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Long-term obeticholic acid treatment leads to reversal or stabilization of fibrosis/cirrhosis in patients with PBC

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The first results from the POISE biopsy sub-study have today confirmed that long-term treatment with obeticholic acid (OCA) leads to the reversal or stabilization of fibrosis/cirrhosis in patients with primary biliary cholangitis (PBC) who have had an incomplete response to ursodeoxycholic acid (UDCA). These results provide the first evidence that improvements in biochemical markers of PBC observed in previous studies are accompanied by anti-fibrotic effects in line with those observed in pre-clinical trials.

"There is strong evidence from clinical trials that OCA leads to significant reductions in alkaline phosphatase (ALP) that are predicted to improve clinical outcomes of patients with PBC who do not respond adequately to or do not tolerate UDCA," said Dr. Christopher Bowlus from the University of California, Davis in the USA, who presented the results today at The International Liver Congress 2018 in Paris, France. "This study offers the first evidence from paired liver biopsies that OCA is indeed a disease-modifying therapy."

Primary biliary cholangitis is a rare autoimmune liver disease characterized by biliary destruction, progressive cholestasis, and, ultimately, the development of fibrosis, cirrhosis, and hepatocellular carcinoma (HCC).The primary medical treatment for PBC is UDCA, however, up to 40% of patients have an insufficient response to this treatment, putting them at risk of potentially life-threatening

complications.

Obeticholic acid is a potent agonist of the farnesoid X receptor (FXR), which regulates bile acid synthesis and transport. Two previously reported Phase 2 studies and a pivotal Phase 3 study (POISE)6 confirmed that OCA, primarily in combination with UDCA, leads to significant reductions in serum ALP and improvements in other biochemical liver markers, leading to the recent approval of the treatment by the US Food and Drug Administration (FDA).

The biopsy sub-study of POISE involved patients undergoing liver biopsies prior to, and after 3 years of, treatment with OCA. Biopsies were centrally read and assessed using a six-tier staging system (from no fibrosis to cirrhosis). Thirteen patients—all receiving treatment with UDCA at baseline—had paired biopsies that were adequate for analysis.

At baseline, nine of the 13 patients (69%) presented with pre-cirrhotic fibrosis and four (31%) with cirrhosis. At the last visit before the final biopsy, serum ALP was reduced and direct bilirubin levels were comparable to baseline (median changes from baseline: -99 U/L and 0.0 μmol/L, respectively). After 3 years of OCA treatment, the majority of patients improved (n=6; 46%) or maintained (n=5; 38%) their histological stage, while two patients (15%) deteriorated. Of the four patients with baseline cirrhosis, three (75%) improved to fibrosis without cirrhosis while receiving OCA treatment.

"Eighty-five percent of the patients with PBC in this study with an incomplete response to UDCA had regression or no worsening of their fibrosis or cirrhosis after 3 years of OCA treatment—a period of time during which we would have expected some degree of fibrosis progression," said Dr. Bowlus. "OCA represents the first new treatment approved for PBC in decades, and these results support the potential of OCA to slow disease progression in this group of patients who have the

greatest need for new treatments. The results of the ongoing COBALT study will determine if the biochemical improvements of the POISE study and the histological results reported here translate to improved clinical outcomes' (NCT02308111).

"Relevant changes are on the way for the management of patients with PBC, for which ursodeoxycholic acid has been the only treatment option for a long time," said Prof. Marco Marzioni from the University Hospital of Ancona, Italy, and EASL Governing Board Member. "Now new medicines are coming and the first of these to be available, obeticholic acid, has been shown to ameliorate surrogate markers of disease progression. The current study, however, reports the first evidence that OCA is also able to halt the deposition of collagen tissue in the liver, a significant outcome for the natural history of PBC."

Provided by European Association for the Study of the Liver

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