Licogliflozin Lowers Liver Enzymes in People With Fatty Liver Disease

Experimental therapy led to weight loss and improved biomarkers of liver health.

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An experimental drug that blocks glucose absorption lowered liver enzyme levels, reduced liver fat and led to modest weight loss in people with non-alcoholic steatohepatitis (NASH) in a mid-stage study, according to a presentation at The Liver Meeting, the annual meeting of the American Association for the Study of Liver Diseases, this month in Boston.

Non-alcoholic fatty liver disease (NAFLD) and NASH, its more severe form, are responsible for a growing proportion of advanced liver disease. Accumulation of fat in the liver triggers inflammation, which over time can lead to fibrosis (buildup of scar tissue), cirrhosis, liver cancer and the need for a liver transplant. Fatty liver disease is increasingly recognized as a manifestation of metabolic syndrome, a cluster of conditions that include abdominal obesity, elevated blood glucose and abnormal blood fat levels.

There are currently no effective medical therapies for NASH, and management relies on lifestyle changes such as weight loss. Over the past few years, several NAFLD/NASH therapies that appeared promising based on biomarkers in early studies ended up not improving clinical outcomes in larger trials.

Stephen Harrison, MD, of Pinnacle Clinical Research in San Antonio, presented interim results from a Phase IIa study of licogliflozin, an inhibitor of sodium-glucose co-transporters 1 and 2 (SGLT1/2) that blocks glucose absorption from the gut and reabsorption in the kidneys.

This randomized trial included 77 people who either had biopsy-confirmed NASH with mild to advanced fibrosis (stage F1 to F3) or were overweight and had type 2 diabetes and elevated ALT liver enzyme levels, a sign of liver inflammation. Individuals with other types of liver disease or severely impaired liver function were excluded.

More than half of the study participants were women, most were white and the median age was about 50. The average body mass index was about 35 (30 and over indicates obesity), and the mean liver fat fraction was about 21%.

Participants were randomly assigned to receive 30 milligrams of licogliflozin (25 people), 150 mg

of licogliflozin (34 people) or a placebo (18 people) for 12 weeks.

ALT levels declined in both licogliflozin groups while remaining stable in the placebo group. At the end of the study, ALT levels were 36% lower in the 30 mg group and 43% lower in the 150 mg group; the latter difference was statistically significant, meaning it was probably not driven by chance. Levels of aspartate AST and GGT liver enzymes declined significantly in both dose groups. Blood glucose levels, as indicated by the HBa1c test, also decreased in both groups.

Body weight declined significantly in both licogliflozin groups—by about 4%—while remaining stable in the placebo group. Waist circumference decreased by an average of 2.44 centimeters and 4.02 cm in the low- and high-dose licogliflozin groups but increased by 1.47 cm in the placebo group.

The amount of liver fat fell by an average of 5.3% and 7.0% from baseline in the 30 mg and 150 mg licogliflozin groups, respectively, compared with -2.6% in the placebo group. At the end of treatment, 63%, 44% and 19% of participants in the respective groups experienced at least a 5% absolute liver fat reduction, while 67%, 40% and 25%, respectively, saw a 30% or greater relative reduction. These differences were significant for the higher-dose group.

Most biomarkers of liver fibrosis did not change significantly in either licogliflozin dose group when looking at all participants. However, some significant decreases were seen when the analysis was limited to those with evidence of more extensive fibrosis at baseline.

Licogliflozin was generally safe and well tolerated. The most common side effects were diarrhea and flatulence. Diarrhea was about twice as common in the 150 mg group compared with the 30 mg and placebo groups (77%, 40% and 39%, respectively), but it was mostly mild, according to Harrison. One person in each group stopped treatment because of adverse events.

“Findings of this interim analysis justify further investigation of licogliflozin in long-term studies and in combination with drugs of different mechanisms of action,” the study authors concluded.

To that end, the ELIVATE study will evaluate licogliflozin plus the FXR agonist tropifexor in people with NASH and liver fibrosis (ClinicalTrials.gov number NCT04065841).

Click here to read the study abstract.
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