Original Article

Asunaprevir/daclatasvir and sofosbuvir/ledipasvir for recurrent hepatitis C following living donor liver transplantation

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Aim: This study aimed to clarify the efficacy and safety of interferon-free therapy using asunaprevir and daclatasvir, or sofosbuvir and ledipasvir for post living donor liver transplantation (LDLT) recipients with hepatitis C virus (HCV).

Methods: A retrospective cohort study of LDLT recipients with HCV genotype 1b treated with asunaprevir (100 mg twice daily) and daclatasvir (60 mg once daily), or sofosbuvir (400 mg/day) and ledipasvir (90 mg/day) was carried out.

Results: Ten patients without mutations in the area of L31 and Y93 completed the treatment with asunaprevir and daclatasvir. Five of them had end-stage chronic kidney disease, including three hemodialysis patients. Of the 10 patients, nine completed the protocol of 24 weeks; one stopped the treatment due to the development of aortic valve stenosis. All nine patients who completed the 24-week treatment protocol achieved end of treatment response. Nineteen patients received treatment with sofosbuvir and ledipasvir. Of the 19 patients, 18 completed the protocol of 12 weeks; one stopped treatment due to severe interstitial pneumonia. All 18 patients who completed the 12-week treatment protocol achieved end of treatment response. All patients in both treatment groups who completed the regimen and reached 3 months after the end of treatment achieved sustained virological response at 12 weeks after treatment. Liver functions were significantly improved at the end of treatment, and no adverse events were observed.

Conclusions: Interferon-free therapy using asunaprevir and daclatasvir, or sofosbuvir and ledipasvir, is highly effective for post-LDLT recipients with HCV genotype 1b.

Key words: asunaprevir, daclatasvir, hepatitis C, ledipasvir, living donor liver transplantation, sofosbuvir

INTRODUCTION

Liver transplant recipients with recurrent hepatitis C virus (HCV) infection have poor transplant prognosis, compared to other recipients without HCV infection. Achieving sustained virological response (SVR) after liver transplantation, which is the most important factor modifiable by clinicians in HCV-positive recipients, can improve the graft and recipient survival, and is of utmost importance, especially after living donor liver transplantation (LDLT) as retransplantation is implausible among LDLT recipients. We previously trialed an aggressive antiviral treatment with a pegylated interferon (PEG-IFN) and ribavirin (RBV)-based regimen for LDLT recipients, however, the SVR rate was only 39.5% with a high incidence of severe adverse events and treatment failure.

The development of direct-acting antiviral drugs (DAA) for the treatment of HCV genotype 1 has improved SVR rates significantly. However, the SVR rates with the triple combination of simeprevir or telaprevir, PEG-IFN, and RBV for recurrent HCV among LDLT recipients were only 56% and 69%, respectively, with an unacceptable high rate of adverse events.

Recently, the combined IFN-free regimens with asunaprevir (ASV)/daclatasvir (DCV) and sofosbuvir (SOF)/ledipasvir (LDV) without the aid of RBV, for the treatment of HCV genotype 1b, were approved by Japan’s
national health insurance program, and have shown promising results among HCV-positive patients. The regimen with ASV and DCV was started in 2014, the first in the world; SOF and LDV combination was introduced in 2015. Accordingly, these regimens started to be used for post-LDLT recipients in Japan, as well as for post-transplant recurrent hepatitis worldwide.

In this study, we evaluated the efficacy of ASV and DCV for 24 weeks and SOF and LDV (without RBV) for 12 weeks in a single-center experience of post-LDLT recipients.

METHODS

Patients

Between January 1996 and August 2016, 147 patients with HCV who underwent LDLT at the University of Tokyo Hospital (Tokyo, Japan) reviewed with regard to anti-HCV treatments following LDLT. Before the introduction of IFN-free DAA treatments, IFN-based regimens were used for all HCV-positive recipients, as reported previously. The IFN-free DAA therapy was started in October 2014. A summary of the antiviral treatments used in our institution is presented in Figure 1. As shown in Figure 1, the regimen with ASV and DCV was used for 12 patients, 11 with null-response or relapse and 1 with fibrosing cholestatic hepatitis. Treatment with SOF and LDV without RBV was given to 19 patients, 16 with null-response or relapse and 3 treatment-naive cases. All are subjects of the present study.

Hepatitis C virus monitoring

The HCV genotype was determined using a genotyping system based on a polymerase chain reaction of the core region, and all patients included in the present study were confirmed to have genotype 1b. We assessed the serum HCV-RNA titers using a real-time polymerase chain reaction-based quantification method for HCV (COBAS AmpliPrep/COBAS TaqMan HCV Test; Roche Molecular Systems, Pleasanton, CA, USA) every 4 weeks from the beginning of therapy. Resistance-associated substitutions in the NSSA region of the HCV genome, including the area of L31 and Y93, were analyzed before therapy by direct sequencing. Liver biopsies were assessed before treatment in all patients. An activity score and a fibrosis score were evaluated using the METAVIR scoring system. The rapid virological response and end of treatment response (ETR) were defined as HCV-RNA undetectable at 4 weeks and at end of treatment, respectively. The SVR12 was defined as the absence of HCV-RNA in the serum for >12 weeks after completing treatment.

Figure 1 Flowchart of patients with recurrent hepatitis C following living donor liver transplantation (LDLT) who were enrolled in this study. *Three patients treated with sofosbuvir (SOF) and ledipasvir (LDV) underwent prior simeprevir therapy and one patient underwent prior telaprevir therapy. ASV, asunaprevir; DCV, daclatasvir; FCH, fibrosing cholestatic hepatitis; HCV, hepatitis C virus; PEG-IFN, pegylated interferon; RBV, ribavirin; SMV, simeprevir; SVR, sustained virological response; TPV, telaprevir.
Interferon-free DAA regimen

The ASV/DCV regimen consisted of ASV (100 mg twice daily) and DCV (60 mg once daily) without RBV for 24 weeks. The SOF/LDV regimen was SOF (400 mg once daily) and LDV (90 mg once daily) without RBV for 12 weeks. The SOF/LDV combination has been considered the first line of treatment since its introduction, however, ASV/DCV was chosen for those with renal insufficiency (estimated glomerular filtration rate <30 mL/min/1.73 m²) or on hemodialysis. Only patients without resistance-associated substitutions in the area of L31 and Y93 were indicated for ASV/DCV.

Management of LDLT

Our management of LDLT, including donor/graft selection, operative procedure, and postoperative management, was described in detail elsewhere. The immunosuppression protocol consisted of calcineurin inhibitors and methylprednisolone in principle, the details of which were described elsewhere. Due to the drug-drug interaction between ASV and cyclosporine A (CsA) based on the same transporting pathway via organic anion-transporting polypeptide, CsA was changed to tacrolimus (Tac) before initiating treatment with ASV/DCV.

On starting the IFN-free treatments, all patients were admitted and underwent strict clinical monitoring following the initiation of DAA. Clinical and biological data were investigated at regular intervals during the treatment at the outpatient clinic. All adverse events were recorded until the last dose was given. Liver function tests (albumin, aspartate aminotransferase [AST], alanine aminotransferase [ALT], and total bilirubin), hemoglobin, and serum creatinine were measured at baseline before treatment initiation and at the end of treatment, and were reviewed.

Statistical analysis

The primary end-point of this study was the proportion of patients who achieved SVR12, defined as undetectable HCV-RNA 12 weeks after treatment completion. The secondary end-points included viral responses, laboratory data, and side-effects. All statistical analyses were carried out using SPSS software (version 22; IBM, Chicago, IL, USA). A paired t-test (two-tailed) was used to detect statistical significance. The confidence interval was 95%. P-values <0.05 were considered statistically significant.

RESULTS

Patients treated with ASV/DCV

Ten patients with HCV genotype 1b who were treated with ASV and DCV since October 2014 were...
the subject of this study, excluding two patients who are still on the treatment. The demographics of the patients are shown in Table 1. We confirmed that all patients with ASV/DCV had no viral mutations. Nine were null-responders or relapsers and one had fibrosing cholestatic hepatitis early after LDLT. Seven patients (70%) were men. One patient was co-infected with HIV and three patients had been on hemodialysis. The median age at the beginning of therapy was 64 years (range, 46–74 years). The median body mass index was 21.5 (range, 16.4–23.1). Graft types were left liver graft in four patients and right liver graft in six patients. The median time to treatment initiation after LDLT was 7.5 years (range, 0.1–15.8 years). Median serum HCV-RNA titers at the initial introduction were 6.5 log IU/mL (range, 5.8–7.5 log IU/mL). Five patients (50%) were treated with Tac-based immunosuppression, and the remaining five patients required conversion from CsA to Tac. No patient had undergone prior DAA therapy.

Of the 10 patients treated with ASV/DCV, nine patients completed the protocol of 24 weeks; one patient stopped the treatment at 16 weeks due to worsening of chronic aortic valve stenosis, which was not a side-effect of DAA. All nine patients who completed the 24-week treatment protocol achieved ETR. In addition, all eight patients who reached 3 months after the end of treatment achieved SVR12, as did one patient who stopped the treatment in mid-course. No relapse has been observed so far. Figures 2 and 3 show the changes in HCV-RNA titers and the virological response in 10 patients with ASV/DCV, respectively. The serum level of HCV-RNA became undetectable within 4 weeks in all patients with an ETR rate of 100%. The dose of drugs and the trough level of Tac were successfully managed and maintained during the treatment without necessitating dose modification in either ASV/DCV or in Tac. No adverse event was encountered during the therapy.

Patients treated with SOF/LDV

Nineteen patients with HCV genotype 1b received treatment with SOF and LDV since October 2015. Sixteen were null-responders or relapers, and three treatment-naïve cases were treated for recurrent HCV. The clinical
Table 2  Characteristics of living donor liver transplantation (LDLT) recipients with hepatitis C treated with sofosbuvir and ledipasvir

<table>
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<tr>
<th>Patient #</th>
<th>Age, years</th>
<th>Sex</th>
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<th>Time from LDLT, years</th>
<th>Previous treatment</th>
<th>HCV-RNA titers, log IU/mL</th>
<th>Liver biopsy</th>
<th>Drug</th>
<th>Dose modification</th>
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**Notes:** BMI, body mass index; CsA, cyclosporine A; ETR, end of treatment response; F, female; HCV, hepatitis C virus; L, left liver graft; M, male; PEG, pegylated interferon; R, right liver graft; RBV, ribavirin; R-lat, right lateral sector graft; RVR, rapid virological response; SMV, simeprevir; SVR12, sustained virological response for 12 weeks after treatment completion; SVR24, sustained virological response for 24 weeks after treatment completion; Tac, tacrolimus; TPV, telaprevir; Null, null responder.

*–, no previous treatment.*
characteristics of those 19 recipients are summarized in Table 2. Nine patients (47%) were men. The median age at the beginning of therapy was 65 years (range, 50–77 years). The median BMI was 23.1 (range, 15.2–29.4). Graft types were left liver graft in eight patients, right liver graft in 10 patients, and the remaining patient received right lateral sector graft. The median time to treatment initiation after LDLT was 8.8 years (range, 0.1–13.8 years). Median serum HCV-RNA titers at the initial introduction were 6.5 log IU/mL (range, 4.7–7.9 log IU/mL).

Resistance-associated variants were found at the L31 (n = 1, 7%) and Y93 (n = 2, 14%) in the NS5A region of the HCV genome before introducing SOF/ LDV. Nine patients (47%) were treated with Tac-based immunosuppression, and the remaining 10 were on CsA. Three patients had treatment failure of PEG-IFN/RBV plus simeprevir therapy, and one patient was of treatment failure of PEG-IFN/RBV plus telaprevir therapy. Of the 19 patients treated with SOF/LDV, 18 patients (95%) completed the protocol of 12 weeks, while one patient stopped the treatment at 4 weeks due to worsening of interstitial pneumonia, which may not be associated with DAA therapy. All 18 patients who completed the 12-week treatment protocol achieved ETR. In addition, all 13 patients who reached 3 months after the end of treatment achieved SVR12. No relapse has been observed so far. Figures 4 and 5 show the changes in HCV-RNA titers and the virological response in 19 patients with SOF/LDV, respectively. The serum level of HCV-RNA became undetectable within 4 weeks in all patients who completed the treatment, with an ETR rate of 100% (18 of 18 patients), excluding the patient who died due to interstitial pneumonia after achieving rapid virological response. Adverse events did not occur during the therapy in all patients.

**Laboratory data**

When compared to baseline values, there was significant improvement in serum AST, ALT, and total bilirubin level at the end of treatment in both groups; only total bilirubin level in the ASV/DCV group did not reach significance. In contrast, no change was observed in hemoglobin level or serum creatinine level after the treatment in both groups.
Laboratory data are summarized in Table 3, comparing results from baseline and the end of treatment.

**DISCUSSION**

In the present study, we established the safety and efficacy of ASV/DCV and SOF/LDV treatment without RBV for the treatment of recurrent HCV among Japanese LDLT recipients, with an ETR of 100% for both regimens among those who completed the treatment. The SVR rates were also 100% for both treatments among those who completed the regimen and reached 3 months after the end of treatment. Biochemical data (AST, ALT, and total bilirubin) were significantly improved at the end of both treatments. No adverse events were observed and there was no impairment in anemia or renal function.

Treatment with ASV/DCV for 24 weeks was the first approved IFN-free DAA regimen in Japan, and is approved for clinical use only. Several case reports of successful use of ASV/DCV for liver transplant recipients have been published from Japanese centers. We started to use ASV/DCV for cases before the introduction of SOF/LDV and for those with severe renal impairment or on hemodialysis for whom SOF/LDV is not indicated. The ETR rate of this treatment was 100% in this study, indicating that ASV/DCV therapy is highly effective in this cohort. It was also shown that ASV/DCV therapy is safe and effective even for liver transplant recipients with renal impairment or on hemodialysis, as previously reported among HCV-positive patients. Recently, Kawakami et al. reported similar safety and efficacy of ASV/DCV therapy for hemodialysis patients with HCV genotype 1 infection when compared to patients with normal renal function, and the plasma concentration of ASV was significantly lower in hemodialysis patients. Unfortunately, we did not measure the ASV and DCV concentration in the present cases. One patient in our study stopped the treatment at 16 weeks due to worsening of chronic aortic valve stenosis, which was not a side-effect of DAA. This was because ASV and verapamil/diltiazem hydrochloride are contraindications for co-administration.

The safety and efficacy of the triple combination regimen with SOF/LDV and RBV for the treatment of HCV after liver transplantation has already been established. However, in Japan, we cannot use RBV with DAA as IFN-free therapy because it has not been approved by the Japanese government’s health insurance scheme. In our study, all patients who completed the treatment achieved ETR without RBV. There is the possibility that the good response to the combination of SOF/LDV may be attributable, at least partly, to all patients in this study having HCV genotype 1b. It is well known that the addition of RBV often results in severe anemia among liver transplant recipients. Very recently, Elfeki et al. reported an SVR12 rate of 100% among 46 liver transplant recipients (HCV genotype 1) with the same dose of SOF/LDV for 12 weeks without RBV. Pungpapong and colleagues also reported the safety and efficacy of SOF/LDV among liver transplant recipients for 12 weeks without RBV. Our study, as well as these previous reports, showed RBV might not be necessary for patients with HCV genotype 1b after LDLT during 12 weeks of treatment with SOF/LDV.

As for safety and tolerance, there were no adverse events associated with DAA in the present cohort, although two patients stopped the therapy due to other reasons. Modification of the dose of Tac or CsA was not required, with a stable trough level during the observation, while the conversion from CsA to Tac was necessitated at the beginning of ASV/DCV treatment.

In conclusion, IFN-free treatments with SOF/LDV for 12 weeks and ASV/DCV for 24 weeks without RBV are highly effective for Japanese patients with recurrent HCV.

<table>
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<th>Table 3</th>
<th>Comparison between baseline laboratory data and end-of-treatment laboratory data in living donor liver transplantation (LDLT) recipients with hepatitis C</th>
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<tr>
<td><strong>Asunaprevir and daclatasvir treatment (n = 10)</strong></td>
<td><strong>Sofosbuvir and ledipasvir treatment (n = 18)</strong></td>
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<tr>
<td>Mean baseline values (± SD)</td>
<td>Mean end of treatment values (± SD)</td>
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<td>AST, IU/L</td>
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<td>ALT, IU/L</td>
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<tr>
<td>Hemoglobin, g/dL</td>
<td>10.1 ± 1.5</td>
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ALT, alanine aminotransferase; AST, aspartate aminotransferase; SD, standard deviation.
hepatitis C after LDLT. The present results are notable in showing the safety and efficacy of DAAs in LDLT recipients and in reporting ASV/DCV treatment results among liver transplant recipients for the first time.

REFERENCES


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