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Strategy for Hepatitis C Treatment in Liver Transplant Settings

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In patients with detectable virus at the time of liver transplantation, hepatitis C virus (HCV) infection always recurs on the graft, and 30% of patients have an aggressive clinical and histologic course with increased morbidity, mortality, and graft loss. Moreover, in some transplantation patients, recurrent HCV infection leads to an aggressive course of disease known as fibrosing cholestatic hepatitis, which is characterized by hepatic decompensation and death. Liver allograft and recipient survival can be substantially improved with successful eradication of HCV. Recent advances in direct-acting antiviral agents have revolutionized the management of HCV infection, and a number of these agents have shown high sustained virological responses, shorter durations of treatment, and much improved tolerability when compared with previous pegylated interferon based therapies in liver transplant settings.

Key Words: Hepatitis C, Direct-acting antiviral agents, Liver transplantation
중심 단어: C형 간염, 직접 작용 항바이러스제, 간이식

INTRODUCTION

In the time since hepatitis C virus (HCV) was initially discovered, our knowledge of the characteristics of infection has advanced rapidly, markedly improving the treatment options available to HCV-infected patients. Oral direct-acting antiviral agents (DAAs) are modern interferon (IFN)-free drug combinations that have dramatically changed the management of HCV infection, especially in patients with the most severe forms of liver disease (decompensated cirrhosis and those who are awaiting or have undergone liver transplantation [LT])(1,2). Management of HCV infection in the latter patients was challenging in the era of IFN-based therapies. Treatment efficacy was poor and treatment-related side effects common; these included hemolytic anemia, pancytopenia, graft rejection, and liver decompensation(3,4). New DAA therapies afford sustained (high-level) virological responses (SVRs) in such patients, with improved tolerability, even in those who have previously failed IFN-based therapies. Elimination of IFN greatly improves the side-effect profile and shortens treatment duration; however, the treatment options for such patients remain limited. Those undergoing LT require immunosuppressive drugs to avoid graft rejection. Such drugs are associated with potential drug–drug interactions (DDIs) and metabolic burdens newly placed on the engrafted liver. Here, we concisely update the treatment options for HCV infection in post-LT patients.

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1. Timing of HCV treatment

Detectable HCV RNA at the time of LT, is always associated with re-infection upon reperfusion(5,6) and is accompanied by a rise in the HCV RNA level peaking about 3～4 months after operation, together with the development of acute hepatitis in most patients(7). Currently, two therapeutic approaches are available. The pre-emptive strategy

features treatment early after LT. Alternatively, treatment may not commence until recurrent disease is clearly established. The potential advantages of early treatment are that the HCV RNA levels and liver fibrosis are minimized(8). Despite the clear benefits afforded by early treatment, such a pre-emptive strategy was historically considered inadvisable because the IFN-based therapies were associated with increased rates of acute allograft rejection and de novo autoimmune hepatitis. Also, such therapies afforded only modest SVR rates in post-LT settings, associated with significant adverse side-effects and poor tolerability(3,4). However, given the development of potent and safe DAA-based therapies, earlier concerns that IFN-related immunomodulation was associated with allograft rejection and poor tolerance when IFN was employed as an anti-HCV therapy after LT is abating. The guidelines of the European Association for the Study of the Liver (EASL) and the Asian-Pacific Association for the Study of the Liver (APASL) recommend that anti-HCV treatment should be initiated early after LT, ideally as "early as possible when the patient is stabilized" (EASL: generally after the first 3 months post-transplantation; APASL: 1～3 months post-transplantation)(9,10). This is because the SVR12 rates are thus diminished in patients with advanced liver disease post-LT. It is likely that DAA-based therapies, affording better tolerability and fewer DDIs than IFN-based therapies, will encourage pre-emptive strategies that will become the standards of care. Also, this is possible even in patients with decompensated cirrhosis and fibrosing cholestatic hepatitis (FCH; a life-threatening form of recurrent HCV infection) in post-LT settings. However, in those, DAA is associated with a reduced likelihood of a SVR(11).

2. Treatment options afforded by DAAs in liver transplant settings

1) Sofosbuvir and ribavirin

The NS5B nucleotide inhibitor, sofosbuvir (SOF), has been repeatedly shown to yield good SVR rates without any need for an additional IFN-based therapy. It is given once daily, and has a good safety profile. Also, it has a high barrier to resistance, a pan-genotypic antiviral effect.

The first study to assess the safety and efficacy of an IFN-free regimen in HCV-infected post-LT patients prescribed a 24-week combination of SOF and ribavirin (RBV) (12). Forty patients with HCV genotypes 1～4 who were at least 6 months after LT were enrolled. The SVR12 rate was 70% (28/40); the safety profile was excellent. Of the 12 patients who experienced virological relapses, 7 succumbed during follow-up week 2, four during week 4, and one during week 12. Although the regimen was suboptimal, the results showed that an IFN-free all-oral regimen could be used to treat liver transplant recipients as effectively as those who did not require transplantation. In a compassionate program, 44 patients with severe HCV recurrences following LT, including FCH, were treated with SOF and RBV, either with (n=12) or without (n=32) peg-IFN for 24 weeks(13). The decision to prescribe peg-IFN was left to the treating physicians. The reported SVR rate was 60% in patients given SOF and RBV and 50% in those taking SOF, RBV, and peg-IFN. Due to the severity of HCV at the time of treatment initiation, 15 patients died of progressive liver disease during treatment. No deaths were attributable to SOF or RBV. Liver function tests (e.g., bilirubin level, and the international normalized ratio) improved upon treatment. Although the trial was small, the data suggest that SOF and RBV are safe and effective when used to treat HCV infection post-LT. However, the SVR12 rate did not attain 90%; the regimen was thus suboptimal.

2) Ledipasvir/sofosbuvir and ribavirin

Ledipasvir/sofosbuvir (LDV/SOF) is a fixed-dose combination of ledipasvir, an inhibitor of HCV NS5A, and SOF. The SOLAR-1 and SOLAR-2 studies recruited patients with end stage liver disease and post LT(14,15). These are phase 2, prospective randomized multicenter studies prescribing a combination of LDV/SOF and RBV for 12 or 24 weeks in patients with HCV genotype 1 or 4.

The SOLAR-1 was conducted across 29 clinical sites in the United States(14). The RBV doses were weight-based for patients without cirrhosis and with Child-Pugh Turcotte (CTP) class A. In CTP class B and C patients, RBV was initiated at 600 mg/day and increased as tolerated. In total, 111 patients exhibited fibrosis of grades F0～F3, whereas 51, 52, and 9 had CTP class A, B, and C cirrhosis, respectively. Among patients without cirrhosis (METAVIR grades F0～F3), the SVR rates were 96% to 98% when

LDV/SOF and RBV were given for 12 or 24 weeks. Among those with cirrhosis, the SVR rates were 96% for those of CTP class A, 85% to 88% for those of class B, and 60% to 75% for those of class C, when LDV/SOF and RBV were given for 12 or 24 weeks. Six patients with FCH, of whom four were treated for 12 weeks and two for 24 weeks, exhibited SVR12 rate of 100%. The response rates in the 12- and 24-week groups were similar. Thirteen patients (4%) discontinued the regimen prematurely due to adverse events; 10 patients died (mainly from complications associated with hepatic decompensation). No rejection or renal insufficiency was noted, and the blood levels of cyclosporine and tacrolimus did not change significantly.

The SOLAR-2 trial was recently conducted at 34 sites across 12 European countries, Australia, Canada, and New Zealand; the patient cohort was similar to that of SOLAR-1(15). Most patients were infected with HCV of genotype 1 (approximately 11% were infected with genotype 4); more than 75% of all patients had failed previous antiviral therapy. Genotype 1 post-LT patients without cirrhosis achieved SVR rates of 93% (42 of 45 patients) and 100% (44 patients) after 12 and 24 weeks of therapy, respectively. Among patients without cirrhosis, the SVR rates were 96% to 98% when LDV/SOF and RBV were given for 12 or 24 weeks. Among patients with cirrhosis, the SVR rates were 96% to 100% for those of CTP class A, 95% to 100% for those of class B patients, and 50% to 80% for those of class C, when LDV/SOF and RBV were given for 12 or 24 weeks. The results of both the SOLAR-1 and SOLAR-2 trials suggest that a short course (12 weeks) of LDV/SOF and RBV is probably sufficient for almost all patients exhibiting genotype 1 HCV recurrence post-LT.

3) Sofosbuvir and daclatasvir with ribavirin

Daclatasvir (DCV) is a first-in-class HCV NS5A replication complex inhibitor exhibiting pan-genotypic activity and a pharmacokinetic profile allowing once-daily dosing.

The ALLY-1 phase 3 study assessed the safety and efficacy of SOF and DCV with RBV (initially 600 mg, adjusted to 1,000 mg) daily for 12 weeks; the trial contained 53 Caucasian LT recipients(16). Thirty-one (58%) were infected with HCV of genotype 1a, 10 (19%) with HCV of genotype 1b, and 11 (21%) with HCV of genotype 3. Liver histology showed that 6 (11%), 10 (19%), 7 (13%), 13 (25%), and 16 (30%) patients had fibrosis of grades F0, F1, F2, F3, and F4, respectively (METAVIR scores). SVR12 was attained in 50 (94%) patients. In terms of the genotypic response, 30 (97%), 9 (90%), and 10 (91%) patients with virus of genotypes 1a, 1b, and 3, respectively, achieved SVR12. One patient with a genotype 3 infection discontinued all medications after 31 days due to headache but nonetheless attained SVR12. The study regimen was compatible with several concomitant immunosuppressive regimens. No dose adjustments were required and no graft rejection was noted. The study showed that the pan-genotypic combination was potent, safe, and tolerable in post-LT patients with HCV infections. The regimen cured most patients, including those infected with the difficult-to-treat genotype 3 HCV.

The largest observational real-life cohort of transplant recipients is the ongoing French CO23 ANRS CUPILT study, which has enrolled 699 patients to date(17). The study assesses the combination of SOF and DCV with or without RBV. Of 137 patients assessed, SVR12 has been attained in 132 (96%), irrespective of the HCV genotype or the duration of treatment (12 weeks vs. 24 weeks). The CUPILT study reports not only high SVR12 rates but also good tolerance, no DDIs, and clinical and biochemical improvements.

4) Ombitasvir/paritritonavir and dasabuvir (Opr+D) with ribavirin

The ombitasvir/paritaprevir/ritonavir and dasabuvir (Opr+D) regimen includes ombitasvir, an NS5A inhibitor; paritaprevir, an NS3/4A protease inhibitor; ritonavir, a CYP3A inhibitor used as a pharmacological booster; and dasabuvir, a non-nucleoside NS5B polymerase inhibitor.

CORAL-1 was a phase 2 open-label study of Opr+D with RBV over 24 weeks in 34 genotype 1 patients presenting with mild fibrosis (METAVIR stages F0～2)(18); all had undergone LT more than 1 year prior to commencing Opr+D with RBV. Because of DDIs with calcineurin inhibitors (CNIs), the starting dosage of tacrolimus was 0.5 mg/week or 0.2 mg every other day and the starting dosage of cyclosporine was one fifth of the pre-treatment total daily dose, administered once a day. The use of mTOR inhibitors (e.g., rapamycin, everolimus) was prohibited. The

dosages of CNIs were adjusted during treatment by reference to the trough levels. SVRs were attained in 97% (33/34) of patients. One patient relapsed on post-treatment Day 3. One patient ceased treatment due to an adverse event but nonetheless attained SVR. Of all patients, 17% (5/29) exhibited tacrolimus levels >15 ng/mL during treatment (mostly attributable to dosing errors) and, in 28% (8/29), one or more measured tacrolimus levels lay below the reference range after treatment ceased. No rejection was noted. Opr+D with RBV did not change the trough levels of either tacrolimus or cyclosporine. Although Opr+D regimen is FDA-approved for use in post-transplant patients, there is the greater likelihood of DDIs with CNIs. Also, safety and efficacy data are lacking for patients with fibrosis METAVIR scores >F2.

These Phase 2/3 and real-world studies have influenced the Korean and international HCV treatment guidelines, which currently recommend IFN-free all-oral DAA regimens for all post-LT patients with HCV infections (Table 1)(9,19,20).

3. Drug-drug Interactions

Before initiation of any DAA, potential DDIs must be considered, including those attributable to both prescription and over-the counter pharmaceuticals. Furthermore, DDIs between DAAs and immunosuppressive drugs, principally CNIs, remain of concern when DAA-based therapies are prescribed. Also, chronic exposure to CNIs may cause progressive declines in renal function, thereby reducing RBV clearance, which may in turn increase the frequency and severity of RBV-associated hemolytic anemia.

Cyclosporine and tacrolimus alter the concentrations of DCV and SOF somewhat, but the changes are not clinically significant(9,21). Although the maximal concentration and exposure to SOF increase 2.5- and 4.5-fold, respectively, when SOF is given with cyclosporine, the increases in SOF concentration and SOF metabolites are not associated with any apparent toxicity. DCV affects neither cyclosporine nor tacrolimus levels, although modest increases in DCV exposure were observed. Concomitant use of SOF, LDV, or DCV with either CNI is considered safe. Also, no SOF, LDV, or DCV dose reductions are recommended for patients

Table 1. Recommended HCV treatment for patients in the liver transplantation setting

	KASL guideline	AASLD/IDSA guideline	EASL guideline
HCV genotype 1 or 4	- LDV/SOF+R/ R* for 12 weeks (R*-decompensated cirrhosis) - SOF+DCV+R* for 12 weeks - LDV/SOF for 24 weeks, if contraindicated or intolerant to RBV - SOF+DCV for 24 weeks, if contraindicated or intolerant to RBV - OPr+D+R for 24 weeks (genotype 1, Metavir stage F0~2) - OPr+R for 24 weeks (genotype 4)	- LDV/SOF+R/ R* for 12 weeks (R*-decompensated cirrhosis) - LDV/SOF for 24 weeks, if contraindicated or intolerant to RBV - SOF+DCV+R* for 12 weeks - SOF+DCV for 24 weeks, if contraindicated or intolerant to RBV - OPr+D+R for 24 weeks (genotype 1, Metavir stage F0~2)	- LDV/SOF+R/ R* for 12 weeks (R*-decompensated cirrhosis) - LDV/SOF for 24 weeks, if contraindicated or intolerant to RBV - SOF+DCV for 24 weeks, if contraindicated or intolerant to RBV
HCV genotype 2	- SOF+DCV+R* for 12 weeks - SOF+DCV for 24 weeks, if contraindicated or intolerant to RBV - SOF+R for 12~24 weeks	- SOF+DCV+R* for 12 weeks - SOF+DCV for 24 weeks, if contraindicated or intolerant to RBV - SOF+R/ R* for 12 weeks (R*-decompensated cirrhosis)	- SOF+DCV+R/ R* for 12 weeks (R*-decompensated cirrhosis) - SOF+DCV for 24 weeks, if contraindicated or intolerant to RBV
HCV genotype 3	- SOF+DCV+R* for 12 weeks - SOF+DCV for 24 weeks, if contraindicated or intolerant to RBV - SOF+R for 24 weeks	- SOF+DCV+R* for 12 weeks - SOF+DCV for 24 weeks, if contraindicated or intolerant to RBV - SOF+R for 24 weeks	- SOF+DCV+R/ R* for 24 weeks (R*-decompensated cirrhosis)

Abbreviations: KASL, Korean Association for the Study of the Liver; AASLD/IDSA, American Association for the Study of Liver Diseases/Infectious Diseases Society of America; EASL, European Association for the Study of the Liver; SOF, sofosbuvir; LDV, ledipasvir; DCV, daclatasvir; R, weight-based ribavirin; R*, ribavirin started from 600 mg/d; OPr, ombitasvir/paritaprevir/ritonavir; D, dasabuvir. Adapted from reference(9,19,20).

with hepatic impairment. However, close monitoring of immunosuppressant trough levels before, during, and after DAA therapy is essential. In the CUPILT study, the dose of one immunosuppressive drug had to be changed in 59% of 130 patients treated with SOF and DCV after LT(17). Opr+D increases the serum cyclosporine and tacrolimus levels; dose adjustments are required(9,18-21). More data are needed on the concomitant use of mTOR inhibitors(e.g., rapamycin, everolimus) and the new DAAs.

CONCLUSION

The rapid advances in hepatitis C treatment have led to a paradigm change. Recurrent HCV infection following LT can accelerate allograft injury that is difficult to treat with peg-IFN-based regimens. Such regimens may be poorly tolerated, afford only modest efficacy, and may interact negatively with immunosuppressive agents. IFN-free all-oral DAA regimens have consistently yielded high SVR rates and better side-effect profiles. Also, treatment courses can be short. Appropriate treatment of HCV infection in the LT setting will minimize graft failure, morbidity, and mortality.

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