New therapy has potential to advance the treatment of pediatric cholestatic liver diseases

22 April 2017

Results presented today from a study of a novel ileal bile acid transport inhibitor, A4250, demonstrated that it reduced levels of blood (serum) bile acids, which are characteristic of many liver diseases and often associated with severe liver damage, in children with cholestatic liver diseases. The data, presented at The International Liver Congress 2017 in Amsterdam, The Netherlands, showed that oral treatment with A4250 also improved pruritus (itching) in 74% of patients and was well tolerated, with mostly mild and transient side effects.

Children can be affected by diseases that either destroy or impair the development of the biliary tree; other diseases alter the ability of liver cells to produce bile. These diseases can lead to progressive liver injury and cirrhosis, even at very early ages and often result in the need for a liver transplant. Among other symptoms or abnormalities, patients may suffer from bile acid retention, which is related to pruritus. Pruritus can be a very debilitating symptom: it is often severe and difficult to treat, while hampering quality of life. Novel therapies for the management of increased bile acid serum levels and pruritus are urgently needed by patients and clinicians. A previous animal study demonstrated that A4250 can reduce elevated levels of serum bile acids without severe side effects,1 and serum bile acid lowering was also shown in a Phase 1 study of A4250 in healthy individuals.2,3

"There is a real need for novel and effective therapies for paediatric cholestatic diseases," said Dr Ulrich Baumann, Hannover Medical School, Germany, and lead author of the study. "The safety and efficacy data from this study show the potential for A4250 to become a significant and novel advance for the treatment of paediatric cholestatic liver diseases."

This study evaluated five doses of A4250 (0.01-0.2 mg/kg), with the dataset including four patients who received each dose. Patients with cholestatic disease and intractable itching were initially administered a single dose of A4250. As there were no safety issues, patients were then given the drug in tablet form for four weeks. If needed, therapy with ursodeoxycholic acid (UDCA) or rifampicin could also be given during the study. The dataset included nineteen patients aged 1-17 years and itching was measured by a visual itch score using patient reported diary data.

Pruritus improved in 14 of 19 cases. Mean levels of serum bile acids were reduced at all doses. In particular, there were substantial reductions in serum bile acids in seven out of nine patients with progressive familial intrahepatic cholestasis, ranging from a 43% to 98% reduction. Most side effects were mild and transient and considered to be unrelated to the drug, and there were no serious side effects.

A4250 is a highly potent inhibitor of the ileal bile acid transporter (IBAT) that acts locally in the gut with minimal systemic exposure.3 It reduces levels of bile acids in serum by blocking the IBAT in the last part of the small intestine in the gut. This interrupts the re-absorption of intestinal bile acids and their re-circulation for further secretion.1

"The study results are crucial as they address pruritus, a significant issue in chronic cholestatic diseases. Currently, there are few therapeutic options with limited efficacy, so new treatment strategies for pruritus are of great importance for clinical practice," said Prof Marco Marzioni, Professor of Gastroenterology, Università Politecnica delle Marche - "Ospedali Riuniti" University Hospital of Ancona, Italy and EASL Governing Board Member.

More information: Abstract: The Ileal Bile Acid Transport inhibitor A4250 decreases pruritus and serum bile acids in cholestatic liver diseases - an ongoing multiple dose, open-label, multicentre study (LBO-04), The International Liver Congress 2017.

References:

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Provided by European Association for the Study of the Liver