Use of direct antiviral agents in liver transplant recipients with hepatitis C virus in Korea: 2-center experience

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INTRODUCTION

Cases of liver transplantation (LT) have increased slowly in Korea, but HCV recurrence in the allograft is nearly universal after LT [1]. In the absence of effective antiviral therapy, HCV recurrence leads to cirrhosis in 10%–25% of recipients at 5 years in the posttransplant period and a 25% reduction in long-term patient survival compared to other indications for LT because recurrent HCV is a major cause of graft dysfunction, graft loss, and patient death [2,3].

Direct antiviral agents (DAAs) have revolutionized HCV treatment in liver transplant recipients. Before the era of DAA agents, IFN-based regimens were the only treatment option. SVR rates of IFN-based regimens were markedly lower in LT recipients than in nontransplant patients due to an inability to tolerate IFN-based regimens and ribavirin (RBV)-induced anemia [4]. Thus, the use of IFN-based regimens has restricted the application of LT [5]. However, achievement of sustained virological response (SVR) results in favorable clinical outcomes in LT recipients [6].

Purpose: The proportion of liver recipients with HCV is gradually increasing in Korea. Limited data are available regarding the efficacy of direct antiviral agents (DAAs) in liver transplant recipients in Asia. We aimed to assess the efficacy and safety of DAAs in HCV-infected liver recipients in Korea.

Methods: Forty HCV-infected patients from 2 centers received DAAs in the pretransplant or posttransplant period between May 2015 and November 2016.

Results: DAA was administered in the pretransplant period in 6 patients and the posttransplant period in 34 patients. Dalastavir and asunaprevir (n = 2) and sofosbuvir/ledipasvir and ribavirin (n = 4) were used in the pretransplant period. HCV RNA was not detected before liver transplantation in all patients. Sustained virological response (SVR) at 12 and 24 weeks after liver transplantation was 100%. In the posttransplant period, 33 of 34 patients received sofosbuvir-based therapy. SVR at 12 weeks in those patients was 94%. Recurrent virologic relapse developed in 2 patients because of HCC recurrence or treatment failure. Adverse events included anemia (n = 2) and abdominal discomfort (n = 1).

Conclusion: DAAs are an effective and well-tolerated treatment for HCV-infected recipients in Korea.

Key Words: Safety, Antiviral agents, Liver transplantation, Treatment outcome
Since the introduction of DAA agents, multiple non-IFN regimens represent an important achievement in HCV treatment, with higher rates of HCV cure and fewer adverse events [7-11]. Three recent observational studies using sofosbuvir-based therapy reported 100% SVR12 rates after completion of therapy [10-12]. However, limited data are available on the efficacy and safety of DAAs in liver recipients in Asia. The outcome for liver transplant recipients in Korea may provide valuable insights into the safety and efficacy of these regimens in Asia. Therefore, we report the results of our 2-center experience in Korea using DAAs for the treatment of HCV patients before and after LT.

METHODS

This is a retrospective observational study that included HCV infected recipients who received DAAs in the pretransplant or posttransplant setting at the Samsung Medical Center (n = 17) and Seoul National University Hospital (n = 23) between May 2015 and November 2016. Electronic medical records were reviewed for patient demographics, including sex, age, transplant type, ABO-incompatibility, coexistence of hepatocellular carcinoma (HCC), coinfection with HBV, HCV genotype, hepatic steatosis of liver graft, ischemic time, HCV RNA estimated by quantitative real time polymerase chain reaction assay (in IU/mL), duration of treatment, interval between LT and treatment initiation, history of prior HCV treatment, and type of immunosuppressive therapy. AST, ALT, and total bilirubin were measured at baseline before treatment initiation and at the end of treatment. HCV RNA was checked before treatment initiation and at the end of treatment.

All patients received tacrolimus and the goal therapeutic range for tacrolimus was 3 to 8 ng/mL. The study was approved and received an exemption from written consent by the Institutional Review Board of Samsung Medical Center (SMC-2017-06-132) and Seoul National University Hospital (H-1706-184-863).

Effectiveness

Serum HCV RNA levels were quantified with a lower limit of quantification of 12 IU/mL. HCV RNA levels were measured prior to treatment, at variable time points throughout treatment, at the end of treatment, and at various times within the 12 weeks following completion of therapy. The primary endpoint was the proportion of patients achieving an undetectable HCV RNA SVR12. The secondary endpoints were virologic relapse after treatment and the incidence of adverse events.

Safety

Safety data were collected prior to initiation of medications, during treatment, and up to 12 weeks after the completion of treatment. Adverse events, graft dysfunction, and graft and patient survival were recorded.

Statistical analysis

The primary end point of this study was the proportion of patients who achieved SVR12, which was defined as an undetectable HCV RNA 12 weeks after treatment completion. The secondary end points included relapse after treatment and side effects. All statistical analyses were performed using IBM SPSS Statistics ver. 22.0 (IBM Co. Armonk, NY, USA). A P-value less than 0.05 was considered statistically significant.

RESULTS

A total of 40 liver transplant recipients from two centers who were infected with HCV with genotypes 1, 2, or 3 were treated with DAA. Six patients were treated with DAAs in the pretransplant period for 12 weeks and 34 patients were treated with DAAs in the posttransplant period for 12 weeks (n = 30) or 24 weeks (n = 4).

For DAA treatment in the pretransplant period, the combination of daclatavir (DCV) and asunaprevir (ASV) (n = 2) and the combination of sofosbuvir/ledipasvir (SOF/LDV) with RBV (n = 4) were used. Demographic and clinical data are summarized in Table 1. HCV RNA was not detected before liver transplantation and the SVR12 and SVR24 rates after liver transplantation were 100% and 100%, respectively.

Ten patients received antiviral treatments before transplantation, in the patients who received DAAs after liver transplantation. Eight patients were treated with a combination of interferon and ribavirin and 2 patients received only interferon therapy. However, we did not have data for the response to antiviral therapies before transplantation. For DAA use in the posttransplant period, 1 patient was treated with the combination of DCV and ASV and the remaining patients (n = 33) were treated with SOF-based therapy. The median time from liver transplantation to DAA use was 105 months (range, 1–161 months) (Table 2). Of the 34 patients treated, 94% (32 of 34) achieved SVR12 and SVR24. Of 21 HCC patients treated with DAA after liver transplantation, 3 patients (14.3%) developed HCC recurrence. When comparing baseline laboratory values and HCV RNA, patients in the posttransplant DAA group (n = 34) showed a significant improvement in serum AST, ALT, total bilirubin, and HCV RNA level (P < 0.05) (Table 3). HCV RNA was undetectable at the end of DAA treatments in 39 of 40 patients.

One patient developed HCV relapse and the other patient experienced treatment failure. Two patients with genotype 1b did not reach SVR12. One patient was treated with SOF/LDV and achieved SVR at the end of treatment, but HCV RNA increased from 8 weeks after the end of treatment. The other patient was treated with a combination of SOF, DCV, and RBV.
but the level of HCV RNA was not decreased.

Biopsy-proven acute rejection developed in 2 patients, who responded to increased immunosuppression. Adverse events were anemia (n = 2) and abdominal discomfort (n = 1). Patients with anemia received RBV. No patients developed graft failure in the last visits, but one patient died because of pneumonia.

**DISCUSSION**

Before the DAA era, treatment options for patients with recurrent HCV in the allograft were limited to pegylated IFN and RBV, which result in very low SVR rates (30%) and a high frequency of side effects, such as hemolysis, pancytopenia, depression, graft rejection, and hepatic decompensation [13,14]. Antiviral treatments in liver recipients prevented liver-related death or the need for retransplantation due to graft failure. Real-world studies have supported high SVR rates and excellent tolerability of DAA regimens in LT recipients with recurrent hepatitis C and mild to moderate fibrosis including combination regimens of SOF/LDV and SOF plus DCV [10-12,15,16].

In this report, we describe our experience of treating HCV-infected patients before and after liver transplantation in Korea with DAs. Six patients were treated with DAs for HCV management before liver transplantation. They bought DAs directly from abroad. One month after liver transplantation, others received DAs in the posttransplant period because their liver enzymes and HCV RNA were elevated or their pathologic results showed liver fibrosis related to HCV reactivation. We

| Variable | Value |
|----------|-------|
| Sex      |       |
| Female   | 4 (66.7) |
| Male     | 2 (33.3) |
| Age (yr) | 68 (45–74) |
| LT type  |       |
| DDLT     | 2 (33.3) |
| LDLT     | 4 (66.7) |
| ABO-incompatible LDLT | 2 (33.3) |
| HCC coexistence | 4 (66.7) |
| Alcohol  | 1 (16.7) |
| HBV coinfection | 1 (16.7) |
| Genotype |       |
| 1b       | 4 (66.7) |
| 2        | 1 (16.7) |
| Unknown  | 1 (16.7) |
| Immunosuppression |       |
| Basiliximab | 4 (66.7) |
| Tacrolimus  | 6 (100) |
| MMF       | 6 (100) |
| mTOR inhibitor | 0 (0) |
| Steatosis (%) |       |
| Macrosteatosis | 3 (0–7) |
| Microsteatosis | 3 (0–5) |
| Cold ischemic time (min) | 73 (49–107) |
| Warm ischemic time (min) | 25 (16–35) |

Values are presented as number (%) or median (range).

| Variable | Value |
|----------|-------|
| Preoperative |       |
| Sex      |       |
| Female   | 9 (26.5) |
| Male     | 25 (73.5) |
| Age (yr) | 60 (27–75) |
| LT type  |       |
| DDLT     | 8 (23.5) |
| LDLT     | 26 (76.5) |
| ABO-incompatible LDLT | 4 (11.8) |
| HCC coexistence | 21 (61.8) |
| Alcohol  | 2 (5.9) |
| HBV coinfection | 3 (8.8) |
| HIV coinfection | 1 (2.9) |
| Genotype |       |
| 1        | 25 (73.5) |
| 2        | 5 (14.7) |
| 3        | 1 (2.9) |
| Unknown  | 3 (8.8) |
| Antiviral treatments before transplantation |       |
| None     | 18 (52.9) |
| Yes      | 10 (29.4) |
| Unknown  | 6 (17.6) |
| Perioperative |       |
| Immunosuppression |       |
| Basiliximab | 26 (76.5) |
| Tacrolimus  | 34 (100) |
| MMF       | 33 (97.1) |
| mTOR inhibitor | 3 (8.8) |
| Duration of DAs (wk) |       |
| 12       | 30 (88.2) |
| 24       | 4 (11.8) |
| Steatosis (%) |       |
| Macrosteatosis | 5 (1–35) |
| Microsteatosis | 5 (0–30) |
| Cold ischemic time (min) | 78 (19–456) |
| Warm ischemic time (min) | 25 (24–55) |
| Time from LT to DAA use (mo) | 10.5 (1–161) |

Values are presented as number (%) or median (range).

DAA, direct antiviral agent; DDLT, deceased donor liver transplantation; LDLT, living donor liver transplantation; HCC, hepatocellular carcinoma; MMF, mycophenolate mofetil; mTOR, mechanistic target of rapamycin.
observed a remarkable SVR12 of 100% for pretransplant use and SVR12 of 94% for post-transplant use. Our results are comparable to previously reported rates in practice [10-12]. The combination of DAAs was well tolerated with a low rate of adverse events. No patient stopped medications prematurely due to adverse events. Anemia was observed in 2 patients and abdominal discomfort was observed in 1 patient. Virologic relapse developed in two patients. One patient failed treatment after LT. HCV RNA was not detected at the end of treatment, but its levels increased when HCC recurrence was diagnosed 1 month after DAA treatment. The relationship between HCC recurrence and HCV reactivation is unclear. The other patient was treated with a combination of SOF, DCV, and RBV, but treatment response was poor because the HCV RNA could not reach an undetectable level. Thus, the patient received DAAs for only 8 weeks.

A decision regarding the optimal time to start antiviral therapy will be needed for every patient waitlisted for liver transplantation. It is worth considering the relative advantages of initiating antiviral therapy before versus after deceased donor liver transplantation in Western countries. Theoretically, the best way to prevent HCV recurrence after liver transplantation is by achieving SVR prior to transplantation [17]. Pretransplant DAA use may be beneficial in the living donor liver transplantation setting, as these are scheduled operations. In addition, DAA use in the pretransplant period in HCC patients who have the additional allocation points in Western countries may be advantageous for preventing HCV recurrence after transplantation.

Posttransplant HCV recurrence was inversely related to the number of days of undetectable HCV RNA before transplantation [17]. Six patients in the present study had an undetectable viral load for more than 1 month prior to liver transplantation. A previous study also reported that 96% of patients with an undetectable viral load for more than 4 weeks prior to LT achieved SVR, whereas 90% of patients with HCV recurrence after transplantation had an undetectable viral load for less than 4 weeks [18]. Our study also suggests that negative HCV RNA due to DAA treatment prior to liver transplantation predicts SVR after liver transplantation.

Evidence from clinical trials that incorporated RBV into the regimens supports the use of RBV when treating patients with recurrent hepatitis C after LT [9,19]. However, in the new DAA era, the role of RBV in the treatment of HCV infection among LT recipients is unclear. Because of hematologic abnormalities associated with RBV, a RBV-free regimen may be considered effective. Limited real-world experiences with SOF-based therapy without RBV suggest similar SVR rates to an RBV-containing regimen [10,11,15]. Avoidance of ribavirin is desirable given the reduction in renal perfusion after liver transplantation due to the use of calcineurin inhibitors and reduced hemoglobin levels.

Several limitations must be considered when interpreting the findings of the present study. First, because of the retrospective observational study design and small sample size, there is considerable heterogeneity in treatment regimens, including previous treatment experience, length of treatment, use of RBV, and time from LT to HCV treatment initiation. Second, we did not have pathologic information, including the degree of fibrosis, because not all patients were biopsied before or after DAA treatment. Third, considering the low number of cases exhibiting treatment failure and relapse, it is difficult to identify factors associated with treatment failure based on our results.

In conclusion, DAAs that included mainly SOF-based therapy achieved high rates of SVR12 and SVR24 in the HCV-infected liver recipients of genotypes 1, 2, and 3. DAAs were well tolerated in all patients. Because of its small sample size and retrospective design, this study needs to be validated in a well-designed prospective study with a homogenous patient population and a large sample size in Asia.

**CONFLICTS OF INTEREST**

No potential conflict of interest relevant to this article was reported.

### REFERENCES

1. Kim JM, Lee KW, Song GW, Jung BH, Lee HW, Yi NJ, et al. Outcomes for patients with HCV after liver transplantation in Korea: a multicenter study. Ann Surg 2016;90:36-42.

2. Chen T. Terrault NA. Perspectives on...
treating hepatitis C infection in the liver transplantation setting. Curr Opin Organ Transplant 2016;21:111-9.

3. Thuluvath PJ, Guidinger MK, Fung JJ, Johnson LB, Rayhill SC, Pelletier SJ. Liver transplantation in the United States, 1999-2008. Am J Transplant 2010;10(4 Pt 2):1003-19.

4. Bzowej N, Nelson DR, Terrault NA, Everson GT, Teng LL, Prabhakar A, et al. PHOENIX: a randomized controlled trial of peginterferon alfa-2a plus ribavirin as a prophylactic treatment after liver transplantation for hepatitis C virus. Liver Transpl 2011;17:528-38.

5. Berenguer M, Palau A, Aguilera V, Rayón JM, Juan FS, Prieto M. Clinical benefits of antiviral therapy in patients with recurrent hepatitis C following liver transplantation. Am J Transplant 2008;8:679-87.

6. Kawecka J, Takahashi S, Kawakami Y, Tsuge M, Hiramatsu A, Imamura M, et al. Sustained virological response to antiviral therapy improves survival rate in patients with recurrent hepatitis C virus infection after liver transplantation. Hepatol Res 2015;45:1047-54.

7. Charlton M, Everson GT, Flamm SL, Kumar P, Landis C, Brown RS Jr, et al. Ledipasvir and sofosbuvir plus ribavirin for treatment of HCV infection in patients with advanced liver disease. Gastroenterology 2015;149:649-59.

8. Forns X, Charlton M, Denning J, McHutchison JG, Symonds WT, Brainard D, et al. Sofosbuvir compassionate use program for patients with severe recurrent hepatitis C after liver transplantation. Hepatology 2015;61:1485-94.

9. Charlton M, Gane E, Manns MP, Brown RS Jr, Curry MP, Kwo PY, et al. Sofosbuvir and ribavirin for treatment of compensated recurrent hepatitis C virus infection after liver transplantation. Gastroenterology 2015;148:108-17.

10. Kwok RM, Ahn J, Schiano TD, Te HS, Potosky DR, Tierney A, et al. Sofosbuvir plus ledipasvir for recurrent hepatitis C in liver transplant recipients. Liver Transpl 2016;22:1536-43.

11. Elfeki MA, Abou Mrad R, Modaresi Esfeh J, Zein NN, Eghtesad B, Zervos X, et al. Sofosbuvir/ledipasvir without ribavirin achieved high sustained virologic response for hepatitis C recurrence after liver transplantation: two-center experience. Transplantation 2017;101:996-1000.

12. Faisal N, Bilodeau M, Aljudaibi B, Hirsch G, Yoshida EM, Hussaini T, et al. Sofosbuvir/ledipasvir without ribavirin achieved high sustained virologic response for recurrent hepatitis C virus infection after liver transplantation: a randomized study. Transplantation 2016;100:1059-65.

13. Korean Association for the Study of the Liver. KASL clinical practice guidelines: management of hepatitis C. Clin Mol Hepatol 2016;22:76-139.

14. Samuel D, Bizollon T, Feray C, Roche B, Ahmed SN, Lemonnier C, et al. Interferon-alpha 2b plus ribavirin in patients with chronic hepatitis C after liver transplantation: a randomized study. Gastroenterology 2003;124:642-50.

15. Saxena V, Khungar V, Verna EC, Levitsky J, Brown RS Jr, Hassan MA, et al. Safety and efficacy of current direct-acting antiviral regimens in kidney and liver transplant recipients with hepatitis C: results from the HCV-TARGET study. Hepatology 2017;66:1090-101.

16. Coilly A, Fougerou-Leurent C, de Ledinghen V, Houssell-Debry P, Duvoux C, Di Martino V, et al. Multicentre experience using daclatasvir and sofosbuvir to treat hepatitis C recurrence - The ANRS CUPILT study. J Hepatol 2016;65:711-8.

17. Curry MP, Forns X, Chung RT, Terrault NA, Brown R Jr, Henkel JM, et al. Sofosbuvir and ribavirin prevent recurrence of HCV infection after liver transplantation: an open-label study. Gastroenterology 2015;148:100-7.

18. Herzode C, Fontaine H, Dorival C, Larrey D, Zoulim F, Canva V, et al. Triple therapy in treatment-experienced patients with HCV-cirrhosis in a multicentre cohort of the French Early Access Programme (ANRS CO20-CUPIC) - NCT01514890. J Hepatol 2013;59:434-41.

19. Kwo PY, Mantry PS, Coakley E, Te HS, Vargas HE, Brown R Jr, et al. An interferon-free antiviral regimen for HCV after liver transplantation. N Engl J Med 2014;371:2375-82.