New modalities in the treatment of HCV in pre and post-transplantation setting

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ABSTRACT
End-stage liver disease and hepatocellular carcinoma (HCC) secondary to hepatitis C virus (HCV) infection are the leading indications for liver transplantation (LT) in developed countries. Recurrence of HCV following LT is universal if the recipient has detectable serum HCV RNA at the time of LT. Recurrent HCV has an accelerated course and is associated with poor long-term patient and graft survival. Interferon (IFN)-based regimens have achieved low Sustained Virological Rates (SVR) in this setting and are associated with a high rate of adverse events, resulting in treatment discontinuation. With advances in understanding the HCV life cycle, drugs targeting specific steps, particularly inhibiting the NS3/4A protease, NS5B RNA dependent RNA polymerase and the NS5A protein, have been developed. Sofosbuvir (SOF), a nucleotide analogue inhibitor of NS5B polymerase was the first compound to enter the market. Combinations of SOF with new HCV antivirals from other classes have allowed for IFN-free regimens with low rates of adverse events and SVR rates >90%. With the availability of newer agents, the approach to the treatment of HCV infection during the pre-and post-liver transplantation period has changed. We will hereby review the current status of HCV treatment and discuss the potential future therapies in the transplant setting.

Keywords: Liver transplantation, direct acting anti-virals, cirrhosis, waiting list, recurrent hepatitis C

INTRODUCTION
Hepatitis C virus (HCV) infection related end-stage liver disease and hepatocellular carcinoma (HCC) are the leading indications for liver transplantation (LT) in the United States and many countries worldwide (1). Chronic HCV infection is a slowly progressive disease. Cirrhosis is seen among 20%-30% of patients with HCV infection 10-20 years after the infection. Ascites, encephalopathy, jaundice, variceal bleeding and failure of synthetic functions characterize the development of decompensation and occur in 2.9%-3.7% of cirrhotic patients annually. In addition, 4%-3.3% of patients with HCV-related cirrhosis develops HCC each year (2). Escalating numbers of patients are likely to need transplantation or experience HCV-related liver failure or HCC over the next 2 decades (3). Recurrent HCV infection following LT is immediate and universal if the recipient has detectable HCV RNA at the time of LT (4). Reinfection of the graft with HCV has a progressive course in immunosuppressed recipient, leading to cirrhosis in up to 20%-30% of recipients only 5 years after LT (5,6).

The optimal way of improving the long-term survival for HCV-infected LT recipients is achieving a sustained virological response (SVR) or HCV cure. In the peri-transplant setting, HCV infection can be treated before transplantation, early after transplantation on preemptive basis or at the time of biopsy-proven recurrent HCV infection during the post-transplant period. Interferon (IFN)-based therapies are not ideal in the transplant setting with reported low SVR rates together with a high incidence of adverse events (AEs), often requiring dis-
continuation of the treatment. Boceprevir and telaprevir, as the first HCV directly acting antivirals (DAAs) introduced in 2011 and inhibiting the HCV protease, NS3A/4A, had to be combined with IFN and ribavirin (RBV). They led to slightly higher SVR rates in return for overlapping toxicities with IFN/RBV and serious drug interactions with immunosuppressive agents. Newer DAAs have allowed for regimens not containing IFN and RBV, and have advanced the management of chronic HCV dramatically in recent years. Evaluation of the safety and efficacy of IFN-free therapies during pre- and post-LT settings has great impact with the expectation of improvements in long term survivals of both the recipients and the grafts. New data reporting encouraging results with sofosbuvir (SOF) and RBV in both pre- and post-transplant setting have been published. We will review the current treatment modalities and discuss the future therapies in these patients.

**Direct-acting antivirals (DAAs)**

With advances in understanding of the HCV life cycle, inhibitors of the NS3/4A protease, NS5B RNA dependent RNA polymerase (nucleoside and non-nucleoside analogs) and NS5A replication complex have been developed (Figure 1) (7). In late 2013, the FDA approved SOF and simeprevir (SIM) for chronic HCV treatment. In January 2014, the American Association for the Study of Liver Diseases (AASLD) and Infectious Diseases Society of America (IDSA) published joint guidelines for the management of chronic HCV infection. In these guidelines, it is recommended to not use telaprevir- or boceprevir-containing regimens. As the initial therapy of HCV genotype 1 infection, SOF+IFN+RBV combination for 12 weeks is recommended. If a patient is not suitable for IFN use, SOF+SIM combination for 12 weeks is recommended. For genotype 2 and 3, SOF+RBV without IFN, is recommended (8). Although not much transplant-specific data are available yet, most of our transplant experience is a reflection of the experience gained among chronic HCV patients. Sofosbuvir is a pan-genotypic HCV-NS5B RNA-dependent RNA-polymerase uridine-analogue nucleotide inhibitor and has high genetic barrier for resistance. No dose adjustment is required for any level of hepatic dysfunction. But due to its renal excretion, SOF is not recommended for those having creatinine clearance ≤30 mL/min or ongoing dialysis (9,10). SIM is a second generation HCV NS3/4 protease inhibitor that is used at a single dose of 150 mg. It has clearly less side effects compared to telaprevir and boceprevir. It is active against genotypes 1, 2, 4-6. Renal impairment does not necessitate any dose adjustment, however it should not be used in severe hepatic impairment (11).

Daclatasvir, a NS5A inhibitor which is active against all genotypes, has been recently approved by European Commission in
Combination with SOF. Asunaprevir, an NS3/4A protease inhibitor, also received regulatory approval in Japan in combination with daclatasvir. In October 2014, FDA approved a fixed-dose pill including ledipasvir 90 mg, an HCV NSSA inhibitor and SOF for treatment of HCV genotype 1. The daily fixed-dose combination of paritaprevir, ritonavir, and ombitasvir with dasabuvir has recently been approved by FDA for the treatment of HCV genotype 1a infection in treatment-naïve patients (8).

Treatment for patients on liver transplantation waiting list
The main aim of treating HCV infection while the patient is on the waiting list is to avoid infection of the new allograft by achieving undetectable HCVRNA at the time of transplantation (12). Another expected benefit of antiviral therapy may be improving the liver function to a point that transplantation is no longer necessary. Although this strategy has been proven for hepatitis-B related cirrhosis, the data in the case of HCV-related cirrhosis remains unclear (13).

IFN-based therapies
Several published studies have examined the role of standard or pegylated IFN (PEG-IFN) in both standard and low accelerating dose regimens with or without RBV for patients on the liver transplant waiting list. Those studies have reported 20%-30% of post-transplantation virological response (pTVR) rates with high incidence of serious adverse effects (SAEs) which were more pronounced among those with high Model for End-Stage Liver Disease (MELD) and Child-Pugh Turcotte (CPT) scores, and lower response rates with genotype 1 patients (14-16). According to a report by Everson et al. (16), treating the patients with Peg-IFN-a2b/RBV in pre-transplant period for more than 16 weeks prevented post-transplant recurrence of HCV infection more effectively in a subgroup of patients. Patients infected with HCV genotypes 2 and 3, and those having the IL28B CC genotype had higher response rates (17). In patients with advanced liver disease, the use of IFN has been associated with severe cytopenias and fatal cases of serious bacterial infections including spontaneous bacterial peritonitis and bacteremia (15). With the addition of boceprevir or telaprevir, SVR rates of 51% and pTVR rate of 67% were reported in patients with genotype 1. The major concern with these regimens was the low tolerability rate. SAEs caused the discontinuation of therapy in 31% of patients (18). In the absence of alternative therapies, IFN-based therapy can only be an option for patients with a chance of better response rates, namely those with genotype 2-3 infection, IL28B CC polymorphism, CPT score <7, MELD<18, or HCC as indication for transplantation (19).

IFN-free regimens of SOF and RBV on pre-transplant setting
Recently, Curry et al. (20) published results of aphaese II, open label study including 61 previously treated patients with HCV GT 1–3 related HCC or cirrhosis with CPT scores of ≤7 (G2-3: 25%). SOF 400 mg/day plus RBV (1000–1200 mg/day) were administered for up to 48 weeks. Forty-six individuals received LT. Forty-three patients (93%) had plasma HCVRNA levels <25 IU/mL at the time of LT. Of these 43 patients, 30 (70%) had pTVR12, 10 (23%) had recurrence of HCV infection and 3 (7%) died (2 from primary graft dysfunction and 1 due to hepatic arterial thrombosis). Recurrence was found to be in inverse relationship with the number of consecutive days of undetectable HCVRNA before LT. The SOF and RBV combination was generally well tolerated. Fatigue (38%), headache (23%) and anemia (21%) were reported as AEs. This study was critically important and showed that when the patient is HCV (-) at the time of LT with this all oral combination, 70% will have pTVR. The major limitation of this study was the lack of decompensated cirrhotic patients in the cohort.

Efficacy of DAA-containing regimens in cirrhosis and future IFN-free regimens in pre-transplant setting
Genotype-1
To increase the efficacy of SOF and RBV particularly in treatment experienced genotype 1 patients, a combination of SOF with NSSA inhibitor (e.g. daclatasvir, ledipasvir) or NS3/4A protease inhibitor (e.g., SIM) has been evaluated. The ELECTRON was the first study to assess the efficiency of SOF, ledipasvir (LDV) and RBV combination in cirrhotic and non-cirrhotic individuals with HCV genotype 1, including both treatment-naïve and null responders. Twelve weeks therapy with LDV/SOF and RBV resulted in SVR 12 rates of 100% for both non-cirrhotic naive and null responders. Among null responder cirrhotic patients, LDV/SOF with or without RBV, achieved SVR rates of 100% and 70%, respectively (21). In the LONESTAR study assessing 12 weeks treatment of LDV/SOF combination with or without RBV in patients with genotype 1.22 (55%) out of 40 enrolled patients were cirrhotic and previously treated with protease inhibitors. Overall SVR rates with and without RBV were reported as 100% and 95%, respectively in this subgroup of patients. The most common AEs were nausea, anemia, upper respiratory tract infection, and headache, with 1 participant experiencing SAE of anemia that was thought to be related to RBV (22).

The ION-1 study enrolled 865 treatment-naive G1-infected patients (16% cirrhotic) to assess the efficacy and safety of LDV/ SOF treatment with or without the addition of RBV for 12 and 24 weeks and reported SVR rates of 97%-99% for all groups. Subgroup analysis revealed SVR rates of 94%-99% for patients with cirrhosis among all groups (23). The ION-II study evaluated the same treatment regimens for previously treated patients, and 20% of patients were cirrhotic. Overall SVR rates were 92% and 98% for cirrhotic and non-cirrhotic patients, respectively. Although SVR rates for 24 weeks treatment (with or without RBV) were similar for non-cirrhotic and cirrhotic patients, SVR12 rates were significantly lower among patients with cirrhosis, being 82% and 86%, with or without RBV, respectively (p=0.007). No treatment discontinuation due to an adverse effect was reported (24). This study suggests that cirrhotic patients need longer duration and/or the addition of RBV to enhance the success rate of treatment.
The COSMOS trial assessed the combination of SIM (150 mg/day) and SOF (400 mg/day) with or without RBV in genotype 1 patients for 12 and 24 weeks. Cohort 1 consisted of non-responders with low fibrosis scores (F1–F2) and cohort 2 consisted of non-responder or naive patients with high fibrosis scores of F3–F4. SVR rates were 95% and 94%, for cohort 1 and 2, respectively. Neither the addition of RBV nor treatment extension to 24 weeks improved the SVR rates significantly in patients with higher fibrosis scores and compensated cirrhosis. This study showed a very good safety profile with 2% incidence of severe AEs and associated drug withdrawal (25).

A phase 3 study of daclatasvir (60 mg/day) and asunaprevir (100 mg/day) for 24 weeks in genotype 1b patients who were treatment-naïve (n:307), previous non-responder (n:205) and ineligible and/or intolerant to Peg-IFN and RBV (n:235) achieved SVR 12 rates of 90%, 82% and 82% in each cohort, respectively. Cirrhosis was present in 49 (16%) naive, 63 (31%) non-responder and 111 (47%) IFN-ineligible and/or intolerant patients. Overall SVR rates were similar for patients with and without cirrhosis (84% vs 85%). HCVRNA levels of less than 25 IU/mL were present by week 4 in 83%, 73% and 68% of naive, non-responder and IFN ineligible and/or intolerant patients, respectively (26).

Recently reported data from the TURQUOISE –II study indicated that the regimen of paritaprevir/ombitasvir and dasabuvir with RBV (paritaprevir, NS5A protease inhibitor; ombitasvir, NS5A inhibitor; dasabuvir, HCV NS5B RNA polymerase inhibitor) in compensated HCV genotype 1-infected Child A cirrhotic patients achieved SVR rates of 91.8% and 95.9% following 12 and 24 weeks of treatment, respectively. SVR rates with this combination were 89%–97% for patients with platelet<100000/mm³ and 84%–89% for patients with hypoalbuminemia (<35 g/L). In this study, 2.1% of the patients discontinued treatment owing to AEs (27).

There are ongoing studies for other new DAAs. Grazoprevir (formerly MK-5177) is a second generation protease inhibitor with potent anti-viral activity and high barrier to resistance. Elbasvir (formerly MK-8742) is a potent NS5A inhibitor. Grazoprevir (100 mg/day) and elbasvir (25 or 50 mg/day) combination with or without RBV was assessed in phase II trial among patients with HCV G1 infection. This grazoprevir-based regimen resulted in high (90%–100%) SVR irrespective of RBV use or extension of treatment duration (12 vs 18 weeks) (28). With 6 weeks of treatment, the addition of SOF to this combination resulted in SVR rates of 80% and 87% in patients with or without cirrhosis, respectively. Treatment for 8 weeks increased the SVR to 95% among cirrhotics (29).

Genotype 2-3
The FUSION study which enrolled previously non-responder G2-3 patients, with one third of them being cirrhotics, to SOF and RBV treatment, reported SVR 12 rates of 60% and 19% following 12 weeks of treatment for G2 and G3 patients, respectively. Extending the treatment to 16 weeks increased SVR 12 rates to 78% for G2 patients and 61% for G3 patients (30). In the VALENCE study which included both treatment naïve and experienced G-2 patients with a cirrhosis ratio of 21%, the SVR rate was reported to be 93% on 12 week treatment with SOF and RBV. However, the SVR rate remained as 85% for G3 patients after 24 weeks of treatment, with even lower response rates in patients with cirrhosis (68% vs 91%) (31). To increase the response rate for G3 patients with cirrhosis, treatment should be extended to 24 weeks.

Decompensated cirrhosis
Data for use of DAAs in HCV-related decompensated cirrhosis are limited to small series or preliminary data. Flamm et al. (32) evaluated LDV, SOF, and RBV treatment in HCV genotype 1 and 4 infected patients with decompensated cirrhosis. According to reported preliminary data, an HCV RNA level of less than 15 IU/mL at week 4 was achieved in 81% and 86% of CPT-B and 100% and 81% of CPT-C patients in the 12 and 24 weeks treatment groups, respectively. SVR 4 rates were 88.9%-91 in Child B and 90.5%–33.3% in Child C patients. Seven CPT-C patients discontinued the study because of LT (n:2), AEs (n:3) and death (n:2). Twenty-eight patients (26%) experienced SAEs during treatment. Four severe events, including anemia, hepatic encephalopathy, and peritoneal hemorrhage, encountered in 4 patients (4%) were regarded as study treatment-associated. Aqeel et al. (33) enrolled 19 patients on the waiting list for LT and having HCV genotype-1 infection and treated them with 12 weeks of SIM/SOF. According to preliminary results, treatment was well tolerated, safe and effective. In total, 70% of patients were HCVRNA negative at week 4 and all were negative at the end of treatment. Lingala et al. (34) reported end of treatment viral response to be achieved in all 25 decompensated cirrhotic patients (18 and 16 of them had ascites and esophageal varices at baseline, respectively) with CPT score of ≥7 after SIM/SOF±RBV treatment with no further decompensation. A proposed algorithm for the treatment of hepatitis C infection in patients on waiting list for LT is shown in Figure 2.

Specific issues for IFN-free regimens in patients awaiting LT
The most important target for pre-transplant treatment of HCV is achieving undetectable HCVRNA at the time of transplantation. In the study by Curry et al., treatment with SOF and RBV resulted in rapid suppression of circulating virus with a median decrease of 3.93 log10 IU/mL in HCV RNA following the first week of treatment. At week 4, 54 of the 58 treated patients (93%) had negative HCV RNA. Importantly, the rate of decline in HCV RNA levels was not affected by prior HCV treatment history or CTP class. pTVR was positively correlated with the number of days with undetectable HCV RNA before the transplantation (20). Treatment with daclatasvir and asunaprevir in a cohort including cirrhotic patients resulted in relatively rapid HCVRNA reductions. HCVRNA of less than 25 IU/mL at week 4
options to provide pre-transplant viral clearance, particularly directly acting antiviral regimens may be potential treatment including only these drugs are not acceptable (37). HCV NS5B polymerase inhibitor, has high genetic barrier to resistance. Because, NS3/4A protease and NS5A inhibitors have low genetic barriers to resistance, combinations because of this, NS3/4A protease and NS5A inhibitors have high genetic barrier to resistance. SOF, as a nucleotide HCV NS5B polymerase inhibitor, has high genetic barrier to resistance. Because, NS3/4A protease and NS5A inhibitors have low genetic barriers to resistance, combinations including only these drugs are not acceptable (37).

Another important issue is risk of viral breakthrough or emergence of resistant variants. HCV replicates with an enormous rate that enables the mutations to occur at every site of the genome (36). Under single drug therapy, resistant variants become dominant and escape from the treatment. SOF, as a nucleotide HCV NS5B polymerase inhibitor, has high genetic barrier to resistance. Because, NS3/4A protease and NS5A inhibitors have low genetic barriers to resistance, combinations including only these drugs are not acceptable (37).

Directly acting antiviral regimens may be potential treatment options to provide pre-transplant viral clearance, particularly for patients waiting for living donor liver transplantation. At our center, HCV (+) recipients of HCV (-) live donors are treated with oral antiviral agents. Liver transplantation from an HCV (-) live donor is scheduled at least 4 weeks after the first HCV RNA negativity of the recipient. For cadaveric recipients, HCV treatment may be postponed to the post-transplantation period to increase the available donor pool by matching the HCV positive candidate to an HCV positive deceased donor. In preliminary data obtained from cadaveric liver transplantation, our group has observed that 40% of HCV-positive recipients have received livers from HCV-positive donors (38).

**Treatment for post-transplantation HCV infection**

Reinfecion of the graft with HCV infection has an accelerated course in immunosuppressed patients (5,19). Recurrent HCV infection leads to cirrhosis in up to 20%-30% of liver recipients only 5 years after LT (6). Decompensation following the cirrhosis is usually rapid in LT recipients, occurring in more than 40% of them at 1 year, in comparison with to less than 5% in immunocompetent patients (39,40). Compared with uninfected recipients, survival is poor for HCV-infected LT recipients (41). Risk factors, including donor age of >40 years, genotype 1 infection, CMV viremia, HIV co-infection, steroid treatment for acute rejections and recipient factors including female sex, older age, metabolic syndrome, race/ethnicity and IL28B non-CC genotype, have been reported to be associated with severe or rapid recurrence of advanced fibrosis (42-50). A high HCV RNA level both at the time of and early after LT is a well-defined predictor for increased risk of progressive recurrent HCV infection and graft loss following liver transplantation (51-53).

**IFN-based therapies**

Treating the recurrent HCV infection with IFN-alfa and RBV after liver transplantation results in low virological response rates, particularly for genotype 1 HCV infection. The combination is not well tolerated, and resulted in high rates of SAEs and treatment discontinuation (54-56). In a randomized controlled study evaluating peg-IFN and RBV treatment for recurrent hepatitis C following LT, SVR rates of 48% were reported in the F1-F2 fibrosis group and 18.5% in the severe fibrosis group (F3-F4 and cholestatic hepatitis) (57). A systematic review (19 studies with 611 patients) evaluating the recurrent hepatitis C treatments, reported mean SVR rate of 30.2% (range 8%-50%) with a mean dose reduction and treatment discontinuation rates of 73% and 27.6%, respectively (58). The addition of first generation protease inhibitors to therapy achieved SVR 12 rates of 50%-63%; however there was an increased incidence of SAEs requiring discontinuation of therapy. The most frequent AE was anemia reaching up to 72% in 1 study (59-61). The use of telaprevir and boceprevir after LT has high potential for toxicity and drug-drug interactions with calcineurin inhibitors (CNIs).

**IFN-free regimens for post-transplant recurrent hepatitis C**

Fontana et al. showed the efficacy of antiviral agents after LT in a case of severe recurrent cholestatic hepatitis C genotype...
1b. The patient had a partial virologic response to peg-IFN/RBV therapy but required re-transplantation. After the second LT, early recurrent cholestatic hepatitis C was treated with daclatasvir 20 mg/day in addition to peg-IFN/RBV for 24 weeks with resulting SVR (62). A year later, the same authors reported a case of recurrent cholestatic hepatitis C which was successfully treated with SOF 400 mg/day and daclatasvir 60 mg/day combination for 24 weeks (63).

The results in 12 patients who received SOF and daclatasvir via expanded access (+RBV for 6 patients) were promising. Patients had severe or advanced liver disease (3 with fibrosing cholestatic hepatitis and 9 with cirrhosis). Nine patients completed 24 weeks of treatment with SOF 400 mg/day and daclatasvir 60 mg/day and all had undetectable HCV RNA levels at the end of treatment. SVR 8 was available for 5 patients with all having undetectable HCV RNA. 3 patients died because of liver failure, gastrointestinal bleeding and sepsis, while 4 patients had severe events (64).

Charlton et al. performed a prospective multicenter open-label pilot study of 40 LT recipients with recurrent HCV of any type. Of those, 83% were infected with genotype 1.40% were compensated cirrhotic patients and 88% were previously treated with IFN-based therapies. Patients received SOF 400 mg/day plus RBV that was initially given at dose of 400 mg/day and regulated according to the creatinine and hemoglobin levels. SVR 12 was achieved in 28/40 (70%). The RBV dose did not influence the SVR rate. Reported AEs were fatigue (30%), diarrhea (28%), anemia (20%) and headache (25%). No viral resistance, death, graft loss or rejection episode was reported. Importantly, no significant drug interaction with immunosuppressant drugs was observed (65).

Kwo et al. allowed 34 liver transplant recipients with no or minimal fibrosis to take paritaprevir (150 mg)/ritonavir (100 mg) and ombitasvir (25 mg) with dasabuvir (250 mg, twice-daily) and weight based RBV for 24 weeks. Of the 34 participants, 33 (97%) had SVR at weeks 12 and 24. Five patients (15%) required erythropoietin. The most frequently encountered AEs were fatigue, headache and cough. No episode of graft rejection was observed. Because of the drug interactions between ritonavir and CNIs, doses of cyclosporine and tacrolimus were needed to be adjusted (66).

A compassionate use program of SOF 400 mg/day and RBV (up to 48 weeks) included 104 LT recipients with recurrent HCV that mostly included cases of severe cholestatic hepatitis, fibrosis score of F32, compensated or decompensated cirrhosis. With treatment, 60 (58%) patients showed clinical and biochemical improvement, while 22 (21%) remained stable. The remaining 22 (21%) patients had progressive disease or died. At the end of treatment, out of 93 patients who had available testing, 76 (82%) had an undetectable HCV RNA level. Out of 85 patients reaching post-treatment follow-up of 12 weeks, 53 (62%) patients achieved SVR. These results were encouraging for severe recurrent hepatitis cases and showed the effect of anti-viral therapy on disease progression (67).

Lutchman et al. reported early data for treatment of 55 post-transplant recurrences of HCV infection with either SOF/RBV or SOF/SIM combinations. Infection with genotype 1 was seen in 75% of the patients. A greater proportion of patients treated with SOF/SIM had undetectable HCV RNA at week 4 compared to the SOF/RBV group (70%–74% vs. 50%); however at week 8, all patients had undetectable HCV RNA, irrespective of genotype or regimen. Nine AEs and 1 SAE (colitis) were reported for the SOF/SIM group; none were reported in the SOF/RBV group (68). In a retrospective analysis of SOF (400 mg/day) and SIM (150 mg/day) combination with or without RBV in 77 recipients, the SVR4 was reported as 92% (69). Leroy et al. assessed the efficacy of SOF and daclatasvir-based regimen that was used for 21 post-transplant patients with mostly decompensated biopsy-proven fibrosing cholestatic hepatitis. The study showed significant improvements in liver functions and ascites in 90% of patients, and undetectable HCV RNA levels in 81% (70). Figure 3 shows suggestions for the future treatment of recurrent HCV infection following LT.

The SOLAR study was a multicenter, randomized controlled study that enrolled treatment-naive and treatment-experienced liver transplant recipients with HCV genotype 1 or 4 (n=223). Histological and clinical severity of recurrence among enrolled patients ranged from F0 to F3 fibrosis (n:111) to compensated CTP-A (n:51) and decompensated CTP B/C cirrhosis (n:61). Patients were randomized to receive LDV (90 mg) and SOF (400 mg) combination in fixed-dose, and RBV for either 12 or 24 weeks. In intention-to-treat analysis, SVR rate was 96% for patients with F0 to F3 fibrosis and compensated cirrhosis, after both the 12- and 24-weeks of treatment. The RBV dose was adjusted according to the weight for patients with F0 to F3 fibrosis and CTP- A cirrhosis. For patients with CTP-B or C cirrhosis, RBV was initiated at a dose of 600 mg/day, and the dose was increased according to the tolerance. Treatment discontinuation due to side effects was observed only in 2% of the patients. The SVR12 rate was lower in CTP-B and C cirrhosis patients, (85% and 60%, respectively) with no significant increase by extension of treatment to 24 weeks. The mortality rate of the study was 10% for individuals with CTP-B or -C cirrhosis (71).

Specific issues for IFN-free regimens in LT patients with recurrent hepatitis C

Drug-drug interactions are important issues in post-transplant period. Unlike the first generation protease inhibitors, new DAAs have less significant drug interactions. For SOF and daclatasvir, no dose adjustment is necessary when co-administered with tacrolimus or cyclosporine (62,65). ABT-450 (paritaprevir)/ritonavir treatment did not affect the CNI level significantly (67). SIM does not need dose adjustment on simultaneous use with tacrolimus (10). In an early data from an ongoing study
Review

When to treat HCV: Before or after transplantation

Treating HCV infection prior to LT can prevent infection of the graft and hepatic and extra-hepatic manifestations of post-transplant recurrent hepatitis C. In some cases, eradication of HCV pre-LT may improve liver function and avoid the need for transplantation entirely. However, treatment may not always be possible because of severe hepatic failure or other co-morbidities such as renal failure. In addition, in order to prevent infection of the allograft, undetectable HCV RNA level must be achieved which typically takes between 4-8 weeks. For some candidates on the waitlist, the timing of transplantation is uncertain and may not be sufficient duration of treatment pre-LT to achieve an undetectable HCV RNA. Finally depending on organ availability in the particular region, one may also consider the donor pool, because delaying treatment post-LT would allow candidates to receive allografts from HCV-infected donors.

In conclusion, both HCV-infected patients on the waiting list and those with recurrent hepatitis C following LT will significantly benefit from HCV treatment prior to transplantation.

HIV/HCV co-infection in liver transplant setting

Effective antiretroviral therapy (ART) achieved significant improvement in the survival of human immunodeficiency virus (HIV) infected patients. HCV-related liver disease is leading cause of morbidity and mortality in these patients. While LT is performed for patients with HIV in several centers of North America and Europe, it is not widely offered mainly because of the low 5-year survival rate (around 50%) among HIV–HCV-co-infected patients (77).

Available data suggest that HIV-HCV patients treated with newer DAAs have responses similar to HCV-mono-infected patients. Therefore, current guidelines recommend that HIV-HCV-co-infected persons should be treated in the same manner as HIV-uninfected patients, after managing interactions with ART.

The Photon-I study evaluated the efficacy and safety of SOF/RBV combination for 12 weeks in HIV-HCV co-infected patients. SVR rates in G1, G2 and G3 were 76%, 88% and 67%, respectively (78). The ERADICATE study evaluated the safety and efficacy of LDV/SOF in 50 non-cirrhotic, genotype 1 HIV-HCV-co-infected patients (13 treatment-naïve, 37 treatment-experienced). The overall SVR12 was 98%, and there were no deaths, treatment discontinuations, or SAEs (79).

The main issue in the HIV-HCV co-infected population is drug-drug interactions. In contrast to first-generation protease inhibitors, the newer HCV DAAs have fewer drug-drug interactions with ART and immunosuppressive agents. No clinically significant drug interaction has been reported to occur between SOF and antiretroviral agents. For SIM, co-administration with antiretroviral potent CYP34A inhibitors (cobicistat, ritonavir-boosted protease inhibitors) or potent inducers (etavirine, efavirenz, nevirapine) is not recommended. Daclatasvir with dose reduction is recommended with specific antiretroviral drugs (78,80). LDV has been shown to increase tenofovir levels, and can therefore increase the risk of tenofovir-associated nephrotoxicity. This effect is potentiated with ritonavir-containing ART, therefore it is recommended that ART should be changed if possible or the use of LDV should be avoided inpatients on tenofovir and ritonavir (8).

Renal failure and HCV treatment during the transplant period

Initial studies have shown that simultaneous liver–kidney (SLK) transplantation can be performed effectively and safely and that renal graft survival in SLK transplantation is greater than that in renal transplant alone. This is thought to be because of the immune protection provided by the liver graft (72,73). HCV-infected kidney transplant recipients were reported to have higher post-transplant mortality and lower renal graft survival (74). HCV treatment is recommended by KDIGO (Kidney Disease: Improving Global Outcomes) for patients who are candidates for kidney transplantation if comorbidities permit (75). In studies with Peg-IFN-α plus low dose RBV, rates of AEs and treatment discontinuation were high. The most common side effect requiring treatment discontinuation was anemia. In mild to moderate kidney dysfunction, (creatinine clearance >30 mL/min), dose adjustment for SOF, SIM, LDV, paritaprevir/r/ombitasvir or dasabuvir is not necessary. For patients with creatinine clearance <30 mL/min, there are limited data, and the use of DAAs is not currently recommended. Ongoing studies will determine the safety and efficacy of DAAs in this setting. These agents may play a role in live donor renal transplantation for achieving viral clearance prior to the scheduled transplant surgery (76).

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Available data suggest that HIV-HCV patients treated with newer DAAs have responses similar to HCV-mono-infected patients. Therefore, current guidelines recommend that HIV-HCV-co-infected persons should be treated in the same manner as HIV-uninfected patients, after managing interactions with ART.

The Photon-I study evaluated the efficacy and safety of SOF/RBV combination for 12 weeks in HIV-HCV co-infected patients. SVR rates in G1, G2 and G3 were 76%, 88% and 67%, respectively (78). The ERADICATE study evaluated the safety and efficacy of LDV/SOF in 50 non-cirrhotic, genotype 1 HIV-HCV-co-infected patients (13 treatment-naïve, 37 treatment-experienced). The overall SVR12 was 98%, and there were no deaths, treatment discontinuations, or SAEs (79).

The main issue in the HIV-HCV co-infected population is drug-drug interactions. In contrast to first-generation protease inhibitors, the newer HCV DAAs have fewer drug-drug interactions with ART and immunosuppressive agents. No clinically significant drug interaction has been reported to occur between SOF and antiretroviral agents. For SIM, co-administration with antiretroviral potent CYP34A inhibitors (cobicistat, ritonavir-boosted protease inhibitors) or potent inducers (etavirine, efavirenz, nevirapine) is not recommended. Daclatasvir with dose reduction is recommended with specific antiretroviral drugs (78,80). LDV has been shown to increase tenofovir levels, and can therefore increase the risk of tenofovir-associated nephrotoxicity. This effect is potentiated with ritonavir-containing ART, therefore it is recommended that ART should be changed if possible or the use of LDV should be avoided inpatients on tenofovir and ritonavir (8).

When to treat HCV: Before or after transplantation

Treating HCV infection prior to LT can prevent infection of the graft and hepatic and extra-hepatic manifestations of post-transplant recurrent hepatitis C. In some cases, eradication of HCV pre-LT may improve liver function and avoid the need for transplantation entirely. However, treatment may not always be possible because of severe hepatic failure or other co-morbidities such as renal failure. In addition, in order to prevent infection of the allograft, undetectable HCV RNA level must be achieved which typically takes between 4-8 weeks. For some candidates on the waitlist, the timing of transplantation is uncertain and may not be sufficient duration of treatment pre-LT to achieve an undetectable HCV RNA. Finally depending on organ availability in the particular region, one may also consider the donor pool, because delaying treatment post-LT would allow candidates to receive allografts from HCV-infected donors.

In conclusion, both HCV-infected patients on the waiting list and those with recurrent hepatitis C following LT will signifi-
cantly benefit from DAAs. Ongoing studies will determine the optimal duration and combination in this unique population.

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