Denifanstat Shows Promise for Advanced Fatty Liver Disease

People treated with the fatty acid synthase inhibitor saw significant improvements in disease activity, liver fibrosis and MASH resolution.

October 24, 2024 By Liz Highleyman

Denifanstat, an oral fatty acid synthase inhibitor, led to significant improvements in people with metabolic dysfunction-associated steatohepatitis (MASH), according to study results published in The Lancet Gastroenterology & Hepatology.

The Phase IIb FASCINATE-2 trial found that people treated with denifanstat were more than twice as likely as placebo recipients to experience an improvement in disease activity, MASH resolution and a reduction in liver fibrosis.

"Patients living with MASH, a complex disease, urgently need treatments that simultaneously address the three main drivers of liver injury: fat accumulation, inflammation and fibrosis," primary investigator Rohit Loomba, MD, of the University of California San Diego, said in a news release. "These data support denifanstat's potential to improve overall liver health by targeting the major pathways responsible for liver injury."

MASH, the new name for non-alcoholic steatohepatitis (NASH), and its earlier stage, metabolic dysfunction-associated steatotic liver disease (MASLD), formerly known as non-alcoholic fatty liver disease (NAFLD), are leading causes of advanced liver disease. Estimates suggest that around a third of people in the United States have MASLD, and about 5% have MASH.

Over time, fat buildup in the liver can trigger inflammation and lead to fibrosis, cirrhosis and liver cancer. The new terminology emphasizes the link with obesity, diabetes and other metabolic abnormalities. In March, the Food and Drug Administration (FDA) approved Madrigal Pharmaceuticals' Rezdiffra (resmetirom) as the first medication for MASH, but management still largely relies on lifestyle changes such as weight loss and exercise.

Developing treatments for fatty liver disease has proved challenging, as the FDA's dual benchmark of MASH improvement without worsening fibrosis and fibrosis improvement without worsening MASH has been difficult to meet. Numerous drug candidates that work by various mechanisms have looked promising in early clinical trials, only to fail in larger studies.

Loomba and colleagues evaluated the safety and efficacy of denifanstat for people with MASH and moderate to advanced fibrosis. Denifanstat, from Sagimet Biosciences, blocks lipogenesis, or fat production, a key pathway driving inflammation and fibrosis. A previous proof-of-concept study that tested two doses of the drug for 12 weeks found that it reduced liver fat and improved multiple biomarkers associated with the disease.

FASCINATE-2 (NCT04906421) enrolled 168 adults at 100 clinical sites in the United States, Canada and Poland between June 2021 and June 2022. About 60% were women, most were white, a third were Latino and the median age was 57 years. The median body mass index was 35.0 (indicating obesity), 60% had type 2 diabetes and half used statins to manage high cholesterol. At baseline, 45% had moderate (F2) fibrosis and 55% had advanced (F3) fibrosis, but they hadn't yet progressed to cirrhosis. The median liver fat percentage was 17.5%; 57% had a NAFLD activity score (NAS) of 4 to 5 and 43% had a score of 6 to 8.

The participants were randomly assigned in a 2:1 ratio to receive either 50 milligrams oral denifanstat or a placebo once daily for 52 weeks.

The first primary efficacy endpoint was at least a two-point improvement in the NAS without worsening fibrosis at week 52; 38% of patients in the denifanstat group met this benchmark, compared with 16% in the placebo group. The second primary endpoint was MASH resolution with at a least two-point improvement in the NAS without worsening fibrosis; 26% and 11%, respectively, met this benchmark.

Denifanstat also led to significant improvement in fibrosis. Nearly a third of denifanstat recipients (30%) saw at least a one-stage reduction in fibrosis without worsening MASH, as did 14% of placebo recipients; 17% and 5%, respectively experienced both MASH resolution and fibrosis improvement. Denifanstat recipients were also more likely to experience at least a two-stage improvement—for example, moving from advanced to mild fibrosis. Some other medications tested for MASH (such as GLP-1 agonists) have been shown to lower liver fat but with no improvement in fibrosis.

What's more, denifanstat reduced liver fat percentages and decreased liver enzymes linked to inflammation. It also improved triglyceride composition and reduced LDL cholesterol, suggesting it might have cardiovascular benefits. Most participants did not experience notable changes in weight or blood sugar.

Treatment was generally safe and well tolerated. There were 13 serious adverse events in the denifanstat group and three in the placebo group, but none were considered related to the study drug. All adverse events deemed drug-related were mild or moderate. Hair loss was more common in the denifanstat group (19% versus 4%), while dry eye symptoms were more common in the placebo group (9% versus 14%). Hair thinning or loss is thought to result from a reduction in lipid synthesis in hair follicles.

"Treatment with denifanstat resulted in statistically significant and clinically meaningful improvements in disease activity, MASH resolution and fibrosis," the study authors concluded.

“The results of this Phase IIb trial support the advancement of denifanstat to Phase III development.”

The FDA recently gave denifanstat a breakthrough therapy designation, indicating that it may demonstrate a substantial improvement over existing therapies for people with a serious or life-threatening disease.

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