AASLD 2013: BMS Interferon-free Combo Cures Over 90% of Genotype 1 HCV in 12 Weeks

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A combination of 3 direct-acting antivirals developed by Bristol-Myers Squibb --daclatasvir, asunaprevir, and BMS-791325 -- cured chronic hepatitis C virus (HCV) infection in over 90% of previously untreated patients in a mid-stage study, Gregory Everson from the University of Colorado reported this week at the 64thAASLD Liver Meeting in Washington, DC. The combination proved equally effective in people with genotype 1a and 1b HCV.

Bristol-Myers Squibb (BMS) is one of several pharmaceutical companies working to develop a highly effective combination of oral direct-acting antivirals that can be used without interferon to cure hepatitis C with 12 to 24 weeks of treatment. Current hepatitis C treatment consists of pegylated interferon and ribavirin combined with a first-generation protease inhibitor, and lasts 24 to 48 weeks.

Interferon-free combinations contain drugs that attack different steps in the HCV lifecycle, so that viral replication can be interrupted and quickly reduced, allowing rapid elimination of HCV from the liver and the blood.

The first interferon-free combination is likely to receive marketing approval for treatment of genotype 2 and 3 HCV in December 2013 (Gilead Sciences' sofosbuvir plus ribavirin). AbbVie is likely to file for approval of its own interferon-free combination for treatment of genotype 1 HCV in the US and Europe in the second quarter of 2014.

BMS is developing a fixed-dose combination containing drugs from 3 classes. Daclatasvir, an NS5A inhibitor active against all HVC genotypes, is being combined with asunaprevir, a protease inhibitor active against genotypes 1, 4, 5, and 6, and BMS-791325, a non-nucleoside polymerase inhibitor active against genotypes 1, 3, 4, 5, and 6. The fixed-dose combination is designed to be taken twice-daily.

Everson presented late-breaking interim results from a Phase 2b dose-comparison study designed to compare 2 doses of BMS-791325 (75 and 150 mg), taken with daclatasvir and asunaprevir, for the purpose of selecting a dose for Phase 3 studies.

The study recruited previously untreated people with genotype 1 chronic hepatitis C; 9% of patients had cirrhosis and they were evenly distributed between the 2 study arms. Patients were also stratified by HCV subtype 1a and 1b. A total of 80 patients were enrolled in the 75 mg arm and 86 in the 150 mg arm. Most patients (82%) had harder-to-treat HCV 1a and 38% had advanced liver disease (stage F3 or F4 fibrosis/cirrhosis as measured by FibroScan).

At 12 weeks after the completion of treatment, 71 of 77 participants (92%) in the 75 mg arm and 77 of 84 (92%) in the 150 mg arm had a sustained virological response (SVR12). There were 3 people lost to follow-up after completion of treatment. A total of 6 cases of virological failure occurred in the 75 mg arm (2 viral breakthroughs and 4 post-treatment relapses) and 5 in the 150 mg arm (3 viral breakthroughs and 2 viral relapses). All viral relapses occurred within 4 weeks of completing treatment.

The 2 doses showed equivalent efficacy across all patient sub-groups (HCV genotype 1a and 1b, IL28B CC and non-CC gene pattern) with the exception of people with cirrhosis, where the 75 mg dose was associated with a higher SVR rate (100% vs 71%) due to 1 treatment discontinuation and 1 viral breakthrough.

The combination was well-tolerated. A single person in each arm discontinued treatment due to an adverse event (1 cancer and 1 episode of severe throat tightness); 1 person experienced grade 3 liver enzyme (AST) elevation which normalized during treatment.

The most frequent side effects were headache (25%), diarrhea (15%), fatigue (11%), and nausea (10%), none of them severe.

The 75 mg dose of BMS-791352 will now be used as part of the 3-drug combination to be tested in Phase 3 studies.

GT Everson, KD Sims, PJ Thuluvath, et al. Phase 2b study of the interferon-free and ribavirin-free combination of daclatasvir, asunaprevir, and BMS-791325 for 12 weeks in treatment-naive patients with chronic HCV genotype 1 infection. 64th Annual Meeting of the American Association for the Study of Liver Diseases (AASLD 2013). Washington, DC, November 1-5, 2013. AbstractLB-1.