COPILOT Study: Second Three-Month Inteferon-Free Abbott Regimen Versus Geno 1 Hep C

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A 12-week regimen of ribavirin plus two experimental drugs from Abbott Laboratories—ABT-450, a once-daily hepatitis C protease inhibitor that requires blood-level boosting using a low dose of the HIV protease inhibitor Norvir (ritonavir), and ABT-333, a twice-daily non-nucleoside polymerase inhibitor—kept hepatitis C virus (HCV) levels undetectable for 12 weeks after completing treatment in over 90 percent of first-time treatment takers and 47 percent of treatment experienced people.

These results, from the Phase II COPILOT study in people with genotype 1 HCV, were presented by Fred Poordad, MD, from Cedars-Sinai Medical Center in Los Angeles and his colleagues on Saturday, April 21, at the 47th Meeting of the European Association for the Study of the Liver (EASL) in Barcelona.

The early data, presented by Poordad's group, documented a sustained virologic response at week 12 following treatment (SVR 12), which is highly predictive of ultimate cure rates or sustained virologic responses at week 24 following treatment completion (SVR 24). All study participants will be followed for 48 weeks to evaluate the durability of their response to interferon-free treatment.

COPILOT enrolled 33 first-time treatment takers and 17 treatment-experienced people. All study participants were given 12 weeks of triple therapy with Norvir-boosted ABT-450, ABT-333 and ribavirin.

Nineteen of the first-time treatment takers received high-dose ABT-450 (250 milligrams) plus 100 mg Norvir; the remaining 14 received lower-dose ABT-450: 150 mg plus 100 mg Norvir.

Treatment-experienced study volunteers all received the lower dose of Norvir-boosted ABT-450.

Most of COPILOT's participants were older than 50 and male, and more than three-quarters of them were white. None had cirrhosis or advanced fibrosis.

Of the first-time treatment takers in the high-dose Norvir-boosted ABT-450 group, most had HCV genotype 1a (89 percent), and half of them had an IL-28B CC genotype. In the low-dose group, 78

percent had HCV genotype 1a, and 35 percent had the IL-28B CC genotype. In the treatment-experienced group, all but one study participant had HCV genotype 1a, and no one had the IL-28B CC genotype; 11 were prior partial responders, and six were prior null responders.

After four weeks of treatment, hepatitis C viral load was undetectable in 90 percent of first-time treatment takers in the high-dose group and 79 percent of the lower-dose group.

SVR 12 rates were 95 percent in the high-dose group of first-time treatment takers and 93 percent in the low-dose group. No viral breakthroughs while on treatment or post-treatment relapses occurred in either dosing group. Two first-time treatment takers did, however, discontinue therapy—one because of liver enzyme increases in the high-dose group and one because of personal reasons in the low-dose group.

In the treatment-experienced group, 73 percent had undetectable HCV levels at week four of therapy. Upon stopping therapy at week 12, 47 percent had undetectable viral loads. However, all 47 percent maintained undetectable HCV levels at the 12-week post-treatment time point.

Overall, 45 percent of the prior partial responders and 50 percent of prior null responders achieved SVR 12. Viral breakthrough during treatment occurred among six people—one due to three weeks of accidental self under-dosing—and three people relapsed two weeks after finishing treatment.

All but one of the nine treatment-experienced study participants who experienced breakthrough or relapse had HCV genotype 1a. The only case of pre-treatment resistance, notably HCV mutations reducing the virus's sensitivity to ABT-450, was found in the person with HCV genotype 1b. Resistance to both protease and polymerase inhibitors after viral breakthrough or relapse was found in eight of nine people; the remaining relapse had no evidence of drug resistance.

Poordad and his team conducted safety assessments during the weekly study visits. At week three, one first-time treatment taker in the high-dose Norvir-boosted ABT-450 group discontinued treatment because of a severe adverse event—a sharp increase in ALT liver enzyme levels, which resolved after treatment was stopped. Although four other study participants experienced severe adverse events—fatigue, vomiting, pain and elevated bilirubin, which was managed by reducing the ribavirin dose—none interrupted or stopped taking their study medications.

Side effects experienced by more than 20 percent of study participants included fatigue, nausea, headache, dizziness, insomnia, itching, vomiting and rash. The rash was mild and in most cases cleared up after stopping treatment.

Laboratory abnormalities were reported only among first-time treatment takers, who experienced elevations in indirect bilirubin (six cases), which were attributed to the effect of Norvir-boosted ABT-450 on bilirubin transporters, and creatinine (two cases, which resolved during treatment) and one case each of elevated sodium and liver enzyme levels.

Poordad and his team explained that neither the HCV subtype (genotype 1a or 1b) nor the IL-28B

genotype affected responses to treatment among first-time treatment takers, although all of the treatment-experienced participants who achieved SVR 12 had HCV genotype 1a; 50 percent had the IL-28B CT genotype, and 40 percent had the IL-28B TT genotype.

The author concluded by underscoring the potential of this 12-week, interferon-free regimen "…to achieve SVR in a high proportion of subjects."

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