

Treatment of Hepatitis C Virus Infection in Liver Transplant Recipients

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Abstract: Chronic hepatitis C virus (HCV) infection is the leading cause of liver transplantation in adults. Although the recurrence of HCV infection after liver transplantation is nearly universal, the recent advances in direct-acting antiviral (DAA) agents have revolutionized the management of HCV infection in the post-transplant setting. A number of these agents have been evaluated in recent clinical trials and have shown high sustained virologic response rates, shorter durations of treatment, and decreased adverse events when compared with the previous treatment of pegylated interferon and ribavirin. This article will review the current literature on the efficacy, tolerability, and potential drug interactions of various DAA agents in patients with recurrent HCV infection posttransplant.

Chronic hepatitis C virus (HCV) infection is the most common indication for liver transplantation in the United States and Europe.¹ Historically, patient and graft survival post-liver transplant (LT) have been poor in the setting of recurrent HCV infection, with up to 30% of patients developing cirrhosis within 5 years posttransplant.²⁻⁷ An aging cohort of HCV patients has led to increased health care utilization to manage decompensated liver disease as well as hepatocellular carcinoma.^{8,9}

Sustained virologic response (SVR) leads to improved clinical outcomes in LT recipients.^{5,10} Until recently, the treatment of HCV infection was limited to ribavirin and pegylated interferon, which resulted in poor SVR rates and high frequency of adverse events, such as depression, hemolysis, pancytopenia, graft rejection, and liver decompensation.¹¹⁻¹⁶ However, new noninterferon-based therapies have been shown to achieve high SVR rates in post-LT patients with improved tolerability and decreased side effects (Figure).¹⁷⁻²²

Due to the relatively recent introduction of direct-acting antiviral (DAA) agents, it can be challenging for health care providers to understand the nuances of treatment with these medications, such as optimal treatment duration, drug-drug interactions, and appropriate use of ribavirin. Although the current literature is still limited,

Keywords

Hepatitis C virus, liver transplant, recurrence, viral hepatitis, direct-acting antiviral agents

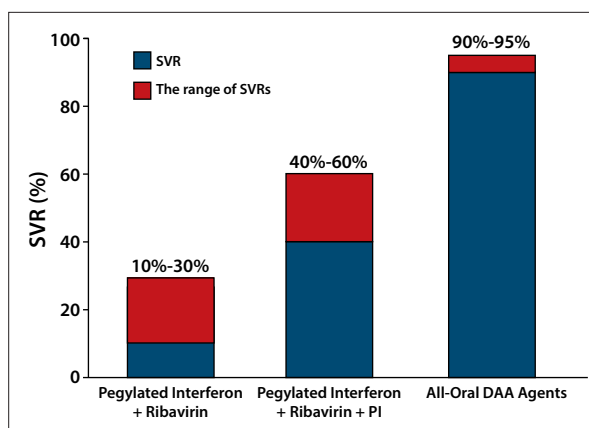


Figure. SVR rates with different treatment strategies.¹¹⁻²²

DAA, direct-acting antiviral; PI, protease inhibitor; SVR, sustained virologic response.

there are several recently published and ongoing trials evaluating the efficacy and tolerability of DAA agents in post-LT patients. This article reviews the current literature and assesses the role of oral DAA agents with or without ribavirin to treat HCV recurrence in post-LT patients.

Review of the Current Literature

Sofosbuvir and Ribavirin

Charlton and colleagues evaluated post-LT patients with compensated recurrent HCV infection who were treated with sofosbuvir (Sovaldi, Gilead) and ribavirin for 24 weeks.²³ Forty patients of any genotype were included in the study; 3% of patients presented with METAVIR stage F0 (no or minimal fibrosis), 35% with stage F1 to F2 (portal fibrosis), 23% with stage F3 (bridging fibrosis), and 40% with stage F4 (cirrhosis). The SVR12 rate was 70% (28/40). Of the 12 patients who experienced virologic relapse, 7 did so during follow-up week 2, 4 during week 4, and 1 during week 12. No patient experienced virologic relapse during treatment. All 28 patients who achieved SVR12 also achieved SVR24. The most common adverse events were fatigue (30%), diarrhea (28%), and headache (25%). Only 2 patients discontinued treatment due to adverse events, both unrelated to treatment. There were no deaths or graft loss, and no net directional changes in the trough levels of tacrolimus or cyclosporine were noted in the study.

Forns and colleagues evaluated the compassionate use of sofosbuvir and ribavirin in post-LT patients with severe recurrent HCV infection.²⁴ Eligible patients had a life expectancy of less than 1 year owing to hepatic failure if left untreated from acute cholestatic hepatitis, severe HCV recurrence, or end-stage liver disease. Patients of all genotypes were included, with the majority being either genotype 1a (35%) or genotype 1b (49%).

Treatment duration was 24 to 48 weeks with the addition of pegylated interferon at the discretion of the investigators. The SVR12 rate was 59% (54/92). Further analysis of treatment regimens showed that patients who received sofosbuvir and ribavirin achieved a SVR12 rate of 56% (39/70), while those who also received pegylated interferon achieved a SVR12 rate of 68% (15/22). Of the patients in whom treatment was initiated less than 12 months posttransplant, the overall SVR12 rate was 73% (35/48). Within this population, patients who received sofosbuvir and ribavirin achieved a SVR12 rate of 74% (25/34), while those who also received pegylated interferon achieved a SVR12 rate of 71% (10/14). In patients in whom treatment was initiated more than 12 months posttransplant, the overall SVR12 rate was 43% (19/44). In this cohort, patients who received sofosbuvir and ribavirin alone as well as those who also received pegylated interferon achieved a SVR12 rate of 43% (16/37 and 3/7, respectively). Overall, the median duration of treatment for the study was 24 weeks, and there was no statistically significant difference with the addition of pegylated interferon. As the study population had baseline liver dysfunction due to severe recurrent HCV infection, severe adverse events were reported in 47% of patients. Hepatic decompensation occurred in 18% of patients. Five percent of patients had severe adverse events that the investigators concluded were secondary to the study drugs. A total of 13 deaths occurred, 8 of which occurred during treatment or within 30 days of treatment completion.

Brown and colleagues presented preliminary data from a multicenter, open-label study evaluating the use of DAA agents for the treatment of HCV infection in the post-LT setting.²⁵ The study evaluated the use of multiple treatment regimens, one of which was the combination of sofosbuvir and ribavirin. Fifty-seven patients were enrolled in this arm, 31 of whom completed treatment at the time of analysis. The SVR4 rates were 90% and 60% in patients with genotype 2 and genotype 3, respectively. Two patients had to stop prematurely due to adverse events. The most common adverse events were fatigue (12%) and anemia (10%).

Sofosbuvir and Ledipasvir

Another study by Charlton and colleagues evaluated the use of sofosbuvir and ledipasvir (Harvoni, Gilead) with ribavirin in patients with both compensated and decompensated liver disease after transplant.²⁶ Patients with Child-Turcotte-Pugh (CTP) class A achieved SVR12 rates of 96% (25/26) and 96% (24/25) when treated for 12 weeks and 24 weeks, respectively. Patients with CTP class B achieved SVR12 rates of 85% (22/26) and 88% (23/26) when treated for 12 weeks and 24 weeks, respectively. Patients with CTP class C achieved SVR12 rates of 60%

(3/5) and 75% (3/4) when treated for 12 weeks and 24 weeks, respectively. Six patients with fibrosing cholestatic hepatitis (FCH), of which 4 were treated for 12 weeks and 2 for 24 weeks, had a SVR12 rate of 100%. There was a high incidence of adverse events, likely owing to many patients having advanced liver disease. Twenty-three percent of patients experienced serious adverse events, most associated with hepatic decompensation. Thirteen patients discontinued treatment prematurely secondary to adverse events. Furthermore, 13 patients died, although the authors concluded that none were related to treatment. Tacrolimus was used for immunosuppression in 76% of the study population. Only 1 patient experienced significantly altered immunosuppressive levels secondary to drug interactions. This patient had increased cyclosporine concentrations, although the authors noted that this may be secondary to improved organ function. Twenty-four other patients required adjustments to immunosuppressive medications that the authors attributed to improvement in hepatic function after viral clearance.

Sofosbuvir and Simeprevir

Sofosbuvir and simeprevir (Olysio, Janssen) is another drug combination that has been evaluated in the post-LT setting.²⁷ Saab and colleagues conducted a single-center retrospective study evaluating sofosbuvir and simeprevir in the post-LT setting in patients with genotype 1 HCV infection. Of the 30 patients included in the study, 28 underwent biopsies; 13 patients (46%) presented with METAVIR stage F0, 2 (7%) with stage F1, 2 (7%) with stage F2, 6 (21%) with stage F3, and 5 (18%) with stage F4. There was a mean time of 71 (± 77.1) months from LT to treatment. Fifty-nine percent of patients (17/27) had undetectable viral loads 4 weeks into treatment. By the end of the treatment period, 100% of patients (30/30) had an undetectable viral load. The SVR12 rate was 93% (28/30). All patients tolerated treatment well, with none requiring growth factors of blood products. Tacrolimus-based immunosuppression was used in 22 patients (73%), whereas a cyclosporine-based regimen was used in 8 patients (27%). Tacrolimus dosing was adjusted in 10 patients with no interruptions in immunosuppressant therapy.

Pungpapong and colleagues conducted a multicenter study evaluating sofosbuvir and simeprevir with and without ribavirin in post-LT patients.²⁸ A total of 123 patients were enrolled, of which 98 received sofosbuvir and simeprevir and 25 also received ribavirin. Treatment was initiated at a median duration of 32 months from LT, and treatment duration was 12 weeks. The SVR12 rates were 90% and 91% in patients receiving sofosbuvir and simeprevir alone and with the addition of ribavirin, respectively; the difference was not statistically significant ($P=1.0$). Patients with advanced fibrosis (METAVIR stage

F3-4) achieved a SVR12 rate of 81% as compared with patients with early fibrosis (stage F0-2), who achieved a SVR12 rate of 93%, which is a statistically significant difference ($P=.05$). Genotype subgroup analysis showed that fibrosis was only a factor for reduced SVR rates in patients with genotype 1a HCV. Patients with genotype 1a and advanced fibrosis achieved a SVR12 rate of 71% as compared with 91% in patients with early-stage fibrosis. Patients with genotype 1b and advanced fibrosis achieved a SVR12 rate of 92%, compared with patients with early fibrosis, who achieved a SVR12 rate of 96%, which was not statistically significant. There was a statistically significant difference ($P=.03$) in SVR12 rates when comparing patients who achieved undetectable viral loads at 4 weeks on treatment (96%) as compared with those who did not (83%). Overall, the treatment regimen was well tolerated with only mild adverse events. Anemia was much more common in patients who received ribavirin than those who did not (75% and 5%, respectively). One death occurred secondary to drug-induced lung injury.

In a single-center retrospective analysis, Gutierrez and colleagues found sofosbuvir and simeprevir effective in the treatment of HCV recurrence in the post-LT setting.²⁹ Sixty-one patients with HCV genotype 1 infection (57% with genotype 1a and 43% with genotype 1b), with a median time of 5.4 years from LT, were treated for 12 weeks. Ribavirin was added in 3 patients. The SVR12 rate was 93.4%. This study also found that patients with HCV genotype 1a and advanced fibrosis (METAVIR stage F3-4) had a statistically significant difference in SVR12 rates compared with patients with minimal fibrosis (stage F0-2; 67% vs 100%; $P=.01$). Patients with genotype 1b achieved a SVR12 rate of 100% regardless of fibrosis severity. No severe adverse events were documented in this study. Most patients, 61%, received tacrolimus-based immunosuppressive therapy, and dose adjustments were required in 26% of patients during treatment and 7% after treatment was discontinued. Only 5% of patients received cyclosporine; thus, the authors were not able to make any conclusions about drug-drug interactions between cyclosporine and simeprevir. No dose adjustments were needed for the patients receiving cyclosporine or sirolimus.

The aforementioned ongoing study by Brown and colleagues also evaluated the use of sofosbuvir and simeprevir with and without ribavirin.²⁵ Patients who were treated with sofosbuvir and simeprevir with or without ribavirin achieved a SVR4 rate of 90% (61/68). Analysis of patients with genotype 1 revealed a SVR4 rate of 87% (48/55). Adverse events were more numerous in the group treated with ribavirin, with 91.7% of patients experiencing an adverse event as compared with 77.0% of the nonribavirin arm. The most common adverse events in the ribavirin group were anemia (9%), headache (7%),

and fatigue (5%). There were 5 serious side effects. In the nonribavirin group, the most common adverse events were fatigue (25%), headache (16%), and infection (16%). There were 8 serious side effects. Two patients died owing to renal/hepatic failure and aspiration pneumonia.

Sofosbuvir and Daclatasvir

An ongoing prospective multicenter study in France evaluating the efficacy of sofosbuvir and daclatasvir (Daklinza, Bristol-Myers Squibb) with or without ribavirin has found high SVR rates in post-LT patients with aggressive recurrent HCV infection.³⁰ The authors have reported data on 130 LT patients who underwent treatment for 12 or 24 weeks. The mean time period between LT and treatment was 74.2 (\pm 73.5) months. Eleven patients received sofosbuvir and daclatasvir without ribavirin for 12 weeks and had a response rate of 100% at the end of treatment as well as a SVR12 rate of 100%. Sixty-four patients underwent this same regimen for 24 weeks and had a response rate of 100% at the end of treatment and a SVR12 rate of 97%. Three patients received sofosbuvir and daclatasvir with ribavirin for 12 weeks; the end-of-treatment response rate was 67%, with a SVR12 rate of 67%. Fifty-two patients underwent the same regimen for 24 weeks and achieved an end-of-treatment response rate of 98% and a SVR12 rate of 96%. The authors concluded that ribavirin did not have a statistically significant influence on SVR and that further prognostic factors needed to be defined. Thirty patients were reported to have experienced severe side effects, with the most common being hematologic toxicity. Two patients died, 1 from diabetic coma and the other from HCV recurrence at 6 weeks posttreatment. Tacrolimus dosing was adjusted in 56% of patients, cyclosporine in 49% of patients, and everolimus in 38% of patients. Leroy and colleagues performed a further subgroup analysis on the same cohort of patients to assess the efficacy of sofosbuvir and daclatasvir on 23 post-LT patients with decompensated FCH.³¹ The regimens studied were sofosbuvir and ribavirin with or without pegylated interferon or sofosbuvir and daclatasvir with or without ribavirin. The duration of treatment was 24 weeks; however, treatment was extended to 48 weeks for 1 patient and 36 to 48 weeks for 3 patients. Patients in the sofosbuvir, ribavirin, and pegylated interferon group achieved a SVR12 rate of 88%, while patients in the sofosbuvir, daclatasvir, and ribavirin group achieved a SVR12 rate of 100%.

A smaller trial evaluated the compassionate use of sofosbuvir and daclatasvir in 12 post-LT patients with severe recurrent HCV infection.³² The mean time from LT to the initiation of treatment was 20 (\pm 17) months. Six patients received ribavirin in addition to DAA agents. Three patients died within the first 12 weeks of treatment.

Of the 9 patients who completed the 24-week course of treatment, 5 received ribavirin. All 9 patients achieved an undetectable viral load at the completion of treatment. The authors published posttreatment virologic data for 5 patients, 2 of whom achieved SVR8 (40%) and 3 SVR4 (60%). No recurrence has yet been reported. No adverse events attributable to study medications were observed, and no modifications to immunosuppressant medications were reported.

A multicenter open-label phase 3 trial evaluated the use of sofosbuvir, daclatasvir, and ribavirin in post-LT patients.³³ Fifty-three patients were enrolled; all were at a minimum of 3 months posttransplant and had no evidence of rejection at the time of enrollment. The treatment duration was 12 weeks. The SVR12 rate was 94% (50/53). Subgroup analysis of patients with genotype 1 infection revealed a SVR12 rate of 95% (39/41). A total of 3 patients relapsed. The most common side effects were headache (19%), fatigue (15%), and anemia (10%). Five patients experienced serious side effects that the authors concluded were not related to study medications. One patient had to discontinue all medications due to adverse events, and 4 patients discontinued ribavirin alone. There were no required dose adjustments of immunosuppressant medications.

Ombitasvir, Paritaprevir With Ritonavir, and Dasabuvir

Kwo and colleagues evaluated 34 LT patients with genotype 1 infection and mild fibrosis (METAVIR stage F0-2) treated with ombitasvir, paritaprevir with ritonavir, and dasabuvir (Viekira Pak, AbbVie; also referred to as the 3D regimen) along with ribavirin for 24 weeks.³⁴ Patients with advanced fibrosis, liver retransplantation, or coinfection with hepatitis B virus or HIV were excluded. The SVR12 rate was 97% (33/34), with these patients remaining virus-free at 24 weeks posttreatment. The most common adverse events were fatigue (17%), headache (15%), and cough (11%). Anemia occurred in 10% of patients, with 5 patients requiring erythropoietin. However, none of the patients required blood transfusions. Only 1 patient discontinued treatment due to adverse events; the patient developed a rash, memory impairment, and anxiety. Immunosuppression was achieved using tacrolimus in 29 patients (85%), while cyclosporine was used in 5 patients (15%). Of the 29 patients who received tacrolimus, 5 were found to have elevated tacrolimus levels. One of these patients developed a mild rash, while the other 4 patients remained asymptomatic. Dosing was based on serum levels, with the majority of patients receiving tacrolimus in doses of 0.5 mg and 0.2 mg at a median frequency of 10 and 5 days, respectively. Eight patients experienced tacrolimus levels below therapeutic range after the completion of treatment, although tacrolimus levels were restored to therapeutic range in all patients

Table 1. Major Trials Evaluating Direct-Acting Antiviral Agents in the Treatment of Post-Liver Transplant HCV Recurrence

Study	Genotype, n (%)	Severity of liver disease, n (%)	Treatment	Duration	SVR12 by Genotype, n (%)	SVR12 by Severity, n (%)
Charlton ^{23,a}	1a: 22 (55) 1b: 11 (28) 3: 6 (15) 4: 1 (3)	F0: 1 (3) F1-2: 14 (35) F3: 9 (23) F4: 16 (40)	Sofosbuvir + ribavirin	24 weeks	1a: 16 (73) 1b: 6 (55) 3: 6 (100)	F0: 1 (100) F1-2: 10 (71) F3: 7 (78) F4: 10 (63)
Forns ^{24,a}	1a: 36 (35) 1b: 49 (47) 2: 1 (1) 3: 7 (7) 4: 7 (7) Multiple: 4 (4)	All patients had either aggressive recurrent disease or cirrhosis	Sofosbuvir + ribavirin	24-48 weeks	N/A	Early recurrence: 35 (73) Cirrhosis: 19 (43)
Charlton ^{26,b}	1a: 164 (72) 1b: 63 (28) 4: 2 (1)	No cirrhosis: 111 (48) CTP A: 51 (22) CTP B: 52 (23) CTP C: 9 (4) FCH: 6 (3)	Sofosbuvir + ledipasvir + ribavirin	12 weeks	N/A	No cirrhosis: 53 (96) CTP A: 25 (96) CTP B: 22 (85) CTP C: 3 (60) FCH: 4 (100)
				24 weeks	N/A	No cirrhosis: 55 (98) CTP A: 24 (96) CTP B: 23 (88) CTP C: 3 (75) FCH: 2 (100)
Saab ^{27,a}	1: all patients	F0: 13 (46) F1: 2 (7) F2: 2 (8) F3: 6 (23) F4: 5 (19)	Sofosbuvir + simeprevir	12 weeks	N/A	Overall SVR12: 28 (93)
Pungpapong ^{28,a}	1a: 74 (60) 1b: 43 (35) Unclear: 6 (5)	F0-2: 85 (70) F3-4: 37 (30)	Sofosbuvir + simeprevir ± ribavirin	12 weeks	1a: 64 (86) 1b: 41 (95)	F0-2: 67 (81) F3-4: 34 (93)
Gutierrez ^{29,a}	1a: 35 (57) 1b: 26 (43)	F0-2: 38 (62) F3-4: 23 (38)	Sofosbuvir + simeprevir ± ribavirin	12 weeks	1a: 31 (89) 1b: 26 (100)	F0-2: 38 (100) F3-4: 19 (83)
Kwo ^{34,b}	1a: 29 (85) 1b: 5 (15)	F0: 6 (18) F1: 13 (38) F2: 15 (44)	Ombitasvir + paritaprevir with ritonavir + dasabuvir	24 weeks	1a: 28 (97) 1b: 5 (100)	N/A
Poordad ^{33,c}	1a: 31 (58) 1b: 10 (19) 3: 11 (21) 6: 1 (2)	F0-2: 23 (43) F3: 13 (25) F4: 16 (30) Not reported: 1 (2)	Sofosbuvir + daclatasvir + ribavirin	12 weeks	1a: 30 (97) 1b: 9 (90) 3: 10 (91) 6: 1 (100)	N/A

CTP, Child-Turcotte-Pugh; FCH, fibrosing cholestatic hepatitis; HCV, hepatitis C virus; SVR, sustained virologic response.

^aReal-life cohort. ^bPhase 2 trial. ^cPhase 3 trial.

with no incidence of graft rejection. Tacrolimus did not alter trough levels of treatment medications.

Grazoprevir and Elbasvir

Recent data from an open-label phase 2 study of grazoprevir and elbasvir (Merck) for the treatment of post-LT patients with cirrhosis showed excellent SVR rates.³⁵

Cirrhotic patients achieved a SVR12 rate of 90%, and noncirrhotic patients achieved a SVR12 rate of 100%. The most frequent side effect was fatigue. Cirrhotic and noncirrhotic patients experienced a similar frequency of adverse events. No patients discontinued therapy due to adverse events. The authors noted that grazoprevir and elbasvir in combination are known to have in vitro

Table 2. Effect of Direct-Acting Antiviral Agents on the Levels of Commonly Used Immunosuppressants

Direct-Acting Antiviral Agent(s)	Cyclosporine	Tacrolimus	Mycophenolate
Daclatasvir	No change in level	No change in level	No change in level
Ledipasvir	No change in level	No change in level	No change in level
Simeprevir	Contraindicated	No change in level	No change in level
Sofosbuvir	No change in level	No change in level	No change in level
3D	Increased levels	Increased levels	Increased levels

3D, combination of ombitasvir, paritaprevir with ritonavir, and dasabuvir.

activity against resistance-associated variants (RAVs) that arise from exposure to first-generation HCV drugs that target the nonstructural (NS) 3 protein, similar to grazoprevir monotherapy. Of the 2 patients who experienced virologic relapse, only NS5A RAVs were noted at baseline. No correlation was seen between the presence of baseline NS3 or NS5A RAVs and SVR12 in this study. According to recent data presented by Kwo and colleagues, although 50% of non-LT patients had RAVs to grazoprevir, their SVR12 rates were not affected.³⁶ However, a decreased SVR12 rate was noted in patients with high-level NS5A RAVs (52%) as compared with patients with no or low-level NS5A RAVs (99%-100%).³⁶

Analysis

The current literature supports the use of DAA agents in the setting of HCV recurrence post-LT. SVR12 rates greater than 90% were consistently achieved in patients with compensated cirrhosis. However, some studies have shown decreased SVR rates in patients with severe liver disease. This was particularly notable in patients with genotype 1a infection.^{28,29} Data are currently limited on further genotype-specific response rates in LT patients; however, it is clear from the current data that both genotype and liver disease severity not only affect response rates individually but also have confounding effects (Table 1). Furthermore, predictors of failure may differ between regimens. For example, hypoalbuminemia predicted failure using sofosbuvir and daclatasvir in pretransplant patients with decompensated liver cirrhosis.³⁵ There may also be patient relapse from RAVs that will likely impact the effectiveness of possible future therapies.³⁶⁻⁴² Treatment duration and the addition of ribavirin are additional factors that have to be further evaluated. Some studies have shown that there may be a benefit in treating patients for a longer course and adding ribavirin in patients with more advanced liver disease.²⁶ The time from transplant to treatment initiation may also play a role; perhaps patients benefit from being treated earlier.²⁴

There are limited data on HCV treatment in LT recipients who have FCH or are coinfecting with HIV. There is a range of SVR in LT recipients. One of the

potential reasons for this variability in SVR is the timing of treatment initiation. Leroy and colleagues described promising response rates in recipients with FCH who were treated with sofosbuvir and ribavirin (SVR12 rate of 88%) as well as those treated with sofosbuvir and daclatasvir (SVR12 rate of 100%).³¹ Patients with FCH who received sofosbuvir and ribavirin had a SVR rate of 80%, according to a study by Fornis and colleagues.²⁴ Saab and colleagues recently conducted a matched analysis of 10 LT recipients with FCH compared with post-LT patients without FCH who were treated with sofosbuvir and ribavirin.³⁷ The SVR12 rate in the FCH cohort was 40% compared with 80% in the non-FCH cohort. The graft survival rates were 80% and 100% in FCH and non-FCH cohorts, respectively. Overall, patient survival was 90% in the FCH cohort and 100% in the non-FCH cohort. The treatment of HIV-coinfecting patients with interferon-free DAA agents has not been fully evaluated in the LT setting. However, the SVR is not believed to be substantially lower in coinfecting LT recipients than in HCV-monoinfecting LT recipients because no dramatic differences have been demonstrated in the nontransplant setting. However, there are concerns and precautions required for potential drug interactions with HIV medications.³⁸

There are a number of unanswered questions regarding treatment for LT recipients. The ideal time to start DAA agents has been investigated in several studies, some of which demonstrate the safety and efficacy of starting DAA agents immediately after LT in patients with aggressive recurrent HCV.^{24,31,37} When the decision to start DAA treatment is elective, the preferred time may be at least 3 to 6 months after LT, at which point readmission and surgical issues that may impact medication drug adherence are less likely. Other studies have evaluated the role of ribavirin. Currently, studies on the 3D regimen and sofosbuvir/ledipasvir have included the use of ribavirin. The effect of these regimens without ribavirin is unknown; additional studies excluding the use of ribavirin are needed, given its poor tolerability in the LT setting.

Overall, the adverse events with DAA agents are mild. Patients with advanced liver disease tend to experience more severe adverse events than patients with minimal disease, partially due to being more ill in general.^{24,26}

This is further compounded by the fact that patients with advanced disease often receive ribavirin in addition to DAA agents. Ribavirin use has consistently been shown to increase adverse events when compared with the use of DAA agents alone. However, the side-effect profile is much improved in comparison with interferon.

Drug-drug interactions with immunosuppressive therapies have been noted in several studies and often required dosage adjustments (Table 2).⁴³ Although the understanding of drug-drug interactions is still incomplete, known interactions have been cataloged and should be considered prior to initiating therapy.⁴³ For example, the use of simeprevir in patients on cyclosporine is contraindicated, as concomitant use has been shown to significantly increase simeprevir concentrations. Several potential interactions that require close monitoring of drug serum levels have also been described. Simeprevir use with tacrolimus has been shown to increase simeprevir concentrations and decrease tacrolimus concentrations. Ledipasvir use with cyclosporine may increase concentrations of both drugs, as both are substrates of P-glycoprotein, which ledipasvir inhibits. Use of ombitasvir, paritaprevir with ritonavir, and dasabuvir has been shown to increase serum tacrolimus levels, and dose modification of tacrolimus is recommended. Sofosbuvir use has not shown any clinically significant interactions with either tacrolimus or cyclosporine. Further study will be required to better qualify these interactions.

There are several limitations of the current available data. Studies evaluating the treatment of patients with advanced liver disease often exclude patients with renal insufficiency; thus, these data may not be generalizable to all patients in clinical practice. Furthermore, only short-term data on DAA use is currently available. It is unclear whether results seen with DAA agents will be sustained. Longitudinal studies will be needed to evaluate patients after achieving SVR to ascertain if clinical outcomes are improved.

Conclusion

Noninterferon-based therapies with oral DAA agents have revolutionized the treatment of HCV recurrence posttransplant. These regimens have consistently demonstrated high SVR rates, shorter treatment courses, and a more favorable side effect profile than interferon-based therapies. Although DAA agents are effective even in advanced liver disease, SVR rates seem diminished when compared with patients with minimal liver disease. The role of ribavirin is still not completely understood, although several studies have shown no benefit with ribavirin in certain cases. Further evaluation of drug-drug interactions with calcineurin inhibitors will be needed as DAA use becomes more common.

Dr Saab is a member of the speakers bureau and serves as a consultant for AbbVie, Gilead, BMS, and Merck. The other authors have no relevant conflicts of interest to disclose.

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