Nature Reviews Gastroenterology & Hepatology | Published online 1 Sep 2016; doi:10.1038/nrgastro.2016.143

THERAPY

Obeticholic acid for PBC

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Results from a new clinical trial show that obeticholic acid decreases serum alkaline phosphatase and bilirubin levels in patients with primary biliary cholangitis (PBC, previously known as primary biliary cirrhosis). However, treatment was associated with increased risk of pruritis in patients receiving higher doses of the drug.

PBC is an autoimmune liver disease characterized by progressive destruction of bile ducts, resulting in cirrhosis and end-stage liver disease. Ursodeoxycholic acid, a secondary bile acid, is currently the only approved treatment for the disease; the lack of therapies for patients not tolerating or responding to this drug has driven investigation of the semi-synthetic bile acid obeticholic acid. However, its use, particularly at doses >10 mg per day, had been associated with severe pruritis in phase II trials.

To address whether obeticholic acid could improve PBC in patients with intolerance or inadequate response to ursodeoxycholic acid, researchers conducted a phase III, randomized, double-blind placebo-controlled trial. Either as monotherapy or in addition to ursodeoxycholic acid, obeticholic acid was given at an initial dose of 5 mg (and up-titrated to 10 mg as necessary) or 10 mg per day. The primary composite end point at 12 months was a serum alkaline phosphatase level <1.67-fold the upper limit of normal (and a reduction of ≥15% from baseline), and a serum bilirubin level at or below the upper limit of normal. Both parameters are validated biomarkers of outcomes in patients with PBC.

46% of patients in the 5–10 mg group ($n = 71$) and 47% of patients in the 10 mg group ($n = 73$) achieved the primary end point, compared with just 10% of the placebo group ($n = 73$; $P < 0.001$ for both comparisons).

"In the 5–10 mg group, around 50% stayed under the 5 mg dose, and the dropout after 1 year due to pruritus was only 1% in this arm", explains author Frederik Nevens. By contrast, dropout rate at 1 year was 10% in the 10 mg group. Notably, 97% of patients in the 5–10 mg group opted to continue treatment during an open-label extension phase at the end of the blinded study. Nevens and colleagues are following-up patients in this study for 5 years to assess long-term tolerance of obeticholic acid and its effect on patients with advanced liver disease (18–20% of the baseline study population).

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ORIGINAL ARTICLE Nevens, F. *et al.* A placebo-controlled trial of obeticholic acid in primary biliary cholangitis. *N. Engl. J. Med.* **375**, 631–643 (2016)