Title
Current Management of Hepatitis C Virus Regimens for Peri-Liver Transplant Patients

Journal
Clinics in Liver Disease, 19(4)

ISSN
1089-3261

Authors
Saxena, Varun
Terrault, Norah

Publication Date
2015-11-01

DOI
10.1016/j.cld.2015.06.007

Peer reviewed

HHS Public Access

Author manuscript

Clin Liver Dis. Author manuscript; available in PMC 2021 May 12.

Published in final edited form as:

Clin Liver Dis. 2015 November ; 19(4): 669–vi. doi:10.1016/j.cld.2015.06.007.

Current Management of Hepatitis C Virus:

Regimens for Peri-Liver Transplant Patients

Varun Saxena, MD, MS, **Norah Terrault, MD, MPH***

Division of Gastroenterology and Hepatology, Department of Medicine, University of California, San Francisco, San Francisco, CA, USA

Keywords

Hepatitis C virus; Liver transplant; Direct-acting antivirals; Recurrent hepatitis C virus; Sofosbuvir; Simeprevir; Ledipasvir; Cholestatic hepatitis

INTRODUCTION

The World Health Organization estimates that about 3% of the world's population has been infected with hepatitis C virus (HCV) and that there are more than 170 million with chronic disease who are at risk of developing liver cirrhosis and/or liver cancer.[1] The prevalence of chronic HCV infection in the United States has been estimated at 2.7 million persons per the most recent National Health and Nutrition Examination Survey (NHANES) data,[2] but a study accounting for high-risk groups underrepresented in NHANES suggested a US prevalence of 5.2 million.[3] Given this burden of disease, is it not surprising that HCV infection remains the most common indication for liver transplant (LT) in the United States.[4]

Recurrence of HCV after LT is universal in viremic patients undergoing LT; in adjusted models, recurrent HCV leads to an approximately 28% (95% confidence interval [CI]: 15%–40%) increase in graft loss and a 17% (95% CI: 3%–32%) increase in recipient mortality compared with LT recipients without HCV.[5] The natural history of recurrent HCV is significantly more aggressive compared with the natural history before LT, with 20% to 54% developing bridging fibrosis/cirrhosis at 5 years[6] and 2% to 9% developing the aggressive and rapidly progressive fibrosing cholestatic HCV within 1 year after LT.[7] On the other hand, successful HCV eradication either before LT or after LT has been shown to improve post-LT outcomes[8] and, therefore, is the goal of HCV treatment in the peri-LT setting.

The development of direct-acting antivirals (DAAs) against HCV has revolutionized the treatment of HCV (Table 1). The first 2 DAAs included the first-generation NS3/4A protease inhibitors (PIs), telaprevir and boceprevir, which were approved by the US Food and Drug Administration (FDA) in 2011 for use in combination with peginterferon (PEG-IFN) and ribavirin (RBV) to treat chronic genotype 1 HCV. With the approval of second-generation NS3/4A PIs and additional DAAs, the first-generation PIs are no longer used in the United

*Corresponding author. University of California, San Francisco, Box 0538, 513 Parnassus Avenue, S357, San Francisco, CA 94143. norah.terrault@ucsf.edu.

States. Simeprevir (SMV), a second-generation PI, was FDA approved for use in combination with PEG-IFN and RBV for genotype 1 HCV in November 2013. Soon thereafter, the first-in-class nucleotide NS5B polymerase inhibitor sofosbuvir (SOF) was FDA approved in December 2013 with pan-genotypic activity. More recently, the FDA approved the fixed-dose combination of ledipasvir (LDV), a NS5A replication complex inhibitor, and SOF in October 2014. This approval was followed closely by the FDA approval of combined ombitasvir (OBV) (an NS5A replication complex inhibitor) and ritonavir (r) boosted paritaprevir (PTV) (a PI), copackaged with dasabuvir (DBV) (the only approved non-nucleoside NS5B polymerase inhibitor) (OBV-PTV-r/DBV). Although not yet approved by the FDA, daclatasvir (DCV), another NS5A inhibitor, was approved in Europe in August 2014 and is anticipated to gain approval in the United States in 2015. With the availability of these and future DAAs (see Table 1), the era of interferon-containing HCV treatment regimens for peri-LT patients is over.

Management of HCV in the peri-LT setting uses several different strategies (Fig. 1). Wait-listed patients can be treated with the goal of achieving pre-LT cure and/or preventing HCV recurrence after LT. In the post-LT setting, HCV treatment can be used either preemptively in the early post-LT period to prevent clinically significant disease or used for patients with established recurrent disease, including those with cirrhosis who have failed prior therapies, all with the intent to achieve cure. In the pre-DAA era when PEG-IFN and RBV were the mainstays for treating HCV, the dominant strategy used was the treatment of post-LT patients who showed evidence of severe or progressive recurrent disease.[9] This approach reflected the diminished tolerability of PEG-IFN and RBV and low rate of sustained virologic response (SVR). Although the addition of first-generation PIs, telaprevir and boceprevir, improved efficacy significantly, the poor tolerability of therapy remained a significant barrier. In contrast, current DAA combination therapies are well tolerated, allowing a broader array of peri-LT patients to be considered for therapy and provide new opportunities to both prevent and treat recurrent HCV disease with high efficacy.

HEPATITIS C VIRUS TREATMENT BEFORE LIVER TRANSPLANT TO ACHIEVE CURE

In general, patients with indications for LT have decompensated cirrhosis. However, patients with hepatocellular carcinoma (HCC) may have compensated cirrhosis. These latter patients can be treated for cure using the same guiding principles as applied to patients who are not wait-listed for LT (see the article by Paul Kwo else-where in this issue). Moreover, because patients with HCC garner exception points that ensure that all patients whose HCC remains within the Milan criteria have access to LT, these patients are ideal patients to treat with DAA combinations before LT with the goal of achieving cure *and* preventing post-LT recurrence (see section Hepatitis C virus treatment before liver transplant to prevent hepatitis C virus recurrence).

For patients with decompensated cirrhosis, the decision to treat for cure is a more complex one. Certainly, there are now DAA combinations that are safe and can offer cure to this previously largely incurable group. Potential gains from achieving cure in patients with

decompensated cirrhosis include a reversal of complications of cirrhosis, improved quality of life, reduced risk of wait-list mortality, and prevention of HCV recurrence after LT (if LT occurs). Most of these potential gains are still theoretic, as long-term studies of outcomes in patients with decompensated cirrhosis are lacking. Moreover, there may be a potential downside of treating patients with decompensated cirrhosis on the wait-list, in that model of end-stage liver disease (MELD) scores may decrease with virologic cure, making LT less likely, but not improving the complications of liver disease sufficiently to make avoidance of LT desirable.

The HCV therapies currently approved in the United States for use in patients with decompensated cirrhosis included SOF/RBV, LDV/SOF with or without RBV, and SMV/SOF (patients with Child-Pugh [CP] class B cirrhosis only). OBV-PTV-r/DBV with or without RBV is not an option. SOF is extensively metabolized in the liver to the pharmacologically active metabolite GS-461203 with eventual dephosphorylation to the inactive metabolite GS-331007.[10] Relative to patients with normal hepatic function, the GS-331007 areas under the curves from 0 to 24 hours ($AUCs_{0–24}$) are 18% and 9% greater in patients with CP class B and C cirrhosis, respectively; no dose adjustments for SOF are needed for patients with advanced cirrhosis.[10] Renal clearance is the major elimination pathway for SOF, via GS-331007; compared with those with normal renal function, SOF $AUC_{0–\infty}$ was 1.7-fold higher and the GS-331007 $AUC_{0–\infty}$ was 4.5-fold higher in those with an estimated glomerular filtration rate (eGFR) less than 30 mL/min/1.73 m^2.[10] Consequently, SOF is not recommended for patients with an eGFR less than 30 mL/min/1.73 m^2.[10] No pharmacokinetic data are available to guide dosing in patients with *combined* liver and renal dysfunction, a frequent clinical scenario in patients with advanced decompensated cirrhosis.

SMV is extensively metabolized by the hepatic cytochrome CYP3A system and eliminated via biliary excretion.[11] Relative to patients with normal hepatic function, SMV $AUC_{0–24}$ values are 2.4-fold and 5.2-fold higher in patients with CP class B and class C cirrhosis, respectively.[12] Higher exposure to SMV has been associated with increased frequency of adverse reactions in clinical trials.[11] As a result, the risks and benefits of SMV use need to be carefully considered in patients with CP class B cirrhosis and avoided in patients with CP class C cirrhosis.[11]

The safety and efficacy of SMV plus SOF in patients with decompensated cirrhosis have been evaluated is real-life cohorts. In a national study of 156 patients (101 with CP class A cirrhosis, 49 with CP class B cirrhosis, and 6 CP class C cirrhosis) treated for 12 weeks with SMV/SOF with (35%) and without (65%) RBV,[13] patients with CP class B or C cirrhosis (vs patients with CP class A cirrhosis) developed further hepatic decompensation more frequently (20% vs 3%; *P* value less than .01) (Table 2) while achieving SVR at 12 weeks after treatment discontinuation (SVR12) less frequently than patients with CP class A cirrhosis (73% vs 91%, *P* value less than .01) (Fig. 2).[13] Similar SVR12 results were reported with compensated and decompensated cirrhosis in the HCV-TARGET cohort (87% and 75%, respectively).[14] Among those with a baseline MELD score greater than 10, HCV-TARGET reported an SVR12 rate of 74% (79 of 107) among those receiving SMV/SOF and 66% (19 of 29) among those receiving SMV/SOF and RBV.[15] In terms of safety and

tolerability, a recent case report suggested SMV/SOF may be associated with worsening hepatic decompensation in patients with CP class C cirrhosis.[16] However, in a controlled study, patients with decompensated cirrhosis treated with SMV/SOF had a similar frequency of hepatic decompensation during treatment to matched controls followed for a similar duration of time (9% vs 10%, $P = .78$),[13] suggesting safety events during treatment may reflect the natural history of decompensated cirrhosis. The complexity of establishing a causal relationship between drug exposures and decompensating events in patients with advanced cirrhosis is well recognized.[17]

In contrast to the pharmacokinetic data for SMV or SOF, the pharmacokinetic data for LDV in subjects with severe renal (eGFR <30 mL/min/m^3) or hepatic (CP class C cirrhosis) impairment suggest no significant differences compared with healthy subjects.[18] Furthermore, safety data are reassuring for use of LDV/SOF in patients with decompensated cirrhosis.[19,20] In the US study of LDV/SOF with RBV (escalating doses starting at 600 mg/d) in 59 patients with CP class B cirrhosis and 49 patients with CP class C cirrhosis (SOLAR-1), SVR12 was achieved in 45 of 52 (87%) patients treated for 12 weeks and 42 of 47 (89%) patients treated for 24 weeks (see Fig. 2).[19] In a similar study from Europe (SOLAR-2), LDV/SOF with RBV resulted in SVR12 rates of 86% (37 of 43) versus 85% (35 of 41) in genotype 1 patients with CP class B/C cirrhosis treated for 12 weeks versus 24 weeks (see Fig. 2).[21] Serious treatment-related adverse events (AEs) were rare. In the SOLAR-1 study, treatment was discontinued early because of AEs in 3 patients, and 6 patients died (4 septic shock, 1 renal failure, 1 cardiac arrest) (see Table 2). Seven patients underwent LT during the study period and were not included in the analysis: one patient died 2 weeks after LT, and 6 achieved a post-transplant virologic response.[19] In a smaller study of 20 SOF treatment-experienced patients retreated with LDV/SOF without RBV, 13 (65%) with CP class B cirrhosis achieved SVR12 after 12 weeks of treatment and 7 relapsed (see Fig. 2).[20] No patients died, and only 2 patients experienced serious AEs: one related to a patient's baseline bipolar disorder and one caused by anemia, chest pain, and cholecystitis (see Table 2).[20] Differences in reported SVR rates between these studies may reflect both the patient populations and the use of RBV. Based on data from patients with compensated cirrhosis,[22] the recommended approach to patients with CP class B/C cirrhosis treated with LDV/SOF is to treat for 24 weeks if RBV is not included and 12 weeks if RBV is included (Table 3).

SOF/RBV was the first all-oral therapy available to treat patients with decompensated cirrhosis and is currently the only treatment approved for genotypes 2 and 3. Real-world data involving patients with cirrhosis and baseline MELD scores greater than 10 from HCV-TARGET show an SVR12 rate of 81% (21 of 26) among genotype 2–infected patients and a rate of 39% (10 of 26) among genotype 3–infected patients.[15] Among 88 patients with cirrhosis and a baseline MELD score greater than 10 treated with SOF/RBV, 27 (31%) had a serious AE and 10 (11%) had hepatic decompensation, but no patients died.[15] For non–genotype 2 or 3 patients, alternative DAA combinations are available for treatment of patients with decompensated cirrhosis and are preferred over SOF/RBV (see Table 3).

Although currently not FDA approved, DCV has been used in Europe in combination with other DAAs in the treatment of HCV. In vitro studies demonstrate that DCV is a substrate of

CYP3A, with CYP3A4 the major cytochrome P isoform responsible for the metabolism.[23] Pharmacokinetic studies show the $AUCs_{0–24}$ are 42.7%, 37.6%, and 51.2% lower in subjects with CP class A, CP class B, and CP class C cirrhosis, respectively.[23] In addition, the $AUC_{0–24}$ of DCV was estimated to be 26.4%, 59.8%, and 79.6% higher in subjects with eGFR values of 60, 30, and 15 mL/min/1.73 m^2.[23] In the French compassionate access program, genotype 3–infected patients with cirrhosis (compensated and decompensated) treated with SOF/DCV ([C21]RBV) for 12 and 24 weeks, achieved SVR4 in 76% (22 of 29) and 88% (52 of 59), respectively.[24] In the National Health Service of England real-life experience treating 171 patients with genotype 1 and 3 cirrhosis (61% and 69% CP class B, 8% and 13% CP class C, respectively) with SOF/DCV ([C21]RBV) for 12 weeks, the SVR12 rates were 80% for genotype 1 and 70% for genotype 3.[25] The ALLY-1 trial examining a 12-week regimen of SOF/DCV with RBV (initial dose of 600 mg/d, adjusted to 1000 mg/d based on hemoglobin levels and creatinine clearance) in a predominantly genotype 1–infected population (genotype 1a: 57%, genotype 1b: 18%) resulted in SVR12 rates of 94% (30 of 32) and 56% (9 of 16) in patients with CP class B and CP class C cirrhosis, respectively (see Fig. 2).[26] Serious AEs occurred in 11 of 60 (17%) patients with cirrhosis, none related to study treatment; there were no deaths (see Table 2).[26] For patients with decompensated cirrhosis in the United States, the future availability of DCV will provide more treatment options for genotype 3–infected patients and additional treatment options for genotype 1– or genotype 4–infected patients.

In a small number of patients with *compensated* cirrhosis who achieved HCV cure with older therapies, liver histology has been shown to improve.[27,28] There is hope that achieving HCV cure in patients with *decompensated* cirrhosis may halt progression of decompensating events and prevent LT. Among 129 HCV-infected patients with decompensated cirrhosis treated with PEG-IFN and RBV, decompensation events occurred in 88% (52 of 59) of the untreated control group, 69% (33 of 48) of the non-SVR group, and 23% (3 of 13) of the SVR group, suggesting a protective effect of cure.[29] Among SOF/LDV-treated patients, the median (range) changes in the CP and MELD scores from baseline to 4 weeks post treatment were −1 (−3 to 2) and −1 (−5 to 10), respectively, among patients with baseline CP class B cirrhosis and was −1 (−3 to 0) and −1 (−6 to 2), respectively, among patients with baseline CP class C cirrhosis. 19 Among patients treated for 24 weeks with SOF/RBV, the mean change from baseline of albumin was 0.4 g/dL, of bilirubin was −0.2 mg/dL, and of MELD score was −1; some patients showed improvement in ascites and hepatic encephalopathy (see Table 2).[30] As most studies with DAA combination therapy have evaluated MELD and clinical benefits at SVR12, longer-term follow-up studies are necessary to determine the benefits of HCV cure among patients with decompensated cirrhosis.

HEPATITIS C VIRUS TREATMENT BEFORE LIVER TRANSPLANT TO PREVENT HEPATITIS C VIRUS RECURRENCE

For patients who achieve SVR before LT, 100% are HCV free after LT.[31] However, a shorter treatment course aimed at achieving an undetectable HCV RNA at the time of LT (rather than SVR) can significantly reduce the risk of post-LT HCV recurrence.[32–38] This HCV

treatment strategy may be especially useful in patients whose time of LT is predictable, such as living-donor LT recipients or those with HCC. This strategy was first established in the Adult-to-Adult Living Donor Liver Transplantation Cohort Study,[36] with patients randomized to a low accelerating dose regimen of PEG-IFN and RBV or observation before LT.[36] The outcome of interest was achieving post-LT virologic response (pTVR) that was defined as an undetectable HCV RNA 12 weeks after LT.[36] Forty-four treated patients underwent LT of which 26 (59%) achieved an undetectable HCV RNA by the time of LT and 11 (25%) achieved pTVR.[36] Importantly, those who were treated for less than 8 weeks, 8 to 16 weeks, or greater than 16 weeks achieved pTVR at 0%, 18%, and 50%, respectively.[36] Despite not directly evaluating the duration of HCV RNA negativity as a predictor of pTVR, this study shows that HCV treatment before LT can prevent HCV recurrence and that duration of therapy (and, therefore, likely the duration of HCV RNA undetectability before LT) was an important predictor of treatment success.[36] With the first-generation PI (telaprevir or boceprevir)-based triple therapy, an improved on-treatment response was seen but offset by the high frequency of treatment-associated AEs.[39,40]

With the availability of the newer DAAs, PEG-IFN no longer has any role in pre-LT antiviral therapy aimed to prevent post-LT HCV recurrence. DAA combinations achieve nearly universal on-treatment virologic responses.[41–43] The time to and duration of HCV RNA negativity are critical elements of using this antiviral strategy to prevent HCV recurrence after LT. The factors potentially influencing the virologic responses on treatment include the severity of cirrhosis, prior treatment experience, and the DAA combination used. The landmark study was a phase 2 pilot study of SOF and weight-based RBV in 61 patients infected with genotypes 1 to 4 and a CP score of 7 or less listed for LT accruing a MELD exception point for HCC.[44] On an intent-to-treat basis, 59% of patients initiating therapy achieved pTVR. However, of the 43 patients who were treated *and* had an undetectable HCV RNA at the time of LT, 30 (70%) achieved pTVR.[44] The duration of continuously undetectable HCV RNA was associated with the likelihood of achieving pTVR, with only 1 of 26 patients with continuously undetectable HCV RNA for at least 30 days before LT developing recurrent HCV.[44] Safety events in this study occurred at similar frequency to what was observed in the registration trials for SOF and weight-based RBV. As a result of this study, SOF and weight-based RBV is FDA approved for patients with HCC awaiting LT with available data supporting a minimum of 4 weeks of HCV RNA negativity before LT to maximize the chance of pTVR.[45]

Available data highlight the heterogeneity of the on-treatment virologic responses. In a study of 25 genotype 1 to 4 HCV–infected patients with CP class A and B cirrhosis and portal hypertension (hepatic venous pressure gradient >6 mm Hg) treated with SOF and RBV,[30] 75% of patients with decompensated cirrhosis achieved an undetectable HCV RNA level by week 4 of treatment (Fig. 3).[30] In a study of 55 patients with decompensated cirrhosis treated with SMV/SOF with or without RBV, 62% achieved an on-treatment response by 4 weeks (see Fig. 3), with a median time to undetectable viral load of 32 days.[13] Among 20 patients with CP class B cirrhosis who underwent LDV/SOF, 75% achieved a negative viral load at treatment week 4% and 100% by week 12 (see Fig. 3).[20] Based on these data, the goal should be to initiate treatment at least 6 to 10 weeks before LT in order to achieve

approximately 4 weeks of HCV RNA negativity before LT and to maximize the likelihood of achieving pTVR.

For patients with compensated cirrhosis, several treatment options exist; but for decompensated cirrhosis, LDV/SOF with/without RBV (genotype 1, 4, and 6) and, until DCV becomes available, SOF and RBV dual therapy (genotypes 2 and 3) should be considered. The treatment duration should be timed to LT if possible, and this is most easily accomplished in patients with living donors or those with exception status (eg, HCC). Because the cost of treatment is closely tied with the duration of therapy, it remains to be determined whether treatment for prevention (with a possibly shorter duration of treatment) is more cost-effective than treatment post-LT.

PREEMPTIVE HEPATITIS C VIRUS TREATMENT AFTER LIVER TRANSPLANT TO ACHIEVE CURE

The preemptive strategy initiates HCV therapy in the immediate or early posttransplant period, before the development of recurrent disease. This therapeutic approach is predicated on the knowledge that HCV viremia rapidly declines with removal of the recipient's cirrhotic liver and increases gradually in the hours to days following LT.[46] Potent DAAs against HCV given immediately at the time of LT, along with removal of the infected organ, may avoid the rapid recurrence of viremia and also allow for shorter and, thus, more cost-effective HCV management. However, the safety and efficacy of DAAs in the immediate transplant period are unknown; the benefits of preemptive versus delayed posttransplant therapy remain to be established. Currently, the CRUSH-C consortium is examining the safety and efficacy of LDV/SOF administered in patients infected with chronic genotype 1 or 4 HCV in the perioperative LT setting (ClinicalTrials.gov NCT02350569).

Another preemptive strategy is to use adjuvant antibody therapy in patients who are on antiviral therapy at the time of LT. In a phase 3, open-label randomized study, 84 HCV-infected wait-listed patients receiving DAAs leading up to transplant were randomized 1:1:1 to hepatitis C immunoglobulin (HCIG) 200 mg/kg, 300 mg/kg, or observation.[47] In preliminary data, 63 patients were treated pre-LT with DAA-based therapy for a median of 63 days with post-transplant reinfection occurring in 1/21 (5%) in the 300 mg/kg, 7/22 (32%) in 200 mg/kg group and 6/20 (30%) controls.[47] These preliminary results suggest use of higher dose HCIG may be beneficial as an adjuvant therapy for patients on HCV therapy undergoing LT.

HEPATITIS C VIRUS TREATMENT AFTER LIVER TRANSPLANT TO ACHIEVE CURE

Achievement of SVR after LT is associated with improved graft and patient survival[48] and is the goal of every LT recipient. Prior treatment guidelines recommended antiviral therapy be initiated after LT only if there is moderate fibrosis (≥F2 on a scale of 4), moderate or severe necroinflammatory activity (≥A3 on scale of 4), or cholestatic hepatitis.[9] Post-LT therapy with PEG-IFN and RBV, started within the first 6 months after LT and before the presence

of fibrosis on protocol biopsies, was no more effective than delaying treatment until disease progression was present.[49] However, with the improved safety profiles of IFN-free therapies, earlier post-LT therapy may be merited to gain full survival benefit from cure and decrease the cost related to monitoring and management of recurrent disease complications.

Significant Fibrosis/Compensated Cirrhosis

SVR rates with PEG-IFN and RBV were approximately 30% for genotype 1 and 60% to 75% for non-1 genotypes.[50] Dose reductions were frequently required, and treatment discontinuation was common; but acute and chronic rejection were infrequent, occurring in 2% and less than 1%, respectively. SVR rates with first-generation PI-based triple therapy were substantially higher with 63% achieving cure.[51] However, tolerability and safety were significant challenges with telaprevir- and boceprevir-based therapy,[51,52] including worsening of renal function in up to 38% of patients.[53] This worsening was possibly related to the degree of anemia or from the result of calcineurin inhibitor toxicity from either altered pharmacokinetics in the setting of CYP3A4/5 inhibition or P-glycoprotein inhibition caused by the PI.[52] Thus, the addition of a DAA substantially increased the success of therapy; however, the side effects of the first-generation PIs plus the need for use of PEG-IFN and RBV resulted in a complex therapy for patients and providers. Although some countries without access to newer DAAs continue to use PI triple therapy with success, in the United States, newer DAA combinations have supplanted its use.

The all-oral antiviral regimens show improved efficacy and safety over the first-generation PI-based triple therapy for LT recipients. In a phase 2 clinical trial, 44 LT recipients with HCV genotypes 1 to 4 who were at least 6 months post-LT received SOF and RBV for 24 weeks.[54] All patients had a CP score of 7 or less and a MELD score of 17 or less, and patients with signs of decompensation were excluded.[54] RBV was started at 400 mg/d and was escalated based on tolerability and degree of anemia.[54] All patients achieved an end-of-treatment response, and 28 (70%) achieved SVR12 (Fig. 4). Average RBV doses did not differ between those who did and did not achieve SVR12.[54] Anemia requiring erythropoietin and/or blood transfusions occurred in 20%,[54] more than half of the frequency seen with first-generation PI-based triple therapy.[51,52] Furthermore, there were no deaths, graft losses, or episodes of rejection or any significant drug-drug interactions between SOF and tacrolimus or cyclosporine.[55] SOF and RBV are currently recommended for post-LT patients with genotype 2 or 3 disease.[45]

Real-world experience with SMV/SOF with or without RBV for genotype 1 LT recipients has been reported. In a study of 123 patients (60% genotype 1A, 30% F3/F4, 80% treatment experienced), SVR12 was achieved in 90%.[56] One patient died of drug-induced lung injury while on treatment.[56] In interim analysis of the HCV-TARGET cohort of 131 LT recipients, 90% achieved SVR4, with 86% SVR4 in those with cirrhosis and 94% in those without.[57] Serious AEs were rare in both studies, and there were no episodes of graft rejection.[56,57] SMV does not seem to have clinically significant interactions with tacrolimus, but cyclosporine increased SMV levels by approximately 6-fold; thus, patients on cyclosporine should not be treated with SMV-containing regimens.[58] SMV/SOF with or without RBV for

12 weeks is one of the recommended regimens for genotype 1–infected LT recipients with compensated liver disease.[45]

LDV/SOF with RBV was evaluated in a phase 2 study of 223 LT recipients with genotype 1 and 4 for 12 or 24 weeks.[19] Fifty percent (n = 111) of the treated patients were without cirrhosis (Metavir fibrosis stage 0–3), 51 (28%) with CP class A cirrhosis, 52 (23%) with CP class B cirrhosis, and 9 (4%) with Child Pugh C cirrhosis.[19] SVR12 was achieved in 96% of F0-F3 patients, 96% with CP class A cirrhosis, and 81% with CP class B/C cirrhosis with SVR rates similar with 12 versus 24 weeks of treatment (see Fig. 4).[19] Fatigue, anemia, headache, and nausea were the most common AEs.[19] Seven patients died of causes judged to be unrelated to treatment.[19] In the European SOLAR-2 study of LDV/SOF with RBV in LT recipients, SVR12 was achieved in 95% with F0–3 fibrosis and 98% with compensated CP class A cirrhosis treated for 12 or 24 weeks (no difference by duration of therapy)[21] (see Fig. 4).[21] Based on these results, LDV/SOF *with* weight-based RBV for 12 weeks is recommended for LT recipients with compensated and decompensated genotype 1 or 4 HCV disease.[45]

In the CORAL-1 study, 34 LT patients with genotype 1 HCV infection and F0–2 fibrosis were treated with OBV-PTV-r/DBV and RBV for 24 weeks.[59] RBV was dosed at the discretion of the treating physician; 600 to 800 mg/d was the most common dosage at baseline (56%) and at the end of treatment (68%). SVR12 was achieved in 97% (see Fig. 4).[59] The one relapse occurred 3 days after treatment discontinuation, and the patient had evidence of NS3, NS5A, and NS5B resistant variants, which were not present at baseline.[59] Serious AEs occurred in 2 patients, and 1 patient discontinued the study drugs because of AEs.[59] Anemia was common and seen in approximately one-third of patients, with 5 patients receiving erythropoietin.[59] Two patients experienced serious AEs: one with hypotension and tachycardia related to tamsulosin administered after elective surgery and one diabetic patient with moderate peripheral edema and pain in extremities.[59] Tacrolimus dosages were modified to 0.5 mg per week or 0.2 mg every 3 days, and cyclosporine dose reductions were to 20% of the pretreated daily dose.[59] No episodes of rejection occurred. Based on these results, OBV-PTV-r/DBV and RBV for 24 weeks is approved for LT recipients with genotype 1 HCV infection with early stage fibrosis (≤F2).[45] A study of this DAA combination in patients with more advanced stages of fibrosis is ongoing (ClinicalTrials.gov NCT01782495).

In the ALLY-1 study, SOF/DCV with RBV for 12 weeks was examined in 53 LT recipients, genotypes 1 and 3, 68% with F0-F3 fibrosis and 30% with CP class A cirrhosis (1 patient missing baseline stage).[26] SVR12 was observed in 50 of 53 (94%). Only 9% experienced serious AEs, and all were unrelated to the study drug.[26] Although SOF/DCV with/without RBV has been used in LT recipients in compassionate access programs,[24,25] efficacy and safety results are not currently available. Coadministration of DCV with cyclosporine or tacrolimus has been investigated in healthy HCV-negative subjects, and DCV did not affect the pharmacokinetics of either calcineurin inhibitor.[60] Although cyclosporine caused a modest increase in DCV exposure with a 40% increase in AUC0–24, dose adjustments for DCV, tacrolimus or cyclosporine are unlikely to be required during coadministration.[60]

Availability of DCV in the United States will provide another NS5A inhibitor option for LT recipients, especially those with decompensated cirrhosis.

Decompensated Cirrhosis

In a compassionate access program for LT recipients with severe recurrence and less than 1-year life expectancy, patients with genotype 1 to 4 and decompensated cirrhosis or severe cholestatic hepatitis received variable duration of SOF and RBV with or without PEG-IFN.[61] Only 72 (69%) patients completed 24 to 48 weeks of treatment; 7 discontinuations caused by AEs, 12 repeat LTs, and 13 deaths were reported.[61] Overall, excluding repeat LT and patients without data available, 62% achieved SVR12.[61]

Data using other DAA combinations are more limited. Drawing on real-world experience, 131 genotype 1–infected LT recipients were treated with SMV/SOF with or without RBV for 12 or 24 weeks with SVR4 reported in 77% of patients with cirrhosis and a MELD score of 10 or greater (see Fig. 4).[62] In LT recipients treated with LDV/SOF with RBV for 12 or 24 weeks, the SVR12 rates were 84% (CP class B cirrhosis, n = 44) and 63% (CP class C cirrhosis, n = 8) (see Fig. 4).[19] Of the 10 patients who did not achieve SVR12, 3 relapsed, 5 died (none thought to be related to treatment), and 1 withdrew consent.[19] Only one patient with decompensated cirrhosis had a treatment-related serious AE (hemolytic anemia), and 3 patients discontinued treatment because of AEs.[19] In the SOLAR-2 study, 35 of 36 (97%) of LT recipients with CP class B cirrhosis and 4 of 6 (67%) of LT recipients with CP class C cirrhosis achieved SVR12 with SVR rates similar with 12 versus 24 weeks of treatment (see Fig. 4).[21] The safety and efficacy of SOF and DCV with or without RBV has been studied in compassionate access settings. Among 12 post-LT patients with severe recurrent HCV (3 with severe cholestatic HCV), 9 patients completing 24 weeks of treatment had undetectable HCV RNA at treatment end and 5 patients with follow-up achieved SVR4.[63] During treatment, 3 deaths occurred: one caused by rapidly progressive liver failure, one caused by gastrointestinal bleeding, and one caused by septic shock and attributed to the severity of the patient's underlying liver disease rather than directly to the antiviral treatment.[63] In another series of 23 patients with post-LT severe cholestatic HCV treated with SOF and daclatasvir, SVR12 was achieved in 96%.[64]

PRETRANSPLANT VERSUS POSTTRANSPLANT THERAPY: WHICH IS BETTER?

HCV treatment in the peri-LT setting needs to be individualized. Factors of importance include patient severity of cirrhosis, presence of HCC, donor options, and regional wait times. Treatment approaches are predicted to change continuously over the next few years, as clinicians gain more experience with using currently approved DAA combinations in patients both before LT and after LT and with a large published experience with peri-LT therapies. A suggested framework for considering the timing of treatment in a moderate to high MELD region is shown in Fig. 5.

Wait-Listed Patients

In patients listed with HCC or with a living donor available, pre-LT treatment with the goal of preventing HCV recurrence is an option to consider. These patients have a fairly predictable time to LT allowing the initiation of therapy in sufficient time to achieve HCV RNA undetectability for 4 or more weeks. Earlier treatment can be considered in patients with HCC and complications of cirrhosis, for whom treatment may improve liver function and facilitate HCC treatment and/or decrease symptoms related to liver decompensation.

For patients with intermediate MELD scores and no living donor option, the benefits and harms of treatment need to be weighed for each patient. Potential benefits of treatment include reversal of decompensation, reduced risk of death on the waiting list, improved quality of life, and avoidance of LT. Potential harms include lack of response and development of resistance, limited access to future therapies, and reduced MELD scores making LT less accessible. Overall, the lack of long-term data on SVR and reversibility of complications of portal hypertension and liver failure are major impediments to decision making. Pre-LT HCV treatment in this group should be considered on a case-by-case basis and may be best suited for those with lower MELD scores (eg, <20) and/or whose complications from portal hypertension are not refractory (see Fig. 5). For those with a high MELD score whose LT is imminent, deferral of HCV treatment until after LT is currently the best option.

Post–Liver Transplant Recipients

In the post-LT setting, patients with severe early recurrence (cholestatic variant) or risk factors for progressive disease should be treated early. As safety and experience with early treatment is acquired, earlier initiation of antiviral therapy is likely. In resource-constrained settings, monitoring of patients with annual liver biopsies or elastography with initiation of treatment if F2 or greater fibrosis is a reasonable strategy. However, the costs and complexity of monitoring and managing patients with recurrent HCV disease need to considered and may justify undertaking treatment at earlier time points after LT.

SUMMARY

In the era of the highly effective and safe all-oral DAA regimens, HCV recurrence after LT is no longer a major clinical challenge; but questions related to the timing of treatment and the most cost-effective approach remain. HCV treatment options before LT are more limited but can decrease the rate of HCV recurrence after LT and may even decrease the need for LT. However, a greater safety experience and longer-term efficacy data are needed in this population to guide decision making. Real-world cohorts of pre-LT and post-LT patients will remain critical in defining optimal HCV treatment regimens.

Acknowledgments

Dr V. Saxena has nothing to disclose. Dr N. Terrault discloses research support from Gilead, Gen-etech/Roche, Vertex, Novartis, Eisai, and AbbVie and has served as consultant for Bristol-Myers Squibb. Dr. V. Saxena is supported in part by T32 DK060414.

REFERENCES

1. WHO. Available at: http://www.who.int/csr/disease/hepatitis/whocdscsrlyo2003/en/index4.html - incidence. Accessed May 23, 2015.
2. Denniston MM, Jiles RB, Drobeniuc J, et al. Chronic hepatitis C virus infection in the United States, National Health and Nutrition Examination Survey 2003 to 2010. Ann Intern Med 2014;160:293–300. [PubMed: 24737271]
3. Chak E, Talal AH, Sherman KE, et al. Hepatitis C virus infection in USA: an estimate of true prevalence. Liver Int 2011;31:1090–101. [PubMed: 21745274]
4. Kim WR, Stock PG, Smith JM, et al. OPTN/SRTR 2011 annual data report: liver. Am J Transplant 2013;13(Suppl 1):73–102. [PubMed: 23237697]
5. Forman LM, Lewis JD, Berlin JA, et al. The association between hepatitis C infection and survival after orthotopic liver transplantation. Gastroenterology 2002;122: 889–96. [PubMed: 11910340]
6. Berenguer M, Schuppan D. Progression of liver fibrosis in post-transplant hepatitis C: mechanisms, assessment and treatment. J Hepatol 2013;58:1028–41. [PubMed: 23262248]
7. Narang TK, Ahrens W, Russo MW. Post-liver transplant cholestatic hepatitis C: a systematic review of clinical and pathological findings and application of consensus criteria. Liver Transpl 2010;16:1228–35. [PubMed: 21031537]
8. Berenguer M, Roche B, Aguilera V, et al. Efficacy of the retreatment of hepatitis C virus infections after liver transplantation: role of an aggressive approach. Liver Transpl 2013;19:69–77. [PubMed: 23008144]
9. Wiesner RH, Sorrell M, Villamil F, International Liver Transplantation Society Expert Panel. Report of the first International Liver Transplantation Society expert panel consensus conference on liver transplantation and hepatitis C. Liver Transpl 2003;9:S1–9.
10. Sofosbuvir [package insert]. Foster City, CA: Gilead Sciences; 2013.
11. Simeprevir [package insert]. Titusville, NJ: Janssen Therapeutics; 2015.
12. Hezode C, Asselah T, Reddy KR, et al. Ombitasvir plus Paritaprevir plus Ritonavir with or without Ribavirin in treatment-naive and treatment-experienced patients with genotype 4 chronic hepatitis C virus infection (PEARL-I): a randomized open-label trial. Lancet 2015;385(9986):2502–9. [PubMed: 25837829]
13. Saxena V, Nyberg L, Pauly MP, et al. Safety and efficacy of simeprevir/sofosbuvir in hepatitis C infected patients with compensated and decompensated cirrhosis. Hepatology 2015. [Epub ahead of print].
14. Jensen DM, O'Leary JG, Pockros PJ, et al. Safety and efficacy of sofosbuvir-containing regimens for hepatitis C: real-world experience in a diverse, longitudinal observational cohort. Program and abstracts of the 65th Annual Meeting of the American Association for the Study of Liver Diseases. Boston (MA), November 7–11, 2014. [abstract: 45].
15. Reddy KR, Lim JK, Kuo A, et al. All oral HCV therapy is safe and effective in patients with decompensated cirrhosis: report from HCV-TARGET. Program and abstracts of the 50th Annual Meeting of the European Association for the Study of the Liver. Vienna (Austria), April 22–26, 2015. [abstract: O005].
16. Stine JG, Intagliata N, Shah NL, et al. Hepatic decompensation likely attributable to simeprevir in patients with advanced cirrhosis. Dig Dis Sci 2015;60: 1031–5. [PubMed: 25373453]
17. Saxena V, Terrault NA, Hepatitis C. Direct antiviral drugs and hepatic decompensation in patients with advanced cirrhosis: culprit or innocent bystander? Dig Dis Sci 2015;60:806–9. [PubMed: 25586091]
18. Ledipasvir/sofosbuvir [package insert]. Foster City, CA: Gilead Sciences; 2015.
19. Charlton M, Everson GT, Flamm SL, et al. SOLAR-1 Investigators. Ledipasvir and Sofosbuvir plus Ribavirin for treatment of HCV infection in patients with advanced liver disease. Gastroenterology 2015. [Epub ahead of print].
20. Gane E, Hyland R, An D, et al. Sofosbuvir/ledipasvir fixed dose combination is safe and effective in difficult-to-treat populations including genotype-3 patients, decompensated genotype-1 patients, and genotype-1 patients with prior sofosbuvir treatment experience. Program and abstracts of the

49th Annual Meeting of the European Association for the Study of the Liver. London (United Kingdom), April 9–13, 2014. [abstract: 06].

21. Manns M, Forns X, Samuel D, et al. Ledipasvir/sofosbuvir with ribavirin is safe and efficacious in decompensated and post-liver transplantation patients with HCV infection: preliminary results of the SOLAR-2 trial. Program and abstracts of the 50th Annual Meeting of the European Association for the Study of the Liver. Vienna (Austria), April 22–26, 2015. [abstract: G02].
22. Reddy KR, Bourliere M, Sulkowski MS, et al. Ledipasvir and Sofosbuvir in patients with genotype 1 hepatitis C virus infection and compensated cirrhosis: an integrated safety and efficacy analysis. Hepatology 2015;62(1):79–86. [PubMed: 25846144]
23. Daclatasvir [package insert]. New York City, NY: Bristol-Myers Squibb; 2014.
24. Hézode C, De Ledinghen V, Fontaine H, et al. Daclatasvir plus sofosbuvir with or without ribavirin in patients with HCV genotype 3 infection: interim analysis of a French multicenter compassionate use program. Program and abstracts of the 50th Annual Meeting of the European Association for the Study of the Liver. Vienna (Austria), April 22–26, 2015. [abstract: LP05].
25. Foster GR, McLauchlan J, Irving W, et al. Treatment of decompensated HCV cirrhosis in patients with diverse genotypes: 12 weeks sofosbuvir and NS5A inhibitors with/without ribavirin is effective in HCV genotypes 1 and 3. Program and abstracts of the 50th Annual Meeting of the European Association for the Study of the Liver. Vienna (Austria), April 22–26, 2015. [abstract: O002].
26. Poordad F, Schiff ER, Vierling JM, et al. Daclatasvir, sofosbuvir, and ribavirin combination for HCV patients with advanced cirrhosis or post-transplant recurrence: ALLY-1 phase 3 study. Program and abstracts of the 50th Annual Meeting of the European Association for the Study of the Liver. Vienna (Austria), April 22–26, 2015. [abstract: L08].
27. D'Ambrosio R, Aghemo A, Rumi MG, et al. A morphometric and immunohisto-chemical study to assess the benefit of a sustained virological response in hepatitis C virus patients with cirrhosis. Hepatology 2012;56:532–43. [PubMed: 22271347]
28. Mallet V, Gilgenkrantz H, Serpaggi J, et al. Brief communication: the relationship of regression of cirrhosis to outcome in chronic hepatitis C. Ann Intern Med 2008; 149:399–403. [PubMed: 18794559]
29. Iacobellis A, Siciliano M, Perri F, et al. Peginterferon alfa-2b and ribavirin in patients with hepatitis C virus and decompensated cirrhosis: a controlled study. J Hepatol 2007;46:206–12. [PubMed: 17125876]
30. Afdhal N, Everson G, Calleja J, et al. Sofosbuvir and ribavirin for the treatment chronic HCV with cirrhosis and portal hypertension with and without decompensation: early virologic response and safety. Program and abstracts of the 49th Annual Meeting of the European Association for the Study of the Liver. London (United Kingdom), April 9–13, 2014. [abstract: O68].
31. Everson GT. Treatment of patients with hepatitis C virus on the waiting list. Liver Transpl 2003;9:S90–4. [PubMed: 14586902]
32. Everson GT, Trotter J, Forman L, et al. Treatment of advanced hepatitis C with a low accelerating dosage regimen of antiviral therapy. Hepatology 2005;42: 255–62. [PubMed: 16025497]
33. Tekin F, Gunsar F, Karasu Z, et al. Safety, tolerability, and efficacy of pegylated-interferon alfa-2a plus ribavirin in HCV-related decompensated cirrhotics. Aliment Pharmacol Ther 2008;27:1081–5. [PubMed: 18346186]
34. Thomas RM, Brems JJ, Guzman-Hartman G, et al. Infection with chronic hepatitis C virus and liver transplantation: a role for interferon therapy before transplantation. Liver Transpl 2003;9:905–15. [PubMed: 12942451]
35. Forns X, Garcia-Retortillo M, Serrano T, et al. Antiviral therapy of patients with decompensated cirrhosis to prevent recurrence of hepatitis C after liver transplantation. J Hepatol 2003;39:389–96. [PubMed: 12927925]
36. Everson GT, Terrault NA, Lok AS, et al. A randomized controlled trial of pretrans-plant antiviral therapy to prevent recurrence of hepatitis C after liver transplantation. Hepatology 2013;57:1752–62. [PubMed: 22821361]

37. Carrion JA, Martinez-Bauer E, Crespo G, et al. Antiviral therapy increases the risk of bacterial infections in HCV-infected cirrhotic patients awaiting liver transplantation: a retrospective study. J Hepatol 2009;50:719–28. [PubMed: 19217183]
38. Massoumi H, Elsiesy H, Khaitova V, et al. An escalating dose regimen of pegy-lated interferon and ribavirin in HCV cirrhotic patients referred for liver transplant. Transplantation 2009;88:729–35. [PubMed: 19741473]
39. Hezode C, Fontaine H, Dorival C, 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. [PubMed: 23669289]
40. Saxena V, Manos MM, Yee HS, et al. Telaprevir or boceprevir triple therapy in patients with chronic hepatitis C and varying severity of cirrhosis. Aliment Pharmacol Ther 2014;39:1213–24. [PubMed: 24654657]
41. Jacobson IM, Gordon SC, Kowdley KV, et al. Sofosbuvir for hepatitis C genotype 2 or 3 in patients without treatment options. N Engl J Med 2013;368:1867–77. [PubMed: 23607593]
42. Osinusi A, Meissner EG, Lee YJ, et al. Sofosbuvir and ribavirin for hepatitis C genotype 1 in patients with unfavorable treatment characteristics: a randomized clinical trial. JAMA 2013;310:804–11. [PubMed: 23982366]
43. Lawitz E, Mangia A, Wyles D, et al. Sofosbuvir for previously untreated chronic hepatitis C infection. N Engl J Med 2013;368:1878–87. [PubMed: 23607594]
44. Curry MP, Forns X, Chung RT, et al. Sofosbuvir and ribavirin prevent recurrence of HCV infection after liver transplantation: an open-label study. Gastroenterology 2015;148:100–7.e1. [PubMed: 25261839]
45. AASLD/IDSA/IAS-USA. Recommendations for testing, managing, and treating hepatitis C. Available at: http://www.hcvguidelines.org. Accessed March 5, 2015.
46. Garcia-Retortillo M, Forns X, Feliu A, et al. Hepatitis C virus kinetics during and immediately after liver transplantation. Hepatology 2002;35:680–7. [PubMed: 11870384]
47. Terrault N, Shrestha R, Satapathy SK, et al. LP17: Novel approach for the prevention of recurrent hepatitis C in liver transplant recipients: preliminary results from ongoing phase III trial with CivacirÒ. J Hepatology 2015;62(Suppl 2):S271–2.
48. Berenguer M, Palau A, Aguilera V, et al. Clinical benefits of antiviral therapy in patients with recurrent hepatitis C following liver transplantation. Am J Transplant 2008;8:679–87. [PubMed: 18294165]
49. Bzowej N, Nelson DR, Terrault NA, 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. [PubMed: 21506241]
50. Wang CS, Ko HH, Yoshida EM, et al. Interferon-based combination anti-viral therapy for hepatitis C virus after liver transplantation: a review and quantitative analysis. Am J Transplant 2006;6:1586–99. [PubMed: 16827859]
51. Burton JR Jr, O'Leary JG, Verna EC, et al. A US multicenter study of hepatitis C treatment of liver transplant recipients with protease-inhibitor triple therapy. J Hepatol 2014;61:508–14. [PubMed: 24801415]
52. Verna EC, Saxena V, Burton JR Jr, et al., for the CRUSH-C Consortium. Telaprevir- and boceprevir-based triple therapy for hepatitis C in liver transplant recipients with advanced recurrent disease: a multicenter study. Transplantation 2015. [Epub ahead of print].
53. Pungpapong S, Aqel BA, Koning L, et al. Multicenter experience using telaprevir or boceprevir with peginterferon and ribavirin to treat hepatitis C genotype 1 after liver transplantation. Liver Transpl 2013;19:690–700. [PubMed: 23696372]
54. Charlton M, Gane E, Manns MP, et al. Sofosbuvir and ribavirin for treatment of compensated recurrent hepatitis C virus infection after liver transplantation. Gastroenterology 2015;148:108–17. [PubMed: 25304641]
55. Tischer S, Fontana RJ. Drug-drug interactions with oral anti-HCV agents and idiosyncratic hepatotoxicity in the liver transplant setting. J Hepatol 2014;60:872–84. [PubMed: 24280292]

56. Pungpapong S, Aqel B, Leise M, et al. Multicenter experience using sofosbuvir and simeprevir with/without ribavirin to treat hepatitis C genotype 1 after liver transplantation. Hepatology 2015;61(6):1880–6. [PubMed: 25722203]
57. Brown RS, Reddy K, O'Leary JG, et al. Safety and efficacy of new DAA-based therapy for hepatitis C post-transplant: interval results from the HCV-TARGET longitudinal, observational study. Program and abstracts of the 65th Annual Meeting of the American Association for the Study of Liver Diseases. Boston (MA), November 7–11, 2014. [abstract: LB-4].
58. Janssen R&D (Posted 2013). A study of pharmacokinetics, efficacy, safety, tolerability, of the combination of simeprevir (TMC435), daclatasvir (BMS-790052), and ribavirin (RBV) in patients with recurrent chronic hepatitis C genotype 1b infection after orthotopic liver transplantation (NCT01938625). Available at: http://www.clinicaltrials.gov/ct2/show/NCT01938625. Accessed September 5, 2014.
59. Kwo P, Mantry P, Coakley E, et al. An interferon-free antiviral regimen for HCV after liver transplantation. N Engl J Med 2014;371(25):2375–82. [PubMed: 25386767]
60. Bifano M, Adamczyk R, Hwang C, et al. Daclatasvir pharmacokinetics in healthy subjects: no clinically-relevant drug-drug interactions with either cyclosporine or tacrolimus. Program and abstracts of the 65th Annual Meeting of the American Association for the Study of Liver Diseases. Boston (MA), November 7–11, 2014. [abstract: 1081].
61. Forns X, Charlton M, Dening J, et al. Sofosbuvir compassionate use program for patients with severe recurrent hepatitis C after liver transplantation. Hepatology 2015;61(5):1485–94. [PubMed: 25557906]
62. Brown RS, Reddy KR, O'Leary JG, et al. Safety and efficacy of new DAA-based therapy for hepatitis C post-transplant: interval results from the HCV-TARGET longitudinal, observational study. American Association for the Study of Liver Diseases (AASLD) Liver Meeting. Boston (MA), November 7–12, 2014. [abstract: LB-4].
63. Pellicelli AM, Montalbano M, Lionetti R, et al. Sofosbuvir plus daclatasvir for posttransplant recurrent hepatitis C: potent antiviral activity but no clinical benefit if treatment is given late. Dig Liver Dis 2014;46:923–7. [PubMed: 24997638]
64. Leroy V, Dumortier J, Coilly A, et al. Efficacy of Sofosbuvir and Daclatasvir in patients with fibrosing cholestatic hepatitis C after liver transplantation. Clin Gastro-enterol Hepatol 2015. [Epub ahead of print].

KEY POINTS

- The primary goal of hepatitis C virus treatment in the peri-liver transplant setting is to prevent liver-related complications and graft loss caused by recurrence of hepatitis C virus after liver transplant.
- Approved direct-acting antivirals against hepatitis C offer a safe and effective option for treatment in the peri-liver transplant period with primary determinants of use guided by renal and liver function.
- Hepatitis C virus treatment in patients with decompensated cirrhosis with newer direct-acting antivirals are generally well tolerated and provide cure rates ranging from 50% to 94%.
- On-treatment virologic responses with newer direct-acting antivirals are almost universal providing the opportunity to treat to achieve at least 4 weeks viral negativity before liver transplant.

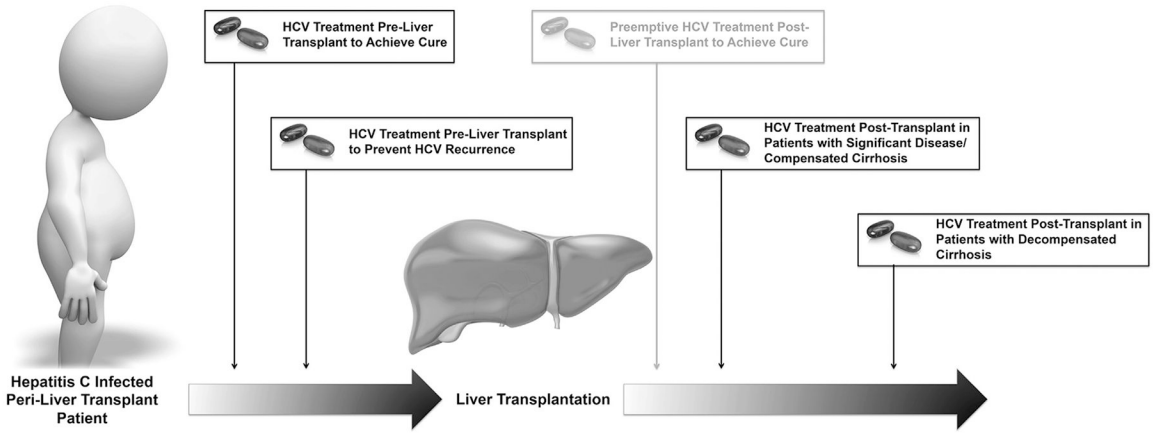

Fig. 1.
HCV treatment strategies for peri-LT patients.

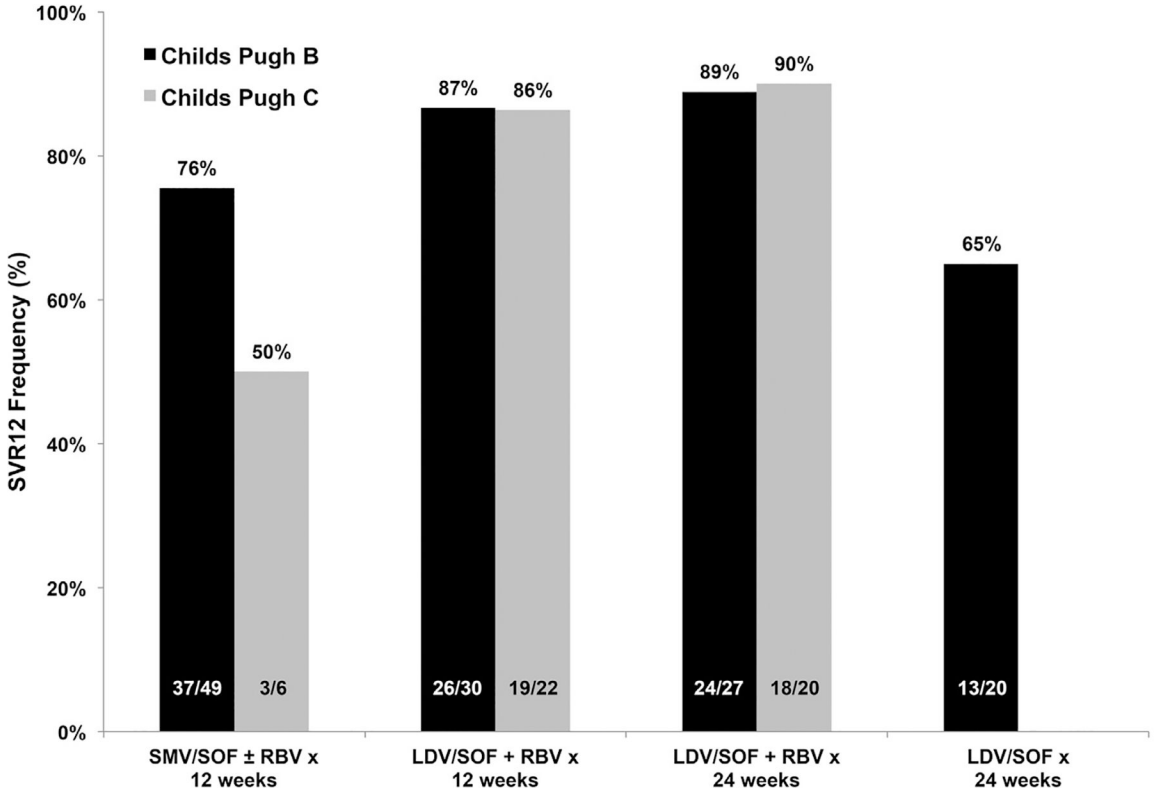

Fig. 2.

Virologic responses with varying regimens in patients with decompensated cirrhosis.

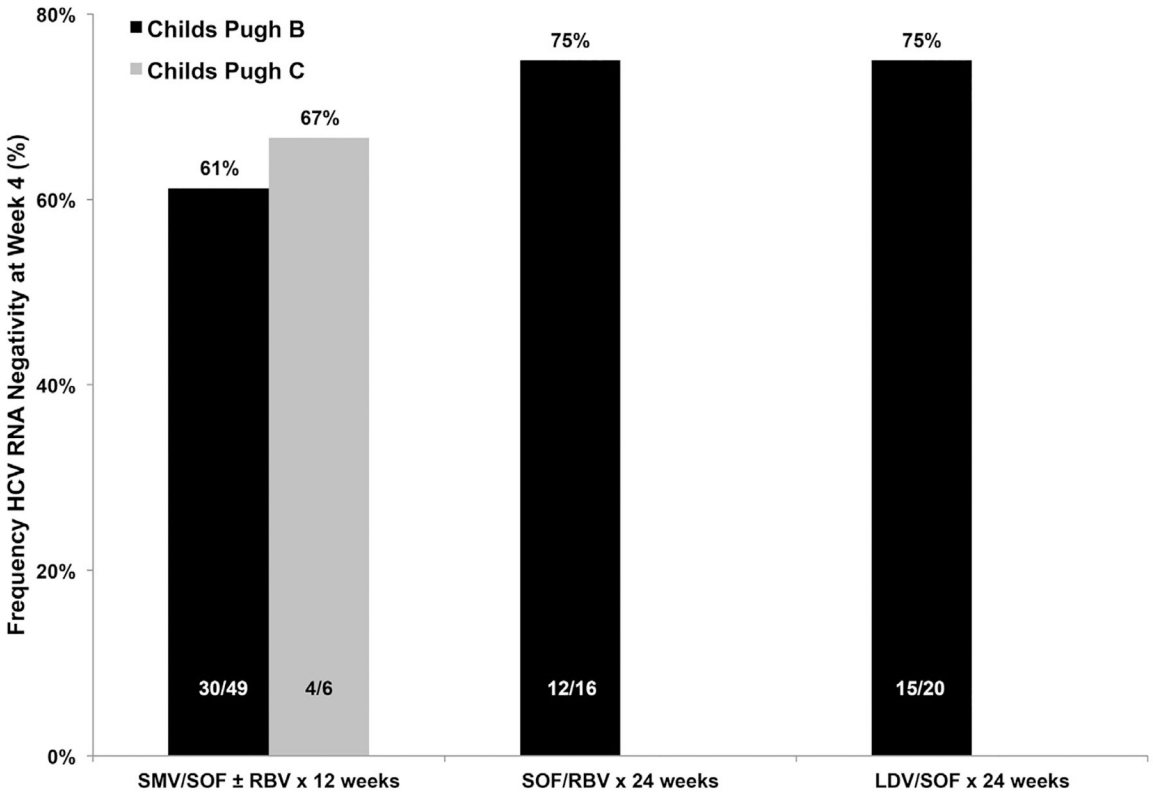

Fig. 3.

On-treatment virologic response at week 4 with varying regimens in patients with decompensated cirrhosis.

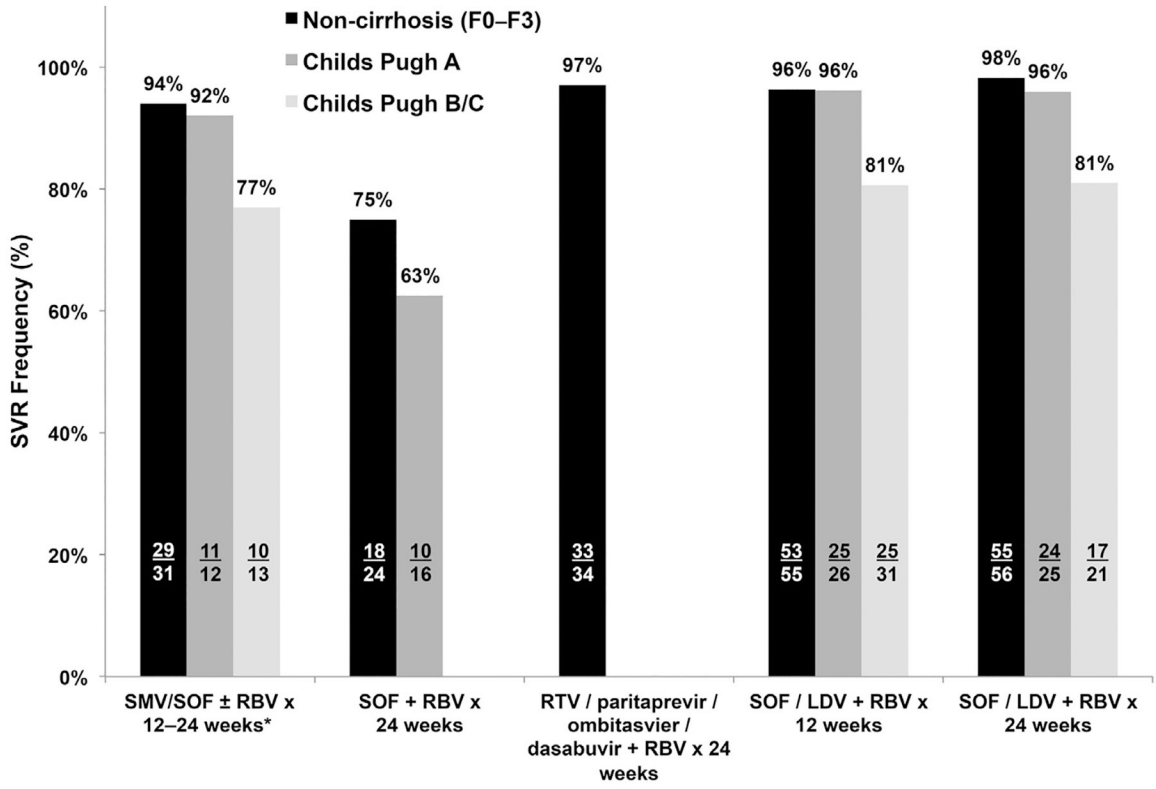

Fig. 4.

Virologic responses in post-LT patients with varying regimens by degree of liver disease. [a] CP class A = cirrhosis with a MELD score less than 10; CP class B/C = cirrhosis with a MELD score of 10 or greater. Of note, results for F0-F3 and CP class A LT recipients in the SOLAR-2 study were presented in a combined format but were included in F0-F3 bars.

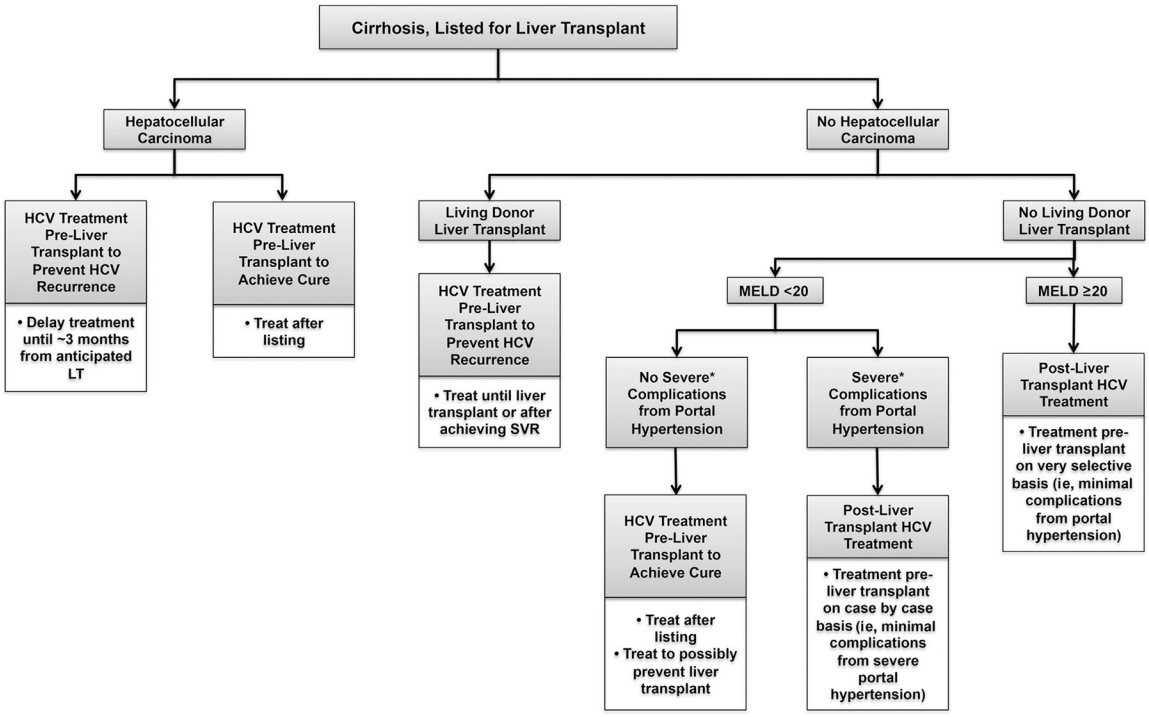

Fig. 5.

Suggested approach to HCV treatment in pre-LT patients. [a] Severe complications from portal hypertension are generally medically refractory ascites or encephalopathy.

Table 1

Characteristics of new DAAs against HCV

DAA	Mechanism of Action	Genotypic Coverage	Special Considerations
Approved			
Telaprevir	NS3/4A protease inhibitor	1	Discontinued in United States
Boceprevir	NS3/4A protease inhibitor	1	To be discontinued in United States December 2015
Simeprevir	NS3/4A protease inhibitor	1, 4	Mild CYP3A inhibition Indirect hyperbilirubinemia
Sofosbuvir	Nucleotide NS5B polymerase inhibitor	Pan-genotypic	Renal clearance
Ledipasvir	NS5A replication complex inhibitor	Pan-genotypic	—
Paritaprevir/ritonavir	NS3/4A protease inhibitor	1, 4	CYP3A inhibition Indirect hyperbilirubinemia
Ombitasvir	NS5A replication complex inhibitor	1, 4	—
Dasabuvir	Non-nucleoside NS5B polymerase inhibitor	1, 4	—
Experimental			
Asunaprevir	NS3/4A protease inhibitor	1, 4	Weak CYP3A induction
Grazoprevir	NS3/4A protease inhibitor	Pan-genotypic	—
Daclatasvir	NS5A replication complex inhibitor	Pan-genotypic	—
GS-5816	NS5A replication complex inhibitor	Pan-genotypic	—
Elbasvir	NS5A replication complex inhibitor	Pan-genotypic	—
Beclabuvir	Non-nucleoside NS5B polymerase inhibitor	1	—

Table 2

Safety outcomes by HCV treatment regimen in patients with decompensated cirrhosis

Regimen	N	Safety Outcomes
SMV/SOF ± RBV × 12 wk[13]	49 CP class B; 6 CP class C	• 11% (6 of 55) early treatment discontinuation • 22% (12 of 55) hospitalized • 20% (11 of 55) infection requiring antibiotics • 20% (11 of 55) further hepatic decompensation • 2% (1 of 55) death
LDV/SOF + RBV × 12–24 wk[18]	59 CP class B; 49 CP class C	• CP and MELD scores improved from baseline in most patients • Low rates of grade 3/4 AEs, serious AEs (more common in 24-wk arm) • No treatment discontinuations in 12-wk arm, 3 in 24-wk arm • 5% (3 of 59) deaths in CP class B, 6% (3 of 49) deaths in CP class C, none attributed to study drugs
LDV/SOF + RBV × 24 wk[19]	13 CP class B	• 2 patients experienced serious AEs: one caused by patient's baseline bipolar disorder and one caused by anemia, chest pain, and cholecystitis • No deaths
SOF/RBV[15]	88 Cirrhosis and MELD >10	• 31% (27 of 88) had a serious AE, 11% (10 of 88) had hepatic decompensation *, 8% (7 of 88) had infections • No deaths
SOF/RBV × 24 wk[24]	15 CP class B; 1 CP class C	• Mean change from baseline of albumin was 0.4 g/dL, of bilirubin was −0.2 mg/dL, and of MELD score was −1 • Improvement of baseline ascites and hepatic encephalopathy
SOF/DCV + RBV × 12 wk[26]	12 CP class A; 32 CP class B; 16 CP class C	• 17% (10 of 60) with serious AEs, all considered unrelated to study treatment • 18% (11 of 60) with grade 3/4 AEs: 4 related to study treatment (anemia, noncardiac chest pain, arthralgia, headache) • 2% (1 of 60) discontinued because of AE: discontinued at time of transplant (attained pTVR) • No deaths

Abbreviations: AE, adverse event; pTVR, post-LT virologic response.

* Combined pre-LT and post-LT patients.

Table 3

Recommended interferon-free regimens by genotype for patients with decompensated cirrhosis

Regimen	Comment
Genotype 1 or 4:	
LDV/SOF + RBV × 12 wk[18]	87% (26 of 30) SVR in patients with CP class B, 86% (19 of 22) SVR in patients with CP class C
LDV/SOF × 24 wk[20]	RBV intolerant; data in patients with decompensated cirrhosis lacking
Genotype 2 or 3:	
SOF/RBV up to 48 wk[39]	Data in patients with decompensated cirrhosis lacking, and exact duration of therapy unknown