

ADVANCES IN HEPATOLOGY

Current Developments in the Treatment of Hepatitis and Hepatobiliary Disease

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Treatment of Hepatitis C Virus Genotype 3 Infection



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G&H How common is genotype 3 among patients with hepatitis C virus infection?

FP Hepatitis C virus (HCV) infection is comprised of 6 genotypes and multiple subtypes. Worldwide, genotype 3 is the second most common HCV genotype after subtype 1B. However, in the United States, genotype 3 comprises only 10% to 12% of all patients infected with HCV.

G&H Does the genotype influence the natural course of HCV in a patient?

FP Yes, it does. Although the demographics of patients with HCV genotype 3 are generally the same as those with other genotypes, studies have shown that genotype 3 is associated with a faster progression to cirrhosis and, thus, a higher likelihood of evolving into hepatocellular carcinoma than the other genotypes.

In addition, HCV genotype 3 has a higher association with fatty liver disease. The mechanism of this association is not well understood, but eradicating the genotype 3 virus has been shown to improve fatty liver.

G&H How effective is treatment for HCV genotype 3 infection?

FP The treatment regimens that have been approved by the US Food and Drug Administration (FDA) for HCV infection were, for the most part, designed for genotype 1. With its recent approval by the FDA, daclatasvir (Daklinza,

Bristol-Myers Squibb) in combination with sofosbuvir (Sovaldi, Gilead) is probably the best choice for HCV genotype 3 patients. This all-oral regimen consists of 60 mg of daclatasvir and 400 mg of sofosbuvir taken once daily for 12 weeks. In the ALLY-3 (Phase III Daclatasvir and Sofosbuvir for Genotype 3 Chronic HCV) trial, which is still ongoing, 96% of noncirrhotic patients with HCV genotype 3 infection experienced an overall sustained virologic response (SVR) with daclatasvir and sofosbuvir, as did 63% of HCV genotype 3 patients with cirrhosis. In addition, SVR was achieved in 90% of treatment-naïve patients and 86% of treatment-experienced patients.

The combination of pegylated interferon, ribavirin, and sofosbuvir can also be effective for HCV genotype 3 infection. Taking this combination for 12 weeks resulted in an overall SVR rate of 83% in both cirrhotic and noncirrhotic patients. However, this regimen is limited by the fact that pegylated interferon is needed.

Combination therapy of just sofosbuvir and ribavirin for 24 weeks has been shown to yield a SVR rate of 85% overall and 62% in cirrhotic patients, but this combination is costly and inconvenient given the long duration.

G&H What is the optimal duration of therapy for genotype 3 patients?

FP The optimal duration of therapy is still in evolution. For noncirrhotic patients, 12 weeks is probably adequate. For cirrhotic patients, the optimal duration, or even the optimal regimen, is still unclear. Currently, the optimal

duration seems to be 24 weeks. However, the use of ribavirin with the combination of daclatasvir and sofosbuvir has been shown to increase efficacy. The ALLY-3 trial is looking at durations of daclatasvir and sofosbuvir beyond 12 weeks, with and without ribavirin, to see if they will yield higher SVR rates.

G&H Are there any predictors of SVR in these patients?

FP The only predictors of response that have been seen thus far are treatment history and cirrhosis. However, the impact of baseline resistance variants on outcomes still has to be fully investigated. This issue is still in its infancy, but clinicians are certainly seeing that, in general, the presence of baseline resistance variants may impact SVR in all genotypes. Resistance testing for genotype 3 infection is not yet commercially available, but it may be within the next year.

G&H If SVR is not achieved in patients infected with HCV genotype 3, how should the patients be managed? Should treatment be extended or the dose increased?

FP Right now, there is no good salvage regimen or secondary solution for patients with HCV genotype 3 who have failed therapy. This is an area of active research, and we recognize that patients who fail current therapy will likely require a different regimen, which we are working to develop. We are hopeful that second-generation direct-acting antiviral agents will become commercially available over the next 2 years and will offer better treatment options for patients who have failed current therapy. Emerging data, such as those recently reported from the ASTRAL-3 (Comparison of Sofosbuvir/Velpatasvir Fixed Dose Combination for 12 Weeks With Sofosbuvir and Ribavirin for 24 Weeks in Adults With Chronic Genotype 3 HCV Infection) study, have shown that 12 weeks of therapy can yield high SVR rates for many patients with genotype 3 infection, although cirrhotic patients still have suboptimal responses.

G&H How common is relapse in these patients?

FP The most common cause of treatment failure is relapse, which occurs in less than 10% of noncirrhotic patients, regardless of whether they are treatment-experienced or -naïve, and 40% of cirrhotic patients who are treatment-experienced. These data come from the recent VALENCE (Sofosbuvir and Ribavirin in Treatment-Naïve and Treatment-Experienced Subjects With Chronic Genotype 2 or 3 HCV Infection) study.

G&H What are the most common adverse events associated with the current treatment options?

FP The all-oral, direct-acting antiviral regimens are very well tolerated and, in general, are considered to be similar to placebo when ribavirin is not used. However, the use of ribavirin and/or interferon is associated with well-known and well-described side effects, such as fatigue, headache, flu-like symptoms, and anemia.

G&H Are there any contraindications to these treatments?

FP There are no absolute contraindications, but there is potential for drug-drug interactions. In these cases, the patient's concomitant medications may need to be adjusted or even discontinued to allow for the minimization of potential negative interactions.

G&H Has there been any research on the real-life cure rates for HCV genotype 3 infection?

FP There have been data published on this issue, some of which were presented by Graham Foster at the last meeting of the European Association for the Study of the Liver. In the European experience, the real-life cure rates were very similar to the SVR rates seen in clinical research trials of treatment-experienced cirrhotic patients.

G&H Has there been any research on the cost-effectiveness of treatment in these patients?

FP I think that most people accept that it is cost-effective to treat all genotypes of HCV not only to decrease the negative sequela of developing cirrhosis and hepatocellular carcinoma, but also to improve extrahepatic morbidity and decrease the potential for indirect costs associated with illnesses related to HCV.

G&H Are there any special considerations that should be kept in mind when treating patients with HCV genotype 3?

FP Clinicians should be aware that the subgroup of treatment-experienced cirrhotic genotype 3 patients is now considered to be one of the harder-to-cure viral groups. Clinicians often underestimate how difficult it is to eradicate genotype 3, and many are unaware that this genotype has a different natural history than other genotypes, in that it leads to a faster progression to cirrhosis. Genotype 3 is sometimes thought of as very similar to genotype 2, which is not true.

When treating patients with genotype 3, it is also important to understand the data and current treatment options prior to engaging in therapy.

G&H What drugs and combinations are currently being examined for treatment of HCV genotype 3?

FP There are several new regimens that are being evaluated for the treatment of genotype 3, including GS-5816 (velpatasvir), ABT-530, and elbasvir. These agents are still in development, but late-stage results are expected over the next coming months.

G&H What are the next steps in research?

FP The next step is to develop second-generation direct-acting antiviral agents that will address both the resistance and treatment failures associated with the first-generation agents. A pangenotypic regimen that covers all genotypes and patient subgroups, and also covers the majority of resistance variants not addressed by current regimens, would be ideal.

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JFC Although the prediction of disease may appear to be an overly ambitious endeavor, it is currently being explored in diseases such as RA, diabetes, and systemic lupus erythematosus. IBD is trailing behind these fields, so there is a strong need for more research. A better understanding of the pathogenesis of the disease in the future may improve the strategies for detecting IBD. For example, if we could identify a signature in the microbiome that is associated with the development of Crohn's disease, then we could add this marker to our preventive metrics. Thus far, the problem is that the main tools that are currently available are serologic markers that are not very sensitive or specific. Nevertheless, this concept is a first step. More prospective studies are needed, as well as studies of cost-effectiveness, feasibility, ethics, and risk/benefit ratios for identifying an at-risk population that could benefit from a preventive approach.

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