Treatment of Patients with Hepatitis C Virus Genotype 3: Where Are We Now?

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The results of several published studies have demonstrated that hepatitis C virus (HCV) genotype (GT) 3 infection may increase the risk of cirrhosis and hepatocellular carcinoma (HCC) as compared with other HCV GTs.^{1,2} Most recently, a retrospective cohort study of approximately 110,000 US veterans with chronic HCV from the Veterans Affairs HCV Clinical Case Registry (collected between 2000 and 2009) was conducted in order to examine the differences among HCV GTs in the risk of progression to cirrhosis and the development of HCC.² The study revealed GT 3 was associated with a significantly higher risk of progression to cirrhosis and HCC as compared to GT 1, independent of age, diabetes, body mass index, or antiviral treatment (Table 1).²

The American Association for the Study of Liver Diseases/ Infectious Diseases Society of America (AASLD/IDSA) guidelines for the management of patients with HCV GT 3 were recently updated,³ and the combination of sofosbuvir + pegylated interferon/ribavirin for 12 weeks is now one of two recommended treatment strategies, because recent evidence has shown it to be more effective than the previously recommended treatment strategy (sofosbuvir + ribavirin for 24 weeks), particularly in patients with cirrhosis.⁴ In the LONESTAR-2 study, sofosbuvir + pegylated interferon/ribavirin for 12 weeks was equally effective with an associated SVR12 (sustained virological response after 12 weeks) rate of 83% in HCV GT 3 treatment-experienced patients with and without cirrhosis.⁵ A recent study evaluated this in a larger fashion, comparing sofosbuvir + pegylated interferon/ribavirin for 12 weeks versus sofosbuvir + ribavirin for 16 or 24 weeks in GT 3 HCV-infected patients (the BOSON study).⁴ The GT 3 SVR12 rates were lowest in the 16-week arm at 71%, were 84% in

the 24-week arm, but highest with the 12 weeks of peginterferon/ribavirin + sofosbuvir at 93%. The greatest disparity between regimens occurred in the treatment-experienced patients with cirrhosis, where the SVR rate was 40% higher with interferon (Figure 1).⁴

Additionally, the combination of daclatasvir + sofosbuvir for GT 3 patients was approved in the US and included in the AASLD/IDSA guidelines as a recommended regimen. The approval was based on data from an open-label phase 3 study (ALLY-3; ClinicalTrials.gov identifier NCT02032901) that evaluated the 12-week regimen of daclatasvir (NS5A inhibitor) + sofosbuvir in HCV GT 3 treatment-naïve and treatment-experienced patients with and without cirrhosis.⁶ The all-oral, 12-week regimen of daclatasvir + sofosbuvir achieved an overall SVR12 rate of 89% (90% in treatment-naïve and 86% in treatment-experienced patients). Importantly, whereas SVR12 was 96% (105/109) in patients without cirrhosis, only 63% (20/32) of patients with cirrhosis were cured.

A recently presented interim analysis of the French Multi-center Compassionate Use Program examining the efficacy of daclatasvir + sofosbuvir with or without ribavirin in patients with HCV GT 3 demonstrated that 12 weeks of daclatasvir + sofosbuvir in HCV GT 3 noncirrhotic patients resulted in high SVR4 rates of 92%. However, patients with cirrhosis required treatment duration of 24 weeks to achieve SVR rates of 88%.⁷

Sofosbuvir + ribavirin for 24 weeks is an approved regimen for the treatment of patients with GT 3 in both treatment-naïve and treatment-experienced patients; however, this yields unacceptably poor response rates in those with advanced fibrosis, and at great expense.³ Currently,

Abbreviations: GT, genotype; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; SVR, sustained virological response.

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Potential conflict of interest: Nothing to report.

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doi: 10.1002/cld.506

TABLE 1 Results of a Multivariate Cox Regression Analysis After Adjustment for Demographic, Clinical, and Antiviral Treatment Factors Indicate an Association Between HCV GT 3 and GT 1 and the Risk of Incident Cirrhosis and HCC

Risk in patients with GT 3 as compared with GT 1	% higher	Adjusted hazard ratio	95% confidence interval
Cirrhosis	31%	1.31	1.22--1.39
HCC	80%	1.80	1.61--2.03

Adapted from Kanwal et al.² **Figure 1** SVR12 in HCV GT 3 patients with cirrhosis by treatment history (adapted from Foster et al⁴). Abbreviations: PEG, pegylated interferon; RBV, ribavirin; SOF, sofosbuvir; SVR, sustained virological response; TE, treatment-experienced; TN, treatment-naïve.

there are limited data on the efficacy of ledipasvir/sofosbuvir with or without ribavirin in patients with HCV GT 3. A single-center study (ELECTRON 2) evaluated ledipasvir/sofosbuvir with or without ribavirin for 12 weeks in treatment-naïve HCV GT 3 patients, of which 19% had cirrhosis. In the ribavirin-containing arm, all 26 patients achieved SVR12 compared with 64% (16/25) of those in the ribavirin-free arm.⁸

Implications and Recommendations for Practitioners

HCV GT 3 is currently the most difficult GT to cure, especially in patients with cirrhosis and past interferon failure; however, the field is rapidly emerging and another promising interferon-free regimen is in late-stage development.

The combination of daclatasvir + sofosbuvir offers a 12-week interferon-free regimen with SVR12 >95% in patients without cirrhosis; however, those GT 3 patients with cirrhosis still cannot achieve SVR12 rates >70%. The US label has a Limitations of Use statement informing prescribers that SVR12 rates are reduced in GT 3 patients with cirrhosis; however, compassionate use experience in Europe dem-

onstrated SVR12 rates of 88% in GT 3 patients with cirrhosis who were treated for 24 weeks with daclatasvir + sofosbuvir with or without ribavirin. Based on this data, the AASLD/IDSA guidelines recommend daclatasvir + sofosbuvir + ribavirin for 24 weeks in GT 3-infected patients with cirrhosis.

C-SWIFT, a proof-of-concept study, assessed grazoprevir/elbasvir + sofosbuvir in HCV GT 3 treatment-naïve patients with and without cirrhosis for 8 or 12 weeks.⁹ This study demonstrated that the combination achieved SVR12 rates of 93% and 100% with 8- and 12-week treatment durations, respectively, in patients without cirrhosis, and a SVR12 rate of 91% with 12-week treatment duration in those with cirrhosis.¹⁰

Combining three potent direct-acting antivirals may be the only viable option for GT 3 patients with cirrhosis in order to achieve SVR12 >90%. This type of potent three-drug combination will likely also be effective in minimizing resistance-associated variants.

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