Treatment of Recurrent HCV Infection following Liver Transplantation

This is a PDF version of the following document:
Module 6: Treatment of Special Populations and Special Situations
Lesson 5: Treatment of Recurrent HCV Infection following Liver Transplantation

You can always find the most up to date version of this document at http://www.hepatitisc.uw.edu/go/special-populations-situations/treatment-post-transplantation/core-concept/all.

Impact of Post-Transplantation HCV Infection

As of January, 2015, roughly 17,000 patients in the United States had been medically approved for liver transplantation and were waiting for donated livers to become available. Hepatitis C virus (HCV) infections cause approximately 40% of all chronic liver disease in the United States and HCV-related cirrhosis is the most frequent indication for liver transplantation in adults. Untreated HCV infection remains an active problem post-successful orthotopic liver transplantation (OLT), and recurrent HCV infection is the leading cause of graft failure in recipients of liver transplant. Infection of the graft occurs nearly universally in patients with untreated HCV infection who receive liver transplantation. Reinfection has been documented to occur as soon as reperfusion of the allograft takes place in the operating room, and viral titers have been detected to reach pre-transplantation levels within 72 hours. Post-transplant, the clinical course of patients with HCV reinfection varies: fewer than 10% may develop severe fibrosing cholestatic hepatitis (50% of whom develop graft loss from recurrent HCV infection within 6 months), 20% have normal or near normal aminotransferase values with minimal inflammation on liver biopsy, and the remainder develop chronic hepatitis, in which cirrhosis develops within 5 to 7 years of transplantation in about 30% of these patients. The course of HCV-related fibrosis progression after liver transplantation is clearly accelerated when compared with the pre-transplant setting. Among post-transplantation patients with untreated hepatitis C infection, 10 to 20% will develop cirrhosis within 5 years post-transplantation. It is not clear whether different genotypes of HCV have different rates of disease progression in post-transplantation organs. Recipient and donor factors (gender, donor age, graft ischemia time, donor liver steatosis) and bolus steroid administration are associated with HCV graft outcomes.

Peginterferon Treatment for HCV in the Post-Transplantation Setting

Until recently, treatment of HCV infection in pre-transplantation and post-transplantation patients was extremely difficult. For patients who were pre-transplant, the extent of their hepatic disease made interferon- or peginterferon-based treatments highly problematic, mainly because of high frequency and severity of adverse events and low sustained virologic response (SVR) rates. Studies have shown varied treatment success, with SVR rates of 10 to 50% reported with peginterferon and ribavirin in this setting. In addition, early post-transplantation treatment with interferon monotherapy was not shown to improve patient and graft outcomes. Currently no indication exists for use of interferon- or peginterferon-based regimens for prophylactic or preemptive therapy following liver transplantation.

Interferon-Free Regimens to Treat Recurrent HCV Infection after Liver Transplantation

Given the high rate of major adverse effects with the use of peginterferon-based regimen when treating HCV following liver transplantation, efforts have shifted to regimens that use all oral direct-acting antiviral agents. The following list of studies emphasizes newer interferon-free regimens.

- **Sofosbuvir plus Ribavirin**: Charlton and colleagues conducted an open-label, phase 2 study of hepatitis C treatment with sofosbuvir and ribavirin in 40 subjects who had received either liver or joint liver and kidney transplant (Figure 1). Eighty percent of study participants had HCV genotype 1, 15% had genotype 3, 1 had genotype 4, and none had genotype 2. Most of the patients (88%) were treatment-experienced. The patients had a range of hepatic fibrosis in the transplanted liver: 40% had cirrhosis, 23% had bridging fibrosis, and 35% had mild-to-moderate fibrosis. Treatment consisted of a 24-week course of sofosbuvir (400 mg once-daily) and ribavirin (starting at 400 mg daily and titrated upward based on hemoglobin levels). Overall, 28 (70%) of the 40 patients achieved an SVR12. No death, graft loss, or episodes of rejection were noted. No interactions were reported between sofosbuvir and any immunosuppressant agents, including tacrolimus, mycophenolate mofetil, prednisone, or cyclosporine, but 4 patients required an increase in their tacrolimus dose. In a separate study, investigators provided a 24 to 48-week course of sofosbuvir and ribavirin in a compassionate use program to treat hepatitis C in patients following liver transplantation. Excluding patients who underwent re-transplantation, 54 (59%) of 92 of patients achieved an SVR12.
- **Sofosbuvir plus Simeprevir**: In a retrospective study performed at the University of California Los Angeles Medical Center, Saab and coworkers reported on their experience with HCV treatment of 30 patients with post-liver transplantation HCV infection (Figure 2). All patients in the report were treated with a 12-week course of simeprevir plus sofosbuvir. Overall, 42% of the patients had F3 or F4 Metavir fibrosis. The treatment regimen of sofosbuvir plus simeprevir was well tolerated and 28 (93%) of 30 patients achieved an SVR12. Of interest, despite the very high SVR12 rate, only 16 (59%) of 27 patients had an undetectable HCV RNA at week 4 of treatment.
- **Ledipasvir-Sofosbuvir Post-Transplantation**: As Cohort B of the SOLAR-1 trial, investigators randomized 229 post-transplant patients with genotype 1 or 4 HCV infection, most of whom had received prior HCV treatment, to receive ledipasvir-sofosbuvir and ribavirin for either 12 weeks or 24 weeks (Figure 3). For patients with F0-F3 fibrosis, 96% achieved an SVR with 12 weeks of therapy compared with 98% in those treated for 24 weeks. Among patients with cirrhosis, the SVR12 responses varied significantly based on the Child-Pugh-Turcotte class. For class A, the 96% of patients achieved an SVR with 12 weeks of therapy and 95% with 24 weeks. For class B, the SVR was 85% with 12 weeks of therapy and 83% with 24 weeks. For class C, the SVR was 60% with 12 weeks and 67% with 24 weeks. There were no specific treatment associated deaths reported.
- **Ombitasvir-Paritaprevir-Ritonavir plus Dasabuvir**: CORAL-1 is a phase 3 trial of an all-oral, interferon-free regimen (ombitasvir-paritaprevir-ritonavir and dasabuvir) with ribavirin for 24 weeks in adult non-cirrhotic liver transplant recipients with recurrent chronic genotype 1 HCV infection; the RBV dosing was left up to the discretion of the investigator (Figure 4). Patients in the study initiated therapy at least 12 months after receiving a liver transplant, had not received other HCV therapy since their liver transplant, and were on a stable immunosuppressant regimen based on either tacrolimus or cyclosporine, for which dose adjustments were advised. A total of 34 patients were enrolled, and 33 (97%) of 34 achieved a sustained virologic response at post-treatment week 12 and 24 (SVR12 and SVR24). During the trial, 15% of patients required erythropoietin. One patient discontinued the study drugs secondary to adverse events after week 18, but had a sustained virologic response regardless.
- **Daclatasvir plus Sofosbuvir plus Ribavirin**: In the phase 3 ALLY-1 trial, Poordad and

coworkers used a 12-week course of sofosbuvir and ribavirin plus the investigational agent daclatasvir to treat 53 patients with recurrent HCV infection following liver transplantation and 60 patients with advanced cirrhosis (Figure 5). The ribavirin dose was initiated at 600 mg per day and then titrated up to 1000 mg/day based on hemoglobin levels and creatinine clearance. Patients in the post-transplant arm of the study were eligible if they had no evidence of rejection at the time of enrollment and were at least 3 months out from the liver transplant. For the patients in the post-transplant arm, 50 (94%) of 53 achieved an SVR12, including 39 (95%) of 41 with genotype 1 HCV infection. In addition, no treated patients had graph rejection and this regimen had a favorable drug interaction profile and did not result in the need to modify the dose of immunosuppressant medications.

Treatment of HCV in the Post-Transplant Setting

Treatment Goals: Treatment of hepatitis C in the post-liver transplantation patient is a rapidly evolving field. When treating hepatitis C in this setting, the main goals of therapy include: (a) cure of HCV chronic infection in the allograft post-transplant, (b) minimize the risk of developing HCV-associated complications in the allograft, such as fibrosing cholestatic hepatitis and allograft failure, and (c) prevent development of hepatic fibrosis and thus preserve the function of the transplanted liver.

Drug Interactions with Immunosuppressant Medications: Several unique and challenging features of this patient population include the unpredictable and fragile nature of their hepatic function and drug-drug interactions between HCV treatment and immunosuppressant medications. The calcineurin inhibitors, such as tacrolimus and cyclosporine, are frequently used as cornerstones in OLT immunosuppressive therapy. Chronic exposure to calcineurin inhibitors may cause a progressive decrease in renal function, thereby reducing ribavirin clearance, which may increase the frequency and severity of ribavirin-associated hemolytic anemia. Potential drug-drug interactions can occur between the calcineurin inhibitors and medications used to treat HCV; accordingly, drug-drug interactions should be carefully reviewed by a pharmacist prior to starting HCV treatment in this setting.

AASLD/IDSA Guidance: The guidance from the American Association for the Study of Liver Diseases (AASLD) and the Infectious Diseases Society of America addresses the treatment of **Patients who Develop Recurrent HCV Infection Post-Liver Transplantation**. All of the AASLD/IDSA recommended regimens for post-transplant treatment of HCV are interferon-free regimens. For a summary of the recommendations for the treatment of Patients who Develop Recurrent HCV Infection Post-Liver Transplantation see the **Summary Box** for this topic. Several key items in the AASLD/IDSA recommended regimens for post-transplant treatment of HCV are outlined below.

- For treatment-naive or -experienced patients with compensated cirrhosis and genotype 1 or 4 infection, the recommended regimens for post-transplantation HCV infection of the allograft are: (a) daclatasvir plus sofosbuvir plus low initial dose of ribavirin (with increase as tolerated) for 12 weeks or (b) ledipasvir-sofosbuvir plus weight-based ribavirin for 12 weeks.
- For treatment-naive patients with genotype 1 or 4 HCV infection who are intolerant or ineligible to receive ribavirin, the recommended regimens for treatment of the HCV-infected allograft are: (a) daclatasvir plus sofosbuvir for 24 weeks or (b) ledipasvir-sofosbuvir for 24 weeks.
- If the patient with genotype 1 HCV infection has early recurrence (Metavir fibrosis F0 to F2) following liver transplantation, a 24-week course of ombitasvir-paritaprevir-ritonavir and dasabuvir plus weight-based ribavirin is also considered an alternative, but the drug-drug interactions between ritonavir and calcineurin inhibitors and between ritonavir and other post OLT medications requires careful consideration and probable dose adjustments.
- For treatment-naive or -experienced patients with genotype 2 or 3 and HCV infection of the allograft and compensated cirrhosis, the recommended regimens are: (a) daclatasvir plus sofosbuvir plus low initial dose of ribavirin (with increase as tolerated) for 12 weeks or (b) 24-week course of sofosbuvir plus weight-based ribavirin. For the patients unable to take or tolerate ribavirin, the recommended regimen is daclatasvir plus sofosbuvir for 24 weeks
- No recommendations have been made for treatment of HCV genotypes 5 or 6 in patients following liver transplantation.

Treatment of HCV in the Post-Transplant Setting of Fibrosing Cholestatic Hepatitis

Treatment of HCV in the Post-Transplant Setting of Fibrosing Cholestatic Hepatitis: Fibrosing cholestatic hepatitis (FCH) is a rare but deadly form of rapidly progressive HCV recurrence post-OLT. It occurs in less than 10% of HCV RNA positive patients post-transplant. Although definitive trials have not been published that address the treatment of fibrosing cholestatic hepatitis in the post-OLT setting, encouraging preliminary data from the following case reports suggest treatment regimens that could be considered for use in this setting. The following summarizes case reports and small series involving patients with post-transplantation fibrosing cholestatic hepatitis received treatment for hepatitis C.

- **Sofosbuvir plus Peginterferon plus Ribavirin**: Delabaudiere and colleagues report the successful treatment of fibrosing cholestatic hepatitis post- liver and kidney transplant in a 66-year-old male infected with HCV genotype 1a using a 24-week treatment course of peginterferon, ribavirin and sofosbuvir. The patient had an undetectable HCV RNA level at week four of treatment, which was maintained through 4 weeks post-therapy. No adverse drug-drug interactions were noted between sofosbuvir and tacrolimus.
- **Sofosbuvir plus Daclatasvir**: Fontana and colleagues reported the successful use of 24 weeks of sofosbuvir and daclatasvir for the treatment of biopsy proven fibrosing cholestatic hepatitis with ascites in a 54-year-old male with genotype 1b recurrent HCV infection 6 months following liver transplantation. At 4 weeks into treatment, the HCV RNA level was undetectable, his AST and ALT normalized, and ascites resolved. At 9 months post-treatment, HCV viral load remained undetectable. No interaction between the HCV regimen and his immunosuppressant medications was noted and tacrolimus levels remained stable.
- **Sofosbuvir plus Ribavirin**: Kim and colleagues describe the successful use of 24 weeks of sofosbuvir and ribavirin in a 49-year-old male with HCV genotype 1A. At 6 months after transplant, the patient developed biopsy proven fibrosing cholestatic hepatitis with an HCV RNA level of 12,000,000 IU/ml. He was initially treated with peginterferon and ribavirin, but this was discontinued after 2 weeks because of medication-related adverse effects. At 16 months post-transplant, he received a 24-week course of sofosbuvir plus ribavirin. The patient had an undetectable HCV RNA at the end of treatment and 2 weeks post-treatment; no SVR12 data was reported. Following treatment of HCV, the patient’s aminotransferase levels normalized and his fatigue and ascites resolved. In a similar report, Borentain and colleagues described successful treatment with sofosbuvir and ribavirin in a patient coinfected with HIV and genotype 4 HCV who developed post-transplantation fibrosing cholestatic hepatitis. After 4 weeks of HCV therapy, the HCV RNA level had markedly declined and the patient had normalization of liver function tests. The patient did not have any complications related to drug-drug interactions between the HCV therapy, HIV antiretroviral medications, and the immunosuppressive regimen.
- **Daclatasvir plus Sofosbuvir**: In the ARNS CO23 CUPILT Study, Leroy and colleagues from France and Belgium reported on treatment of recurrent HCV infection after liver transplant in 23 patients with fibrosing cholestatic hepatitis. In this prospective cohort study, 15 patients were treated with a 24-week course of daclatasvir plus sofosbuvir and 8 with 24 weeks of sofosbuvir plus peginterferon plus ribavirin; most patients had genotype 1 infection. Among the patients treated with daclatasvir and sofosbuvir, 15 (100%) of 15 obtained an SVR12 compared with 7 (88%) of 8 treated with sofosbuvir plus peginterferon plus ribavirin.
- **Daclatasvir plus Peginterferon plus Ribavirin**: Fontana and colleagues described the use of the peginterferon alfa-2a and ribavirin, in combination with daclatasvir, in a 49-year-old female who developed severe recurrent HCV genotype 1b infection 4 months post-OLT, with severe cholestasis evident on liver biopsy. Three months after her second OLT, she was treated with daclatasvir (20 mg/day), peginterferon alfa-2a (180 mcg/week), and ribavirin (800 mg/day); serum HCV RNA became undetectable at treatment week 3 and remained undetectable through 24 weeks of therapy, as well as at post-treatment weeks 12 and 24.

Timing of Post-Transplantation HCV Treatment

Treatment of chronic hepatitis C prior to liver transplantation may be an option in some patients and is ideal if possible. For patients who develop post-transplantation HCV infection, the ideal time to initiate HCV treatment has not been well characterized, and most of the clinical trials have enrolled patients at least 3 months (or many years) following liver transplantation. There are typically many dose changes to the immunosuppression regimen in the first 3 months after transplantation. In this circumstance, there are drug-drug interactions to consider, such as ombitasvir-paritaprevir-ritonavir plus dasabuvir and ribavirin co-administered with a calcineurin inhibitor, or simeprevir co-administered with cyclosporine. Fortunately, there are no significant drug-drug interactions identified thus far with ledipasvir-sofosbuvir and the immunosuppressive medications. In addition, renal dysfunction is very common in patients before liver transplantation, and renal function may decline initially after liver transplantation due to acute kidney injury following surgery in conjunction with the use of calcineurin inhibitors. Impaired renal function impacts the dosing of ribavirin due to risk of drug-induced hemolytic anemia. Thus, it is reasonable to wait at least 3 months after transplantation before considering initiation of hepatitis C treatment, allowing for stabilization and reduction of immunosuppression and renal function. In patients with aggressive recurrence of hepatitis C, such as fibrosing cholestatic hepatitis C, however, treatment should be initiated as soon as possible, given the high risk of graft loss with this condition.

Summary Points

- Treatment of HCV infection following liver transplantation has historically been challenging using interferon- and peginterferon-based therapies, primarily due to poor SVR rates, frequent adverse drug effects, and significant drug-drug interactions.
- Interferon-free treatments are showing promise for treatment of HCV following liver transplantation, with high SVR rates and few drug-related adverse effects.
- A 24- to 48-week course of sofosbuvir and ribavirin in post-liver transplantation patients with genotypes 1, 3 or 4 has shown SVR12 rates of 59 to 70%.
- Using ledipasvir-sofosbuvir in post-liver transplantation patients with genotypes 1 or 4, SVR12 rates were 96 to 98% for non-cirrhotic patients and 60 to 96% for patients with cirrhosis, with response rates depending on the degree of cirrhosis.
- In patients with hepatitis C genotype 1 infection with only early stage fibrosis following transplantation, treatment with a 24-week course of ombitasvir-paritaprevir-ritonavir and dasabuvir (with ribavirin) showed an SVR12 rate of 97%. The regimen was well tolerated, but requires dose modification of calcineurin inhibitors.
- Successful treatment of patients with a variety of new non-interferon-based therapies in fibrosis cholestatic hepatitis has been reported in case reports and small series; additional studies may be necessary to verify findings in these initial reports.
- The ASLD/IDSA hepatitis C guidance recommended treatment for recurrent genotype 1 or 4 HCV infection following liver transplantation is a 12-week course of ledipasvir-sofosbuvir plus ribavirin; for patients unable to receive ribavirin, the guidance recommends a 24-week course of ledipasvir-sofosbuvir. Sofosbuvir plus simeprevir is an alternative for genotype 1.
- For patients with genotype 2 or 3 HCV reinfection following liver transplantation, the AASLD/IDSA guidance recommends a 24-week course of sofosbuvir plus weight-based ribavirin; this recommendation includes patients with compensated cirrhosis.
- Treatment of HCV in patients who are post liver transplantation is an actively evolving field and recommendations may change as new data emerge and new additional oral agents become available.

References

- AASLD/IDSA. Recommendations for testing, management, and treating hepatitis C. Unique patient populations:patients who develop recurrent HCV post-liver transplantation. [AASLD/IDSA Hepatitis C Guidance] -

- Angelico M, Petrolati A, Lionetti R, et al. A randomized study on Peg-interferon alfa-2a with or without ribavirin in liver transplant recipients with recurrent hepatitis C. J Hepatol. 2007;46:1009-17.
[PubMed Abstract] -

- Babatin M, Schindel L, Burak KW. Pegylated-interferon alpha 2b and ribavirin for recurrent hepatitis C after liver transplantation: From a Canadian experience to recommendations for therapy. Can J Gastroenterol. 2005:359-65.
[PubMed Abstract] -

- Beckebaum S, Cicinnati VR, Zhang X, et al. Combination therapy with peginterferon alpha-2B and ribavirin in liver transplant recipients with recurrent HCV infection: preliminary results of an open prospective study. Transplant Proc. 2004;36:1489-91.
[PubMed Abstract] -

- Belli LS, Volpes R, Graziadei I, et al. Antiviral therapy and fibrosis progression in patients with mild-moderate hepatitis C recurrence after liver transplantation. A randomized controlled study. Dig Liver Dis. 2012;44:603-9.
[PubMed Abstract] -

- Berenguer M. Natural history of recurrent hepatitis C. Liver Transpl. 2002;8:S14-8.
[PubMed Abstract] -

- Bifano M, Adamczyk R, Hwang C, Kandoussi H, Marion A, Bertz RJ. An open-label investigation into drug-drug interactions between multiple doses of daclatasvir and single-dose cyclosporine or tacrolimus in healthy subjects. Clin Drug Investig. 2015;35:281-9.
[PubMed Abstract] -

- Borentain P, Colson P, Dhiver C, et al. Successful treatment with sofosbuvir of fibrosing cholestatic hepatitis C after liver transplantation in HIV-HCV coinfected patient. Antivir Ther. 2014 Aug 8. [Epub ahead of print]
[PubMed Abstract] -

- Castells L, Vargas V, Allende H, et al. Combined treatment with pegylated interferon (alpha-2b) and ribavirin in the acute phase of hepatitis C virus recurrence after liver transplantation. J Hepatol. 2005;43:53-9.
[PubMed Abstract] -

- Chalasani N, Manzarbeitia C, Ferenci P, et al. Peginterferon alfa-2a for hepatitis C after liver transplantation: two randomized, controlled trials. Hepatology. 2005;41:289-98.
[PubMed Abstract] -

- 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;149:649-59.
[PubMed Abstract] -

- 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 Abstract] -

- Coilly A, Roche B, Duclos-Vallée JC, Samuel D. Optimal therapy in HCV liver transplant patients with direct acting antivirals. Liver Int. 2014 Nov 6. [Epub ahead of print]
[PubMed Abstract] -

- 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;148:100-107.
[PubMed Abstract] -

- Delabaudière C, Lavayssière L, Dörr G, et al. Successful treatment of fibrosing cholestatic hepatitis with pegylated interferon, ribavirin and sofosbuvir after a combined kidney-liver transplantation. Transpl Int. 2014 Aug 27. [Epub ahead of print]
[PubMed Abstract] -

- Dickson RC, Caldwell SH, Ishitani MB, et al. Clinical and histologic patterns of early graft failure due to recurrnet hepatitis C in four patients after liver transplantation. Transplantation. 1996;61:701-5.
[PubMed Abstract] -

- Dumortier J, Boillot O, Scoazec JY. Natural history, treatment and prevention of hepatitis C recurrence after liver transplantation: past, present and future. World J Gastroenterol. 2014;20:11069-79.
[PubMed Abstract] -

- Dumortier J, Scoazec JY, Chevallier P, Boillot O. Treatment of recurrent hepatitis C after liver transplantation: a pilot study of peginterferon alfa-2b and ribavirin combination. J Hepatol. 2004;40:669-74.
[PubMed Abstract] -

- Fagiuoli S, Ravasio R, Lucà MG, et al. Management of hepatitis C infection before and after liver transplantation. World J Gastroenterol. 2015;21:4447-4456.
[PubMed Abstract] -

- Fishman JA. Infection in solid-organ transplant recipients. N Engl J Med. 2007;357:2601-14.
[PubMed Abstract] -

- Fontana RJ, Hughes EA, Appelman H, Hindes R, Dimitrova D, Bifano M. Case report of successful peginterferon, ribavirin, and daclatasvir therapy for recurrent cholestatic hepatitis C after liver retransplantation. Liver Transpl. 2012;18:1053-9.
[PubMed Abstract] -

- Fontana RJ, Hughes EA, Bifano M, et al. Sofosbuvir and daclatasvir combination therapy in a liver transplant recipient with severe recurrent cholestatic hepatitis C. Am J Transplant. 2013;13:1601-5.
[PubMed Abstract] -

- Forns X, Charlton M, Denning J, et al. Sofosbuvir compassionate use program for patients with severe recurrent hepatitis C after liver transplantation. Hepatology. 2015;61:1485-94.
[PubMed Abstract] -

- Gane EJ, Agarwal K. Directly acting antivirals (DAAs) for the treatment of chronic hepatitis C virus infection in liver transplant patients: "a flood of opportunity". Am J Transplant.

2014;14:994-1002.
[PubMed Abstract] -

- Gane EJ. The natural history of recurrent hepatitis C and what influences this. Liver Transpl. 2008;14 Suppl 2:S36-44.
[PubMed Abstract] -

- García-Reyne A, Lumbreras C, Fernández I, et al. Influence of antiviral therapy in the long-term outcome of recurrent hepatitis C virus infection following liver transplantation. Transpl Infect Dis. 2013;15:405-15.
[PubMed Abstract] -

- 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 Abstract] -

- Grassi A, Ballardini G. Post-liver transplant hepatitis C virus recurrence: an unresolved thorny problem. World J Gastroenterol. 2014;20:11095-115.
[PubMed Abstract] -

- Gurusamy KS, Osmani B, Xirouchakis E, Burroughs AK, Davidson BR. Antiviral therapy for recurrent liver graft infection with hepatitis C virus. Cochrane Database Syst Rev. 2009;(1):CD006803.
[PubMed Abstract] -

- Gurusamy KS, Tsochatzis E, Toon CD, Xirouchakis E, Burroughs AK, Davidson BR. Antiviral interventions for liver transplant patients with recurrent graft infection due to hepatitis C virus. Cochrane Database Syst Rev. 2013;12:CD006803.
[PubMed Abstract] -

- Herzer K, Papadopoulos-Köhn A, Walker A, et al. Daclatasvir, simeprevir and ribavirin as a promising interferon-free triple regimen for HCV recurrence after liver transplant. Digestion. 2015;91:326-33.
[PubMed Abstract] -

- Ikegami T, Yoshizumi T, Kato M, et al. Reduced-dose telaprevir-based triple antiviral therapy for recurrent hepatitis C after living donor liver transplantation. Transplantation. 2014;98:994-9.
[PubMed Abstract] -

- Joshi D, Pinzani M, Carey I, Agarwal K. Recurrent HCV after liver transplantation-mechanisms, assessment and therapy. Nat Rev Gastroenterol Hepatol. 2014;11:710-21.
[PubMed Abstract] -

- Kim B, Trivedi A, Thung SN, Grewal P. Case report of successful treatment of fibrosing cholestatic hepatitis C with sofosbuvir and ribavirin after liver transplantation. Semin Liver Dis. 2014;34:108-12.
[PubMed Abstract] -

- Kwo PY, Mantry PS, Coakley E, et al. An interferon-free antiviral regimen for HCV after liver transplantation. N Engl J Med. 2014;371:2375-82.
[PubMed Abstract] -

- 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.
[PubMed Abstract] -

- Moreno Planas JM, Rubio Gonzalez E, Boullosa Graña E, et al. Peginterferon and ribavirin in patients with HCV cirrhosis after liver transplantation. Transplant Proc. 2005;37:2207-8.
[PubMed Abstract] -

- Mukherjee S, Rogge J, Weaver L, Schafer DF. Pilot study of pegylated interferon alfa-2b and ribavirin for recurrent hepatitis C after liver transplantation. Transplant Proc. 2003;35:3042-4.
[PubMed Abstract] -

- Nair S, Lipscomb J, Eason J. Efficacy of interferon based antiviral therapy for recurrent hepatitis C in patients who received steroid free immunosuppression for liver transplantation. Transplantation. 2008;86:418-22.
[PubMed Abstract] -

- Neff GW, Montalbano M, O'Brien CB, et al. Treatment of established recurrent hepatitis C in liver-transplant recipients with pegylated interferon-alfa-2b and ribavirin therapy. Transplantation. 2004;78:1303-7.
[PubMed Abstract] -

- Neumann U, Puhl G, Bahra M, et al. Treatment of patients with recurrent hepatitis C after liver transplantation with peginterferon alfa-2B plus ribavirin. Transplantation. 2006;82:43-7.
[PubMed Abstract] -

- Oton E, Barcena R, Moreno-Planas JM, et al. Hepatitis C recurrence after liver transplantation: Viral and histologic response to full-dose PEG-interferon and ribavirin. Am J Transplant. 2006;6:2348-55.
[PubMed Abstract] -

- Perrakis A, Yedibela S, Schuhmann S, et al. The effect and safety of the treatment of recurrent hepatitis C infection after orthotopic liver transplantation with pegylated interferon α2b and ribavirin. Transplant Proc. 2011;43:3824-8.
[PubMed Abstract] -

- Poordad F, Schiff ER, Vierling JM, et al. Daclatasvir with sofosbuvir and ribavirin for hepatitis C virus infection with advanced cirrhosis or post-liver transplantation recurrence. Hepatology. 2016;63:1493-505.
[PubMed Abstract] -

- Raziorrouh B, Jung MC, Schirren CA, et al. Antiviral therapy for recurrent hepatitis C after liver transplantation: sustained virologic response is related to genotype 2/3 and response at week 12. Eur J Gastroenterol Hepatol. 2008;20:778-83.
[PubMed Abstract] -

- Rodriguez-Luna H, Khatib A, Sharma P, et al. Treatment of recurrent hepatitis C infection after liver transplantation with combination of pegylated interferon alpha2b and ribavirin: an open-label series. Transplantation. 2004;77:190-4.
[PubMed Abstract] -

- Rodriguez-Luna H, Vargas HE. Management of hepatitis C virus infection in the setting of liver transplantation. Liver Transpl. 2005;11:479-89.
[PubMed Abstract] -

- Saab S, Greenberg A, Li E, et al. Sofosbuvir and simeprevir is effective for recurrent hepatitis

C in liver transplant recipients. Liver Int. 2015 Apr 24. [Epub ahead of print]
[PubMed Abstract] -

- 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;41:328-39.
[PubMed Abstract] -

- Terrault N. Liver transplantation in the setting of chronic HCV. Best Pract Res Clin Gastroenterol. 2012;26:531-48.
[PubMed Abstract] -

- Toniutto P, Fabris C, Fumo E, et al. Pegylated versus standard interferon-alpha in antiviral regimens for post-transplant recurrent hepatitis C: Comparison of tolerability and efficacy. J Gastroenterol Hepatol. 2005;20:577-82.
[PubMed Abstract] -

- Verna EC, Brown RS Jr. Hepatitis C virus and liver transplantation. Clin Liver Dis. 2006;10:919-40.
[PubMed Abstract] -

- Wright TL, Donegan E, Hsu HH, et al. Recurrent and acquired hepatitis C viral infection in liver transplant recipients. Gastroenterology. 1992;103:317-22.
[PubMed Abstract] -

Figures

Figure 1 (Image Series) - Sofosbuvir plus Ribavirin Treatment of HCV following Liver Transplantation (Image Series) - Figure 1 (Image Series) - Sofosbuvir plus Ribavirin Treatment of HCV following Liver Transplantation
Image 1A: Study Design

Patients received a 24-week course of sofosbuvir plus weight-based ribavirin (started at 400 mg per day and increased up to 1200 mg per day as tolerated).

Source: 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.

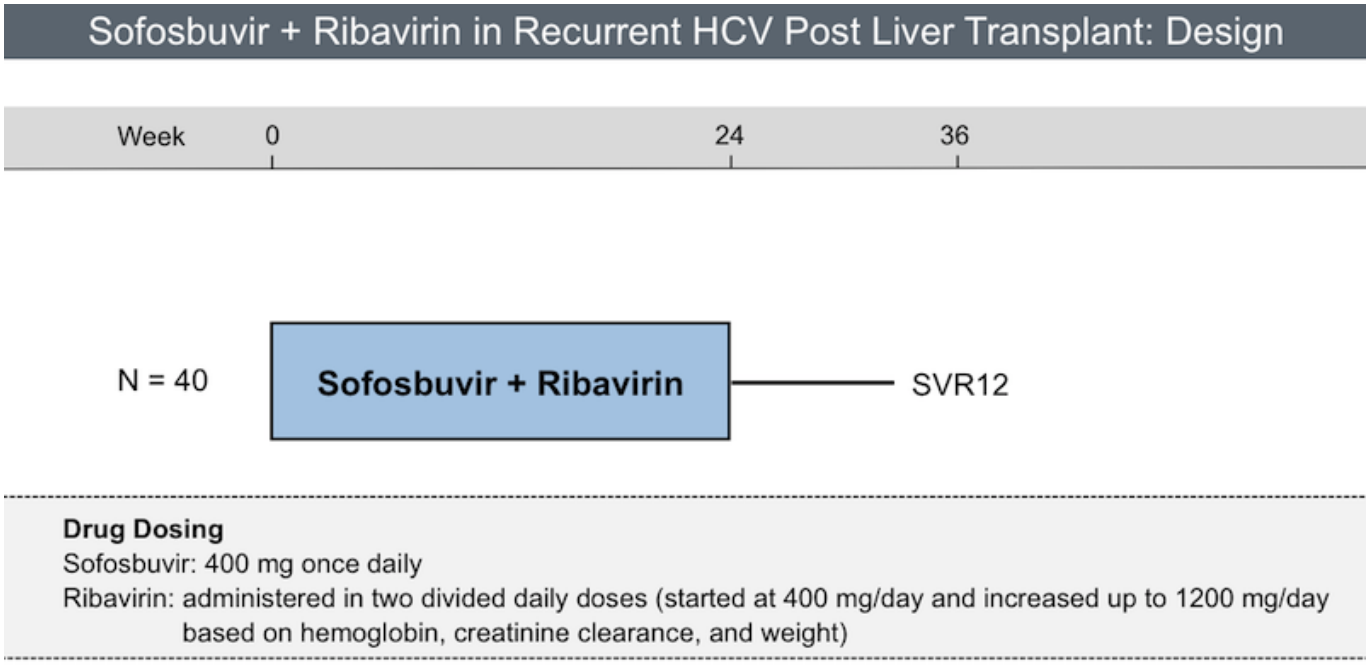


Figure 1 (Image Series) - Sofosbuvir plus Ribavirin Treatment of HCV following Liver Transplantation
Image 1B: Virologic Response to Treatment

Source: 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.

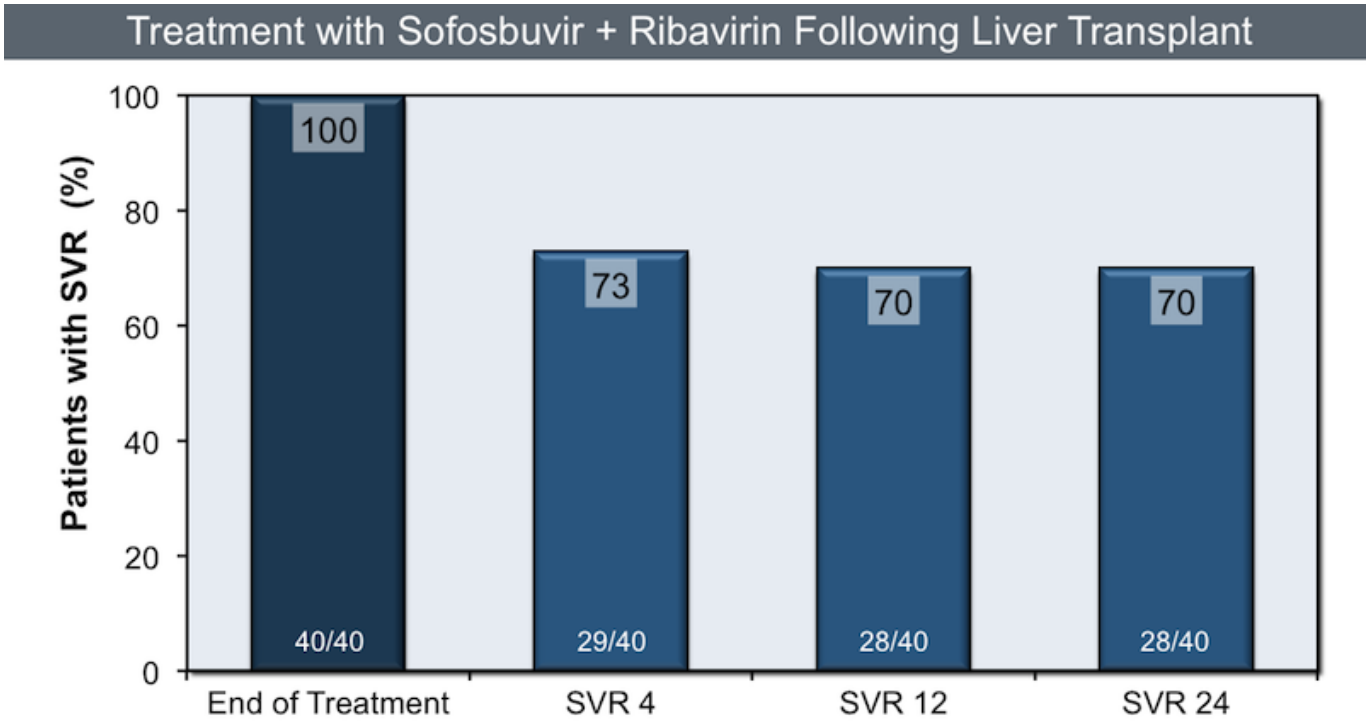


Figure 2 (Image Series) - UCLA Study: Sofosbuvir and Simeprevir for HCV in Post-Transplant Setting (Image Series) - Figure 2 (Image Series) - UCLA Study: Sofosbuvir and Simeprevir for HCV in Post-Transplant Setting
Image 2A: Study Design

In this retrospective study, investigators at the UCLA liver transplant center summarized their experience using sofosbuvir and simeprevir to treat 30 patients with recurrent HCV infection following liver transplantation.

Saab S, Greenberg A, Li E, et al. Sofosbuvir and simeprevir is effective for recurrent hepatitis C in liver transplant recipients. Liver Int. 2015 Apr 24. [Epub ahead of print]

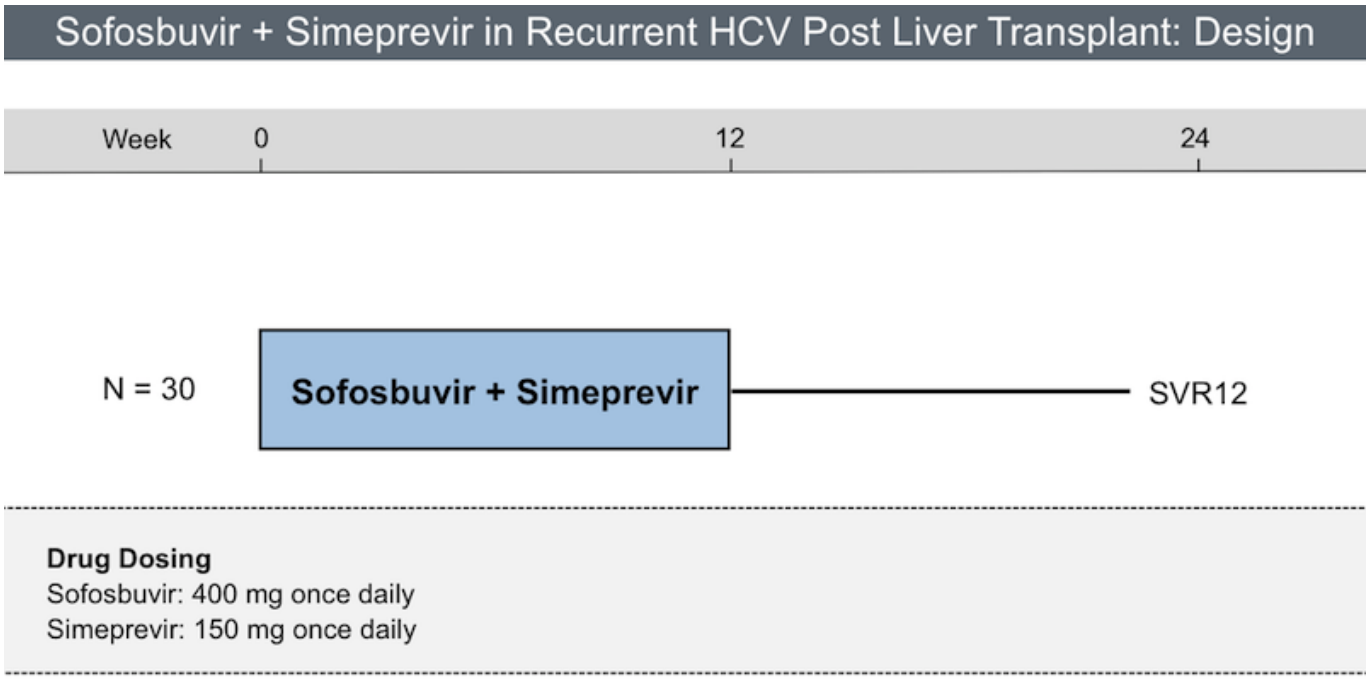


Figure 2 (Image Series) - UCLA Study: Sofosbuvir and Simeprevir for HCV in Post-Transplant Setting
Image 2B: Virologic Response to Therapy

Saab S, Greenberg A, Li E, et al. Sofosbuvir and simeprevir is effective for recurrent hepatitis C in liver transplant recipients. Liver Int. 2015 Apr 24. [Epub ahead of print]

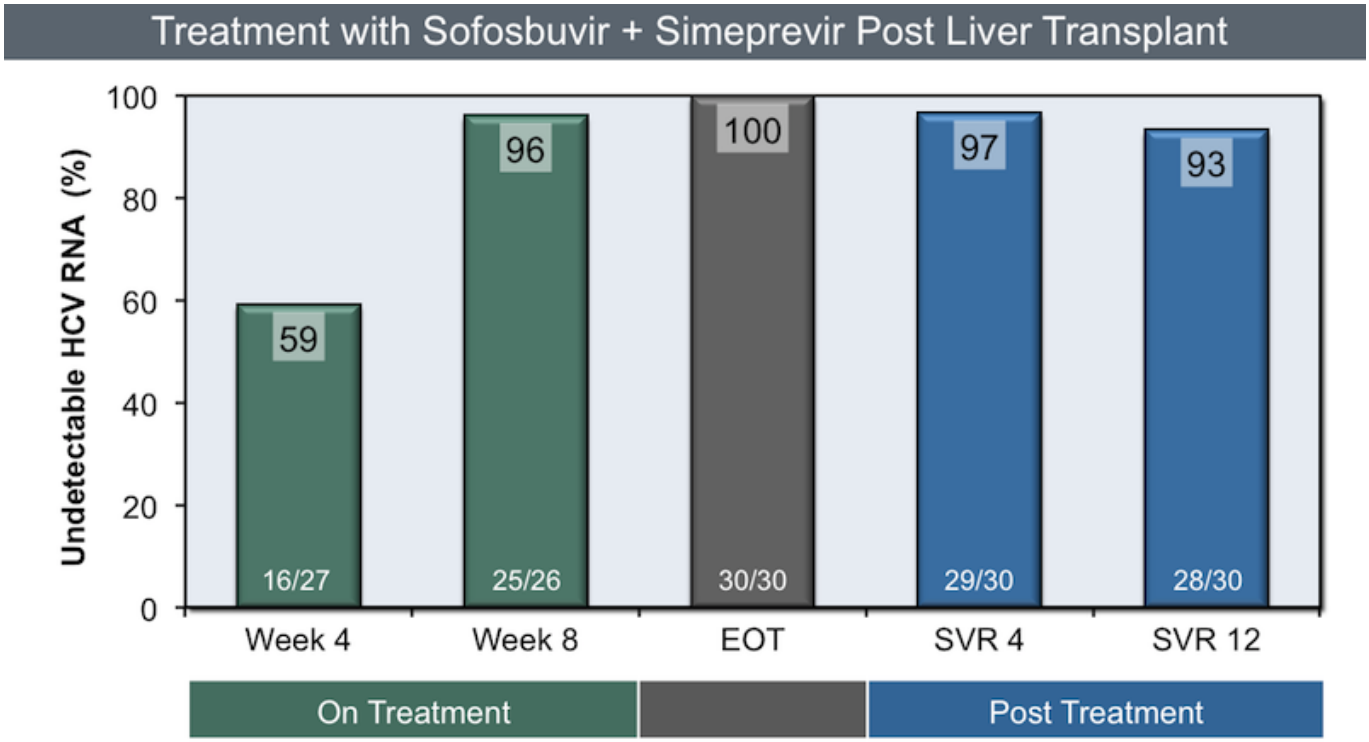
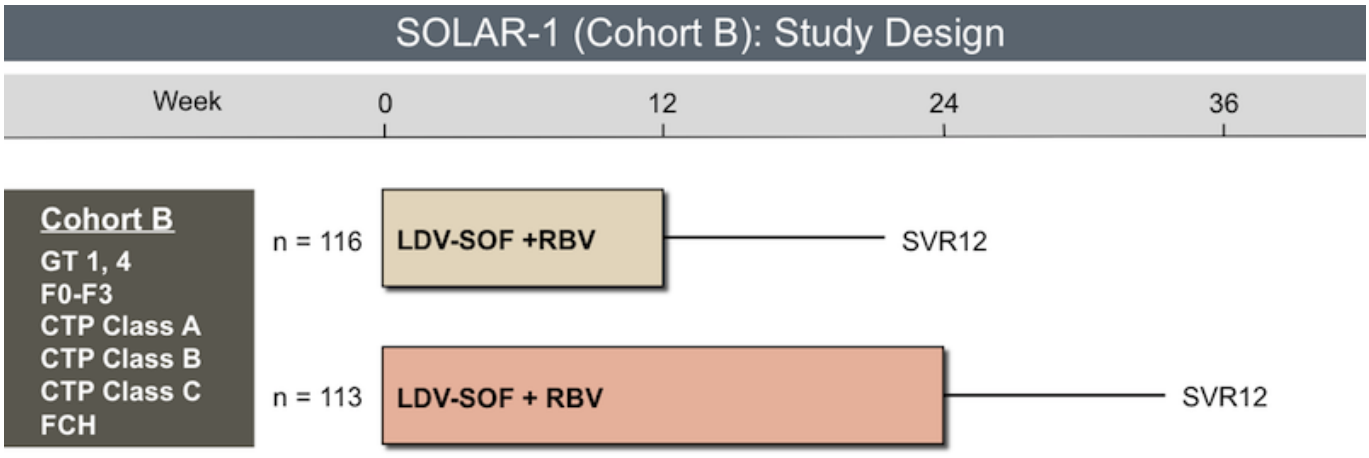


Figure 3 (Image Series) - Ledipasvir-Sofosbuvir plus Ribavirin Treatment of HCV following Liver Transplantation (Image Series) - Figure 3 (Image Series) - Ledipasvir-Sofosbuvir plus Ribavirin Treatment of HCV following Liver Transplantation
Image 3A: Study Design

Source: 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 May 15. [Epub ahead of print]

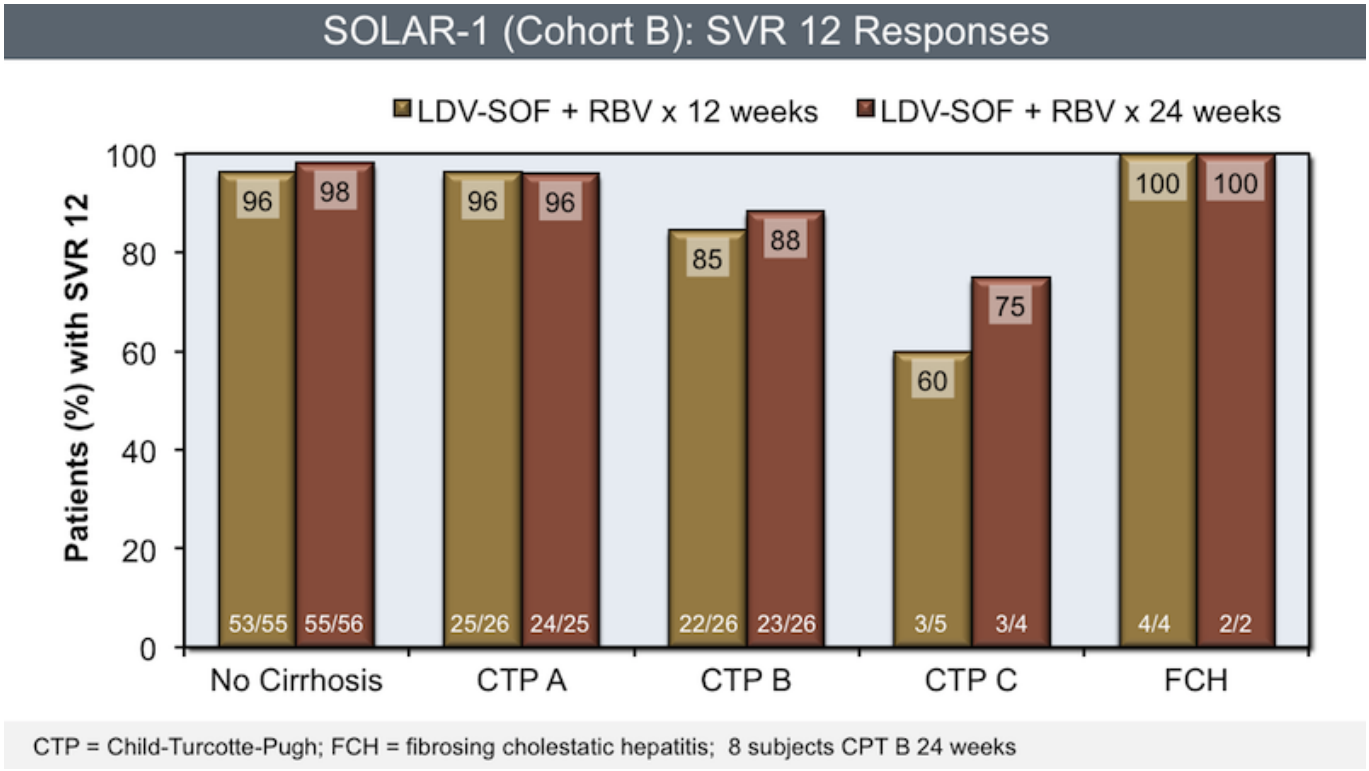


Abbreviations: CTP=Child-Turcotte-Pugh; FCH=fibrosing cholestatic hepatitis; LDV=ledipasvir; SOF=sofosbuvir; RBV=ribavirin

Drug Dosing
Ledipasvir-sofosbuvir (90/400 mg): fixed dose combination; one pill once daily
Ribavirin Dosing
- No cirrhosis; FCH: weight-based and divided bid (1000 mg/day if < 75 kg or 1200 mg/day if ≥ 75 kg)
- CTP B, C: started at 600 mg/day and escalated up to maximum of 1200 mg/day

Figure 3 (Image Series) - Ledipasvir-Sofosbuvir plus Ribavirin Treatment of HCV following Liver Transplantation
Image 3B: SVR12 Response Rates

Source: 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 May 15. [Epub ahead of print]



CTP = Child-Turcotte-Pugh; FCH = fibrosing cholestatic hepatitis; 8 subjects CPT B 24 weeks

Figure 4 (Image Series) - 3D Treatment of HCV following Liver Transplantation (Image Series) - Figure 4 (Image Series) - 3D Treatment of HCV following Liver Transplantation Image 4A: Study Design

Source: Kwo PY, Mantry PS, Coakley E, et al. An interferon-free antiviral regimen for HCV after liver transplantation. N Engl J Med. 2014;371:2375-82.

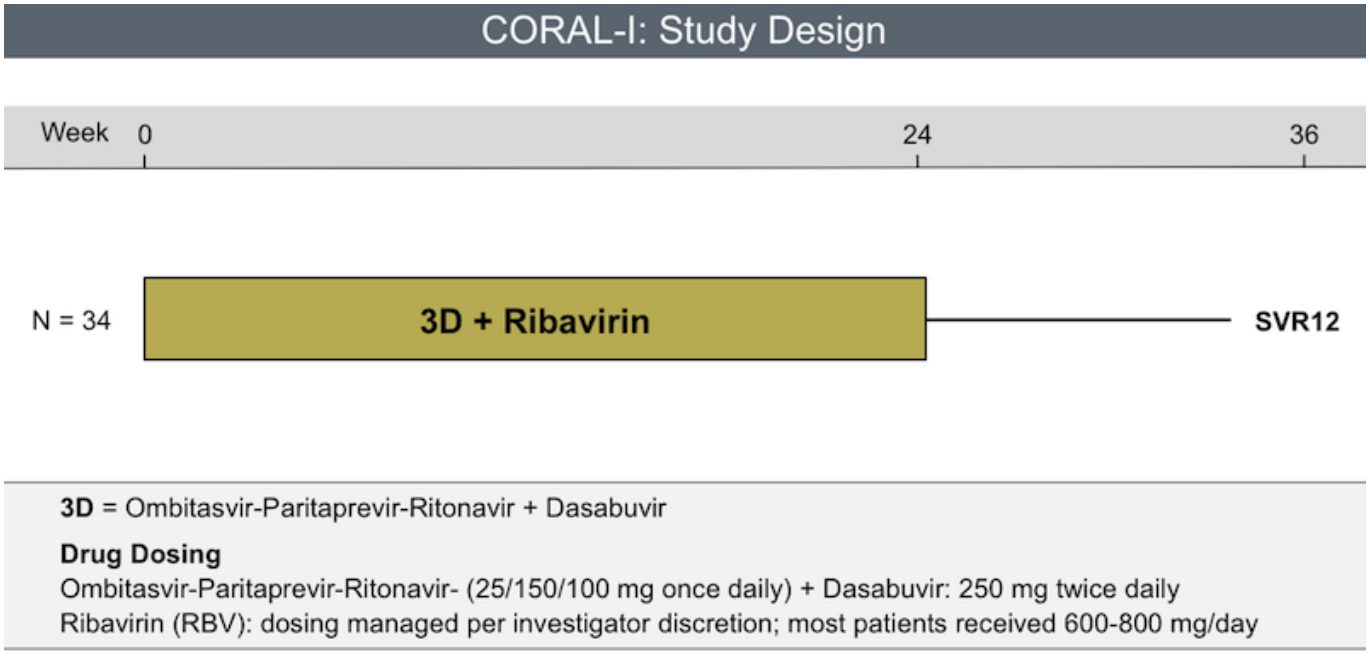


Figure 4 (Image Series) - 3D Treatment of HCV following Liver Transplantation
Image 4B: Virologic Response to Therapy

Source: Kwo PY, Mantry PS, Coakley E, et al. An interferon-free antiviral regimen for HCV after liver transplantation. N Engl J Med. 2014;371:2375-82.

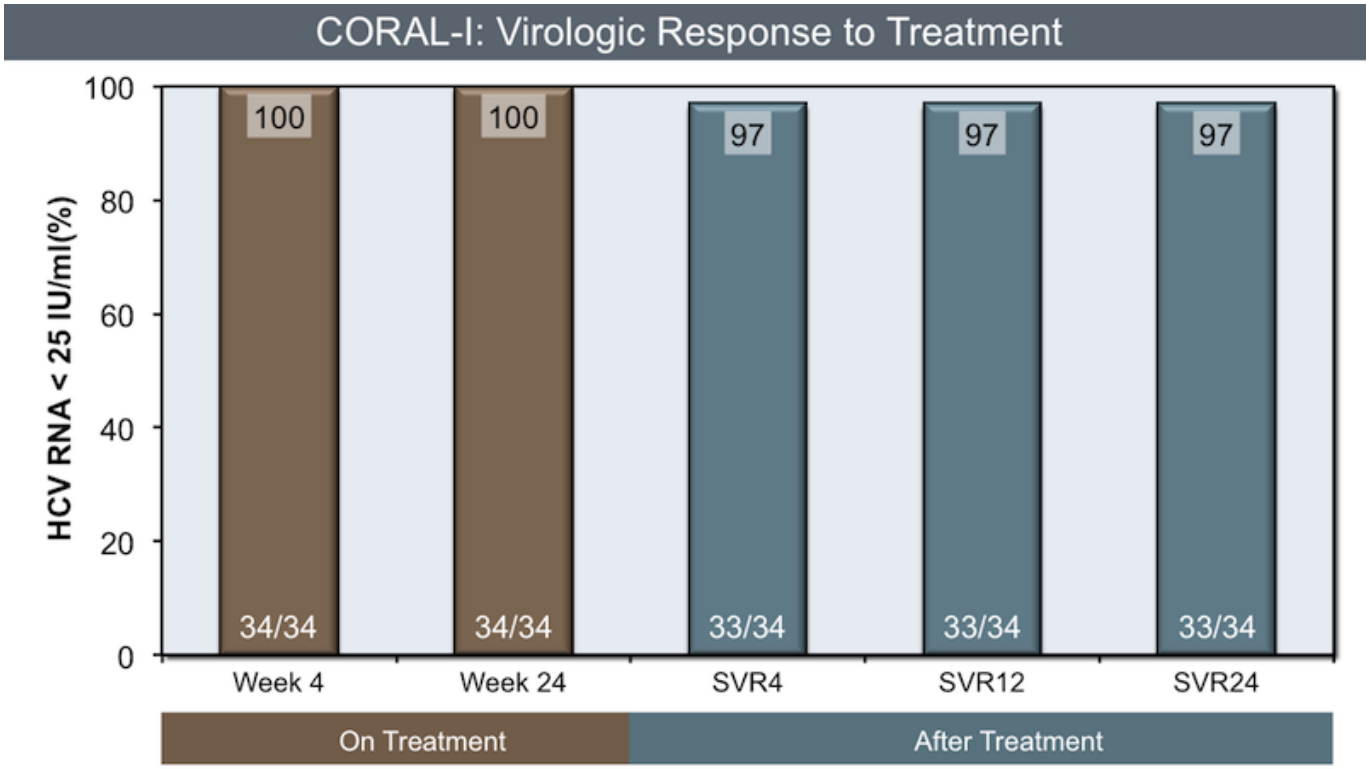


Figure 5 (Image Series) - Daclatasvir and Sofosbuvir and Ribavirin to Treat Post Transplant HCV Infection (Image Series) - Figure 5 (Image Series) - Daclatasvir and Sofosbuvir and Ribavirin to Treat Post Transplant HCV Infection
Image 5A: ALLY 1: Study Design

Source: 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. 50th Annual Meeting of the European Association for the Study of the Liver; April 22-26, 2015; Vienna, Austria. Abstract L08.

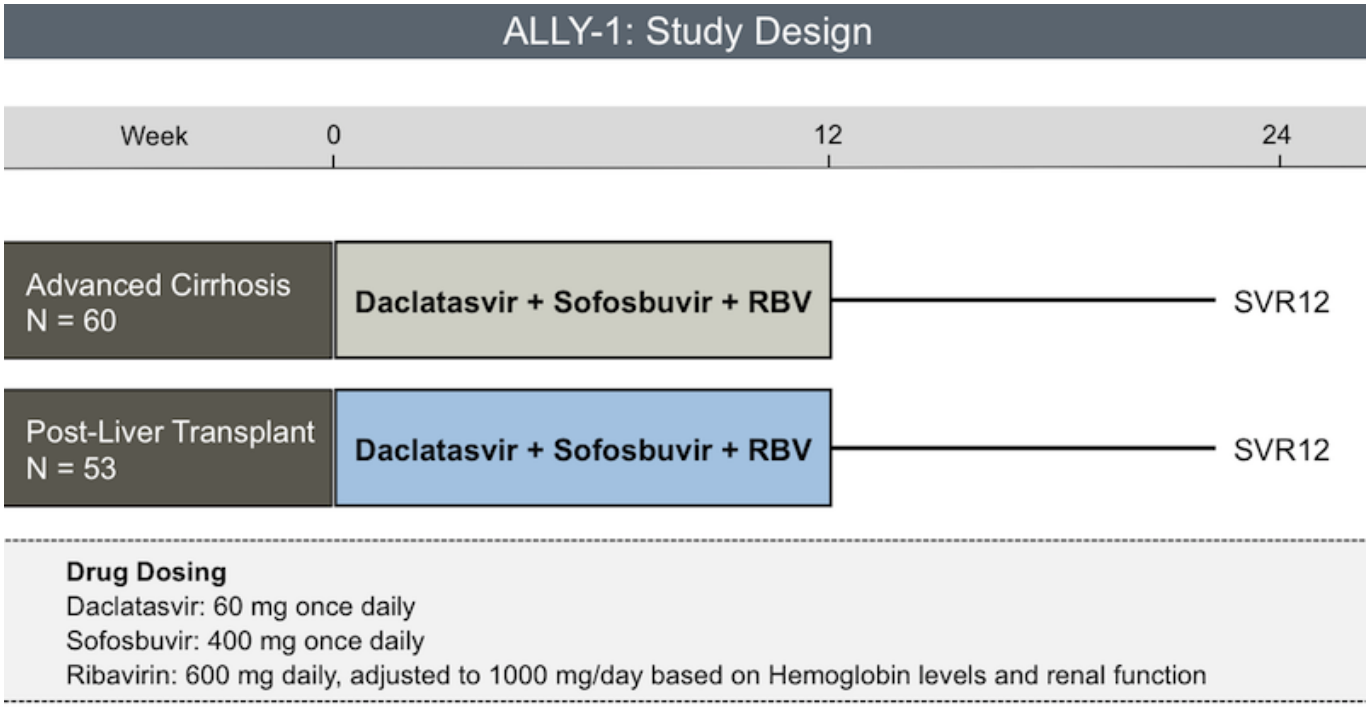


Figure 5 (Image Series) - Daclatasvir and Sofosbuvir and Ribavirin to Treat Post Transplant HCV Infection
Image 5B: ALLY 1: Results

Results for the post-transplant arm of the study are shown here.

Source: 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. 50th Annual Meeting of the European Association for the Study of the Liver; April 22-26, 2015; Vienna, Austria. Abstract L08.