Grazoprevir and Elbasvir Once-Daily Oral Combination Clears Hepatitis C in 95%

Miriam E. Tucker

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VIENNA — Clearance rates at 12 weeks were high in patients with hepatitis C genotype 1, 4, or 6 infections who were treated with an investigational fixed-dose combination of grazoprevir and elbasvir, a phase 3 trial shows.

The once-daily tablet, which consists of grazoprevir 100 mg, an NS3/4A protease inhibitor, and elbasvir 50 mg, an NS5A inhibitor, is interferon-free and ribavirin-free.

If the fixed-dose combination from Merck & Co. is approved by regulatory bodies in Europe and the United States, it will be in competition with two combinations already approved for the treatment of adults with chronic genotype 1 hepatitis C infection: ledipasvir plus sofosbuvir (*Harvoni*, Gilead Sciences); and ombitasvir, paritaprevir, ritonavir, plus dasabuvir (*Viekira Pak*, AbbVie).

However, the grazoprevir–elbasvir combination "has a few advantages" over AbbVie's fixed-dose combination, said study author Paul Pockros, MD, from the Scripps Translational Science Institute in La Jolla, California. Grazoprevir is a pan-genotypic protease inhibitor that does not require ritonavir boosting, he pointed out.

"The competition will further reduce cost," Dr Pockros told*Medscape Medical News*. "Merck intends to use their product in combination with a nucleoside NS5b polymerase inhibitor that is as potent as sofosbuvir. This would shorten the duration of therapy further and likely not require ribavirin in any patients, including treatment-failure cirrhotics," he explained.

The randomized double-blind placebo-controlled clinical was presented by Stefan Zeuzem, MD, from Goethe University Hospital in Frankfurt, Germany, here at the European Association for the Study of the Liver (EASL) International Liver Congress 2015. Results were published online in the *Annals of Internal Medicine* to coincide with the presentation.

New Regimen, High Cure Rate

"It's a new regimen that will supplement the regimens we already have" and "the data look promising," said Markus Peck-Radosavljevic, MD, who is secretary-general of the EASL.

"It's always good to have a third player on the market that provides a cure on its own," he told*Medscape Medical News*. "The protease inhibitor from this regimen is pretty good, but so

are others. We are talking about treatments that have close to a 100% cure. So if there's a 1 or 2 percentage point difference, oftentimes it's other reasons than just the potency of the drug."

In their study, Dr Zeuzem and colleagues recruited treatment-naive cirrhotic and noncirrhotic patients with chronic hepatitis C genotype 1, 4, or 6 from general medical clinics at 60 trial centers in nine countries on four continents. The 421 patients were randomly assigned, in a 3:1 ratio, to 12 weeks of immediate therapy with the grazoprevir–elbasvir combination or to deferred therapy.

Four weeks after the completion of therapy, patients in the deferred group received open-label grazoprevir–elbasvir for 12 weeks.

The 73% rate of unquantifiable hepatitis C RNA at 12 weeks derived from previous studies was used for efficacy. The deferred group served as a control group for safety.

Of the 316 patients in the immediate group, 299 patients (95%) achieved a sustained viral response at 12 weeks — the primary efficacy outcome. This varied by genotype, ranging from eight of 10 (80%) for those with genotype 6 to 18 of 18 (100%) for those with genotype 4.

For patients with cirrhosis, 97% achieved a sustained viral response at 12 weeks; for patients without cirrhosis, 94% did.

The treatment was slightly less successful for patients with levels of hepatitis C RNA above 800,000 IU/mL than for those with lower levels (92% vs 100%).

There were no significant effects on treatment outcome for age, sex, race, ethnicity, or IL28B genotype.

Virologic failure occurred in 13 patients (4%); in four patients, this was unrelated to the efficacy of the combination (two patients died, one patient experienced adverse events, and one patient dropped out). When those patients were excluded from the analysis, 94% of patients with genotype 1a achieved a sustained viral response at 12 weeks, as did 99% of those with genotype 1b.

The data suggest an association between virologic failure and the presence of resistance-associated variants, although the numbers were small and virologic failure was most pronounced in patients with genotype 1a resistance-associated variants who had high viral loads at baseline.

"That makes one wonder if the addition of ribavirin and longer therapy would overcome this resistance," said Dr Pockros. "However, it was such a small number that the only way to identify those cases would be to treat with a salvage regimen in the few who failed."

The grazoprevir–elbasvir combination was generally well tolerated, and the safety profile was similar in the treatment and placebo groups.

The rate of drug-related adverse events was lower in the treatment group than in the placebo group (36.1% vs 39.0%). The rate of serious adverse events was similar in the treatment and placebo groups (2.8% vs 2.9%), and none were considered to be drug-related.

Although pan-genotype coverage is an advantage, "it only covers three genotypes — 1, 4, and 6," Dr Peck pointed out. Although treatment for genotype 3 is still needed, this is "an important regimen," he added. "We are looking forward to it."

This study was sponsored by Merck & Co. Dr Pockros reports financial relationships with Merck, Gilead Sciences, Bristol-Myers Squibb, AbbVie, and Janssen. Dr Peck reports financial relationships with AbbVie, ArQule, Bayer, BMS, Gilead, Lilly MSD, Boehringer-Ingelheim, and Roche.

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