Perspective

Management of Advanced Fibrosis in the Context of Hepatitis C Virus Infection

Advanced fibrosis may be present in a substantial proportion of individuals with asymptomatic, chronic hepatitis C virus (HCV) infection, including those who have been newly diagnosed. HCV treatment improves all-cause and liver-related mortality in individuals with advanced fibrosis, and there is some evidence that reversal of decompensated liver disease may occur in those with a sustained virologic response. HCV treatment is also crucial for individuals undergoing liver transplantation, as recurrent HCV infection posttransplantation is associated with accelerated fibrosis progression and increased risk of poor outcomes. This article summarizes a presentation by Elizabeth C. Verna, MD, at the IAS–USA continuing education program, Management of Hepatitis C Virus in the New Era: Small Molecules Bring Big Changes, *held in New York, New York, in September 2015.*

Keywords: HCV, hepatitis C virus, hepatitis C, fibrosis, sustained virologic response, SVR, cirrhosis, hepatocellular carcinoma, liver transplantation

Identifying Advanced Fibrosis

Currently, the most common methods for staging of fibrosis on liver biopsy specimens are the 4-point Metavir and 6-point Ishak scoring systems. A Metavir score of F4 and an Ishak score of 6 indicate cirrhosis; a Metavir score of F2 and an Ishak score of 3 or 4 indicate moderate fibrosis.

Data indicating that even moderate fibrosis may be associated with worse outcomes in the context of hepatitis C virus (HCV) infection come from the HALT-C (Hepatitis C Antiviral Long-Term Treatment Against Cirrhosis) trial, which examined the effect of maintenance therapy with peginterferon alfa among individuals with chronic HCV infection and fibrosis. The 6-year cumulative incidence of first clinical event was 5.6% for Ishak stage 2; 16.1% for Ishak stage 3; 19.3% for Ishak stage 4; 37.8% for Ishak stage 5; and 49.3% for Ishak stage 6.[1,2]

In a report evaluating a cohort of 4 large provider networks, biopsy results or Fibrosis-4 (FIB-4) scoring indicated fibrosis of Metavir stage F2 or higher in more than 50% of individuals without decompensated cirrhosis who were assessed for HCV treatment.[3] Thus, it is common for some individuals presenting to care for the first time after HCV diagnosis to already have fibrosis even if they are asymptomatic and have laboratory values and physical examination findings within normal limits.

Dr Verna is Assistant Professor of Medicine at Columbia University and Director of Clinical Research at the Center for Liver Disease and Transplantation in New York, New York.

Numerous serologic tests have been developed to detect liver fibrosis, including the aspartate aminotransferase (AST)-to-platelet ratio index (APRI), FIB-4 scoring, and various serum biomarker tests. However, none of these tests is very sensitive or specific, when used alone, for differentiating degree of fibrosis; they can be useful in determining the absence of fibrosis or presence of cirrhosis but are less useful in diagnosing intermediate grades of fibrosis. These tests may be even less accurate for individuals who have very marked liver inflammation or certain types of liver disease that affect the markers used in different ways.

Staging of fibrosis using imaging technology is likely to become the standard of care in the coming years. At present, the most common imaging modality in the United States for staging of fibrosis is transient elastography, but other modalities include magnetic resonance elastography (MRE), shear wave elastography (SWE), and cross-sectional imaging. Transient elastography, a major advance in the staging of fibrosis, generally performs much better than serologic markers and makes it easier to follow the same individual's response to different therapies over time; however, it is not perfect. The advantages of transient elastography are that it is increasingly available, inexpensive, fast, and predictive of clinical outcomes, and that it has been tested in the context of many disease stages. The disadvantages of transient elastography are that it is operator dependent and that imaging findings, as with all types of ultrasound imaging, may be skewed by factors such as an individual's body habitus and the presence of extensive inflammation or extensive fatty infiltration of the liver. MRE may be more accurate but is much more expensive and less available at present than transient elastography. Conventional cross-sectional imaging and ultrasound are considered inadequate for accurate staging of fibrosis. Transient elastography values for each fibrosis stage are shown in Table 1.

A combination of serologic testing and imaging is likely the best option for staging of fibrosis at this time. Liver biopsy confirmed the findings of serum biomarker testing

Table 1. Transient Elastography Values for Each Metavir Fibrosis Stage in Individuals With Chronic Hepatitis C Virus–Related Liver Disease

Transient Elastography Value	Metavir Fibrosis Stage
2.5-7.4 kPa	F0-F1 (no or mild fibrosis)
7.5-9.4 kPa	F2 (moderate fibrosis)
9.5-12.4 kPa	F3 (severe fibrosis)
>12.4 kPa	F4 (cirrhosis)

Table 2. Recommended Changes to HCV Regimens for Treatment-Naive and -Experienced Persons With Compensated Cirrhosis, by Genotype[a]

	Regimen	Treatment-Naive Persons	Treatment-Experienced Persons
HCV genotype 1	Daclatasvir plus sofosbuvir[b]	Extend to 24 weeks with or without ribavirin	Extend to 16-24 weeks with or without ribavirin
	Elbasvir/grazoprevir[c] for 12 weeks	No change	No change
	Ledipasvir/sofosbuvir for 12 weeks	No change	Extend to 24 weeks or with ribavirin
	Paritaprevir/ritonavir/ombitasvir plus dasabuvir (with ribavirin for genotype 1a) for 12 weeks[d]	Extend to 24 weeks for genotype 1a No change for genotype 1b	Extend to 24 weeks for genotype 1a No change for genotype 1b
	Simeprevir plus sofosbuvir with or without ribavirin[b]	Extend to 24 weeks	Extend to 24 weeks
	Sofosbuvir/velpatasvir for 12 weeks	No change	No change
HCV genotype 2	Daclatasvir plus sofosbuvir[b]	Extend to 16-24 weeks with or without ribavirin	Extend to 24 weeks with or without ribavirin
	Sofosbuvir/velpatasvir for 12 weeks	No change	No change
HCV genotype 3	Daclatasvir plus sofosbuvir with or without ribavirin	Extend to 24 weeks with or without ribavirin	Extend to 24 weeks with or without ribavirin
	Sofosbuvir/velpatasvir for 12 weeks	No change	No change
HCV genotype 4	Elbasvir/grazoprevir for 12 weeks	No change	No change
	Ledipasvir/sofosbuvir for 12 weeks	No change	Extend to 24 weeks or add ribavirin
	Paritaprevir/ritonavir/ombitasvir plus dasabuvir for 12 weeks	No change	No change
	Sofosbuvir/velpatasvir for 12 weeks	No change	No change

Abbreviation: HCV, hepatitis C virus. Adapted from the American Association for the Study of Liver Diseases and the Infectious Diseases Society of America.[5]

[a]Slash indicates a coformulation.

[b]Regimen is recommended as an alternative.

[c]For individuals with HCV genotype 1a infection, 12 weeks if there are no baseline resistance-associated variants and extend to 16 weeks if there are baseline resistance-associated variants.

[d]This regimen is recommended for individuals with HCV genotype 1b infection and is an alternative regimen with ribavirin for individuals with HCV genotype 1a infection.

and transient elastography, used in combination, for 84% of individuals with fibrosis of Metavir stage F2 or higher, 95% of those with Metavir stage F3 or higher, and 94% of those with Metavir stage F4.[4] Although there remains a role for liver biopsy, the era of routine liver biopsy to confirm that an individual does not yet require HCV treatment has yielded to an era in which liver biopsies are infrequent, reflecting the beliefs that all HCV-infected individuals should receive treatment and that the risks associated with biopsy should be avoided when possible. Liver biopsy still plays an important role when the findings of noninvasive tests are discrepant or when other forms of chronic liver disease are suspected.

Widely used prognostic models for individuals with cirrhosis include the Child-Turcotte-Pugh (CTP) and Model for End-Stage Liver Disease (MELD) scores. In general, both CTP and MELD scoring should be used to help determine the appropriateness and safety of HCV treatment and evaluation for liver transplantation.

HCV Treatment

Recommendations for changes in HCV treatment in individuals with compensated cirrhosis according to HCV genotype are shown in Table 2.[5] Extended duration of treatment or the addition of ribavirin is recommended for many regimens and particularly for treatment-experienced individuals with HCV genotype 1 disease, and more changes are recommended based on HCV genotype subtype (1a vs 1b). Similarly, extended treatment and the addition of ribavirin are recommended for individuals with HCV genotype 2 or 3 disease and compensated cirrhosis.

An integrated analysis of phase II and III studies of treatment with ledipasvir/sofosbuvir (slash indicates a coformulation) with or without ribavirin for participants with HCV genotype 1 infection and compensated cirrhosis showed high rates of sustained virologic response (SVR).[6,7] A somewhat lower SVR rate was observed among treatment-experienced participants who received only 12 weeks of ledipasvir/sofosbuvir without ribavirin. Findings in the integrated analysis indicated little difference in SVR rates according to method of determination of cirrhosis, transient elastography score, or albumin level. However, SVR rates were lower among treatment-naive and -experienced participants with platelet counts below 75 $\times 10^3$/μL, suggesting that individuals with borderline decompensated cirrhosis may have been included in the studies and in the analysis.

Table 3. Recommended HCV Regimens for Persons With Decompensated Cirrhosis, by Genotype[a]

	Regimen	Duration
HCV genotype 1 or 4	Daclatasvir plus sofosbuvir plus ribavirin[b]	12 weeks 24 weeks (without ribavirin[c])
	Ledipasvir/sofosbuvir plus ribavirin[b]	12 weeks 24 weeks (with ribavirin for prior failed treatment with sofosbuvir, or without ribavirin[c])
	Sofosbuvir/velpatasvir plus ribavirin	12 weeks 24 weeks (without ribavirin[c])
HCV genotype 2 or 3	Daclatasvir plus sofosbuvir plus ribavirin[b]	12 weeks
	Sofosbuvir/velpatasvir plus ribavirin	12 weeks

Abbreviation: HCV, hepatitis C virus. Adapted from the American Association for the Study of Liver Diseases and the Infectious Diseases Society of America.[5]

[a]Slash indicates a coformulation.

[b]Low-dose ribavirin starting at 600 mg daily and increased as tolerated.

[c]If riboflavin is ineligible.

For individuals with decompensated cirrhosis and CTP class B or C disease, hepatic impairment represents a contraindication to the use of some anti-HCV drugs, including simeprevir, paritaprevir (part of the regimen of paritaprevir/ritonavir/ombitasvir plus dasabuvir), and grazoprevir (part of the regimen of elbasvir/grazoprevir), owing to degree of hepatic metabolism and reports of liver injury. Current recommendations for HCV treatment for individuals with decompensated cirrhosis are shown in Table 3.[5] Many of the recommended regimens include ribavirin, reflecting the goal of improving the chances for an SVR despite the potential worsening of anemia in some individuals. Some experts suggest initiating ribavirin at 600 mg (not weight based) and titrating the dose according to tolerability.

The best data on treatment with ledipasvir/sofosbuvir plus ribavirin for individuals with CTP class B or C disease come from the SOLAR-1 and SOLAR-2 studies (Figure 1).[8,9] There was no marked difference in SVR rates with 12 or 24 weeks of treatment, and there was some suggestion of lower SVR rates among participants with CTP class C disease. The safety profile was quite favorable, particularly given the degree of illness in these participants. Adverse events of any grade included fatigue (41%), anemia (20%), and headache (27%), and grade 3 or 4 adverse events occurred in 24% of participants; 4% of participants discontinued due to adverse events. No deaths were considered to be related to the study drugs.

Impact of SVR on Treatment Outcomes

Findings from several studies have made it clear that SVR in individuals with advanced fibrosis is associated with reduced risk of hepatic decompensation and death. In an analysis of 530 individuals with advanced fibrosis, SVR versus no SVR was associated with improvements in all-cause mortality (8.9% vs 26.0%), liver-related mortality or liver transplantation (1.9% vs 27.4%), hepatocellular carcinoma (HCC; 5.1% vs 21.8%), and liver failure (2.1% vs 29.9%).[10] Whether hepatic decompensation can be transformed into "recompensation" after an SVR has been achieved has not been definitively determined. However, some data indicate that an SVR is associated with improvement in MELD or CTP score in many but not all individuals.[8] Nevertheless, some individuals have progressive liver disease despite an SVR, and little is known about how to determine whose disease will or will not progress.

Complications of Cirrhosis and Evaluation for Liver Transplantation

Complications of cirrhosis include HCC and complications of portal hypertension, such as variceal bleeding, encephalopathy, hepatorenal syndrome, and synthetic dysfunction. Such complications have a marked impact on disease prognosis and should prompt an evaluation for liver transplantation.

Screening is recommended for variceal bleeding and HCC for all individuals with cirrhosis, because early intervention can lead to better outcomes. An esophagogastroduodenoscopy (EGD) should be performed at the time of diagnosis of cirrhosis to screen for variceal bleeding, with surveillance interval depending on clinical status: EGD should be repeated every 2 to 3 years for individuals with compensated cirrhosis

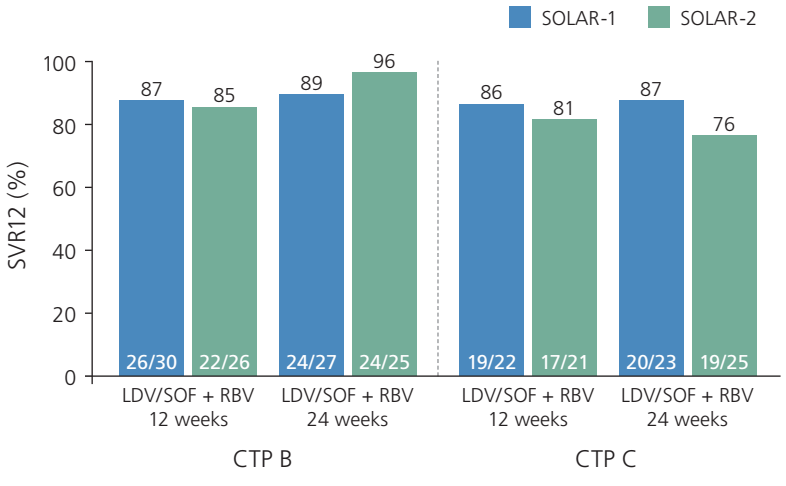

Figure 1. Rates of sustained virologic response 12 weeks after cessation of treatment with coformulated (/) ledipasvir/sofosbuvir plus ribavirin among hepatitis C virus–infected participants with Child-Turcotte-Pugh (CTP) class B or C disease in the SOLAR-1 and SOLAR-2 studies. Efficacy was comparable between the 2 studies. Adapted from Charlton et al and Manns et al.[8,9]

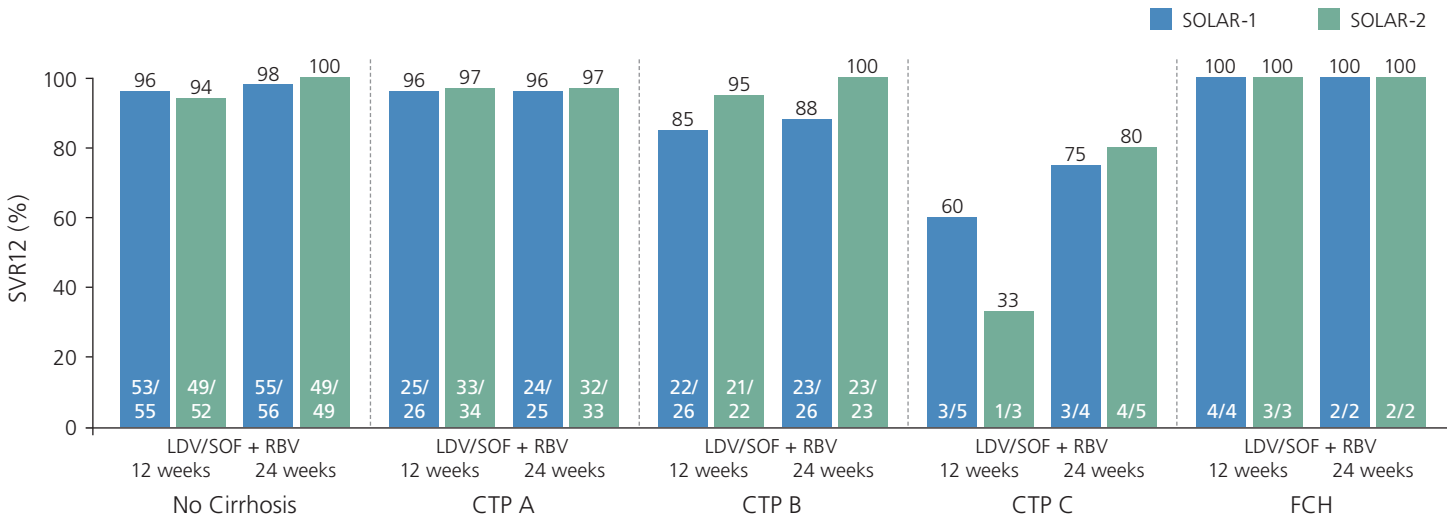

Figure 2. Rates of sustained virologic response 12 weeks after cessation of treatment with coformulated (/) ledipasvir/sofosbuvir plus ribavirin among hepatitis C virus (HCV)-infected individuals with HCV genotypes 1 and 4 post–liver transplantation, by Child-Turcotte-Pugh (CTP) class in the SOLAR-1 and SOLAR-2 studies. Adapted from Charlton et al and Manns et al.[8,9]

who have no varices, every 1 to 2 years if small varices are present, and annually for individuals with decompensated cirrhosis. Nonselective β-blockers or band ligation (for very large esophageal varices) may be used to substantially reduce the incidence of variceal hemorrhage. Individuals with HCV-related cirrhosis should be screened for HCC via ultrasound every 6 months, as there is evidence that screening for HCC in high-risk populations, including those with viral hepatitis infection, is associated with reduced mortality.[11,12]

HCC can still occur in the context of an SVR. In some cases, HCC may be present but relatively undetectable before initiation of HCV treatment. Local-regional therapy for HCC is not considered to be curative, although some individuals who undergo chemoembolization do not appear to experience recurrence. Screening for HCC using α-fetoprotein (AFP) testing alone is no longer recommended, as it is not considered sensitive or specific enough and a substantial proportion of individuals with HCC have normal results on AFP testing. The current indications for liver transplantation in the context of HCV disease are the presence of cirrhosis or a MELD score of 15 or higher and any decompensating event (eg, HCC, ascites, hepatic encephalopathy, variceal hemorrhage, or hepatopulmonary syndrome).

Treatment for HCV infection in liver transplant recipients is crucial because the natural history of recurrent HCV infection after transplantation is accelerated (cirrhosis occurs in up to 25% of individuals by 5 to 10 years after liver transplantation, and complications of cirrhosis are more common). SVR improves survival rates among liver transplant recipients. In an ideal world, all HCV-infected individuals would receive treatment and achieve an SVR before liver transplantation, eliminating the risk for recurrence. In reality, an SVR is not always achieved before liver transplantation, and response rates in individuals with CTP class C disease are lower than in other subgroups receiving HCV treatment, including in those with compensated cirrhosis posttransplant. Further, depending on the region of the United States, access to a new organ may be difficult for individuals in whom HCV treatment has cleared the virus (eg, if MELD score drops from 27 to 18 after HCV treatment in an

Table 4. HCV Regimens Post–Liver Transplantation[a] Including Patient With Recurrent Compensated Cirrhosis

	Regimen	Duration
Recommended for HCV genotype 1 or 4	Daclatasvir plus sofosbuvir with or without ribavirin	12 weeks (with ribavirin) 24 weeks (without ribavirin)
	Ledipasvir/sofosbuvir with or without ribavirin[b]	12 weeks (with ribavirin) 24 weeks (without ribavirin)
Alternatives for HCV genotype 1	Paritaprevir/ritonavir/ombitasvir plus dasabuvir and ribavirin[c]	24 weeks
	Simeprevir plus sofosbuvir with or without ribavirin	12 weeks
Recommended for HCV genotype 2 or 3	Daclatasvir plus sofosbuvir plus ribavirin	12 weeks (with ribavirin) 24 weeks (without ribavirin)
	Sofosbuvir plus ribavirin[b]	24 weeks

Abbreviation: HCV, hepatitis C virus. Adapted from the American Association for the Study of Liver Diseases and the Infectious Diseases Society of America.[5]

[a]Slash indicates a coformulation.

[b]Currently recommended for persons with HCV genotype 2 infection or decompensated recurrent liver disease.

[c]Only recommended for patients with early stage recurrent fibrosis (F0-2).

individual with decompensated cirrhosis, that individual may be ineligible for liver transplantation in some locations). Thus, communication with local transplant groups regarding individuals with a moderate MELD score but several disease complications in whom it is believed that HCV treatment will not achieve complete recompensation should be considered.

Data are now emerging on the use of perioperative treatment immediately before or after liver transplantation. A small phase II study examined treatment with sofosbuvir plus ribavirin given immediately before transplantation to individuals with any HCV genotype, HCC, and CTP class A or B disease.[13] Among 43 evaluable participants, 65% achieved a posttransplantation VR. However, perioperative treatment is not generally recommended at this time due to high relapse rates with sofosbuvir plus ribavirin in individuals with HCV genotype 1 infection. It is not known whether this approach would be more effective with currently recommended regimens. More recently, a small group of individuals was treated with ledipasvir/sofosbuvir in the immediate postoperative setting for only 4 weeks, and SVR was achieved in 14 of 16 individuals.[14]

Important considerations regarding HCV treatment immediately after liver transplantation include potential drug-drug interactions with anti-HCV drugs, particularly between HCV protease inhibitors and calcineurin inhibitors (eg, cyclosporine, tacrolimus), and the potential need for treatment interruption due to complications in the setting of high-dose immunosuppression. Most experience with HCV treatment in the posttransplantation setting is with ledipasvir/sofosbuvir plus ribavirin (in part because of the lower likelihood of drug interactions than with other HCV regimens). Data from the SOLAR-1 and SOLAR-2 studies among participants with HCV genotype 1 or 4 infection show that HCV treatment during the early period after liver transplantation produced high SVR rates 12 weeks after cessation of treatment (SVR12) in those with CTP class A or B disease (Figure 2); although rates were lower in those with CTP class C disease, SVR was still achieved in the majority of participants.[8,9] Current recommendations for HCV treatment after liver transplantation are shown in Table 4.[5]

Conclusion

Individuals with advanced fibrosis and liver transplant recipients are among those with the highest priority for HCV treatment owing to their high risk for severe complications. SVR among individuals with advanced liver disease may reduce the risk of life-threatening decompensation. However, even individuals with cirrhosis and preserved liver function remain at risk for decompensation and must be monitored indefinitely. Safe and effective HCV treatment with direct-acting antiviral drugs has revolutionized the care of liver transplantation candidates and recipients with HCV infection, although treatment must currently be individualized based on stage of disease, comorbidities, and access to a liver allograft.

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