Laboratory assessment for the patients with post-transplant hepatitis was performed when necessary. The eGFR was calculated using the following formula: 194 × serum creatinine (-1.094) × age (-0.287) × 0.739 (if female), Japanese equation (equation 4; 12). HCV RNA levels were measured using a COBAS TaqMan HCV assay (Roche Diagnostics K.K., Tokyo, Japan). The HCV genotype was determined before transplantation. The interleukin 28B (IL28B) genotype rs8099917 was checked with the Invader assay (Third Wave Technologies, Madison, WI) (*13*). The NS3 and NS5A regions of HCV were evaluated as resistance-associated variants using direct - sequencing methods before the induction of the therapy. Liver biopsy was done which was evaluated by a pathologist based on the Metavir score (*14*).

2.3. *Immunosuppression*

The strategy after the transplantation comprised steroid induction with tacrolimus or cyclosporine. The dose of each drug was gradually tapered over 6 months after LDLT. The methylprednisolone dose was tapered from 3 mg/kg on the first postoperative day to 0.05 mg/kg at the sixth postoperative month. All the five patients are continuing to use methylprednisolone with a maintenance dose (2-4 mg).

2.4. *Ethics statement*

The study protocol was approved by the Postgraduate School of Life Science at the Kumamoto University of Research Ethics Committee.

2.5. *Statistical analysis*

The SPSS 17.0 statistical software was used (SPSS Inc., Chicago, IL) to analyze the relevant data. The effect of treatment on eGFR and immunosuppressant trough levels were analyzed by the Mann-Whitney U test. A p-value < 0.05 was considered significant.

3. Results and Discussion

The characteristics of the recipients are shown in detail (Table 1). The model for end-stage liver disease score was 15 in median (range 9-23). One case received an ABO – incompatible liver graft. None were co-infected with HIV. Two (40%) had hepatocellular carcinoma which was satisfying the Milan criteria. The HCV profile are shown also in Table 1. All the patients completed the therapy. The HCV load became undetectable at week 2 (n = 1), 4 (n = 3), and 8 (n = 1; Table 1). No remarkable adverse events were observed. There was no significant change in eGFR before (median 68 [range 65~90] mL/min/1.73 m^2) or after the therapy (median 70 [range 57~90] mL/min/1.73 m^2; p = 0.78). No patients needed a dose reduction, blood transfusion, or granulocyte-colony stimulating factor. None exhibited increased bilirubin levels. Immunosuppression was not changed before the therapy, and the immunosuppessant trough levels did not change significantly before (median 5.8 [range 2.1~8.4] ng/mL) or after (median 5.8 [range 1.9~7.7] ng/mL) introduction of the therapy (p = 0.24). No episodes of acute or chronic rejection were recognized during the treatment.

The introduction of pegylated interferon and ribavirin improved the virological efficacy for recurrent HCV in post-transplant patients. Although the SVR rate for liver transplantation patients with a history of HCV genotype 1 infection was improved to 30-50% (*5,15,16*), more than 50% of the recipients suffered from recurrent HCV infection. The use of protease inhibitors in LDLT recipients is limited due to strong drug-to-drug interactions. Here we report the experience with five patients treated with combined ledipasvir and sofosbuvir for recurrent post-liver transplantation hepatitis caused by HCV genotype 1.

Ledipasvir is a potent inhibitor of HCV NS5A. NS5A is a viral protein with an important role in viral replication. Sofosbuvir is a nucleotide analog inhibitor of NS5B polymerase. NS5B is the key enzyme mediating HCV replication. Combined therapy with the two agents produces a high virological response in patients with

Table 1. Patinets' characteristics

Patients	1	2	3	4	5
Age (years)	57	57	50	66	58
Gender	Male	Female	Male	Female	Male
Height (cm)/weight (kg)	176/87	157/46	159/45	147/42	169/69
Donor age (years)	49	29	36	62	29
Donor relationship	Spouse	Child	The third party*	Spouse	Child
Calcineurin inhibitor	FK	FK	FK	FK	FK
MMF	Yes	No	Yes	No	No
Splenectomy at LT	Yes	Yes	Yes	Yes	No
Pretreatment activity†	A2	A1	A3	A1	A1
Pretreatment fibrosis†	F1	F1	F3	F1	F1
Baseline clinical chemistry at the therapy					
Total bilirubin (mg/dL)	2.1	1.3	0.4	1	1
Alanine aminotransferase (IU/mL)	631	888	306	690	257
Creatinine (mg/dL)	0.62	0.71	0.96	0.47	0.86
eGFR (mL/min)	> 90	65	66	> 90	68
Prothrombin time (International normalized ratio)	1.15	0.85	1.12	0.98	0.99
Hemoglobin (g/dL)	11.1	9.8	10	12	14
Leukocytes (/μL)	6,000	7,400	5,600	4,900	4,800
Platelets (/μL)	18.9	36.5	16,6	12	16
HCV genotype	1b	1b	1a	1b	1b
NS5A mutation	No	No	No	No	No
NS3 mutation	No	No	No	No	No
IL28B Recipient	TT	TT	GG	TG	TT
Pretransplant antiviral therapy	None	None	Relapse	Relapse	None
Baseline HCV RNA pre-LT (log10 IU/mL)	4.3	3.9	5.5	6.1	2.7
Pre-treatment (mo) since LT	4	3	83	81	109
HCV RNA at the therapy (log10 IU/mL)	6.5	7.5	5.9	6.2	6.1
HCV response for the therapy					
HCV RNA at w1	3.3	3.1	ND	ND	2.1
HCV RNA at w2	LLOQ	2.3	UD	1.5	LLOQ
HCV RNA at w4	UD	UD	UD	LLOQ	UD
HCV RNA at w8	UD	UD	UD	UD	UD
HCV RNA at w12	UD	UD	UD	UD	UD

FK, tacrolimus; eGFR, estimated glomerular filtration rate; LLOQ, lower limit of quantification (LLOQ), < 1.2 log10 IU/mL; ND, no data; UD, not detectable. *that of domino transplantation. †as per Metavir.

genotype 1 HCV infection (*10*). Currently, in Europe, treatment with ledipasvir-sofosbuvir plus ribavirin for 24 weeks is indicated for genotype 1 patients with decompensated cirrhosis and/or those who have undergone liver transplantation. Findings from the SOLAR-1 (*10*) and SOLAR-2 (*11*) trials suggest that 12 - week treatment with ledipasvir-sofosbuvir is sufficient for almost all patients with genotype 1 HCV recurrence after liver transplantation.

In the 2015 HCV treatment guidelines, the European Association for the Study of the Liver (EASL) recommend a 12 -week treatment with ledipasvir-sofosbuvir plus ribavirin as a first-line option for HCV genotype 1 patients with advanced liver disease which includes those with decompensated cirrhosis before or after liver transplantation (*17*). As another first-line therapy, EASL guidelines recommend a 12-week treatment with sofosbuvir plus daclatasvir with ribavirin for 12 weeks in HCV genotype 1-infected patients with decompensated cirrhosis and/or after liver transplantation (*18*). The Infectious Diseases Society of America and the American Association for the Study of Liver Diseases (*19*) have made the same recommendations.

The small size of the study cohort and the retrospective design were limitations of the present study. This is the first study, to our knowledge, to provide such detailed insight into the combined treatment with ledipasvir and sofosbuvir for LDLT recipients.

In conclusion, combined treatment with ledipasvir and sofosbuvir is effective for recurrent HCV infection in patients after liver transplantation. The 12 -week treatment should become a standard of care for patients with recurrent genotype 1 chronic hepatitis C after liver transplantation.

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