

Management of hepatitis C in the pre- and post-transplant setting: then and now

Abstract

The prevalence and accelerated course of recurrent hepatitis C infection after liver transplantation is associated with significant morbidity and mortality. Use of dual therapy with interferon/ribavirin or triple therapy with first-generation NS3/4 protease inhibitors for the treatment of hepatitis C in cirrhotic and post-transplant patients has yielded only modest sustained virologic response (SVR) rates. The advent of multiple new direct-acting antiviral agents has led to improved treatment outcomes in patients with chronic hepatitis C; all while minimizing undesired side effects and adverse reactions. This review describes the treatment of hepatitis C in cirrhotic patients awaiting transplantation and in patients with recurrent HCV after transplantation and the role of new all-oral therapy in both of these patient populations.

Keywords: recurrent hepatitis C, liver transplantation, interferon-free regimen, direct-acting antiviral agents

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George F Protopapas, Kiran V Rao, Nikolaos Pyrsopoulos

Division of Gastroenterology and Hepatology, New Jersey Medical School, USA

Correspondence: Nikolaos Pyrsopoulos, Division of Gastroenterology and Hepatology, New Jersey Medical School, Room H 538, 185 South Orange Avenue, Newark, NJ 07103, USA, Tel 973-972-5252, Email pyrsopni@njms.rutgers.edu

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Abbreviations: HCV, hepatitis C virus; OLT, orthotopic liver transplantation; IFN/RBV, Interferon/Ribavirin; PIs, protease inhibitors; PEG-IFN, pegylated interferon; IDSA, infectious diseases society of America; AASLD, American Association for the Study of Liver Diseases; CUPIC, compassionate use of protease inhibitors in viral C cirrhosis; HCC, hepatocellular carcinoma

Introduction

Recurrent hepatitis C virus (HCV) infection after liver transplantation is the most frequent cause of death and graft and represents two-thirds of graft failures.¹ The recurrence of hepatitis C virus in a patient after liver transplant is associated with significant morbidity. It is estimated that at one year after orthotopic liver transplantation (OLT), more than 50% of patients with a history of hepatitis C prior to transplant will show histological evidence of HCV recurrence.² Of particular significance is the accelerated course of HCV recurrence in this setting.³ Recurrence of HCV infections in the graft has been seen as early as four weeks after liver transplantation. It is estimated that 10% to 40% of patients will progress to cirrhosis within 5-10 years of transplant.^{4,5} Previous studies have shown that HCV genotype 1b-infected liver recipients are at a high risk of developing graft cirrhosis in the first 5 years after transplantation, especially those with previous rejection episodes.⁶ Certain factors have been proposed to be associated with an accelerated progression of fibrosis in patients with recurrent HCV infection, resulting in graft loss.⁷ High HCV RNA levels in both serum and the graft at the time of or early after transplantation are associated with an increased risk of progression to cirrhosis, graft loss and death.⁸ Other factors associated with poorer outcomes include female gender, older donor age, steatosis of the graft, the degree of HLA matching, and the IFN λ 3 of the donor and the recipient.^{9,10} Furthermore, rates of decompensation in patients with graft cirrhosis are particularly high, at approximately 42% at 12 months, further adding to morbidity.¹¹

The impact of preservation injury on the severity of recurrent hepatitis C after OLT has also been evaluated. A review of patients undergoing OLT for hepatitis C infection showed that the duration of ischemic rewarming during graft implantation was significantly

associated with the severity of recurrent hepatitis C.¹² In their study, cold ischemia time did not correlate with the severity of hepatitis C. In the post-transplant setting, use of intravenous steroids for management of acute allograft rejection has been associated with an earlier recurrence of hepatitis.¹³ The type of calcineurin inhibitor used in the post-OLT setting and its effects on progression of fibrosis has also been assessed. Several prospective studies have concluded that there is no difference in incidence of advanced fibrosis with use of cyclosporine versus tacrolimus-based immunosuppressive regimens.¹⁴⁻¹⁶ A retrospective review of 141 patients undergoing OLT for hepatitis C cirrhosis looked at the effect of sirolimus-based immunosuppressive regimens on post-transplant HCV recurrence in these patients.¹⁷ Of note, sirolimus did not significantly affect the timing or severity of HCV recurrence and in fact, sirolimus-treated patients had lower progressive activity and fibrosis level on serial biopsy. The effect of OKT3 on hepatitis C recurrence has been well-documented. Cohort studies have shown earlier and more severe allograft hepatitis in patients receiving OKT3, with patients exhibiting greater histological severity scores.¹⁸ Although obtaining an SVR in patients with HCV recurrence in the post-transplant setting can greatly improve overall survival, this has only been reported in approximately one-third of patients (20-30 % in genotype 1 and 40-50 % in genotype 3) [19]. Up until recently, dual therapy with interferon/ribavirin (IFN/RBV) or triple therapy with first-generation NS3/4 protease inhibitors (PIs) were considered the most potent options available to these patients. Recently, multiple, new direct-acting antiviral agents have entered the hepatitis C arena. This review describes the treatment of HCV in cirrhotic patients awaiting transplantation and recurrent HCV after transplantation and the role of new all-oral therapy in both of these patient populations.

Treating hepatitis C in the pre-transplant period

The current approach to the management of chronic HCV-infected patients undergoing transplantation includes pre-transplant antiviral therapy given in an attempt of preventing reinfection. Simply decreasing the HCV viral load prior to transplantation may not be enough to alter the course of HCV recurrence in the post-

transplant setting [20]. Viral undetectability and achieving an SVR prior to transplantation has been shown to eliminate the risk of HCV recurrence [21]. Thus, it has been the primary goal in this particular setting.

The use of traditional agents in the pre-transplant period

Until 2011, dual therapy with pegylated interferon (PEG-IFN) and ribavirin (RBV) was the standard of care. The limitations of this therapy were that treatment was restricted to patients with compensated cirrhosis, given serious complications associated with treatment of decompensated cirrhotic patients. Despite the improvement after dual therapy, the SVR was lower in patients with compensated cirrhosis (43%-50%) than in patients without cirrhosis (57%-65%), with genotype 1 patients faring rather poorly with an SVR of 11%.²²

Two well-known trials looking at dual therapy (IFN/RBV) for patients with HCV cirrhosis were by Everson and Forns. Everson treated 124 decompensated cirrhotic patients with a mean MELD of 11, with IFN/RBV as part of the LADR regimen (low-accelerating dose regimen).²³ Similar to prior studies, patients with HCV genotype 1 had worse SVR rates (24% in genotype 1 versus 50% in patients with genotypes 2/3). Fifty-seven patients were HCV RNA negative at the end of treatment with 27 patients achieving an SVR. Thirty patients recurred for a relapse rate of 53%. In another study, Forns treated 30 patients for a median of 12 weeks of IFN/RBV. SVR only occurred in 30% of patients and two-thirds of that subset being free of HCV recurrence in the post-transplant period. This further solidifies the notion that viral undetectability is key. Dose reductions were required in 60% and 20% stopped their therapy prematurely.²⁴

In this population, adverse reactions reduced adherence to therapy and resulted in dose modifications that resulted in less response. Dose reductions were required in more than half of patients that were treated. This belabors the point of interferon-related adverse reactions. These typically include bone marrow depression, flu-like symptoms, neuropsychiatric disorders, and autoimmune syndromes among others. The major issues that patients on ribavirin encounter are hemolytic anemia and rash. Because of the side effects, 10-20% withdraws from therapy prematurely and upwards of 20-30% of patients have required dose modifications.²⁵ Treatment-related decompensation is also a serious concern and has made providers gun-shy in proceeding with treatment. Table 1 refers to some of the most common adverse reactions associated with use of PEG-IFN and ribavirin.

Table 1 Common adverse reactions associated with use of peg-IFN and Ribavirin

| Adverse reactions | Incidence |
|-------------------|-----------|
| Anemia | 20-30% |
| Headaches | 47-62% |
| Fevers | 40-46% |
| Myalgias | 37-56% |
| Rigors | 24-48% |
| Arthralgias | 24-34% |
| Nausea | 35-43% |
| Depression | 22-31% |
| Weight Loss | 29% |

Table continued...

| Adverse reactions | Incidence |
|-----------------------------|-----------|
| Insomnia | 33-40% |
| Alopecia | 21-36% |
| Rash/dermatitis | 20-24% |
| Injection site inflammation | 25% |
| Pruritus | 25-29% |
| Dyspnea | 26% |
| Fatigue | 48-64% |

Two first-generation protease inhibitors (PI), boceprevir and telaprevir, were FDA-approved in 2011 for patients infected with HCV genotype 1 in treatment naïve, non-responders and relapsers. But in December 2012, a black box warning was placed on telaprevir in that some rashes may lead to death.²⁶ Boceprevir and telaprevir were each paired up with IFN/RBV as part of a triple regimen and results have seemed promising in the registration trials, as SVRs increased by 30 % with triple therapy compared to PEG-IFN/RBV in treatment-naïve patients and by 25-60% in treatment-experienced genotype 1 patients.²⁷⁻³⁰ However, such results came a significant cost, as new issues once again surfaced. A two-fold increase in anemia was seen as well as the emergence of new adverse reactions. Dysgeusia was observed in nearly one-third of patients on boceprevir and a cutaneous rash in 55% of patients on telaprevir.^{27,28} In patients with advanced fibrosis and cirrhosis, the triple regimen was a step up from the dual regimen, as this was an additional option that increased SVR in comparison to IFN/RBV regimens in genotype 1 patients with compensated cirrhosis. However, limitations included: (1) patients required careful monitoring, (2) previous non-responders would likely not benefit and (3) triple therapy would not be recommended in patients with decompensated cirrhosis.³¹

Crippin's observations in a pilot study of antiviral therapy in HCV infected patients awaiting liver transplantation noted that more than half of the patients awaiting liver transplantation had one or more contraindications to treatment with interferon with or without ribavirin.³² The study also observed a high incidence of adverse events in patients with decompensated cirrhosis during treatment with antiviral therapy, thus concluding that anti-viral therapy is poorly tolerated in this population.

Another study looking at the tolerability and safety of antivirals and the first generation protease inhibitors was the CUPIC (Compassionate Use of Protease Inhibitors in viral C cirrhosis) cohort study which looked at treatment-experienced cirrhotic patients with genotype 1.³³ In the intent to treat analysis, in the 292 patients treated with telaprevir, RNA was undetectable in 55.1%, 80.5%, 78.8%, and 67.1% at weeks 4, 8, 12, and 16. In the 42 patients treated with a lead-in phase, 9.5%, 76.2%, 71.4% and 59.5% were undetectable. In the 250 patients treated without a lead-in phase, 62.8%, 81.6%, 80.0%, and 68.4% had a response rate. At week 16, the response rate was significantly higher in relapsers (74%) than in partial responders (66.2%) and in null responders (45%). In patients treated with boceprevir, 2.4%, 37.6%, 54.6% and 58% showed response at 4, 8, 12 and 16 weeks. At week 16, response rate was significantly higher in relapsers (69.0%) than in partial responders (50.0%) and in null responders (22.2%).³³

The safety profile was noted to be poor, with severe infection and hepatic decompensation in approximately 6% of patients. The CUPIC study suggested that treatment-experienced patients with compensated cirrhosis with platelet counts < 100,000/mm³ and serum albumin < 35 g/L may not benefit from triple therapy regimens.³³

The current wave of treatment in the pre-transplant period

The current wave of NS3/4A protease inhibitors and NS5B polymerase inhibitors have seen several advantages over the first generation PI's. They include a higher barrier to resistance, better effectiveness with pan-genotypic activity, more convenient dosing, reduced pill burden, and better safety and tolerability.³⁴⁻³⁶ In a large phase 2b study of 462 total patients, 83 treatment-experienced genotype 1 patients with cirrhosis were treated with simeprevir (TMC435) 100 or 150 mg QD with PEG-IFN/RBV for 12, 24 or 48 weeks, followed by PEG-IFN/RBV until week 48 if needed vs PEG-IFN/RBV for 48 weeks.³⁷ SVR24 was noted to be higher in the simeprevir regimen than with PEG-IFN/RBV. The SVR rate in patients with cirrhosis was reported to be 70-73% in patients with relapse, 15-82% in partial responders and 31-46% in non-responders.

Phase 3 data from QUEST 1 and QUEST 2 illustrated that simeprevir in combination with IFN/RBV, led to SVR12 rates of approximately 60% in HCV patients with METAVIR scores of F4.^{38,39} In phase 3 data from the PROMISE study of patients who had previously experienced a relapse after prior treatment with IFN based therapy achieved a SVR 12 in 74% of patients with a METAVIR score of F4.⁴⁰

In the NEUTRINO trial, NS5B pyrimidine nucleotide analogue, sofosbuvir 400 mg daily plus IFN/RVB was used for 12 weeks in 327 treatment-naïve patients with genotypes 1, 4, 5 or 6. Of these patients 17% had cirrhosis with a robust 81% response rate noted in the genotype 1 patients with cirrhosis. In the FISSION trial, sofosbuvir 400 mg daily plus RBV was used for 12 weeks in genotype 2 and 3 patients.⁴¹ Twenty percent of the 256 patients that underwent this treatment had cirrhosis. The response rate was noted to be lower in genotype 3 than in those with genotype 2 (56% vs 97% respectively) and were lower for patients with cirrhosis than for those without cirrhosis (47% vs 72 %). This highlights the continued difficulty in treating this population of patients.

As illustrated above, sofosbuvir has proven to have potent antiviral activity across all HCV genotypes. An open-label phase 2 study (2025) enrolled 61 compensated cirrhotic patients who were listed for transplantation due to hepatocellular carcinoma (HCC). Seventy-three percent of the patients were genotype 1.³⁷ Patients received sofosbuvir 400 mg daily plus weight-based ribavirin 1,000-1,200 mg daily for a duration of 48 weeks, with the last dose given on day of transplant and the standard immunosuppressive medication used post-transplant.⁴² Ninety-three percent of patients had an undetectable viral load at the time of transplantation, irrespective of the duration of the treatment. In those patients with an undetectable viral load at time of transplant, two-thirds of patients maintained viral suppression at 12-weeks post-transplant. A multivariate analysis showed that duration of viral undetectability was the only factor to significantly predict SVR and no HCV recurrence.⁴²

The LONESTAR study looked at 40 patients of which about half with cirrhosis who were not able to achieve a cure with the standard of care at that time, triple therapy (PI + PEG IFN/RBV). These patients were treated with sofosbuvir 400 mg and ledipasvir 90 mg daily with or without RBV for 12 weeks. The SVR12 was 91 % in the cirrhotic patients. This proves that for a large portion of patients that RBV can be removed without affecting the SVR.⁴³

In the meantime, recent AASLD guidelines state that treatment-naïve patients with compensated cirrhosis, including those with

HCC, should receive the same treatment as recommended for patients without cirrhosis. This regimen consists of daily sofosbuvir, 400mg plus weight-based RBV for up to 48 weeks.⁴⁴ This was supported by Curry in his reporting that 93% of patients having undetectable RNA at the time of transplantation with two-thirds maintaining viral suppressions at 12 weeks post-transplantation.⁴² Figure 1 summarizes the effect of various treatment regimens on SVR rates in patients with hepatitis C and advanced fibrosis.

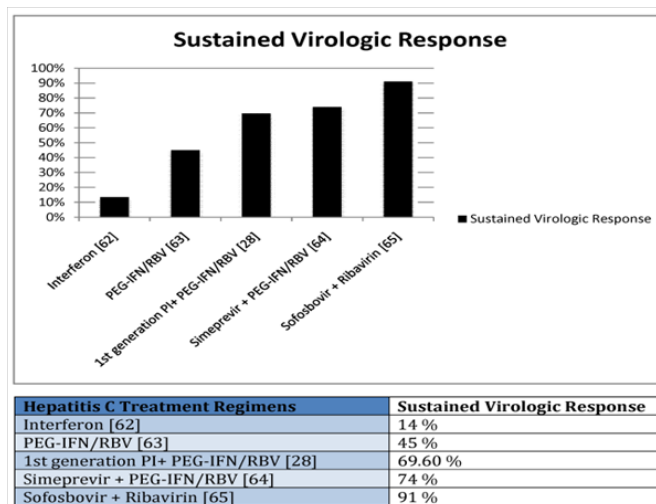


Figure 1

Traditional approaches to HCV management in the post-transplant setting

Obtaining a sustained virological response has been the primary goal in liver transplant recipients with recurrent hepatitis C, as this can greatly improve graft survival.¹⁹ Unfortunately, achieving an SVR in this subset of patients is especially difficult. In the past, there have been two general approaches to treatment in the post-transplant setting: (1) a prophylactic treatment approach and (2) initiation of treatment after documentation of HCV recurrence and associated graft fibrosis. The PHOENIX study group sought to evaluate the prophylactic approach with 115 liver transplant recipients with HCV being randomized to peginterferon/ribavirin versus observation.⁴⁵ Significant HCV recurrence at 120 weeks, graft survival rates, and biopsy-proven acute cellular rejection were similar in the two groups, with anemia being the most common adverse event leading to treatment withdrawal.

A small prospective study of 47 liver transplant patients with recurrent hepatitis C were treated with 12 months of PEG-IFN and ribavirin.⁴² An SVR of only 23% was achieved in this study, highlighting the well-known difficulties in treating these patients. The authors note the predominance of genotype 1b patients (93%), as well as the decision to initiate treatment only when a clear evidence of chronic hepatitis was identified on liver biopsy. Once stage 1 or 2 fibrosis has been identified on liver biopsy, the antiviral regimen for HCV recurrence in OLT patients has generally consisted of pegylated interferon (IFN) and ribavirin.⁴³ Improvement in hepatic inflammation and fibrosis has been associated with a durable SVR.⁴⁴ Logistic regression analysis as part of a retrospective review of 99 OLT patients treated with IFN/ribavirin for HCV recurrence identified the following three variables as being predictors of SVR: donor age <60 years, viral genotype other than 1, and the use of cyclosporine as the immunosuppressive agent during treatment.⁴⁵⁻⁴⁹

Triple therapy with a first-generation protease inhibitor for the treatment of recurrent hepatitis C in the post-OLT patient has had relative success when compared to traditional dual therapy.⁵⁰ A cohort of 37 OLT patients with recurrent HCV, genotype I, were treated with triple therapy with either telaprevir or boceprevir, with end of treatment responses of 40% and 72% respectively.⁵¹ The most common adverse event in the study was anemia (92%), highlighting again one of the limitations of a ribavirin-based regimen. The inherent risk of infection in the immunocompromised OLT patient as well as drug-drug interactions made implementation of such triple regimens especially difficult. Premature discontinuation of triple therapy for HCV recurrence in the post-OLT setting has been as high as 20%, despite fairly decent SVR12 rates.⁵² The CRUSH-C multicenter study was undertaken to evaluate protease inhibitor-based triple therapy in a cohort of liver transplant recipients. Adverse events were common in this cohort, with 11% discontinuing treatment and 21% of patients experiencing serious adverse events requiring hospitalization.⁵³ More recently, the REFRESH study, a phase 2B, prospective, multicenter study, assessed the efficacy of telaprevir in combination with PEG-interferon and ribavirin in liver transplant patients with genotype 1 chronic HCV infection who did not have cirrhosis.⁵⁴ An interim analysis at week 16 was presented at AASLD in 2013. Conclusions included that the CYP3A4 inhibitory activity of telaprevir required substantial dose adjustments for each of the calcineurin inhibitors

being studied. Tacrolimus required greater modifications of dose and dosing intervals than did cyclosporine. This is further evidence that the use of protease inhibitors in the post-transplant setting requires constant dose adjustments. This is also relevant in the setting of combined liver-kidney transplant recipients with recurrent hepatitis C,⁴⁷ where treatment for hepatitis C has generally been avoided due to interactions between available antiviral agents and immunosuppressive medications.

New approaches to treatment in the post-transplant setting

The last two years has seen the development of multiple new direct-acting antiviral agents for the treatment of hepatitis C. Table 2 refers to some of the newer agents being evaluated for the treatment of hepatitis C. Charlton et al.,^{8,54} recently reported an open-label phase 2 study of 40 OLT patients, with more than 80% exhibiting HCV genotype 1 and the overwhelming majority being treatment-experienced.⁵⁵ Their patients were treated with once daily sofosbuvir (400mg daily) plus ribavirin (started at 400mg daily, gradually increased based on tolerability). Taking into account its potentially limited clinical utility, SVR4 rates were noted to be 77% in their patient population. Of note, no interactions were reported between sofosbuvir and any immunosuppressant agents.

Table 2 Traditional, new, and upcoming protease inhibitors

| Antiviral agent | Class | Targeted genotypes | Studied in pre-OLT setting | Studied in post-OLT setting |
|-----------------|--|---------------------|----------------------------|-----------------------------|
| Telaprevir | NS3/4A protease inhibitor | Genotypes 1,4 | Yes | Yes |
| Boceprevir | NS3/4A protease inhibitor | All genotypes | Yes | Yes |
| Simeprevir | NS3/4A protease inhibitor | Genotypes 1,2,4,5,6 | Yes | Yes |
| Asunaprevir | NS3/4A protease inhibitor | Genotype 1b | Yes | No |
| Daclatasvir | NS5A replication inhibitor | Genotype 1b | Yes | Yes |
| Ledipasvir | NS5A replication inhibitor | Genotype 1 | Yes | No |
| Sofosbuvir | NS5B nucleoside inhibitor | All genotypes | Yes | Yes |
| ABT-333 | NS5B non-nucleoside polymerase inhibitor | Genotype 1 | Yes | No |
| ABT-450 | NS3/4A protease inhibitor | Genotype 1 | Yes | No |
| ABT-267 | NS5A replication inhibitor | Genotype 1 | Yes | No |

Strategies for implementation of these new direct-acting antiviral agents have also included IFN-free, ribavirin-free, combination therapy. The NS5B nucleoside inhibitor, sofosbuvir, has been shown in multiple studies to lead to high SVR rates without the need for interferon-based regimens.^{41,56} Daclatasvir, a potent oral NS5A inhibitor, has been paired up with sofosbuvir for the treatment of recurrent HCV. Sulkowski et al.,⁵⁶ conducted an open-label study of more than 200 patients assigned to sofosbuvir and daclatasvir, with or without ribavirin, for duration of 24 weeks.⁵⁷ SVR rates were consistently 90% or greater across genotypes 1, 2, and 3, including patients with no response to prior therapy with telaprevir or boceprevir.

Such a regimen has crossed over to the post-OLT setting as well. Fontana et al.,⁵⁷ reported the first ever use of an interferon-free, all oral 24-week regimen of daily sofosbuvir and daclatasvir in an OLT patient with recurrent cholestatic hepatitis C.⁵⁸ Viral load was undetectable within 4 weeks of treatment and the patient achieved sustained viral response, all the while his immunosuppression (tacrolimus) remaining unscathed. Studies focusing on the pharmacokinetics of newer DAAs such as daclatasvir have emphasized the lack of clinically-evident

drug-drug interactions associated with its use alongside calcineurin inhibitors.⁵⁹ Understandably, SVR4 rates are not the best predictors of treatment success but the trial has pointed to an all-oral, IFN-free regimen as a treatment option for HCV recurrence in the post-transplant setting.

Entering the arena as of late has been the emergence of ABT combination therapy for the management of recurrent hepatitis C. In an ongoing phase II study, Kwo et al.,⁶⁰ are evaluating 34 post-liver transplant patients with recurrent genotype 1 HCV infection, who are receiving ABT-450 (an NS3/4A protease inhibitor), ritonavir, ombitasvir (an NS5A inhibitor), with dasabuvir (an NS5B RNA polymerase inhibitor) and ribavirin for a duration of 24 weeks. RVR was 100% and SVR12 has been reported to be 96% in this ongoing study.

In early 2014, the American Association for the Study of Liver Diseases (AASLD), in collaboration with the Infectious Diseases Society of America (IDSA), presented their recommendations for patients who develop recurrent HCV infection post-liver

transplantation. For treatment-naïve patients with HCV genotype I in a compensated allograft liver, daily sofosbuvir (400mg) plus simeprevir (150mg), with or without ribavirin (initial dose 600mg, increased monthly as tolerated to weight-based dose), for 12 to 24 weeks was recommended [Class IIB, Level C recommendation].⁴⁴ This recommendation is, in part, supported by evidence from the COSMOS study, with data showing that 12 or 24 weeks of simeprevir plus sofosbuvir with or without ribavirin is generally well tolerated and can lead to greater than 90% sustained viral response rate in patients who are prior null responders with chronic hepatitis C, genotype I.⁶¹ Furthermore, for treatment-naïve genotype 1 patients, an alternative regimen of daily sofosbuvir (400mg) and ribavirin (initial dose 600 mg/day, with subsequent monthly increases to a weight-based dose of 1000-1200mg, with consideration of the patients CrCL and hemoglobin levels), with or without pegylated interferon, is recommended for a duration of 24 weeks in patients with compensated allograft HCV genotype I infection (Class IIB, Level C recommendation). For treatment-naïve patients with HCV genotype 2 or 3 in the compensated allograft liver, daily sofosbuvir (400mg) and ribavirin (initial dose 600 mg/day with subsequent monthly increases, with consideration of a patient's CrCl and hemoglobin), for 24 weeks was recommended (Class IIB, Level C recommendation).⁴⁴ One of the bolder statements in the recent AASLD recommendations is that telaprevir or boceprevir-based regimens should not be used for patients with compensated allograft hepatitis C infection. This further supports concerns regarding adverse effects and drug-drug interactions associated with first generation protease inhibitors in this patient population.

We closely follow the AASLD's recommendations when treating our own post-transplant patients with evidence of recurrent hepatitis C infection. Genotype 1 patients are typically started on daily sofosbuvir and simeprevir for a duration of 12 to 24 weeks. Daily sofosbuvir and ribavirin for a duration of 12 and 24 weeks is used for our genotype 2 and 3 patients, respectively. In parallel with the AASLD recommendations, we do not use of telaprevir or boceprevir in this patient population.

Conclusion

Patients in the pre- and post-OLT setting with HCV recurrence may stand to benefit from implementation of new, recently-approved direct-acting antiviral agents. This is especially important given that the management of OLT patients, from the standpoint of immunosuppression management, is becoming more and more sophisticated with new agents continuously being developed. Appropriate treatment of recurrent hepatitis C in the pre- and post-transplant setting will certainly help minimize graft failure and prevent morbidity and mortality, especially if these new agents can peacefully co-exist with immunosuppression. Unequivocally, we are in the dawn of a new era for this special population of patients.

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Conflicts of interest

Authors declare that there is no conflict of interest.

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