AASLD 2015: Daclatasvir + Sofosbuvir with Ribavirin Cures 90% of Genotype 3 Hepatitis C Patients

November 19, 2015
by Liz Highleyman

An all-oral combination of daclatasvir, sofosbuvir, and ribavirin taken for 12 or 16 weeks led to high sustained virological response rates for people with hard-to-treat hepatitis C virus (HCV) genotype 3 and advanced liver fibrosis or cirrhosis, according to findings from the ALLY-3+ study presented at the 2015 AASLD Liver Meeting this week in San Francisco.

Interferon-free direct-acting antiviral therapy has revolutionized treatment for chronic hepatitis C, but better options are still needed for people with genotype 3, which is the most difficult type to cure in the post-interferon era. Genotype 3, which accounts for an estimated 30% of all hepatitis C cases worldwide, is associated with faster liver disease progression and is more likely to lead to cirrhosis and liver cancer than other genotypes.

Vincent Leroy from Centre Hospitalier Universitaire de Grenoble presented late-breaking results from the ALLY-3+ trial, a Phase 3b study evaluating Bristol-Myers Squibb's pangenotypic HCV NS5A replication complex inhibitor daclatasvir (Daklinza), Gilead Sciences' HCV polymerase inhibitor sofosbuvir (Sovaldi), and ribavirin for genotype 3 patients with advanced liver disease.

In the previous ALLY-3 study, daclatasvir plus sofosbuvir taken for 12 weeks led to a sustained virological response rate of 96% for people without cirrhosis, but only 63% for those with cirrhosis. ALLY-3+ assessed the whether adding ribavirin to this combination for 12 or 16 weeks could improve outcomes for patients with advanced fibrosis or cirrhosis.
ALLY-3+ (AI444326) enrolled 50 genotype 3 chronic hepatitis C patients. Most (80%) were men, almost all were white, and the mean age was 54 years. About three-quarters had prior treatment experience, including 12% who relapsed after taking sofosbuvir plus ribavirin (with or without interferon); people who had previously used NS5A inhibitors were excluded. Over a quarter (28%) had advanced fibrosis (stage F3) while 72% had compensated cirrhosis (stage F4). About half had high HCV viral load at baseline (≥6 million IU/mL).

Participants in this open-label trial were randomly assigned (1:1) to take 60 mg daclatasvir and 400 mg sofosbuvir once-daily plus 1000-1200 mg/day weight-based ribavirin for either 12 or 16 weeks.

Results

- Overall sustained virological response rates at 12 weeks post-treatment (SVR12) were 88% in the 12-week treatment arm and 92% in the 16-week arm in an intention-to-treat analysis -- not a significant difference.
- 100% of people with advanced fibrosis achieved SVR12 in both the 12-week and 16-week treatment arms.
- Among people with cirrhosis, SVR12 rates were 83% in the 12-week arm and 89% in the 16-week arm.
- Looking at treatment history, SVR12 rates were 92% for treatment-naive people (88% for treatment-naive cirrhotics) and 89% for treatment-experienced patients (86% for treatment-experienced cirrhotics).
- There were no viral breakthrough during treatment, but 4 people relapsed after finishing therapy (2 in each arm).
- 8 participants had NS5A resistance-associated variants (RAVs) at baseline, and among these 88% achieved SVR12.
- 2 of the relapsers had also previously relapsed on sofosbuvir plus ribavirin; however, no sofosbuvir-associated NS5A RAVs were detected at either baseline or relapse.
- Treatment was generally safe and well-tolerated, with no treatment-related serious adverse events or discontinuations due to adverse events; there was 1 treatment-unrelated death.
- The most common adverse events were insomnia (30%), fatigue (26%), and headache (24%).

- 1 patient in the 16-week arm developed grade 3 anemia.
- All 6 people who reduced their ribavirin dose went on to achieve SVR12, while the 4 relapsers had no dose reductions.

Based on these findings the researchers concluded, "Daclatasvir + sofosbuvir + ribavirin for 12 or 16 weeks is a highly efficacious therapy for genotype 3-infected patients with advanced fibrosis or compensated cirrhosis, a population in urgent need of treatment."

Leroy said that 12 and 16 weeks of treatment "probably perform the same," and it is not yet known whether extending therapy to 24 weeks would further reduce relapses.

A pair of real-world studies presented at the Liver Meeting also showed good results for patients with advanced liver disease treated with daclatasvir plus sofosbuvir, with or without ribavirin, in compassionate use programs.