CROI Roundup: News From the Front

Researchers presented findings from clinical trials of both investigational and approved hepatitis C therapies at the 2014 Conference on Retroviruses and Opportunistic Infections (CROI).

April 15, 2014 By Benjamin Ryan

Periodically throughout the year, researchers descend upon major medical meetings to announce the latest and greatest results from studies about hepatitis C virus (HCV) treatments. The 2014 Conference on Retroviruses and Opportunistic Infections (CROI), which took place March 3 to 6 in Boston, is typically dominated by news about HIV. But hep C research findings also made a significant showing this time around as the drug pipeline swells with a diverse range of therapies that promise to accelerate the ongoing revolution in hep C treatment.

For more information about any of the studies mentioned in this article, click on the imbedded hyperlinks. You can also check out Hepmag.com's CROI page here.

Six-Week Sovaldi Combo Treatment

You read that right. Just six weeks of Gilead Sciences' hotly anticipated combination pill of the NS5A inhibitor ledipasvir and the FDA-approved nucleotide analog polymerase inhibitor Sovaldi (sofosbuvir), given with or without the NS5B site 2 polymerase inhibitor GS-9669 or the NS3 protease inhibitor GS-9451, cured 95 to 100 percent of people with genotype 1 of hep C in a small pilot study called SYNERGY.

Making these results all the more promising, the 20 study participants had characteristics that made them traditionally difficult to treat. Most had genotype 1a and high hep C viral loads, and about 25 to 30 percent had advanced liver disease. (Genotype 1 is the most common in the United States.) About 80 percent were African Americans, who traditionally have not responded as well to treatment.

BMS: Daclatasvir Combos

Bristol-Myers Squibb (BMS) presented two promising studies of its NS5A inhibitor daclatasvir at CROI.

In a Phase IIb open-label trial of daclatasvir, plus the protease inhibitor asunaprevir and the non-nucleoside NS5B polymerase inhibitor BMS-791325 ('325), 92 percent of those with genotype 1 were cured after 12 weeks of therapy. The findings support two Phase III trials of a fixed dose pill of the triple-drug regimen.

Another trial gave 12 to 24 weeks of daclatasvir and Janssen's Olysio, with or without ribavirin, to 147 study participants with genotype 1b, including 104 treatment-naive participants and 43 prior null responders. Another part of the study included 21 people with genotype 1a, who received all three drugs for 24 weeks.

Eighty-one percent of the treatment-naive 1b's who received 12 weeks of the two-drug treatment and 89 percent who received 24 weeks of that regimen were cured. The cure rates for those who received three drugs were 75 percent in the 12-week group and 74 percent in the 24-week group.

Among the null-responder participants with genotype 1b, 65 percent of those who took the two-drug regimen and 95 percent who took the three-drug cocktail were cured.

The cocktail cured just 67 percent of the participants with genotype 1a.

BMS submitted new drug applications for daclatasvir and asunaprevir to the U.S. Food and Drug Administration (FDA) on April 7. The applications requested approval for the two drugs to be used in combination to treat genotype 1b, and also for daclatasvir to be used in combination with other hep C drugs to treat multiple genotypes. Meanwhile, Gilead applied for approval of the ledipasvir and Sovaldi combination pill on February 10, with an expected answer from the FDA coming October 10. This suggests that the end of 2014 could see another one-two punch of newly approved hep C therapies akin to the Sovaldi and Olysio (simeprevir) approvals of late 2013. Plus, AbbVie is probably not far behind in submitting for approval of its combination therapy.

BMS expects to file for approval of the triple combination of daclatasvir, asunaprevir and '325 in the first quarter of 2015.

AbbVie's Arsenal

AbbVie's so called "three-D" combination therapy is gearing up to give Gilead's offerings a run for their money. A combination of the ritonavir-boosted protease inhibitor ABT-450/r (a coformulated pill of the two drugs), the NS5A inhibitor ABT-267 and the non-nucleoside NS5B inhibitor ABT-333, given with or without ribavirin, cured 99 percent of 419 people with genotype 1b of hep C after 12 weeks of therapy.

The major adverse side effects were headache, fatigue, itching, nausea and weakness, with rates of the latter two side effects significantly greater among those taking ribavirin. The good news is that the researchers concluded that ribavirin offered no advantage, indicating that the drug could be eliminated from the regimen.

Coinfection Treatment

Recent studies have shown that, thanks to newer HCV treatments, HIV no longer reduces the likelihood of a hep C cure for someone coinfected with both viruses. (For a feature article on advances in treatment of hep C among coinfected people, click here.) Several clinical trials presented at CROI both underlined this fact and gave clues as to how well both the approved and the investigational therapies may work in other subgroups of the hep C population.

One Phase III trialinvestigated Sovaldi plus ribavirin in coinfected study participants with genotypes 1, 2 and 3 of hep C.

Seventy-five percent of treatment-native participants with genotype 1 were cured after receiving 24 weeks of therapy, which is the treatment duration that the FDA recommends for their genotype when taking this interferon-free regimen.

The genotype 2 and 3 participants received 12 weeks of treatment if they were treatment naive and 24 weeks if they were prior non-responders to treatment. (The FDA specified in its December approval of Sovaldi that 24 weeks is the preferred treatment length for all people with genotype 3 taking this regimen, however.) Eighty-eight percent of the treatment-naive genotype 2s were cured, compared with just 67 percent of those with genotype 3. Treatment-experienced genotypes 2 and 3 had higher cure rates: a respective 92 and 94 percent.

A Phase II trial of Merck's NS3/4A protease inhibitor MK-5172 and its NS5A replication complex inhibitor MK-8742 boasted near-perfect preliminary results, which were equivalent between those who were mono- or coinfected with hep C. A treatment-naive, non-cirrhotic participant pool randomly received the two drugs for 12 weeks either with or without ribavirin.

At the end of treatment, 100 percent of the coinfected participants who took ribavirin and 90 percent of those who did not take that drug had undetectable hep C, indicating a good likelihood that tests 12 weeks down the line would show that they have been cured. Among the monoinfected participants, 94 percent of those who took ribavirin and 100 percent of those who did not achieved an undetectable viral count.

Merck intends to present further results of this study at the European Association for the Study of the Liver (EASL), taking place April 9 to 13 in London. Check back with Hepmag.com for news from that conference.

Boehringer Ingelheim's protease inhibitor faldaprevir also cures people coinfected with HIV and HCV as effectively as those with just hep C, according to a Phase III study of the drug in people with genotype 1. The trial, however, included interferon, which will likely be phased out for the treatment of most people with hep C by early next year, making it unlikely that such a regimen would ever be preferred over others.

In the study, a coinfected group that included over three-quarters of treatment-naive people and 22 percent of prior relapsers took faldaprevir plus pegylated interferon alfa-2a and ribavirin. Those who were taking HIV protease inhibitors took a 120 milligram daily dose of faldaprevir for 24 weeks, while those who were taking Sustiva (efavirenz) to treat HIV took double the dose of faldaprevir for either 12 or 24 weeks. The participants treating their HIV with Isentress (raltegravir) or who were not taking HIV therapy were randomly assigned to take 12 or 24 weeks of the faldaprevir combination.

Seventy-one percent of those who received the lower dose of faldaprevir for 24 weeks and 72

percent of those on the higher dose were cured.

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