Mini-Review

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# Direct-acting agents for hepatitis C virus before and after liver transplantation

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**Summary** **Chronic hepatitis C virus (HCV) infection remains a widespread public health concern and many people are infected with HCV. HCV is one of the leading indications for liver transplantation. Direct-acting antiviral agents (DAAs) against HCV have changed the course of chronic HCV infection, however, making it a curable disease. DAA treatment may be initiated before or after liver transplantation. In the present review, we present the available data on DAA treatment of HCV in liver transplant recipients.**

***Keywords:*** Liver transplantation, living donor, hepatocellular carcinoma

## 1. Introduction

Chronic hepatitis C virus (HCV) infection is a serious public health concern worldwide and 130-150 million people are estimated to be infected with HCV (*1*). Chronic HCV infection remains the leading indication for liver transplantation. In the United States in 2011 (*2*), HCV-related cirrhosis was the most common indication for liver transplantation, accounting for approximately 28% to 40% of all liver transplantations.

HCV recurrence after transplantation is inevitable if HCV is not eradicated before transplantation (*3*). HCV reinfection causes significant damage to the liver graft, however, resulting in poor patient survival (*4*). Patients transplanted for HCV-related cirrhosis have a worse 5-year survival than those with other indications (*5*). One postoperative life -threatening condition is cholestatic hepatitis C, which occurs in approximately 5% of patients within the first year after transplantation (*6*).

Direct-acting antiviral agents (DAAs) have changed the outlook for HCV-infected patients. HCV recurrence and poorer graft survival have led to the use of DAA agents in the liver transplantation setting (*7*). The present review discusses the clinical management of interferon-free regimens in patients with HCV in the liver transplantation setting.

## 2. Pre-transplant use

Treatment with DAAs substantially improves liver function in some patients with decompensated cirrhosis. Therefore, some patients on the waiting list can be delisted and avoid or postpone transplantation.

### 2.1. *Sofosbuvir-based therapy*

Sofosbuvir and simeprevir was well-tolerated, resulting in a sustained viral response for 12 weeks (SVR12) of 74% and 100% in patients with genotype 1a and 1b, respectively (*8*). In a multicenter study (*9*) with the same regimen in decompensated and compensated patients reported an SVR12 of 74% and 91%, respectively.

The SOLAR-I (*10*) and SOLAR II (*11*) studies disclosed that patients with advanced liver diseases and Child Pugh B or C cirrhosis who were waiting for liver transplantation treated with sofosbuvir, ledipasvir, and ribavirin had an SVR12 and SVR24 of 85-89% and 78-96%, respectively. In the ALLY-1 phase 3 study (*12*), 60 patients with cirrhosis and multiple genotypes (1, 2, 3, 4, and 6) were treated and an SVR12 was achieved in 92% of patients with Child-Pugh class A cirrhosis, 94% of patients with Child-Pugh class B, and 56% of

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patients with Child-Pugh class C, respectively.

A UK study (*13*) reported an SVR12 from 60% to 92% in patients with decompensated cirrhosis with genotype 1 or 3 and a Child-Pugh score of more than 7 after administration of sofosbuvir with ledipasvir or daclastavir with or without ribavirin therapy. In another study (*14*), liver transplant candidates with hepatitis C cirrhosis underwent interferon-free therapy (sofosbuvir + ribavirin, sofosbuvir + daclastavir ± ribavirin, sofosbuvir + simeprevir ± ribavirin) and 88% of the patients with decompensated cirrhosis achieved an SVR12. Administration of new combination of sofosbuvir and velpatasvir for 12 weeks provided decompensated cirrhotic patients an SVR of 88% (*15*). In the ASTRAL-4 study (*16*), patients with decompensated cirrhosis and HCV genotypes 1, 2, 3, 4, and 6 underwent combined sofosbuvir and daclatasvir administration with or without ribavirin for 12 weeks or without ribavirin for 24 weeks and the SVR12 was 87%.

Donato *et al*. (*17*) reported that of 31 patients treated with sofosbuvir (400 mg/day) and ribavirin (600-1200 mg/day) for 24 to 48 weeks before liver transplantation, HCV was eradicated in 12 before liver transplantation.

### 2.2. *Gazaprevir and elbasvir*

The C-SALT study part A (*18*) revealed that gazaprevir and elbasvir in patients with Child Pugh class B decompensated cirrhosis yielded an SVR12 of 90%. There are no data on patients with Child Pugh class C decompensated cirrhosis. A European study (*19*) reported that 143 Child Pugh class B patients and 22 class C patients underwent sofosbuvir/daclastavir treatment with or without ribavirin for 24 weeks and achieved an SVR12 of 86% and 76%, respectively.

A recent study (*20*) analyzed the outcome of various DAAs for patients with HCV-related cirrhosis on the waiting list for transplantation. After treatment with DAAs for 6 months, HCV inactivation was achieved in 16% of the patients, but none of the patients were delisted. The model for end-stage liver disease scores improved by a median of 3.4 points and the Child-Turcotte-Pugh (CTP) scores improved by 2 points. Another study showed that 36% of the patients had a biologic response with regression to CTP class A after a 12 -week follow-up. In a study of subjects with hepatocellular carcinoma and well-compensated cirrhosis treated with sofosbuvir and ribavirin, 30 patients underwent transplantation and achieved an SVR12 (*21*). It is important to note, however, that no patients with decompensated cirrhosis were enrolled in that study.

### 2.3. *HCC recurrence*

A recent study (*22*) demonstrated higher rates of HCC recurrence following HCV eradication by DAA agents. More recent prospective data , however, showed that the risk of HCC recurrence was comparable to that of the previous therapy with interferon.

### 2.4. *Benefit of pre-transplant use of DAA*

The benefits of pre-transplant use of DAA, however, remain uncertain. In cases of diseased donor liver transplantation, the improved MELD score after DAA therapy may lead to a loss of priority or even eligibility for liver transplantation. The 2016 EASL guidelines for HCV treatment advised postponing DAA therapy for patients with MELD scores ≥ 18. The use of costly DAAs in patients with a risk of progressive liver disease may be problematic. Furthermore, in cases with HCC, the risk of HCC recurrence may be increased after DAA therapy (*22,24*). Further prospective studies are needed to address several difficult questions in the pre-liver transplant cohort.

## 3. Treatment after transplantation

DAA is effective for the treatment of HCV in liver transplantation patients. Sofosbuvir and ribavirin were administered to 40 post-transplant patients for 24 weeks with recurrent HCV (all genotypes) and an SVR12 of 70% was achieved (*16*).

### 3.1. *Sofosbuvir and ledipasvir*

In the ALLY-1 study (*12*), daclastavir, sofosbuvir, and ribavirin were administered to patients. Of the study participants, 55% had advanced fibrosis or cirrhosis. A total of 53 patients with genotype 1a (58%), 1b (19%), and 3 (21%) were treated with daclatasvir (60 mg/day), sofosbuvir (400 mg/day), and ribavirin and achieved an SVR12 of 94%. Similarly, Letvitsky *et al*. (*25*) reported that 37 patients treated with sofosbuvir and ledipasvir achieved an SVR of 97%.

The SOLAR studies (*10,11*) recruited post-transplant patients with HCV infection (and also those with end-stage liver disease) having genotype 1 or 4. In the SOLAR 1 study (*10*), the cohort was post-transplant patients in the United States that were non-cirrhotic ($n$ = 111) or cirrhotic having various extents of liver dysfunction (Child-Pugh class A, $n$ = 51; Child Pugh class B, $n$ = 52; and Child Pugh class C, $n$ = 9). They received sofosbuvir and ledipasvir for 12 or 24 weeks and achieved an SVR12 of 96%, 98%, 86%, and 60%, respectively, after 12-week treatment, and of 96%, 98%, 88%, and 75%, respectively, after 24-week treatment.

In the SOLAR 2 study conducted in Europe, Canada, and New Zealand (*11*), the subjects also comprised non-cirrhotic ($n$ = 89) or cirrhotic patients with various extents of liver dysfunction (Child Pugh class A, $n$ = 58; Child Pugh class B, $n$ = 40; and Child

Pugh class C, *n* = 7, but those with a Child Pugh score greater than 13 were excluded from the study. All the patients received sofosbuvir, ledipasvir, and ribavirin. The SVR12 when treated for 12 weeks was 93%, 100%, 95% and 50%, respectively, and the SVR12 when treated for 24 weeks was 100%, 96%, 100%, and 80%, respectively.

A report was published on a Japanese multicenter experience. A total of 53 patients who underwent liver transplantation for HCV (genotype 1b) cirrhosis were the subjects of the study. The regimen was sofosbuvir and ledipasvir without ribavirin for 24 weeks and the SVR12 was 98%. Saab *et al*. (*26*) reported the UCLA experience. The SVR12 was 85% after treatment with sofosbuvir and ledipasvir with or without ribavirin for 12 weeks, and 94% after treatment with sofosbuvir and ledipasvir without ribavirin for 12 weeks. Globke *et al*. (*27*) reported the Charite Campus Virchow experience in which the SVR12 was 100% in 51 patients.

### 3.2. *Sofosbuvir and simeprevir*

Sofosbuvir and simeprevir treatment has been evaluated in several studies, and demonstrates good tolerability and efficacy. The SVR12 in transplant patients was 88% (*28,29*).

In the HCV-TARGET study (*30*), 151 post-transplant patients infected with HCV genotype 1 were enrolled and received sofosbuvir and simeprevir with (*n* = 32) and without (*n* = 119) ribavirin for 12 (*n* = 136) or 24 weeks (*n* = 15). The SVR 12 was 88%. A similar study (*31*) reported an SVR12 of 90% in 123 transplant patients treated with sofosbuvir and simeprevir. In a similar study (*21*), 28 patients received a combination of sofosbuvir and simeprevir for 12 weeks and the SVR was 93%. Due to DAAs, graft survival for patients with HCV will improve compared with those undergoing transplantation for other indications for which recurrence may not be easily controlled.

The phase II SATURN study (*32*) demonstrated a 91% SVR12 in 35 post-transplant patients with HCV genotype 1. The regimen was a combination of simeprevir, daclastavir, and ribavirin.

### 3.3. *Ombitasvir, paritaprevir-ritonavir, dasabuvir*

Some clinical trials have reported the effectiveness of combined treatment with ombitasvir, paritaprevir-ritonavir, dasabuvir, and ribavirin. In the CORAL I study, 34 post-liver transplant patients underwent this combination therapy for 24 weeks. In patients with genotype 1a and 1b, the SVR12 was 97% and 100%, respectively. The livers of the patients exhibited normal to mild fibrosis, however, and no cirrhotic patients were included in the study. Another study (*34*) revealed a 100% SVR12 in 9 post liver transplant patients on this regimen. In the AMBER-CEE study (*35*), the regimen was ombitasvir, paritaprevir-ritonavir, and dasabuvir with or without ribavirin. A total of 35 patients (91% genotype 1b, 77% at fibrosis stage ≥ F2) underwent the regimen and the SVR12 was 100%.

### 4. Daclastavir-based regimens

In a Spanish multicenter study (*36*), 331 post-transplant patients underwent anti-HCV treatment consisting of daclastavir-sofosbuvir with or without ribavirin and daclastavir-simeprevir with or without ribavirin. Of note, 49% of the patients had advanced fibrosis (F4). The intention -to-treat SVR was 93%.

### 5. Fibrosing cholestatic hepatitis

Fibrosing cholestatic hepatitis (FCH) is a more severe form of HCC recurrence that occurs in less than 10% (*6*) of liver transplant recipients for HCV cirrhosis. FCH is characterized by a high viral load and divergent quasispecies (*37*). FCH results in progressive liver dysfunction and its prognosis is poor with more than 90% mortality (*38,39*). FCH can also occur after liver transplantation for hepatitis B cirrhosis and cytomegalovirus infection.

In the interferon era, the treatment response was poor, resulting in graft and patient loss. DAA is useful for FCH (*40,41*). In one study (*41*), sofosbuvir and ribavirin were administered to 10 FCH patients for 24 or 48 weeks and the SVR12 was 80%. Another study (*42*) showed that a 24-week treatment with simepredvir and sofosbuvir provided 80% SVR12. In the SOLAR 1 study (*10*), six patients with FCH underwent 12-or 24-week treatment with ledipasvir and sofosbuvir, which led to a significant decline in the total bilirubin level. A total of 23 patients with FCH received either sofosbuvir and daclatasvir (*n* = 15) or sofosbuvir and ribavirin (*n* = 8) for 24 weeks. At week 36, 22 patients (96%) had a complete clinical response (*14*). There was no death in the cohort. The CO23 ANRS CUPOT study (*40*) reported 23 patients with FCH treated with sofosbuvir-based regimens (sofosbuvir + ribavirin, pegylated interferon + sofosbuvir ± ribavirin, sofosbuvir + daclastavir ± ribavirin). Clinical improvement was achieved after 24 weeks of therapy without the need for re-transplantation. A recent multicenter study (*43*) also reported an SVR12 of 94% (*n* = 117) and 98% (*n* = 45) after ledipasvir and sofosbuvir treatments, respectively, with and without ribavirin regimens.

### 6. Timing of DAA use

The optimal time to initiate DAA treatment remains to be clarified. Patients should be treated before HCV recurrence. In the ALLY1 trial (*12*), subjects were 4 months to 13 years post transplantation and in the SOLAR trials (*10,11*), subjects were more than

3 months post transplantation. Most centers initiate DAA therapy 6 months post transplantation (*3*). The feasibility of a preemptive approach should be evaluated.

## 7. Interactions between DAA and immunosuppressive drugs

Drug-to-drug interactions between most of recently devised new generation DAAs and immunosuppressive drugs is not a significant issue (*44*). The trough levels of immunosuppressive drugs, however, should be closely monitored. After a period of DAA use, the dose of tacrolimus should be increased to maintain a trough level because of improved function of the liver graft.

One exception is ritonavir in ombitasvir, paritaprevir-ritonavir, dasabuvir, and ribavirin therapy. Due to the inhibitory effect of ritonavir on CYP3A-4 to metabolize cyclosporine or tacrolimus, the trough level of the drugs increase (tacrolimus, 57-86 fold, cyclosporine, 4.3-5.8 fold) (*45*). Simeprevir is reported to increase the level of cyclosporine 6-fold (*46*). Grazoprevir and elbastavir have drug-to-drug interactions with tacrolimus, increasing the level to 143%, as well as with cyclosporine, increasing the level to 115% (*7*).

## 8. Future perspective

Due to the introduction of DAAs for HCV, the need for transplantation for chronic HCV will be reduced as a result of the improved liver function (*47*). A recent study showed that the proportion of HCV-infected patients on the waiting list for HCC and decompensated cirrhosis will decrease whereas the proportion of patients with non-alcoholic steatohepatitis on the waiting list will increase (*48*). Fibrosing cholestatic hepatitis as an indication for re-transplantation may be significantly reduced because of DAA treatment. It is unlikely that the total volume of deceased donor liver transplantation will decrease, however, because this is regulated by the number of the deceased donors (*47*).

## 9. Conclusions

The currently available DAAs achieve a satisfactory SVR12 in post-liver transplantation patients. Drugs with a maximum SVR12 and minimum interaction with immunosuppressive and adverse events would be ideal, and this goal is very nearly met by the current DAAs. Optimal timing of the DAA treatment is not yet established, but it may be appropriate to consider DAA treatment after the patients' condition and graft function become stable.

## References

1. van Tilborg M, Maan R, van der Meer AJ, de Knegt RJ. Interferon-free antiviral therapy for chronic hepatitis C among patients in the liver transplant setting. Best Pract Res Clin Gastroenterol. 2017; 31:219-25.
2. Kim WR, Lake JR, Smith JM, Skeans MA, Schladt DP, Edwards EB, Harper AM, Wainright JL, Snyder JJ, Israni AK, Kasiske BL. OPTN/SRTR 2015 annual data report: Liver. Am J Transplant. 2017; 17(Suppl 1):174-251.
3. Jothimani D, Govil S, Rela M. Management of post liver transplantation recurrent hepatitis C infection with directly acting antiviral drugs: A review. Hepatol Int. 2016; 10:749-761.
4. Samuel D, Feray C. Recurrent hepatitis C after liver transplantation: Clinical and therapeutical issues. J Viral Hepat. 2000; 7:87-92.
5. Berenguer M, Lopez-Labrador FX, Wright TL. Hepatitis C and liver transplantation. J Hepatol. 2001; 35:666-678.
6. 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; 16:1228-1235.
7. Bhamidimarri KR, Satapathy SK, Martin P. Hepatitis C virus and liver transplantation. Gastroenterol Hepatol (N Y). 2017; 13:214-220.
8. Modi AA, Nazario H, Trotter JF, Gautam M, Weinstein J, Mantry P, Barnes M, Habib A, McAfee J, Teachenor O, Tujague L, Gonzalez S. Safety and efficacy of simeprevir plus sofosbuvir with or without ribavirin in patients with decompensated genotype 1 hepatitis C cirrhosis. Liver Transpl. 2016; 22:281-286.
9. Saxena V, Nyberg L, Pauly M, Dasgupta A, Nyberg A, Piasecki B, Winston B, Redd J, Ready J, Terrault NA. Safety and efficacy of simeprevir/sofosbuvir in hepatitis C-infected patients with compensated and decompensated cirrhosis. Hepatology. 2015; 62:715-725.
10. Charlton M, Everson GT, Flamm SL, *et al*. Ledipasvir and sofosbuvir plus ribavirin for treatment of HCV infection in patients with advanced liver disease. Gastroenterology. 2015; 149:649-659.
11. Manns M, Samuel D, Gane EJ, *et al*. Ledipasvir and sofosbuvir plus ribavirin in patients with genotype 1 or 4 hepatitis C virus infection and advanced liver disease: A multicentre, open-label, randomised, phase 2 trial. The Lancet Infectious diseases. 2016; 16:685-697.
12. Poordad F, Schiff ER, Vierling JM, Landis C, Fontana RJ, Yang R, McPhee F, Hughes EA, Noviello S, Swenson ES. Daclatasvir with sofosbuvir and ribavirin for hepatitis C virus infection with advanced cirrhosis or post-liver transplantation recurrence. Hepatology. 2016; 63:1493-1505.
13. Foster GR, Coppola C, Derbala M, Ferenci P, Orlandini A, Reddy KR, Tallarico L, Shiffman ML, Ahlers S, Bakalos G, Hassanein T; GUARD-C Study Group. Impact of safety-related dose reductions or discontinuations on sustained virologic response in HCV-infected patients: Results from the GUARD-C Cohort. PLoS One. 2016; 11:e0151703.
14. Coilly A, Roche B, Duclos-Vallee JC, Samuel D. Optimum timing of treatment for hepatitis C infection relative to liver transplantation. The lancet Gastroenterology & hepatology. 2016; 1:165-172.
15. Coilly A, Roche B, Duclos-Vallee JC, Samuel D. News and challenges in the treatment of hepatitis C in liver transplantation. Liver Int. 2016; 36 (Suppl 1):34-42.
16. 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; 148:108-117.
17. Donato MF, Morelli C, Romagnoli R, Invernizzi F, Mazzarelli C, Iemmolo RM, Montalbano M6, Lenci I7, Bhoori S, Pieri G, Berardi S, Caraceni P, Martini S; ITACOPS-SOF Bridging Study Group. Prevention of hepatitis C recurrence by bridging sofosbuvir/ribavirin from pre- to post-liver transplant: A real-life strategy. Liver Int. 2017; 37:678-683.
18. A SPECIAL MEETING REVIEW EDITION: Advances in the Treatment of Hepatitis C Virus Infection From EASL 2015: The 50th Annual Meeting of the European Association for the Study of the Liver * April 22-26, 2015 * Vienna, AustriaSpecial Reporting on:* Daclatasvir, Sofosbuvir, and Ribavirin Combination for HCV Patients With Advanced Cirrhosis or Posttransplant Recurrence: Phase 3 ALLY-1 Study* Efficacy and Safety of Grazoprevir and Elbasvir in Hepatitis C Genotype 1-Infected Patients With Child-Pugh Class B Cirrhosis (C-SALT Part A)* Ledipasvir/Sofosbuvir With Ribavirin Is Safe and Efficacious in Decompensated and Post Liver Transplantation Patients With HCV Infection: Preliminary Results of the Prospective SOLAR 2 Trial* Retreatment of Patients Who Failed 8 or 12 Weeks of Ledipasvir/Sofosbuvir-Based Regimens With Ledipasvir/Sofosbuvir for 24 Weeks* Sofosbuvir + Peginterferon/Ribavirin for 12 Weeks Vs Sofosbuvir + Ribavirin for 16 or 24 Weeks in Genotype 3 HCV Infected Patients and Treatment-Experienced Cirrhotic Patients With Genotype 2 HCV: The BOSON Study* Safety and Efficacy of the Combination Daclatasvir-Sofosbuvir in HCV Genotype 1-Mono-Infected Patients From the French Observational Cohort ANRS CO22 HEPATHER* C-SWIFT: Grazoprevir/Elbasvir + Sofosbuvir in Cirrhotic and Noncirrhotic, Treatment-Naive Patients With Hepatitis C Virus Genotype 1 Infection for Durations of 4, 6 or 8 Weeks and Genotype 3 Infection for Durations of 8 or 12 WeeksPLUS Meeting Abstract Summaries With Expert Commentary by: Steven L. Flamm, MD Chief, Liver Transplantation ProgramProfessor of Medicine and SurgeryNorthwestern University Feinberg School of MedicineChicago, Illinois. Gastroenterol Hepatol (N Y). 2015; 11(6 Suppl 3):1-23.
19. Welzel TM, Petersen J, Herzer K, Ferenci P, Gschwantler M, Wedemeyer H, Berg T, Spengler U, Weiland O, van der Valk M, Rockstroh J, Peck-Radosavljevic M, Zhao Y, Jimenez-Exposito MJ, Zeuzem S. Daclatasvir plus sofosbuvir, with or without ribavirin, achieved high sustained virological response rates in patients with HCV infection and advanced liver disease in a real-world cohort. Gut. 2016; 65:1861-1870.
20. Belli LS, Berenguer M, Cortesi PA, *et al*. Delisting of liver transplant candidates with chronic hepatitis C after viral eradication: A European study. J Hepatol. 2016; 65:524-531.
21. 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.
22. Reig M, Marino Z, Perello C, Inarrairaegui M, Ribeiro A, Lens S, Díaz A, Vilana R, Darnell A, Varela M, Sangro B, Calleja JL, Forns X, Bruix J. Unexpected high rate of early tumor recurrence in patients with HCV-related HCC undergoing interferon-free therapy. J Hepatol. 2016; 65:719-726.
23. EASL Recommendations on treatment of hepatitis C 2016. J Hepatol. 2017; 66:153-194.
24. Conti F, Buonfiglioli F, Scuteri A, Crespi C, Bolondi L, Caraceni P, Foschi FG, Lenzi M, Mazzella G, Verucchi G, Andreone P, Brillanti S. Early occurrence and recurrence of hepatocellular carcinoma in HCV-related cirrhosis treated with direct-acting antivirals. J Hepatol. 2016; 65:727-733.
25. Levitsky J, Verna EC, O'Leary JG, Bzowej NH, Moonka DK, Hyland RH, Arterburn S, Dvory-Sobol H, Brainard DM, McHutchison JG, Terrault NA. Perioperative ledipasvir-sofosbuvir for HCV in liver-transplant recipients. N Engl J Med. 2016; 375:2106-2108.
26. Saab S, Rheem J, Jimenez MA, *et al*. Effectiveness of ledipasvir/sofosbuvir with/without ribavarin in liver transplant recipients with hepatitis C. J Clin Transl Hepatol. 2017; 5:101-108.
27. Globke B, Raschzok N, Teegen EM, Pratschke J, Schott E, Eurich D. Treatment of hepatitis C virus recurrence after transplantation with sofosbuvir/ledipasvir: The role of ribavirin. Transpl Infect Dis. 2017; doi: 10.1111/tid.12647.
28. Gutierrez JA, Carrion AF, Avalos D, O'Brien C, Martin P, Bhamidimarri KR, Peyton A. Sofosbuvir and simeprevir for treatment of hepatitis C virus infection in liver transplant recipients. Liver Transpl. 2015; 21:823-830.
29. Nguyen NH, Yee BE, Chang C, Jin M, Lutchman G, Lim JK, Nguyen MH. Tolerability and effectiveness of sofosbuvir and simeprevir in the post-transplant setting: Systematic review and meta-analysis. BMJ open gastroenterology. 2016; 3:e000066.
30. Brown RS, Jr., O'Leary JG, Reddy KR, *et al*. Interferon-free therapy for genotype 1 hepatitis C in liver transplant recipients: Real-world experience from the hepatitis C therapeutic registry and research network. Liver Transpl. 2016; 22:24-33.
31. Pungpapong S, Aqel B, Leise M, Werner KT, Murphy JL, Henry TM, Ryland K, Chervenak AE, Watt KD, Vargas HE, Keaveny AP. Multicenter experience using simeprevir and sofosbuvir with or without ribavirin to treat hepatitis C genotype 1 after liver transplant. Hepatology. 2015; 61:1880-1886.
32. Forns X, Didier S, Mutimer D, *et al*. Efficacy of telaprevir-based therapy in stable liver transplant patients with chronic genotype 1 hepatitis C. Ann Hepatol. 2016; 15:512-523.
33. Kwo PY, Mantry PS, Coakley E, *et al*. An interferon-free antiviral regimen for HCV after liver transplantation. N Engl J Med. 2014; 371:2375-2382.
34. Yu ML, Chen YL, Huang CF, Lin KH, Yeh ML, Huang CI, Hsieh MH, Lin ZY, Chen SC, Huang JF, Dai CY, Chuang WL. Paritaprevir/ritonavir/ombitasvir plus dasabuvir with ribavirin for treatment of recurrent chronic hepatitis C genotype 1 infection after liver transplantation: Real-world experience. J Formos Med Assoc. 2017; pii: S0929-6646(17)30292-9.
35. Tronina O, Durlik M, Wawrzynowicz-Syczewska M, *et al*. Real-world safety and efficacy of ombitasvir/paritaprevir/ritonavir/+dasabuvir±ribavirin (OBV/PTV/r/+DSV±RBV) therapy in recurrent hepatitis C virus (HCV) genotype 1 infection post-liver transplant: AMBER-CEE study. Ann Transplant. 2017; 22:199-207.
36. Salcedo M, Prieto M, Castells L, *et al*. Efficacy and safety of daclatasvir-based antiviral therapy in hepatitis C virus recurrence after liver transplantation. Role of cirrhosis and

genotype 3. A multicenter cohort study. Transpl Int. 2017; 30:1041-1050.
37. Satapathy SK, Sclair S, Fiel MI, Del Rio Martin J, Schiano T. Clinical characterization of patients developing histologically-proven fibrosing cholestatic hepatitis C post-liver transplantation. Hepatol Res. 2011; 41:328-339.
38. Verna EC, Abdelmessih R, Salomao MA, Lefkowitch J, Moreira RK, Brown RS, Jr. Cholestatic hepatitis C following liver transplantation: An outcome-based histological definition, clinical predictors, and prognosis. Liver Transpl. 2013; 19:78-88.
39. Antonini TM, Sebagh M, Roque-Afonso AM, Teicher E, Roche B, Sobesky R, Coilly A, Vaghefi P, Adam R, Vittecoq D, Castaing D, Samuel D, Duclos-Vallée JC. Fibrosing cholestatic hepatitis in HIV/HCV co-infected transplant patients-usefulness of early markers after liver transplantation. Am J Transplant. 2011; 11:1686-1695.
40. Leroy V, Dumortier J, Coilly A, *et al*. Efficacy of sofosbuvir and daclatasvir in patients with fibrosing cholestatic hepatitis C after liver transplantation. Clin Gastroenterol Hepatol. 2015; 13:1993-2001.e1-2.
41. Forns X, Charlton M, Denning J, *et al*. Sofosbuvir compassionate use program for patients with severe recurrent hepatitis C after liver transplantation. Hepatology. 2015; 61:1485-1494.
42. Issa D, Eghtesad B, Zein NN, Yerian L, Cruise M, Alkhouri N, Adams R, Hanouneh IA. Sofosbuvir and simeprevir for the treatment of recurrent hepatitis C with fibrosing cholestatic hepatitis after liver transplantation. Int J Organ Transplant Med. 2016; 7:38-45.
43. Kwok RM, Ahn J, Schiano TD, T, *et al.* Sofosbuvir plus ledispasvir for recurrent hepatitis C in liver transplant recipients. Liver Transpl. 2016; 22:1536-1543.
44. Bunchorntavakul C, Reddy KR. Management of hepatitis C before and after liver transplantation in the era of rapidly evolving therapeutic advances. J Clin Transl Hepatol. 2014; 2:124-133.
45. Hepatitis C guidance: AASLD-IDSA recommendations for testing, managing, and treating adults infected with hepatitis C virus. Hepatology. 2015; 62:932-954.
46. EASL Recommendations on treatment of hepatitis C 2015. J Hepatol. 2015; 63:199-236.
47. Durand F, Francoz C. The future of liver transplantation for viral hepatitis. Liver Int. 2017;37(Suppl 1):130-135.
48. Goldberg D, Ditah IC, Saeian K, Lalehzari M, Aronsohn A, Gorospe EC, Charlton M. Changes in the prevalence of hepatitis C virus infection, nonalcoholic steatohepatitis, and alcoholic liver disease among patients with cirrhosis or liver failure on the waitlist for liver transplantation. Gastroenterology. 2017; 152:1090-9.e1.

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