ADVANCES IN HEPATOLOGY

Current Developments in the Treatment of Hepatitis and Hepatobiliary Disease

Section Editor: Eugene R. Schiff, MD

Update on the Treatment of Hepatitis C Virus Infection in Patients With Cirrhosis

Paul J. Pockros, MD
Director, Liver Disease Center and SC Liver Research Consortium, Scripps Clinic
Clinical Director of Research, Scripps Translational Science Institute
La Jolla, California

G&H What is the prevalence of cirrhosis in patients with hepatitis C virus infection, and has it changed over time?

PP It is generally accepted that approximately 20% of patients with untreated hepatitis C virus (HCV) infection develop cirrhosis after 20 years of infection and approximately 40% after 40 years of infection. Thus, it is not unusual for patients with HCV infection who were Baby Boomers (ie, born between 1945 and 1965) to develop cirrhosis.

However, patients with HCV infection are now typically younger than they were before, a result of the opioid epidemic and intravenous drug use. Thus, they generally have had the disease for a much shorter period of time, and much fewer have cirrhosis than before. It is difficult to know the exact rate of cirrhosis now because the demographics are changing rapidly. However, a nationwide chart audit done in 2017 at the offices of physicians who typically treat HCV infection showed that only 15% of patients have cirrhosis, which is a smaller percentage than that previously reported.

G&H What are the challenges of treating patients who have both conditions?

PP Cirrhotic patients were always harder to treat—starting with interferon, subsequently with protease inhibitors, and then with the newer direct-acting antiviral drugs—and so required longer-duration therapy (sometimes with ribavirin for many of the older therapies).

In addition, cirrhotic patients with HCV infection have to be managed differently because they need to be screened with routine ultrasound for hepatocellular carcinoma (HCC) before, during, and after HCV therapy, and it has not been determined when and if screening can be stopped. These patients also need to undergo endoscopy for esophageal varices and signs of portal hypertension.

G&H How does the stage of cirrhosis affect HCV treatment?

PP There are 3 stages of cirrhosis: Child-Pugh A, B, and C. Child-Pugh A is compensated cirrhosis, while B and C are decompensated cirrhosis. Patients with decompensated cirrhosis generally are much more difficult to treat. Typically, these patients are referred to a liver center to determine their Model for End-Stage Liver Disease (MELD) score and whether they are candidates for liver transplantation. If their MELD score is above a certain level—generally, the cutoff is 18 to 20, although it varies from site to site—it may be decided that their HCV infection should not be treated until after liver transplantation. It is essentially contraindicated for patients with Child-Pugh B and C cirrhosis to receive protease inhibitor–based therapy, including elbasvir/grazoprevir (Zepatier, Merck), glecaprevir/pibrentasvir (Mavyret, AbbVie), and sofosbuvir/velpatasvir/voxilaprevir (Vosevi, Gilead). Only sofosbuvir-based regimens without protease inhibitors can be used safely in these patients.

In contrast, patients with Child-Pugh A cirrhosis can be safely treated with protease inhibitors. Until very

recently, the standard of care was 12 weeks of treatment with glecaprevir/pibrentasvir, ledipasvir/sofosbuvir (Harvoni, Gilead), daclatasvir/sofosbuvir, or sofosbuvir/velpatasvir (Epclusa, Gilead) with or without ribavirin depending on the regimen and genotype. This past September, the US Food and Drug Administration (FDA) expanded the label for glecaprevir/pibrentasvir (without ribavirin) to 8 weeks of treatment in this patient population.

G&H How effective and safe are the 12-week treatment regimens?

PP With 12 weeks of treatment, glecaprevir/pibrentasvir and sofosbuvir/velpatasvir (the most commonly used regimens in the United States) have excellent efficacy rates in patients with Child-Pugh A cirrhosis (ie, cure rates above 95%). The main adverse events for both regimens are fatigue and headache (20%-25%). Otherwise, the treatments are very well tolerated, and almost no patients discontinue therapy due to adverse events.

G&H Could you outline how treatment duration has evolved for patients with compensated cirrhosis?

PP Originally, glecaprevir/pibrentasvir was studied in detail in all genotypes in noncirrhotic patients and treatment-naive or treatment-failure patients, and was shown to be effective with 8 weeks of therapy and was labeled accordingly. This regimen was not initially studied for 8 weeks in cirrhotic patients. Instead, it was studied for 12 weeks in cirrhotic patients and was shown to have the same benefit and efficacy as 8 weeks in noncirrhotic patients.

Results from a subsequent study, EXPEDITION-8, were presented by Dr Robert S. Brown Jr at the 2018 American Association for the Study of Liver Diseases (AASLD) meeting. This was a single-arm, open-label, phase 3b study of 343 treatment-naive HCV patients, genotypes 1 through 6, with compensated cirrhosis. Eight weeks of glecaprevir/pibrentasvir was found to work just as well in these patients as 12 weeks. Glecaprevir/pibrentasvir is the first regimen that showed that 8 weeks of treatment in patients with compensated cirrhosis was just as effective as 12 weeks. That is what led to the label expansion.

G&H What were the key efficacy and safety findings from EXPEDITION-8?

PP The sustained virologic response (SVR) rate was 98% in the intent-to-treat population and 100% in the per-protocol population, which were extremely high rates. The mean FibroScan (Echosens) score in these patients was 23.7, which suggests that they definitely had cirrhosis as opposed to F3 fibrosis.

In addition, EXPEDITION-8 showed that treatment for 8 weeks was safe in patients with compensated cirrhosis. Only 1 of the treated patients experienced relapse, and there were no treatment discontinuations because of adverse events. The most common adverse events were fatigue, pruritus, and headache.

G&H Has there been any research on other 8-week HCV treatments in the setting of compensated cirrhosis?

PP Virtually all of the regimens that are approved have been studied for 8 weeks, but failed to match their 12-week data. In other words, 8 weeks of treatment worked, but 12 weeks worked better. Glecaprevir/pibrentasvir is the first treatment regimen whose 8-week data in compensated cirrhosis matched their 12-week data, and I think that shortening the treatment duration is certainly an advantage.

G&H What are the main benefits of having a shorter treatment duration?

PP We have found that both patients and payers prefer shorter treatment durations. They are easier and usually less expensive, and adherence is better. Those are the main benefits, and physicians have had a good deal of experience using 8 weeks of therapy rather than 12 weeks because glecaprevir/pibrentasvir and ledipasvir/sofosbuvir have been approved for 8 weeks of HCV treatment in noncirrhotic patients for several years. We therefore have a good understanding of patient preference and adherence.

G&H Are there any possible challenges or concerns with shortening treatment?

PP The worry is that patients might relapse if they are inadequately treated because they do not have a long enough duration of therapy. If I were worried that a particular patient might relapse, I would probably treat him or her for 12 weeks instead of 8 weeks with glecaprevir/pibrentasvir, as this regimen is still approved for 12 weeks.

G&H What should follow-up care consist of for cirrhotic patients who have achieved SVR?

PP My colleagues and I published an article last year that suggested that using FibroScan every 6 months and showing reversal of fibrosis on FibroScan is not adequate to stop screening for HCC, and that many of those patients still have advanced fibrosis. Guidelines from the

AASLD and the American Gastroenterological Association still recommend indefinite screening for HCC after HCV cure until it can be proven that it is safe to stop. If patients have a platelet count of less than 150,000/μL, or their FibroScan score is greater than 20 kPa, they need to undergo endoscopy at certain intervals, according to the AASLD guidelines on complications of portal hypertension. It is not necessary to screen for HCC or esophageal varices in patients without cirrhosis or advanced fibrosis.

G&H Could you discuss the recent FDA drug safety communication involving HCV treatment in patients with cirrhosis?

PP The drug safety communication stated that the use of glecaprevir/pibrentasvir, elbasvir/grazoprevir, and sofosbuvir/velpatasvir/voxilaprevir in patients with moderate to severe liver impairment could result in rare cases of worsening liver function. This occurred most commonly in the first 4 weeks of therapy, and most of the patients had Child-Pugh B or C cirrhosis. However, some patients did not have apparent decompensated cirrhosis, and had mild liver impairment such as Child-Pugh A cirrhosis, although they did have evidence of decreased platelet counts or increased portal vein pressure.

More details may be released by the 2019 AASLD meeting. There is no question that the patients with Child-Pugh B and C cirrhosis should not have been treated with protease inhibitor–based regimens; that was provider error. However, more information is needed about the cases that did not appear to have decompensated cirrhosis but may have had impaired liver function. Also, the FDA implies in the report that platelet count and portal vein pressure might predict outcome, but does not specify how.

Based on the information currently available, I am recommending, at least for my own center, that patients with cirrhosis and HCV infection who have a platelet count of less than 150,000/μL or who have a FibroScan score above 20 kPa should undergo endoscopy before starting therapy. If esophageal varices are identified, I am planning to choose a regimen without a protease inhibitor, such as sofosbuvir/velpatasvir for 12 weeks, to avoid the risk that has been reported. Any other patients with Child-Pugh A cirrhosis, I am willing to treat with 8 weeks of glecaprevir/pibrentasvir because it makes sense, but I will monitor them carefully in the first 4 weeks because that is when the events occurred. That probably means bringing patients back at week 4 for an office visit and adding another set of laboratory tests at week 2 to make sure that they are okay, and then just proceeding as usual.

Dr Pockros has received research grants paid to Scripps Health from, and has served on speaking and advisory boards for, Gilead, AbbVie, and Intercept. He has also served on the data monitoring committee for Assembly Biosciences and ContraVir Pharmaceuticals.

Suggested Reading

Asselah T, Bourgeois S, Pianko S, et al. Sofosbuvir/velpatasvir in patients with hepatitis C virus genotypes 1-6 and compensated cirrhosis or advanced fibrosis. *Liver Int.* 2018;38(3):443-450.

Brown RS Jr, Hezode C, Wang S, et al. Preliminary efficacy and safety of 8-week glecaprevir/pibrentasvir in patients with HCV genotype 1-6 infection and compensated cirrhosis: the EXPEDITION-8 study [AASLD abstract LB-7]. *Hepatology.* 2018;68(suppl 1).

Forns X, Lee SS, Valdes J, et al. Glecaprevir plus pibrentasvir for chronic hepatitis C virus genotype 1, 2, 4, 5, or 6 infection in adults with compensated cirrhosis (EXPEDITION-1): a single-arm, open-label, multicentre phase 3 trial. *Lancet Infect Dis.* 2017;17(10):1062-1068.

Pan JJ, Bao F, Du E, et al. Morphometry confirms fibrosis regression from sustained virologic response to direct-acting antivirals for hepatitis C. *Hepatol Commun.* 2018;2(11):1320-1330.

Pockros PJ. Management of patients who have achieved sustained virologic response for hepatitis C virus infection. *Gastroenterol Hepatol (N Y).* 2018;14(5):305-307.

US Food and Drug Administration. FDA warns about rare occurrence of serious liver injury with use of hepatitis C medicines Mavyret, Zepatier, and Vosevi in some patients with advanced liver disease. https://www.fda.gov/drugs/drug-safety-and-availability/fda-warns-about-rare-occurrence-serious-liver-injury-use-hepatitis-c-medicines-mavyret-zepatier-and. Published August 28, 2019. Accessed September 9, 2019.