EDITORIALS

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Most current article

Therapy With Direct-Acting Antivirals for Genotype 3 Patients: Interferon's Last Gasp?

See "Efficacy of ledipasvir and sofosbuvir, with or without ribavirin, for 12 weeks in patients with HCV genotype 3 or 6 infection," by Gane EJ, Hyland RH, An D, et al, on page 1454; and "Efficacy of sofosbuvir plus ribavirin with or without peginterferon-alfa in patients with Hepatitis C Virus genotype 3 infection and treatment-experienced patients with cirrhosis and Hepatitis C Virus genotype 2 infection," by Foster GR, Pianko S, Brown A et al, on page 1462.

Hepatitis C virus (HCV) genotypes (GTs) 2 and 3 account for approximately 40% of infections by this virus worldwide.[1] Patients with HCV GT3 have more rapid disease progression and are less responsive to treatment than those with GT2,[2] and GT3 infection is considered relatively difficult to cure with the available direct-acting antivirals (DAAs).[3,4]

In the United States, 2 interferon-free regimens have been approved for HCV GT3, namely, sofosbuvir plus ribavirin for 24 weeks and daclatasvir plus sofosbuvir for 12 weeks. The main limitation of DAA combinations for GT3 is the low sustained virologic response (SVR) rates in patients with cirrhosis, particularly treatment-experienced ones. Another option is the combination of sofosbuvir plus peginterferon and ribavirin for 12 weeks, but it is less attractive because of the adverse effects and monitoring requirements of peginterferon. In Europe, 3 regimens are recommended for HCV GT3: sofosbuvir plus peginterferon and ribavirin for 12 weeks, sofosbuvir and ribavirin for

24 weeks, or sofosbuvir and daclatasvir for 12 weeks in noncirrhotic patients.[4,5] Response rates for all-oral regimens in GT3 patients with cirrhosis are well below the 90% rates seen in patients with other HCV GTs. For this reason, sofosbuvir plus peginterferon and ribavirin for 12 weeks, or sofosbuvir plus daclatasvir with or without ribavirin for 24 weeks are preferred in treatment-experienced cirrhotic patients. However, these options have been recommended based on limited information that must be confirmed in further studies.

In this issue of *Gastroenterology*, 2 important papers offer new data on GT3 patients: Gane et al[5] describe the safety and efficacy of ledipasvir/sofosbuvir regimens with or without ribavirin for 12 weeks in a study including 126 GT 3 or 6 patients, and Foster et al[6] report the efficacy of sofosbuvir plus ribavirin with or without peginterferon alfa in a population of GT3 patients. Gane et al performed a phase II open-label, uncontrolled trial, in which GT3 treatment-naïve patients were assigned randomly to receive ledipasvir/sofosbuvir with or without ribavirin for 12 weeks, whereas treatment-experienced patients received ledipasvir/sofosbuvir and ribavirin for 12 weeks. SVR12 rates were 100% and 82% in treatment-naïve and experienced patients, respectively, treated with ledipasvir/sofosbuvir and ribavirin. SVR rates were only 64% in treatment-naïve individuals receiving ledipasvir/sofosbuvir without ribavirin, suggesting that ribavirin cannot be omitted from this regimen without a considerable loss of efficacy. Addition of ribavirin to ledipasvir/sofosbuvir reduced the relapse rate from 8% to 0% in treatment-naïve individuals, whereas relapse was 8% in treatment-experienced patients. Patients who relapsed were predominantly males with cirrhosis. Ledipasvir/sofosbuvir has been approved for treating HCV GT3 by the European Medicines Agency (EMEA), but not the US Food and Drug Administration (FDA), and the European Association for the Study of the Liver guidelines do not currently recommend the use of this combination.[4]

Based on the results of the All-Oral 12-Week Treatment With Daclatasvir Plus Sofosbuvir in Patients With Hepatitis C Virus Genotype 3 Infection (ALLY-3) trial, another NS5A complex inhibitor, daclatasvir, in combination with sofosbuvir has been approved by both the FDA and EMEA for treating GT3 patients.[7] In ALLY-3, daclatasvir plus sofosbuvir for 12 weeks resulted in SVR rates of 90% in treatment-naive and 86% in treatment-experienced patients. SVR was high in patients without cirrhosis (97% and 94%, respectively) and substantially lower in those with cirrhosis (58% and 69%, respectively). Almost all patients who did not achieve SVR relapsed. The reason for the higher relapse rate in GT3 cirrhotic patients is uncertain. Cirrhosis may affect the therapy response owing to drug-related factors such as changes in drug delivery and metabolism resulting from major disruptions in hepatic blood flow.[8] These changes could lead to suboptimal drug levels in some regions of the liver, favoring viral reservoirs. It has been reported that the hepatic steatosis frequently found in GT3 patients may alter drug metabolism.[9] Factors related to the host immune response could also contribute to relapse. In patients with cirrhosis, particularly those with low albumin levels, there is an increase in the risk of infection, possibly via prostaglandin E2 inhibition of macrophages.[10] In addition, a recent report in noncirrhotic patients has shown that interferon-free therapy normalizes natural killer cell function.[11]

There are no head-to-head studies comparing ledipasvir/sofosbuvir versus daclatasvir and sofosbuvir. In vitro findings suggest that the antiviral potency of daclatasvir against HCV GT3 is superior to that of ledipasvir.[12] The results obtained by Gane et al[5] when ribavirin was added to ledipasvir/sofosbuvir are better than would be expected, enabling a reduction in the duration of therapy to 12 weeks in treatment-naïve patients, including those with cirrhosis. However, the study was performed only in New Zeeland and it contains a small number of cirrhotic patients. To put the value of ledipasvir into perspective, Gane et al's results can be viewed against those obtained with sofosbuvir and ribavirin for 12 weeks in GT3 treatment-naïve (Fission study)[13] and experienced (Fusion study) patients.[14] With all the limitations of this type of comparison, ledipasvir/sofosbuvir for 12 weeks increased SVR rates by 9% relative to sofosbuvir and ribavirin in naïve patients, and with the addition of ribavirin, by approximately 40% in naïve and experienced patients. However, daclatasvir and sofosbuvir without ribavirin for the same duration has provided even higher SVR rates than ledipasvir/sofosbuvir (90%), except in patients with cirrhosis.[7] In the early access program in UK in decompensated GT3 patients,[15] SVR12 was 59% (36/61) for ledipasvir/sofosbuvir plus ribavirin for 12 weeks and 70% (80/114) for daclatasvir and sofosbuvir plus ribavirin for 12 weeks. SVR rates were lower in the small number of patients receiving the same combination without ribavirin. Several lessons have been learned in studies with DAAs: (1) GT3 patients with cirrhosis are still difficult to cure, (2) ribavirin is needed to increase SVR rates, and (3) lengthy therapy is required, ≥16 or 24 weeks even when using combinations of sofosbuvir and an NS5A inhibitor.

In the phase III, open-label, multicenter study by Foster et al[6] included in this issue of *Gastroenterology*, 48 GT2 treatment-experienced patients and 544 GT3 treatment-naïve and experienced patients were randomized to receive sofosbuvir and ribavirin for either 16 or 24 weeks, or sofosbuvir plus peginterferon and ribavirin for 12 weeks. In GT2, SVR rates were 87% and 100% for 16 and 24 weeks of sofosbuvir and ribavirin, respectively, and 94% for sofosbuvir, peginterferon, and ribavirin for 12 weeks. In GT3 patients, SVR12 was 71% and 84% in those receiving 16 or 24 weeks of sofosbuvir and ribavirin, respectively, and 93% in those receiving sofosbuvir, peginterferon, and ribavirin for 12 weeks. Among the major patient subgroups, including treatment-naïve and treatment-experienced patients, those with and without cirrhosis, and in subgroups by combined treatment history and cirrhosis status, SVR12 rates were least among patients receiving 16 weeks of sofosbuvir and ribavirin and greatest among patients receiving 12 weeks of sofosbuvir plus peginterferon and ribavirin. Eighty-three
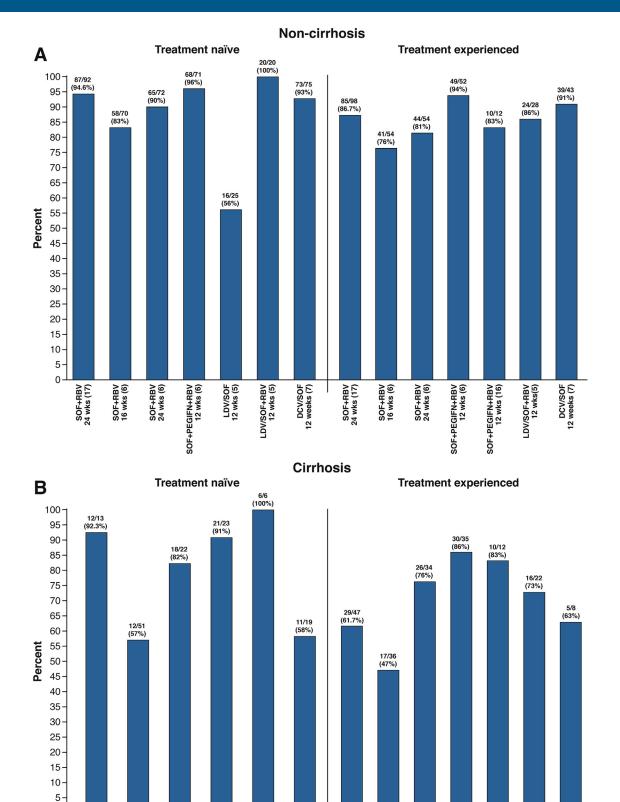
Figure 1. Sustained virologic response rates with different therapeutic regimens (*A*) in patients without cirrhosis (*B*) in patients with cirrhosis.

patients had virologic relapse, 50 (28%) in the group receiving 16 weeks of sofosbuvir and ribavirin, 24 (13%) of those receiving 24 weeks of sofosbuvir and ribavirin, and 9 (5%) patients receiving 12 weeks of sofosbuvir plus peginterferon and ribavirin. Baseline factors associated with relapse were male sex, cirrhosis, and interleukin (IL)-28B non-CC haplotype in patients receiving 16 weeks of sofosbuvir and ribavirin. This results support the preliminary data of a phase II study,[16] suggesting that the combination of sofosbuvir, peginterferon, and ribavirin remains the best option in terms of efficacy and duration in GT3 patients with cirrhosis, yielding SVR rates of >85%. SVR12 rates in various studies using the approved DAA combinations are shown in Figure 1.

The main drawback of interferon is its associated side effects. Nonetheless, the 12-week regimen of sofosbuvir plus peginterferon and ribavirin in Foster's study unexpectedly showed few differences in terms of adverse events compared with 16 to 24 weeks of sofosbuvir and ribavirin. Some interferon-associated side effects were more common in patients receiving this drug (fatigue, myalgia, flu-like symptoms), but only 1 patient discontinued therapy.[6]

An advantage of the interferon-based regimen used in this study was that none of the patients who relapsed harbored NS5B resistance-associated variants such as S282T, V321A, or V321A, suggesting that interferon use prevents their emergence. In the sofosbuvir and ribavirin arms, relapsers did not show the S282T resistance-associated variant, but L159F was identified in 8 patients and V321A in 1. Data from Gane et al on RAVs by deep sequencing in the 17 patients who relapsed to ledipasvir/sofosbuvir with or without ribavirin showed no Y93H variants associated with NS5A resistance, whereas the S282T variant was detected in 2 patients.[5] This contrasts with previous findings in HCV GT1.[17,18] Both these observations support a lower potency of ledipasvir against HCV GT3. NS5A RAVs (Y93H) were also detected in 9 of 19 patients who failed daclatasvir and sofosbuvir in the ALLY-3 study.[7]

Emergence of RAVs can compromise salvage therapy, but there is little available information to date on rescue therapy in this scenario. Retreatment with sofosbuvir plus daclatasvir is a potential option in noncirrhotic GT3 patients who fail sofosbuvir and ribavirin, as was seen in 5 of 7 patients included in the ALLY-3 study. However, in treatment-experienced patients (including failure to peginterferon and ribavirin, and sofosbuvir and ribavirin), the best current salvage therapy in those who tolerate interferon is the combination of sofosbuvir, peginterferon, and ribavirin.[19] Very few data are available on rescue therapy with sofosbuvir and daclatasvir, but this combination may also have potential efficacy in patients harboring NS5A RAVs.[20]

Difficult-to-cure HCV GT3 infection may prompt the last revival of interferon-based therapy, in combination with sofosbuvir and ribavirin. For interferon-ineligible patients, ribavirin is an important tool to increase SVR rates in the interim until new, more potent DAAs against GT3 come on the market.

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Diagnosing Minimal Hepatic Encephalopathy: From the Ivory Tower to the Real World

> See "Minimal hepatic encephalopathy and critical flicker frequency are associated with survival of patients with cirrhosis," by Ampuero J, Simón M, Montoliú C, et al, on page 1483.

Hepatic encephalopathy (HE) is one of the major, unsolved complications of cirrhosis. Even its subtle form, termed minimal HE (MHE), is associated with increased mortality, risk of hospitalization, quality of life impairment, and caregiver burden. Detection of MHE may guide treatment, which has the potential to improve outcomes and quality of life.[1] However, testing of patients with cirrhosis for MHE remains uncommon in clinical practice. In this issue of *Gastroenterology*, Ampuero et al[2] studied the impact of MHE using two validated techniques and found that the critical flicker frequency (CFF), a neurophysiologic test for MHE, was associated independently with survival. These important findings should spur further debate as to how to integrate MHE into the context of overall survival analysis of subjects with cirrhosis and define barriers to this being a reality.

Ampuero et al found that a decreased CFF predicted mortality in a well characterized cohort of 117 patients with cirrhosis, independent of Model for End-stage Liver Disease (MELD) score.[2] The confirmation of this finding in a multicenter validation cohort of 114 subjects followed every 6 months is a key strength of this study. During a 5-year follow-up period, they found that a clear separation of mortality occurred in those with abnormal CFF performance. MHE identified based on CFF in the setting of a low MELD score did not impact mortality of subjects; however, this significantly changed with worsening liver disease severity. The team also studied a paper-and-pencil battery, the Psychometric Hepatic Encephalopathy Score (PHES), which did not add independently to the mortality risk. Of note, these cohorts did include patients with prior overt HE events that have been shown to carry a worse prognosis. However, even in cirrhotic subjects without prior overt HE, a similar impact on survival and hospitalizations was noted, independent of the liver disease severity in a prior study.[3] The striking differences in the survival curves between subjects of comparable MELD with or without abnormal CFF in the current study provides further evidence that patients with MHE are a subset of patients with cirrhosis whose guarded prognosis cannot be predicted readily using the MELD score, serum albumin, or other relevant biomarkers.[2–4] It could also suggest that cognitive impairment can legitimately be considered as an additional variable to refine priority for liver transplantation in a "sickest first" allocation system. These results expand on others from the United States, Europe, and Asia and go one step further to demonstrating that specialized testing for HE could be a "value-added" proposition to the overall prognostication for cirrhosis patients.[3,5,6]

Traditionally in hepatology practice, specialized HE testing has taken a backseat to other measures such as screening for varices and hepatocellular cancer. Despite increasing evidence of the importance of MHE and