Press Release

Bile acid research: Basis for new therapeutic concepts

UDCA and norUDCA: two bile acids with a future, not just in hepatology

The interest was enormous: The XXV Bile Acid Meeting of the Falk Foundation e.V. in Dublin was attended by 520 scientists from about 40 countries – more than ever before. This underlines the increasing importance of bile acid research, not only for basic researchers, but also for clinical research. A whole series of bile acids, bile acid analogs, FXR and TGR5 agonists and antagonists are in clinical development, with the potential to influence hepatological and gastrointestinal diseases favorably. There are also promising new findings for the two bile acids UDCA and norUDCA. UDCA has long since become an established part of the front-line therapy of primary biliary cholangitis. According to initial in-vitro results, which show a positive effect on intestinal barrier disorders, this bile acid could also be useful for inflammatory bowel diseases such as ulcerative colitis. norUDCA, on the other hand, is raising interest in the therapy of primary sclerosing cholangitis. To date, there is still no effective treatment available for this "black box" of hepatology. After the very successful results of a phase-II-study, which were presented by Professor Dr. Michael Trauner, Vienna (Austria), the results of an about to be launched phase-III-study are eagerly awaited. In addition, norUDCA shows positive effects on metabolic liver diseases such as non-alcoholic fatty liver disease (NAFLD).

Even though bile acid research is running at full speed: So far, only two substances are available that therapeutically intervene with the complex system of bile acid metabolism and bile acid signaling: Ursodeoxycholic acid (e.g. Ursofalk®) is the bile acid that has been used in medicine for the longest time. It is used for the therapy of cholestasis in primary biliary cholangitis (PBC) and is still the first-line therapy for this indication. The FXR agonist obeticholic acid has recently become available as a combination partner for non-responders. To date, no substance has been approved for the therapy of primary sclerosing cholangitis (PSC). UDCA was proven to be only moderately effective against PSC. This is not the case with norUDCA: It was very successful in a phase-II-study with PSC and will be examined in a phase-III-study shortly.

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UDCA and norUDCA: don't lump them together

Trauner emphasized that norUDCA and UDCA are two completely different molecules with substantial differences in their pharmacological profiles. The side chain of the newly developed norUDCA is shortened, making conjugation only possible to a limited extent. This leads to cholehepatic shunting with induction of a bicarbonate-rich choleresis, which protects against toxic bile acids. UDCA, on the other hand, passes through the enterohepatic cycle. In addition, anti-inflammatory and anti-fibrotic effects are being observed for norUDCA. So far, immunomodulatory effects have been observed for norUDCA, but not for UDCA. This further emphasizes the status of norUDCA as an independent active agent.

norUDCA already in phase-III-study for PSC

norUDCA has produced impressive results against PSC in a European, multicenter, placebo-controlled phase-II-study with a total of 161 patients. In daily doses of 500 mg, 1,000 mg and 1,500 mg, the bile acid caused a substantial improvement in the cholestasis. Within 12 weeks, there was a significant reduction of the ALP (alkaline phosphatase) level in comparison to placebo, explained Trauner. This effect was dose-dependent, with the best effect being achieved at the maximum dose of 1,500 mg/day (ALP reduction: -26% vs. -17.3% vs. -12.3% vs. +1.2%). The efficacy of norUDCA was independent from a previous treatment with UDCA or a response to UDCA. In other words: Even UDCA non-responders benefited from the therapy. The safety profile was at placebo level (Fickert P et al., J Hepatol 2017; 67: 549-558). These results gave rise to further investigation in a phase-III-study.

Treating NAFLD to prevent progression

Moreover, norUDCA shows favorable effects on metabolic liver diseases such as NAFLD, which involves an increased risk of NASH (non-alcoholic steatohepatitis), fibrosis and cirrhosis. This is shown by a randomized, placebo-controlled and double-blind phase-IIa-study, which compared norUDCA 500 mg/day and 1,500 mg/day with placebo. On the daily dose of 1,500 mg, there was a significant reduction of alanine aminotransferase (ALT) (-17.4% vs. -4.2% vs. +10.4%; $p<0.0001$) within 12 weeks. This effect is corroborated by sub-group analyses on liver stiffness and hepatic steatosis. In experimental studies on animals, the positive effect on the fatty liver was accompanied by anti-atherosclerotic effects. In a mouse model with ApoE $^{-/-}$ mice, norUDCA achieved a substantial reduction of hepatic steatosis and inflammation, and a reduction of aortic plaques and macrophage infiltration, explained Dr. Tarek Moustafa, Graz (Austria).

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UDCA even for ulcerative colitis?

Not only liver and bile diseases, but possibly also intestinal disorders can be influenced by UDCA. In-vitro and in-vivo studies show a positive effect of UDCA on intestinal barrier function and the release of inflammatory cytokines from epithelial cells of the colon. The bile acid also promotes the restitution of epithelial wounds, explained Dr. Stephen J. Keely, Dublin (Ireland). The expert said that this poses the question of whether UDCA has the potential to be a new therapy option for ulcerative colitis.

Source: Symposium 211 " **XXV International Bile Acid Meeting: Bile Acids in Health and Disease 2018**" of the Falk Foundation e.V., 06-07 July 2018 in Dublin

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