Study finds adverse effects in treatment for primary sclerosing cholangitis

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Primary sclerosing cholangitis (PSC) is an uncommon chronic liver disease characterized by progressive inflammation and destruction of the bile ducts. The disease progresses slowly, usually leading to biliary cirrhosis, portal hypertension and liver failure over a 10-15 year period. PSC is a common cause of adult cholestatic liver diseases and a primary source behind many of the liver transplantations in U.S. adults. At least 70% of PSC cases are associated with chronic inflammatory bowel disease (IBD), usually ulcerative colitis. Currently, there is no cure for PSC and prospective treatments remain ineffective.

A recently ceased study, led by Keith Lindor, M.D., from the Fiterman Center for Digestive Diseases at the Mayo Clinic, determined that PSC patients treated with high-dose Ursodeoxycholic Acid (UDCA) had poorer clinical results compared to those not receiving the therapy. More patients developed esophageal or gastric varices (enlarged veins), died, or became eligible for liver transplantation in the group receiving UDCA compared to the placebo group despite improvement in liver tests. Findings from this study are published in *Hepatology*, a journal of the American Association for the Study of Liver Diseases.

One hundred fifty adult PSC patients entered the study at seven U.S. sites over a three-year period. Half of the participants in the double-blind controlled trial were given high-dose UDCA (28-30 mg/kg/day), while the others received a placebo. Liver biopsy and imaging of the bile ducts were performed to monitor patients' response to the therapy. The primary outcome measure was development of cirrhosis, varices,

cholangiocarcinoma-a bile duct cancer, meeting minimal listing criteria for transplant, liver transplantation or death.

"Our results showed patients on UDCA had a 2.1 times greater chance for death, transplantation or meeting minimal listing criteria than for those in the placebo group," explained researchers. Patients treated with UDCA were more likely to suffer serious adverse effects from the therapy then those who did not receive treatment (63% vs. 37%). Previous studies projected UDCA to be a safe and beneficial therapy.

According to researchers, the Food and Drug Administration (FDA) approved a UDCA dose of 13-15 mg/kg/day for patients with primary biliary cirrhosis and those patients did not suffer more adverse effects when treated with higher doses of the drug up to 25 or 30 mg/kg/day. Pilot studies in PSC patients using doses ranging from 17-25 mg/kg/day did not have an increased risk of adversities. "The findings in our study were surprising and quite unanticipated," said Dr. Lindor. "It is unclear how a drug that has a reputation for such safety would have these paradoxical effects in this condition."

Researchers speculate that higher doses of UDCA allowed unabsorbed drug to enter the colon, modifying into hepatotoxic bile acids and recommend further evaluation of this theory. "At this time, UDCA in a dose of 25-30 mg/kg/day should not be used due to the increased risk to PSC patients," advises Dr. Lindor. "We hope a safe and effective therapy for patients with PSC will be developed, but high-dose UDCA cannot be recommended."

More information: "High Dose Ursodeoxycholic Acid for the Treatment of Primary Sclerosing Cholangitis," Keith D. Lindor, Kris V. Kowdley, Velimir A. C. Luketic, M. Edwyn Harrison, Timothy McCashland, Alex S. Befeler, Denise Harnois, Roberta Jorgensen, Jan Petz, Jill Keach, Jody Mooney, Carol Sargeant, Julie Braaten, Tamara Bernard, Debra King,

Ellen Miceli, Jeff Schmoll, Tanya Hoskin, Prabin Thapa, Felicity Enders, *Hepatology*, 2009 (DOI: 10.1002/hep.23082)