

Obeticholic Acid Shows Efficacy in Primary Biliary Cholangitis

Obeticholic acid, a farnesoid X receptor agonist, improves primary biliary cholangitis in a phase 3 trial.

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July 6, 2017 – In patients with primary biliary cholangitis (PBC), dosing with the bile acid derivative obeticholic acid (OCA) showed an improvement in baseline symptoms compared to placebo, as noted in a recent phase 3 clinical study.

Frederik Nevens, MD, PhD, with the University Hospitals KU Leuven in Leuven, Belgium, and colleagues reported their findings in the August 18, 2016 issue of the *New England Journal of Medicine*.

The researchers mentioned, “obeticholic acid is a selective farnesoid X receptor (FXR) agonist that is derived from the bile acid chenodeoxycholic acid”, and “[OCA] has an approximately 100 times greater potency in activating FXR than chenodeoxycholic acid”. FXR signaling promotes anti-inflammatory pathways and protects against bile acid toxicity.

Previous phase 2 studies indicated that high doses of OCA reduced expression of alkaline phosphatase and bilirubin, both indicative of PBC progression; however, side effects were present compared to placebo when OCA daily dosage surpassed 10mg. This randomized phase 3 trial thus examined the efficacy and adverse effects of OCA at doses of 5mg to 10mg per day on PBC compared to placebo.

A total of 217 patients were randomly assigned in a 1:1:1 ratio daily doses of placebo, OCA at an initial dose of 5mg up to 10mg (5-10mg group), or OCA at 10mg (10mg group); the study was followed for 12 months. All doses were administered in combination with the PBC-approved drug ursodiol per standard of care, or administered without ursodiol in patients intolerant to its side effects.

The primary composite endpoint of reduced alkaline phosphatase level was reached in 46% of the 5-10mg group (-113 ± 14 U per liter) (given in least-squares mean \pm SE), 47% of 10mg group (-130 ± 15 U per liter), and 10% of placebo-treated patients (-14 ± 15 U per liter) ($P < 0.001$ for both comparisons to placebo).

Patients treated with OCA saw a reduced bilirubin level in the 5-10mg group (-0.02 ± 0.04 mg per deciliter) and 10mg treatment groups (-0.05 ± 0.04 mg per deciliter), while bilirubin levels increased with placebo treatment (0.12 ± 0.04 mg per deciliter) ($P < 0.001$ for both comparisons vs. placebo). Endpoint evaluation was recorded after 12 months of treatment.

The authors indicated that the most common side effect across all groups was pruritus, reported in 39 patients (56%) of the 5-10mg group, 50 patients (68%) of the 10mg group, and 28 patients (38%) of the placebo group. Serious adverse events were limited at 16% and 11% for 5-10mg and 10mg treatment, respectively, vs. 4% for placebo.

“Obeticholic acid is effective at considerably lower doses [than ursodiol],” mentioned Dr. Nevens. He and his colleagues also wrote that “[the] effects [on biochemical markers] were sustained for 2 years, and patients who crossed over from placebo to obeticholic acid had similar improvements after 1 year,” further providing support for this PBC treatment.

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