Cotadutide Improves NASH Biomarkers in Overweight People With Diabetes

The experimental drug led to significant reduction in body weight but was accompanied by nausea and vomiting.

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Cotadutide, a drug that affects glucose and lipid metabolism, significantly reduced body weight and improved metabolic and cardiovascular biomarkers in people with overweight or obesity and type 2 diabetes. These findings from a Phase IIb clinical trial were presented at the Digital International Liver Congress.

An advanced form of non-alcoholic fatty liver disease (NAFLD), non-alcoholic steatohepatitis (NASH) results from fat accumulation in the liver. NAFLD and NASH are responsible for a growing proportion of advanced liver disease worldwide. Due to inflammation, NAFLD can lead to the formation of scar tissue (fibrosis), cirrhosis (advanced scarring) and even liver cancer. Considered the fastest rising liver disease around the world, NAFLD affects some 25% of the world's population. About one in five people with NASH develop cirrhosis. While researchers are exploring underlying mechanisms such as lipid metabolism in search of a fix, there are no effective approved medical therapies, and disease management is currently dependent on weight loss and other lifestyle changes.

NAFLD and NASH are linked to obesity and type 2 diabetes. Developed by AstraZeneca, cotadutide is a dual receptor agonist that stimulates glucagon and glucagon-like peptide-1 activity. The drug's dual nature promotes weight loss through appetite control and impacts liver fat content and related inflammation.

Philip Ambery, MD, of AstraZeneca in Gothenburg, Sweden, and colleagues conducted a study to evaluate the efficacy and safety of administering cotadutide to a group of people with overweight or obesity and type 2 diabetes (ClinicalTrials.gov NCT03235050).

The study population included 834 individuals. More than half were women, and the median age was approximately 57 years. They had a body mass index (BMI) of at least 25, with a median of about 35, and they were taking metformin to control their diabetes.

The participants were randomly assigned to receive a daily dose of cotadutide by subcutaneous injection (either 100, 200 or 300 micrograms), the GLP-1 receptor agonist liraglutide or a placebo.

The researchers tracked changes in body weight and liver enzymes, including alanine aminotransferase (ALT) and aspartate aminotransferase (AST), from the time of study entry to week 54. They also took note of the participants' NAFLD fibrosis score and FIB-4 index (indicators or liver scarring) and fatty liver index, a predictor of NAFLD.

The researchers found that weight loss occurred with all three cotadutide doses compared with the placebo. The 300 mcg dose significantly lowered body weight in comparison with liraglutide. By week 54, the average weight loss was 3.70%, 3.22% and 5.02% with increasing doses of cotadutide compared with 3.33% with liraglutide.

Moreover, levels of ALT and AST fell with increasing doses of cotadutide over the 54 weeks. For ALT, the average drops were 7.52% with 100 mcg, 12.01% with 200 mcg and 14.15% with 300 mcg compared to 3.21% with liraglutide. The corresponding AST declines were 1.77%, 6.22% and 9.15% compared with a rise of 0.35% with liraglutide. These changes were independent of any weight loss.

The researchers also noted a drop in the blood sugar marker HbAc1, especially for cotadutide compared with the placebo. The drops were greater with higher doses of cotadutide and reached their maximum after 14 weeks. Triglyceride levels also decreased with cotadutide, especially in the intermediate and high dose groups, while changing little in the liraglutide group and rising in the placebo group.

At the beginning of the study, more than 90% of participants had fatty liver disease and 13% had advanced liver fibrosis. By week 54, the participants' fibrosis scores had decreased. The researchers observed significantly greater improvement in the NAFLD fibrosis score with the highest cotadutide dose, and significant improvement in the FIB-4 score with the high and intermediate doses, in comparison with the placebo.

Most participants in all groups experienced some kind of treatment-related adverse event. About a quarter of those receiving cotadutide did not complete treatment, including those who stopped due to side effects such as nausea and vomiting. Adverse events led to treatment discontinuation in 13.0%, 15.2% and 21.5% of those on the lowest to highest cotadutide doses, compared with 1.8% of those the liraglutide arm and 4.5% in the placebo arm. Among those who received the 300 mcg dose of cotadutide, 41.0% experienced nausea, compared with 23.0% and 33.2% in the low and intermediate dose groups, 15.5% in the liraglutide group and 10.7% in the placebo groups. The researchers suggest that dose optimization may help attenuate side effects.

"The improvements seen in the NAFLD fibrosis score and FIB-4 are encouraging, and support the need for prospective clinical trials with cotadutide in patients with NASH," Ambery said in a press release.

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