Outcomes of treatment with daclatasvir and asunaprevir for recurrent hepatitis C after liver transplantation

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Aim: The development of direct-acting oral agents has dramatically changed the treatment strategy of hepatitis C virus (HCV) infection. Here we aimed to reveal the efficacy and safety of daclatasvir (DCV) and asunaprevir (ASV) for recurrent HCV genotype 1 infection after liver transplantation (LT).

Methods: A retrospective study was undertaken on nine patients who underwent a 24-week DCV/ASV treatment regimen for recurrent HCV genotype 1 infection. Five of the patients were men; four had failed treatment with pegylated interferon (Peg-IFN)/ribavirin, two had failed simeprevir/Peg-IFN/ribavirin, one had the resistance-associated variant Y93H in the NS5A region, and one underwent maintenance dialysis.

Results: Median time to treatment initiation following LT was 70 months. Of the nine patients treated with DCV/ASV, eight (88.9%) achieved a sustained viral response 12 weeks after completion of therapy (SVR12). The patient with virologic failure had failed simeprevir/Peg-interferon/ribavirin therapy 4 months before undergoing the DCV/ASV treatment regimen. In addition, a resistance-associated variant D168E in the NS3 region was detected in the patient after discontinuation of the DCV/ASV regimen. The trough level of tacrolimus tended to decrease, and renal function showed no significant changes during treatment. Adverse events occurred in two patients (22.2%), but no severe adverse events occurred during treatment.

Conclusions: The DCV/ASV regimen was well tolerated, resulting in high rates of sustained viral response 12 weeks after completion of therapy for LT patients with recurrent HCV genotype 1 infection.

Key words: daclatasvir and asunaprevir, direct-acting antiviral drugs, hepatitis c, liver transplantation

INTRODUCTION

Liver transplantation (LT) is an effective treatment option for end-stage liver disease. Hepatitis C virus (HCV)-related chronic liver disease is the most common indication for adult LT. Recurrence of HCV occurs immediately after LT in recipients with viremia prior to transplantation, which results in the progression of fibrosis and graft loss.1,2 Firpi et al. reported that liver graft cirrhosis occurred in 50% of LT recipients within 5 years, and hepatic decompensation occurred in 30% 1 year after the development of cirrhosis.3 Combined treatment with pegylated interferon (Peg-IFN) and ribavirin (RBV) for 48 weeks is the standard therapeutic approach for patients with HCV genotype 1, but a sustained viral response (SVR) is achieved in only approximately 40–50% of patients.4,5 The SVR rate achieved using the Peg-IFN/RBV-based regimen in a treatment-naive cohort increases to 68–89% when combined with the protease inhibitor telaprevir, boceprevir, or simeprevir (SMV).6–8 Antiviral therapy using a Peg-IFN/RBV-based regimen in LT recipients, however, is more difficult due to drug–drug interactions and a high prevalence of intolerance with frequent adverse events.9–11 Several therapies with IFN-free oral direct-acting antiviral (DAA) drugs were recently developed, leading to a high SVR rate with a shorter therapy duration and a lower rate of adverse events.12 Combined therapy with the non-structural protein (NS)5A replication complex inhibitor daclatasvir (DCV) and the selective NS3 protease inhibitor asunaprevir (ASV) has shown robust antiviral activity and a high SVR rate, with no clinically significant
Because of its efficacy and tolerability, DCV/ASV use was initiated in Japan in 2014 and provides a high SVR rate in patients with HCV genotype 1 infection, including those who did not respond to prior IFN-based therapy. The efficacy and safety of DCV/ASV for recurrent hepatitis C following LT are not yet clear. Here we report the clinical course of nine patients treated with DCV/ASV for recurrent HCV genotype 1 infection after LT.

**METHODS**

**Patients and study design**

**BETWEEN DECEMBER 1998 and March 2016, 449 patients underwent 471 LT at Kumamoto University Hospital (Kumamoto, Japan). Of these, 96 recipients underwent LT for HCV infection-related indications, including 49 patients with hepatocellular carcinoma. Liver biopsy was carried out 3, 6, 12, 24, and 36 months after transplantation. Drug therapy was started when hepatitis recurrence was diagnosed on biopsy, with concomitantly increased levels of HCV RNA and transaminase. A total of nine patients received DCV/ASV therapy, and were the subjects of the present study. All of the patients underwent living-donor LT. Daclatasvir (60 mg) was given orally once daily and ASV (100 mg) was given orally twice daily for 24 weeks. Before initiating the treatment, HCV RNA and the interleukin-28B (IL28B) genotype (rs8099917) were analyzed. At that time, L31 and Y93 in the NS5A region, and V36, T54, R155, A156, and D168 in the NS3 region of the HCV genome were evaluated as resistance-associated variants (RAVs) using a direct sequencing method, as described previously. Briefly, the viral RNA was extracted from the patient’s serum using a QIAamp Viral RNA Mini Kit (Qiagen, Hilden, Germany), and reverse-transcribed and amplified by polymerase chain reaction using a PrimeScript RT Reagent Kit with gDNA Eraser (TaKaRa, Shiga, Japan) with the primer pairs. The PCR products were purified and sequenced using an automated DNA sequencer (3130 Genetic Analyzer; Applied Biosystems, Foster City, CA, USA). The HCV amino acid sequences predicted from the sample were compared with the HCV-J strain sequence as a reference (GenBank, accession no. AJ238799.1). If minor RAV sequences were detected in more than 10% of the major sequence, it was considered RAV-positive.

None of the patients showed evidence of advanced liver fibrosis (Metavir score ≤ F2) on liver biopsy. Characteristics of the study group are shown in Table 1. The entire LT protocol was approved by the institutional review committee. The study was carried out according to the Ethical Guidelines for Clinical Research published in 2009 by the Ministry of Health, Labor and Welfare of Japan.

**Surgical procedure**

The transplant procedures used in our institution were described previously. Briefly, hepatic and portal veins were reconstructed under a surgical loupe, and hepatic arteries were reconstructed under a microscope. Except in LT recipients with biliary atresia, duct-to-duct biliary reconstruction was routinely performed.

<table>
<thead>
<tr>
<th>Case</th>
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<tbody>
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<td>57/66</td>
<td>51/57</td>
<td>63/70</td>
<td>58/60</td>
<td>66/67</td>
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<td><strong>Gender</strong></td>
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<td>Ma</td>
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<tr>
<td><strong>BMI, kg/m²</strong></td>
<td>20.4</td>
<td>23.6</td>
<td>19.3</td>
<td>24.6</td>
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<td>+</td>
<td>–</td>
<td>+</td>
<td>+</td>
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<td>–</td>
<td>+</td>
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<tr>
<td><strong>Previous Tx</strong></td>
<td>PR</td>
<td>PR</td>
<td>PR</td>
<td>PR + SMV</td>
<td>PR + SMV</td>
<td>–</td>
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<td><strong>Time to Tx, months</strong></td>
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<td>13</td>
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<td>3</td>
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<td><strong>HCV RNA, log IU/mL</strong></td>
<td>4.9</td>
<td>6.2</td>
<td>4.7</td>
<td>6.3</td>
<td>5.7</td>
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<td><strong>IL28 (rs8099917) genotype</strong></td>
<td>TT</td>
<td>TT</td>
<td>TT</td>
<td>TG</td>
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<td><strong>Metavir score</strong></td>
<td>A1 F2</td>
<td>A1 F1</td>
<td>A1 F2</td>
<td>A1 F1</td>
<td>A2 F1</td>
<td>A1 F1</td>
<td>A0 F1</td>
<td>A2 F1</td>
<td>A0 F1</td>
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<tr>
<td><strong>Immunosuppression</strong></td>
<td>M</td>
<td>F + M</td>
<td>F + M</td>
<td>M</td>
<td>F + M</td>
<td>F + M</td>
<td>F</td>
<td>C + P</td>
<td>F + M</td>
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<tr>
<td><strong>NS5A variants</strong></td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>Y93H</td>
</tr>
<tr>
<td><strong>NS3 variants</strong></td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
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<tr>
<td><strong>eGFR, mL/min/1.73 m²</strong></td>
<td>7 (HD)</td>
<td>59</td>
<td>56</td>
<td>50</td>
<td>73</td>
<td>78</td>
<td>60</td>
<td>68</td>
<td>66</td>
</tr>
</tbody>
</table>

BMI, body mass index; C, cyclosporine A; eGFR, estimated glomerular filtration rate; F, tacrolimus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; HD, hemodialysis; IL28, interleukin-28; M, mycophenolate mofetil; NS, non-structural protein; P, prednisolone; PR, pegylated interferon + ribavirin; SMV, simeprevir; Tx, therapy.
**Immunosuppression**

The immunosuppressive regimen comprised tacrolimus and low-dose steroids. Target trough levels of tacrolimus were between 10 and 15 ng/mL during the first 2 weeks, ~10 ng/mL during the next 2 weeks, and between 5 and 10 ng/mL thereafter. Treatment with steroids was initiated by an injection of methylprednisolone (10 mg/kg) prior to graft perfusion during surgery. Recipients received an i.v. injection of 1 mg/kg methylprednisolone during postoperative day (POD) 1-3, 0.5 mg/kg during POD 4-6, and 0.3 mg/kg at POD 7. The steroid dose was then tapered off at ~3 to 6 months. Mycophenolate mofetil was added case by case to reduce the dose of calcineurin inhibitor (CNI). The CNI was switched from tacrolimus to cyclosporine A in cases where posterior leukoencephalopathy or thrombotic microangiopathy was suspected. Some patients who had suffered from renal dysfunction discontinued the CNI if their liver function was stable. Immunosuppression therapy was continued at the same dose without pre-emptive adjustment when DCV/ASV therapy was initiated.

**Efficacy and safety assessment**

Serum HCV RNA levels were evaluated using the COBAS TaqMan HCV assay (Roche Molecular Systems, Pleasanton, CA, USA). Hepatitis C virus RNA was monitored at least every 2 weeks until no longer detected, and tested every 4 weeks until 12 weeks after patients completed the DCV/ASV regimen. Patients were followed closely by the LT surgeon and hepatologist every 2 weeks during treatment. Standard blood tests, including blood cell counts, liver and renal function tests, HCV RNA, and trough levels of immunosuppressive drugs, were evaluated. Changes in renal function during the treatment were also evaluated.

Safety assessment was carried out by asking patients about potential adverse events at each visit. An adverse effect was defined according to the Common Terminology Criteria for Adverse Events version 4.0. Undetectable HCV RNA at 4 weeks was defined as a rapid virologic response. The SVR12 was defined as the absence of HCV RNA at 12 weeks after the completion of treatment.

**Statistical analysis**

Continuous variables are expressed as mean values ± standard deviations. Data were analyzed using the two-tailed Wilcoxon signed-rank test or two-tailed Friedman test as appropriate for continuous data. A P-value <0.05 was considered statistically significant. The statistical package PASW Statistics 18 (IBM, Tokyo, Japan) was used for statistical analyses.

**RESULTS**

**Patient characteristics**

The patients comprised five men and four women, with a mean age of 59.8 ± 4.4 years at LT. Mean age at the start of DCV/ASV therapy was 64.7 ± 4.6 years. Median time to DCV/ASV treatment initiation after LT was 70 months (range, 3–121 months). Five patients had HCV combined with hepatocellular carcinoma before LT. Overall, four patients (44.4%) had been treated with Peg-IFN/RBV and two patients (22.2%) had been treated with SMV/Peg-IFN/RBV following LT. The mean HCV RNA load before the treatment was 6.11 ± 0.85 (log IU/mL). Six patients had an IL28B (rs8099917) TT genotype and two patients had an IL28B TG genotype; the status of one patient could not be determined. Based on the graft liver biopsies obtained before the treatment, two patients were classified with F2. One patient (case 7) showed an RAV of Y93H in the NS5A region before treatment with DCV/ASV. Due to the small Y93H RAV population in this patient, treatment with DCV/ASV was initiated. Our study cohort included one maintenance dialysis patient (case 1).

**Immunosuppression**

Seven patients (77.8%) were treated with CNI-based immunosuppression (tacrolimus, six patients; cyclosporine, one patient). Mycophenolate mofetil was used in seven patients (77.8%) with or without CNI. Few dose adjustments in the CNI were required during the DCV/ASV treatment to maintain the trough level, and all patients received the same dosage of CNI before and after the DCV/ASV treatment. The time course of the tacrolimus trough level in six patients tended to decrease during DCV/ASV treatment (Fig. 1a). The average trough level differed significantly between before treatment and 24 weeks after treatment initiation (3.80 ± 1.10 vs. 2.57 ± 1.06 ng/mL, P = 0.0392), and between 4 weeks after treatment initiation and 24 weeks after treatment initiation (2.97 ± 1.19 vs. 2.57 ± 1.06 ng/mL, P = 0.0045; Fig. 1b).

**Renal function**

Changes in renal function during treatment were evaluated because the effects of DCV/ASV on renal function in LT patients are unclear. The average estimated glomerular filtration rate (eGFR; mL/min/1.73 m²) before treatment was 57.4 ± 20.8 (range, 7–78). The patient undergoing maintenance hemodialysis showed no interaction or adverse events related to dialysis, and completed 24 weeks of treatment. The time course of eGFR in nine patients
showed no dynamic changes (Fig. 2a). The average eGFR did not differ significantly between before treatment and 4 weeks or 24 weeks after the DCV/ASV treatment initiation (Fig. 2b).

**Efficacy**

Eight patients, including the maintenance dialysis patient, completed 24 weeks of DCV/ASV treatment (Table 2). In all but one patient (case 4) HCV RNA became undetectable during the DCV/ASV treatment, at a median of 4 weeks (range, 2–8 weeks; Fig. 3a). The HCV RNA load decreased significantly 4 weeks after the initiation of DCV/ASV treatment (Fig 3b; $6.11 \pm 0.85$ before treatment vs. $1.12 \pm 1.65 \log_{10} \text{IU/mL}$ at 4 weeks, $P < 0.0001$). Four patients (44.4%) achieved a rapid virologic response. The response rate remained at 88.9% at 8 weeks, at 12 weeks, and at the end of treatment (Fig. 3c). Eventually, an SVR12 was achieved by 88.9% of the patients, including all eight patients who completed the 24-week treatment regimen. The patient who discontinued treatment at 10 weeks (case 4) showed no response with DCV/ASV. This patient had failed SMV/Peg-IFN/RBV treatment due to viral breakthrough 4 months before starting the DCV/ASV therapy. After discontinuation of the DCV/ASV treatment, a D168E RAV in NS3 was detected in case 4, although RAVs in the NS3 and NS5A regions were not detected before treatment with DCV/ASV. The patient who had the Y93H RAV in the NS5A region (case 7) achieved an SVR12.

**Safety**

Overall, two patients experienced adverse events (Table 2). One patient (case 1) experienced mild anorexia (grade 1) but was able to continue treatment. One patient (case 7)
Table 2  Efficacy and safety of daclatasvir and asunaprevir in nine patients with recurrent hepatitis C after liver transplantation

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<th>Case</th>
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<tbody>
<tr>
<td>Duration of Tx, weeks</td>
<td>24</td>
<td>24</td>
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<td>24</td>
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<td>24</td>
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<tr>
<td>Time when HCV RNA became undetectable, weeks</td>
<td>4</td>
<td>2</td>
<td>3</td>
<td>–</td>
<td>5</td>
<td>4</td>
<td>8</td>
<td>6</td>
<td>8</td>
</tr>
<tr>
<td>Adverse events</td>
<td>Anorexia</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>ALT AST elevation</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Response</td>
<td>SVR12</td>
<td>SVR12</td>
<td>SVR12</td>
<td>NR</td>
<td>SVR12</td>
<td>SVR12</td>
<td>SVR12</td>
<td>SVR12</td>
<td>SVR12</td>
</tr>
</tbody>
</table>

–, not applicable; ALT, alanine transaminase; AST, aspartate transaminase; HCV, hepatitis C virus; NR, no response; SVR12, sustained viral response 12 weeks after completion of treatment; Tx, therapy.

Figure 3  (A) Time course of hepatitis C virus (HCV) RNA in nine patients after liver transplantation during 24 weeks of treatment with daclatasvir and asunaprevir (DCV/ASV). All but one patient (case 4) accomplished undetected HCV RNA during the DCV/ASV treatment. (B) Average HCV RNA was compared before treatment and 4 weeks after the initiation of treatment. (C) Time course of the response rate during DCV/ASV treatment at 4, 8, 12, and 24 weeks, and 12 weeks after treatment. Data represent mean ± standard deviation. [Colour figure can be viewed at wileyonlinelibrary.com]

had a transiently elevated transaminase (grade 1) level, which peaked at 6 weeks (aspartate transaminase 85 U/L, alanine transaminase 81 U/L) and persisted until the completion of treatment. The patient completed the treatment with a dose reduction in ASV (from 200 mg/day to 100 mg/day). None of the patients experienced acute cellular rejection during the DCV/ASV treatment. None of the patients in our cohort discontinued the treatment due to adverse events.

DISCUSSION

RECURRENT HEPATITIS C after LT may occur under immunosuppression, or in relation to other transplant-related complications, including rejection, and vascular and biliary complications. The therapeutic strategy for HCV has been drastically changed by the introduction of DAA, and several studies recently confirmed the efficacy and safety of IFN-free therapy after LT.18–24
present study, 88.9% of the patients treated with DCV/ASV for recurrent hepatitis C genotype 1 infection after LT achieved SVR12. This therapeutic drug regimen was well tolerated with a shorter treatment duration, fewer adverse effects, and significant efficacy.

When using DAA in LT recipients, it is important to consider drug interactions because most DAAs are substrates of cytochrome P450 3A4, which is an enzyme responsible for the metabolism of CNI. 24 Daclatasvir has no known drug interaction with CNI. Ueda and Uemoto reported that the median concentration / dose ratio of tacrolimus significantly increased in the first week after DCV/ASV treatment, and significantly decreased 2 weeks after treatment initiation. 25 The increase in the concentration / dose ratio in the first week was considered to be caused by drug–drug interactions, while the decrease in the concentration / dose ratio at 2 weeks was considered to result from effective viral clearance and a subsequent improvement in metabolism. Consistent with this report, the tacrolimus trough level also tended to decrease during DCV/ASV treatment in our study. To prevent the development of rejection, close monitoring of liver function and immunosuppressant trough levels is important.

In the IFN era, a meta-analysis revealed a 17% to 30% discontinuation rate in hemodialysis patients treated with IFN monotherapy. 26,27 Renal function is a major concern when considering the DAA regimen for LT recipients because renal failure may occur more easily due to the toxicity of CNI, HCV infection, and metabolic disorders such as new-onset diabetes. 28,29 Recent studies reported a strong effect of a sofosbuvir-based regimen with a high SVR rate in patients with F3–4 cirrhosis, RAVs, and LT. 30–33 Sofosbuvir, however, showed a 2-fold greater area under the concentration curve in patients with a GFR less than 30 mL/min/1.73 m² than in patients with normal renal function, and thus sofosbuvir is not recommended for patients with renal failure. Both DCV and ASV are metabolized in the liver and excreted into the bile duct, and therefore renal dysfunction does not affect the safety and efficacy of DCV/ASV therapy even if under hemodialysis. 34–36 These studies showed the high SVR12 rate (95.5–100%) in dialysis patients and DCV/ASV therapy was well tolerated, even in patients with liver cirrhosis and NS5A RAVs. In accordance with these results, our study showed few time course changes in the eGFR and interactions with other parameters during DCV/ASV therapy, including in a maintenance dialysis patient. Therefore, a DAA regimen of DCV/ASV can be recommended for LT patients with renal failure.

Pre-existing RAVs reportedly influence the virologic outcome in patients undergoing DCV/ASV therapy. In a phase III multicenter study, the overall SVR rate was 84%, but the SVR rate for patients with L31 or Y93 substitutions was only 38–41%. 14 Furthermore, Iio et al. reported that a history of SMV therapy was associated with virologic failure in DCV/ASV therapy, resulting in the emergence of multiple RAVs. 37 Consistent with this report, one patient (case 4) with virologic failure in the present study had also failed SMV/Peg-IFN/RBV therapy. A recent study showed that in cases of treatment failure, baseline D168E and/or Q80K in NS3 were prevalent with prior SMV treatment. 38 Uchida et al. reported that NS5A R30Q/H/I and NS5A Y93H mutations at baseline determined the therapeutic efficacy of DCV/ASV, but rare NS5A RAVs (P29del and P32del) developed frequently in patients with previous SMV therapy. 39 The D168E RAV in NS3 was detected in the patient who failed therapy in our cohort after the discontinuation of DCV/ASV. Treatment with DCV/ASV may be less effective in patients who failed prior therapy using SMV, which is an NS3 protease inhibitor, due to emergence of RAVs in NS5A and/or NS3. At present, it is not clear whether these minor substitutions affect retreatment using NS5A and NS3 protease inhibitors, but future analysis is expected to reveal the detailed mechanisms. Liver transplantation patients with these RAVs should be assessed to optimize future DAA regimens.

Regarding adverse effects, only one patient (case 7) showed increased transaminase levels (grade 1). Fortunately, the patient completed the 24-week DCV/ASV treatment and achieved SVR12. Increased transaminase levels are a common adverse event in the DCV/ASV regimen, which seems to be related to ASV, but not DCV. 40,41 Although the exact mechanisms of hepatotoxicity are unclear, they are thought to be due to immune-allergic reactions. Our patient (case 7) showed slight and transient elevation of transaminase levels without fever, C-reactive protein elevation, and eosinophilia. As described above, DCV/ASV treatment tends to decrease the trough level of the tacrolimus. Therefore it would be very important for LT recipients to distinguish the graft rejection and immune-allergic reactions by means of liver biopsy in case the elevation of transaminase levels is severe and uncontrollable. In our case, we reduced the dose of ASV first and the patient recovered from increased transaminase levels. The trough level of tacrolimus did not change dramatically before or after dose reduction of ASV (2.7 to 2.3 ng/mL), thus dose adjustment of tacrolimus was not carried out. We did not undertake liver biopsy because the patient’s clinical course was favorable, hence the exact types of liver injuries could not be clarified. It is also possible that immune-allergic liver injury might be prevented in
patients receiving immunosuppressive therapies. In any case, the possibility of adverse events including the graft rejection should be taken into account when starting DCV/ASV therapy and liver function should be closely monitored during the follow-up period.

All oral DAAs have significantly improved the efficacy and safety of the treatment for HCV genotype 1 infection. New DAAs including sofosbuvir/ledipasvir, ombitasvir/paritaprevir/ritonavir, and grazoprevir/elbasvir have been approved in Japan. These regimens, which are a once-daily oral for 12 weeks, are simpler and shorter for the treatment periods compared to DCV/ASV. Meanwhile the appearance of these new regimens results in a high cost for the treatment of HCV infection. Some studies have shown the regimen of sofosbuvir/ledipasvir for 12 weeks is highly effective for genotype 1 hepatitis C including post-LT cohorts. Baseline RAVs in NS5A have minimal effects on patient responses to sofosbuvir/ledipasvir, but the regimen is not recommended for patient with renal dysfunction, as described. The regimen of ombitasvir/paritaprevir/ritonavir also showed high SVR12 rates in a Japanese cohort, however, this regimen has a weak point for LT recipients. Because of the presence of drug–drug interactions between ritonavir and CNI, blood levels of CNI should be monitored closely and the dosage must be modified appropriately. The regimen of grazoprevir/elbasvir is known to be little-affected by renal function. Roth et al. showed an SVR12 rate of 98.9% in dialysis patients with no discontinuation. This regimen would be one of the options for the treatment of HCV genotype 1 infection, in particular, in LT patients with renal dysfunction. The drug–drug interactions between grazoprevir/elbasvir and CNI should be monitored as a treatment precaution. Still fewer data are available for the treatment of HCV infection after LT, thus further examination is needed on these new DAAs for LT patients.

Our study has two limitations: its retrospective nature and small size. We believe that our data from the cohort are reliable, however, because the treatment practices and follow-up strategy are standardized, and this study includes useful information regarding clinical outcomes. A prospective and multicenter study is needed to further clarify the efficacy and safety of DCV/ASV in detail.

In conclusion, anti-HCV treatment with dual DAAs (DCV/ASV) showed high antiviral efficacy in patients with recurrent HCV genotype 1 infection after LT. Combination therapy with DCV/ASV is feasible for LT patients with little effect on drug interactions or renal function.

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