Treating Hepatitis C Virus in Patients With Decompensated Cirrhosis: Why Is It So Difficult and Does a Sustained Response Rate Rescue the Patient From Liver Transplantation?

Paul Kwo, M.D.,* and Saurabh Agrawal, M.D.,*†

Hepatitis C remains the most common indication for orthotopic liver transplant (OLT) worldwide. In the era of all oral direct-acting antiviral (DAA) therapy, sustained response rates (SVRs) greater than 95% have been observed across multiple populations with compensated liver disease including the majority of previously designated “special populations.” This is especially important in patients with cirrhosis where SVR is associated with improvements in survival and reduction in risk for hepatocellular cancer and decompensation requiring OLT.^{1–3} Recent studies in those with hepatitis C–related decompensated cirrhosis have demonstrated that SVRs can indeed be achieved in the majority of these individuals, and short-term follow-up from these studies has shown that SVR is often accompanied by improvement in measures of decompensation including Model for End-Stage Liver Disease (MELD) score and Child-Turcotte-Pugh (CPT) score. Moreover, because hepatitis C recurrence after OLT is associated with worse outcomes, achieving SVR before transplant in a decompensated population with chronic hepatitis C will likely allow these patients to achieve long-term outcomes not different from non-HCV-infected populations.⁴ In the SOLAR-1 and SOLAR-2 studies, those with decompensated cirrhosis with genotypes 1 and 4 were randomized to receive sofosbuvir/ledipasvir with low-dose ribavirin for 12 or 24 weeks.^{5,6} No difference was seen in SVRs in the 12- or 24-week arms, and the therapy was well tolerated (Fig. 1). Similar results were reported in the ALLY-1 study where the combination of sofosbuvir/daclatasvir and low-dose ribavirin for 12 weeks in cirrhotic patients was described across all genotypes (Fig. 2).⁷ Moreover, these studies both reported improvement in MELD and CPT scores 4 weeks after ther-

apy had been stopped with longer-term follow-up results expected. These studies have been complemented by real-world data from the United Kingdom where SVRs in Childs B/C patients were from 60% to 86% in genotype 1 and 43% to 71% in genotype 3 patients receiving 12 weeks of sofosbuvir with ledipasvir or daclatasvir $\pm$ ribavirin.⁸

The reasons for the lower SVRs in patients with decompensated cirrhosis compared with compensated liver disease are not well defined. The presence of clinically significant portal hypertension may reduce hepatic exposure of DAAs by significant portosystemic shunting, although one report demonstrated that intrahepatic sofosbuvir and ribavirin metabolite levels are sufficient in cirrhotic livers from those who underwent OLT.⁹ The presence of cirrhosis may alter the metabolism of DAAs in the liver as well, although for protease inhibitors, higher area under the curve values have been observed in those with decompensated cirrhosis and to date, no protease inhibitors have been approved in the therapy of those with hepatitis C and decompensated liver disease (http://www.rxabbvie.com/pdf/viekirapak_pi.pdf, <https://www.olyzio.com/shared/product/olyzio/prescribing-information.pdf>). For paritaprevir/ombitasvir/dasabuvir, a recent update to the label was made contraindicating the use of this set of DAAs in the treatment of those with decompensated liver disease, as opposed to not recommending their use in decompensated liver disease, which was in the original label, based on recent safety reports. Finally, higher doses of ribavirin than the 600 mg may be beneficial, although the anemia is more difficult to manage in those with decompensated liver disease. Another possibility is that the fibrotic matrix may create viral reservoirs that are difficult for DAAs to penetrate, with

Abbreviations: CPT, Child-Turcotte-Pugh; DAA, direct-acting antiviral; DCV, Daclatasvir; HVPg, hepatic venous pressure gradient; MELD, Model for End-Stage Liver Disease; OLT, orthotopic liver transplant; SVR, sustained response rate.

From the *Department of Medicine, Indiana University School of Medicine, Indianapolis, IN 46202; and †Purdue University West Lafayette, IN.

Potential conflict of interest: Advisory Board: Abbvie, Bristol Myers Squibb, Gilead, Janssen, Merck; Funded Research: bbvie, Bristol Myers Squibb, Gilead, Janssen, Merck.

View this article online at wileyonlinelibrary.com

© 2016 by the American Association for the Study of Liver Diseases

doi: 10.1002/cld.519

Figure 1 SVRs with sofosbuvir/ledipasvir and ribavirin in decompensated cirrhosis. Abbreviations: Hep, hepatitis; LDV, ledipasvir; RBV, ribavirin; SOF, sofosbuvir.

sufficiently large viral reservoirs remaining after therapy is discontinued that relapse occurs. Whether longer exposure to DAAs in the setting of decompensated cirrhosis or additional DAAs will improve further SVRs remains to be determined.

Another question that remains to be answered is whether achieving SVR will rescue patients and prevent OLT. Across all of the studies in decompensated patients, achieving SVR is associated with improvement in albumin and bilirubin levels, as well improvements in MELD and CPT scores, although it is not yet clear what the long-term magnitude of improvement will be. To date, the long-term effects of DAA therapy in decompensated cirrhotic patients with HCV infection on mortality are not yet available. In addition, the long-term outcome in those with clinically significant portal hypertension remains to be determined. A reduction in CPT score or MELD score is obviously desirable, but if the ascites or encephalopathy improves from poorly controlled to better controlled only after SVR, these patients may still require OLT. Recent studies from the interferon era suggest that it may take years to reverse clinically significant portal hypertension, with one recent report noting eight individuals with compensated cirrhosis and clinically significant portal hypertension, in whom the hepatic venous pressure gradient (HVPG) was >10 mm Hg, who achieved SVR having reductions in HVPG of 5 mm Hg from baseline, with three converting to HVPG less than 10 mm Hg after 5 years of follow-up.¹⁰ Thus far, large trials of patients with cirrhosis have yet to demonstrate significant reductions in SVRs based on platelet counts, an indirect measure of portal hypertension.^{11,12} A recent report evaluated the changes in the hepatic vein pressure gradient in patients with hepatitis

Figure 2 Sofosbuvir/Daclatasvir in cirrhosis with and without decompensation. Abbreviations: DCV, daclatasvir; RBV, ribavirin; SOF, sofosbuvir.

C with cirrhosis receiving DAAs. In this study, 50 patients have been randomized to receive 48 weeks of sofosbuvir and ribavirin. In those who received 48 weeks of sofosbuvir and ribavirin, 8 of 33 individuals had at least a 20% reduction in their hepatic vein portal gradient that correlated with improvements in liver chemistries, CPT score, and MELD score, with final results of this study yet to be reported.¹³

Currently, for patients who are OLT candidates, the inability to predict who with decompensation will improve to avoid OLT makes managing patients with decompensated hepatitis C challenging. Although SVR may lead to modest improvements in MELD score, it may also reduce the likelihood of undergoing OLT, particularly in the era of share 35 where MELD scores greater than 30 are often required to receive a liver. Although there are no multicenter data, a MELD “purgatory” can exist post SVR where patients do not have MELD scores that allow them to undergo OLT, yet do not improve to the point where they can be removed from the transplant list and return to productive lives because they still have evidence of decompensation. Moreover, there have been reports of further hepatic decompensation in Childs B/C patients receiving DAAs. One study from the Target registry noted good SVRs with combinations of sofosbuvir/simeprevir with or without ribavirin, as well as sofosbuvir/ribavirin, although episodes of decompensation were noted.¹⁴ Notably, simeprevir administration is not recommended in Childs B/C patients. And although the preliminary report from the United Kingdom noted SVR could be achieved in Childs B/C patients receiving sofosbuvir with daclatasvir or ledipasvir, those with albumin levels less than 3.5 g/dL and age younger than 65 years were noted to have

Figure 3 Potential algorithm for management of decompensated patients with hepatitis C. Abbreviations: Hep, hepatitis; HTN, hypertension.

higher rates of decompensation with MELD scores increasing by 2 points in these populations more frequently than those who were older than 65 years.⁸ Thus, while considering treatment options in decompensated cirrhotic patients, those younger than 65 years with low albumin levels should be carefully counseled before initiating therapy. However, multicenter data will be required to determine whether

MELD score or CPT cutoffs or other variables can be determined where DAA therapy in cirrhotic patients is futile, and it is better to proceed with OLT and subsequent hepatitis C therapy. This is especially true for those patients who are able to undergo OLT in a timely manner because SVRs after OLT are higher than in those who have decompensated liver disease who are treated with DAAs.^{5,7} And, of course, withholding DAA therapy in individuals who face difficult odds of obtaining a liver because of geographic shortage is also problematic because they may decompensate further with little opportunity to undergo OLT. It is our practice to proceed with OLT if the MELD score is greater than 15 and withhold therapy at our center, although this will vary from center to center. Because there is much variability across the world, and until there is more uniform access to organs, these decisions are currently individualized, although long-term studies will be required to delineate what improvement can be expected in those with significant portal hypertension and synthetic dysfunction (Fig. 3).■

CORRESPONDENCE

Paul Kwo, Indiana University School of Medicine, 975 W. Walnut, IB 327, Indianapolis, IN 46202-5121. E-mail: pkwo@iu.edu

References

- Shiratori Y, Ito Y, Yokosuka O, Imazeki F, Nakata R, Tanaka N, et al. Antiviral therapy for cirrhotic hepatitis C: association with reduced hepatocellular carcinoma development and improved survival. *Ann Intern Med* 2005;142:105-114.
- Bruno S, Stroffolini T, Colombo M, Bollani S, Benvegnù L, Mazzella G, et al. Sustained virological response to interferon- α is associated with improved outcome in HCV-related cirrhosis: a retrospective study. *Hepatology* 2007;45:579-587.
- van der Meer AJ, Veldt BJ, Feld JJ, Wedemeyer H, Dufour JF, Lammert F, et al. Association between sustained virological response and all-cause mortality among patients with chronic hepatitis C and advanced hepatic fibrosis. *JAMA* 2012;308:2584-2593.
- Forman LM, Lewis JD, Berlin JA, Feldman HI, Lucey MR. The association between hepatitis C infection and survival after orthotopic liver transplantation. *Gastroenterology* 2002;122:889-896.
- Charlton M, Everson GT, Flamm SL, Kumar P, Landis C, Brown RS Jr, et al. Ledipasvir and sofosbuvir plus ribavirin for treatment of HCV infection in patients with advanced liver disease. *Gastroenterology* 2015;149:649-659.
- Manns M, Forns X, Samuel D, Denning J, Arterburn S, Brandt-Sarif T, et al. G02: 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. *J Hepatol* 2015;62:S187-S188.
- Poordad F, Schiff ER, Vierling JM, Landis C, Fontana RJ, Yang R, et al. LO8: Daclatasvir, sofosbuvir, and ribavirin combination for HCV patients with advanced cirrhosis or posttransplant recurrence: Phase 3 ALLY-1 study. *J Hepatol* 2015;62:S261-S262.
- Foster G, McLauchlan J, Irving W, Cheung M, Hudson B, Verma S, et al. O002: Treatment of decompensated HCV cirrhosis in patients with diverse genotypes: 12 weeks sofosbuvir and NS5A inhibitors with/without ribavirin is effective in HCV genotypes 1 and 3. *J Hepatol* 2015;62:S190-S191.
- Babusis DM, Curry MP, Denning J, Park Y, Murakami E, Afdhal N, et al. Nucleotide analog levels in liver explants from HCV infected subjects undergoing liver transplantation after up to 24 weeks sofosbuvir (GS-7977) with ribavirin treatment. *Hepatology* 2013;58:111.
- Lens S, Rincón D, García-Retortillo M, Albillos A, Calleja JL, Bañares R, et al. Association between severe portal hypertension and risk of liver decompensation in patients with hepatitis C, regardless of response to antiviral therapy. *Clin Gastroenterol Hepatol* 2015;13:1846-1853.
- Poordad F, Hezode C, Trinh R, Kowdley KV, Zeuzem S, Agarwal K, et al. ABT-450/r-ombitasvir and dasabuvir with ribavirin for hepatitis C with cirrhosis. *N Engl J Med* 2014;370:1973-1982.
- Bourlière MJ-PB, de Ledinghen V, Hézode C, Zoulim F, Mathurin P, Tran A, et al. Ledipasvir/Sofosbuvir fixed-dose combination is safe and efficacious in cirrhotic patients who have previously failed protease-inhibitor based triple therapy. *Hepatology* 2014;60:1270A.
- Afdhal N, Everson GT, Calleja JL, McCaughan G, Bosch J, Denning J. LP13: Effect of long term viral suppression with sofosbuvir + ribavirin on hepatic venous pressure gradient in HCV-infected patients with cirrhosis and portal hypertension. *J Hepatol* 2015;62(suppl 2):S269-S270.
- Reddy R, Lim JK, Kuo A, Di Bisceglie AM, Vargas HM, Galati JS, et al. O007: All oral HCV therapy is safe and effective in patients with decompensated cirrhosis: interim report from the HCV-target real world experience. *J Hepatol* 2015;62:S193.