Adding Viread to Baraclude for Hep B Treatment Shows Limited Benefit

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Earlier studies exploring combination therapy have presented mixed results. For example, in a study comparing Epivir (lamivudine) to Epivir plus Hepsera (adefovir), there was significantly better long-term HBV viral load suppression as well as a decreased number of treatment failures in people using both drugs. However, the rate of hepatitis B “e” antigen (HBeAg) seroconversion—a primary goal of treatment, as it means that viral suppression will likely continue and that therapy can end—was similar in both groups. And in a study comparing the Hepsera monotherapy to Hepsera plus Emtriva (emtricitabine)—a drug similar to Epivir—rates of HBV viral load were higher among those using both drugs, but so too were significant viral load rebounds while on combination treatment.

The latest data, reported by Anna Lok, MD, of the University of Michigan Health System and her colleagues, don’t go further in clarifying whether combination therapy—at least among those starting hepatitis B treatment for the first time—improves effectiveness.

The 96-week data highlighted by Lok’s group come from the BE-LOW study, a Phase III clinical trial comparing Baraclude (0.5 milligrams once daily) with Baraclude plus Viread (300 mg once daily) in 379 chronic HBeAg-positive and HBeAg-negative hepatitis B participants starting therapy for the first time.

In short, no major difference was observed between the two treatment groups with respect to the primary goal of the study: an undetectable HBV viral load (below 50 IU/mL or 300 copies/mL) by the end of the study. Among those in the Baraclude monotherapy group, 76.4 percent had undetectable HBV viral loads, compared with 83.2 percent of those receiving a combination of both groups. The difference between the two groups was not statistically significant, meaning it was small enough to have occurred by chance.

Looking solely at HBeAg-positive patients, there appeared to be a moderate advantage to using both drugs instead of just Baraclude. About 70 percent of HBeAg-positive patients in the Baraclude monotherapy group had undetectable HBV viral loads after 96 weeks of treatment, compared with 80 percent of those who were receiving combination treatment. This difference was statistically significant, meaning it wasn’t likely due to chance.

Further analysis suggested that this difference could be accounted for by the subset of patients with a high pre-treatment viral load, notably those with viral loads in excess of 100 million IU/mL. Whereas there was no statistically significant difference in HBeAg-positive patients with viral loads

below this level, 62 percent of Baraclude monotherapy patients with high pre-treatment viral loads, compared with nearly 79 percent of combination therapy patients with high pre-treatment viral loads, had undetectable HBV levels after 96 weeks of treatment.

Results for HBeAg-negative patients were also reported. HBeAg-negative chronic hepatitis differs considerably from those who experience a HBeAg-to-hepatitis B “e” antibody seroconversion, either naturally or as a result of treatment. HBeAg-negative chronic hepatitis generally means that HBV viral load is still detectable and is often associated with persistently high liver enzyme levels, liver damage and a increased risk of liver failure or liver cancer. HBeAg-negative hepatitis is believed to be caused by HBV strains with mutations that prevent “e” antigen expression. Treatment for HBeAg-negative hepatitis has been discouraging; indefinite treatment is generally required.

Among HBeAg-negative patients in BE-LOW, suppression of HBV viral load was similar in both groups: 91.1 percent among those receiving Baraclude alone, compared with 89.8 percent of those receiving both drugs.

Secondary efficacy goals measured in the study included normalization of the liver enzyme alanine aminotransferase (ALT) and HBeAg seroconversion. ALT normalization was observed in roughly 82 percent of participants receiving Baraclude monotherapy, compared with 69 percent of those in the combination treatment group. HBeAg seroconversion was documented in 32.5 percent of the monotherapy group, versus 21.7 percent of the combination group.

The overall side effect profiles were similar in the two groups. A total of three deaths occurred among treated patients, all in the combination therapy group.

Two people in the Baraclude monotherapy group and seven in the combination therapy group experienced viral load rebounds while on therapy. Encouragingly, however, no recognized drug-resistance mutations were observed in either treatment group.

“In these 96-week data comparing entecavir [Baraclude] monotherapy to combination of entecavir plus tenofovir [Viread], we found that combination therapy did not result in statistically significant difference in virologic response compared to entecavir monotherapy,” concluded Lok. “The BE-LOW study data confirmed the results of previous studies showing limited or no benefit of combination therapy compared to monotherapy for treatment-naive patients with chronic hepatitis B.”
