High doses of ursodeoxycholic acid ineffective for NASH patients

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A study conducted by researchers at Johann Wolfgang Goethe University in Frankfurt, Germany found that high doses of ursodeoxycholic acid (UDCA), suggested by some studies to have a beneficial effect on nonalcoholic steatohepatitis (NASH), does not improve overall histology in these patients. Full findings of this study are published in the August issue of *Hepatology,* a journal of the American Association for the Study of Liver Diseases (AASLD).

According to the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), NASH ranks as one of the major causes of cirrhosis in America, behind hepatitis C and alcoholic liver disease. Liver transplantation is the only treatment for advanced cirrhosis with liver failure, and transplantation is increasingly performed in people with NASH. Currently, there are no specific therapies for NASH.

Small, open label clinical studies have shown that UDCA positively influenced liver function tests and liver histology in NASH patients, but a two-year prospective double-blind trial with 166 patients at the dosage of 13□□mg/kg body weight per day failed to confirm these results. To determine if the dosage of UDCA may have been too low and a reduction of body weight could have contributed to the results, the German research team initiated a multicenter, placebo-controlled double-blind trial with a high dose of UDCA and without weight-lowering diet.

A UDCA dose of 23-28 mg/kg body weight or placebo was administered daily in three divided doses to 147 randomized patients of both sexes,

aged 18 years and older. No special diet was recommended and the body weight of the patients remained constant during the study period. The total treatment time for each patient was 18 months. The primary objective was improvement of liver histology by at least 3 points. Secondary criteria were single histological variables and liver biochemistry.

Pre- and post-treatment liver biopsies from each patient were evaluated according to a modified Brunt score (including steatosis, hepatocellular ballooning, lobular inflammation, and portal/lobular fibrosis) as well as the nonalcoholic fatty liver disease activity score (NAS). Using the modified Brunt score, 185 patients with histologically proven NASH were randomized (intention to treat: ITT), 147 were treated per protocol (PP). Using the NAS, 137 patients were confirmed as having NASH, 48 were borderline NASH, and 1 was not NASH.

The results were the same for both scoring systems—no significant improvement in overall histology was detected. Of the single variables, only lobular inflammation improved using both the modified Brunt and NAS scores. In subgroup analyses, significant improvement of lobular inflammation was also observed in males, patients less than 50 years of age, slightly overweight patients, in patients with hypertension and an increased histology score. The fibrosis scores did not change.

"Our study has shown that the high dose of 23 to 28 mg UDCA/kg body weight per day, over a treatment time of 18 months, was unable to improve liver histology and overall liver function when compared to placebo and thus confirms the results of an earlier study using a lower dose over a period of 24 months," concluded study leader Dr. Ulrich F.H. Leuschner.

"Previous investigations may have shown positive results, because, first of all, in most of the studies the number of patients was too small,

treatment time was too short, or a control group was missing," he explains. "Secondly, the positive effect of UDCA on the suggested pathogenetic mechanisms has been shown in only a few investigations with a small number of experimental animals and in few patients. Finally, the anticipation of an effect of UDCA in NASH probably depends on an incorrect assumption. Up to now positive effects of UDCA have only been observed in primary biliary cirrhosis, but NASH does not present with features of biliary liver diseases."

More information: "High-Dose Ursodeoxycholic Acid Therapy of Nonalcoholic Steatohepatitis. A Double-Blind, Randomized Placebo-Controlled Trial." Ulrich F.H. Leuschner, Birgit Lindenthal, Günter Herrmann, Joachim C. Arnold, Martin Rössle. Hepatology; Published Online: April 23, 2010 (DOI: 10.1002/hep.23727); Print Issue Date: August 2010.

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