Novel Thyroid Hormone Receptor Agonists Show Promise for MASH

VK2809 and ALG-055009 led to reductions in liver fat and blood lipids associated with cardiovascular risk.

November 27, 2024 By Liz Highleyman

Two experimental thyroid hormone receptor agonists, VK2089 and ALG-055009, led to significant improvements in people with metabolic dysfunction-associated steatohepatitis (MASH), according to late-breaking study results presented at the American Association for the Study of Liver Diseases Liver Meeting 2024.

One study showed that up to 75% of people treated with VK2809, from Viking Therapeutics, achieved MASH resolution with no worsening of liver fibrosis at 52 weeks. In another study, Aligos Therapeutics' ALG-055009 led to a reduction in liver fat at 12 weeks, supporting further evaluation.

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, or NAFLD), are leading causes of advanced liver disease worldwide. Over time, fat buildup in the liver can trigger inflammation, leading to fibrosis, cirrhosis and liver cancer. The new terminology emphasizes the link with obesity, diabetes and other metabolic abnormalities, and management has relied on lifestyle changes such as weight loss and exercise.

Developing treatments for fatty liver disease has proved challenging, as the dual benchmark of MASH improvement without worsening fibrosis and fibrosis improvement without worsening MASH is difficult to meet. In March, the Food and Drug Administration (FDA) granted accelerated approval of the first medication for MASH, Madrigal Pharmaceuticals' resmetirom (Rezdiffra), a selective thyroid hormone receptor beta agonist. Newer drugs in this class, which activate hormones that play a role in fat metabolism, are in the pipeline.

VK2809

Rohit Loomba, MD, of the University of California San Diego, presented final 52-week results from the Phase IIb VOYAGE trial (NCT04173065), which evaluated VK2089, a selective thyroid hormone beta receptor agonist that targets the liver. Selective activation of this receptor in liver tissue is thought to favorably affect cholesterol and lipoprotein levels via multiple mechanisms, including

increasing the expression of genes associated with lipid metabolism and clearance, according to a Viking news release.

The study enrolled 221 people with biopsy-proven MASH (at least 8% liver fat content) and liver fibrosis. More than half were women, most were white and the mean age was 53 years. About a third had advanced (Stage F3) fibrosis, but they had not yet progressed to cirrhosis (Stage F4). Up to 25% could have mild (Stage F1) fibrosis if they also had additional risk factors, such as diabetes or obesity.

The participants were randomly assigned to receive oral VK2809 at doses of 1.0 mg, 2.5 mg or 5.0 mg once daily, 10.0 mg VK2809 every other day or a placebo for 52 weeks. Age, weight and body mass index were similar across treatment groups. Magnetic resonance imaging proton density fat fraction (MRI-PDFF) scans were done at the start of the study, week 12 and week 52, and liver biopsies were performed at baseline and the end of treatment.

As previously reported, people randomized to the three higher VK2809 doses saw significantly greater reductions in liver fat at 12 weeks, the study's primary endpoint. The new data showed that benefits were maintained at 52 weeks. The median relative fat reduction was 34% in the 1.0 mg group, 54% in the 2.5 mg group, 47% in the 5.0 mg group and 56% in the 10.0 mg group, compared with just 9% in the placebo group, demonstrating "robust durability," according to Loomba.

What's more, people assigned to VK2809 were significantly more likely to experience at least a 30% decrease in liver fat, ranging from 64% in the 1.0 mg group to 88% in the 10.0 mg group, compared with 27% in the placebo group. This level of liver fat reduction is predictive of improved liver tissue health.

The proportion of study participants who achieved MASH resolution with no worsening of fibrosis ranged from 63% to 75% in the VK2809 groups, compared with 29% in the placebo group; these differences were significant for the three higher dose groups.

People in the two highest VK2089 dose groups were significantly more likely to see their fibrosis improve by at least one stage with no worsening of MASH (52% and 57%) compared with the placebo group (34%); 41% and 48%, respectively, in the higher dose groups experienced both fibrosis improvement and MASH resolution, compared with 20% of placebo recipients. Similar improvements were observed among people with more advanced fibrosis at baseline.

Looking at noninvasive biomarker tests, VK2809 recipients experienced greater reductions in low-density lipoprotein (LDL) cholesterol, lipoprotein(a), triglycerides and other markers associated with cardiovascular risk.

Treatment was generally safe and well tolerated, and most treatment-emergent adverse events were mild or moderate. Across all four VK2809 groups, 29% experienced drug-related adverse events. Rates of gastrointestinal side effects, such as nausea or diarrhea, were similar in the

VK289 and placebo groups. Just 6% of VK2089 recipients discontinued treatment due to adverse events, compared with 9% in the placebo group. Weight changes did not differ significantly across groups.

“The potent reductions in liver fat, impressive NASH resolution rates and improvements in fibrosis suggest an attractive potential treatment option for patients,” Loomba said in the news release. “In addition, the observed improvements in plasma lipids indicate a potential long-term cardioprotective effect, a valuable benefit in this setting.”

ALG-055099

Loomba also presented results from the Phase IIa HERALD trial (NCT06342947), which evaluated ALG-055009, a “purpose-built” next-generation thyroid hormone receptor beta agonist. The study included 102 people with presumed MASH, at least 10% liver fat content and Stage F1 to F3 fibrosis. Again, more than half were women, and the mean age was about 50 years. Nearly half were Latino, a group with a higher prevalence of fatty liver disease.

Just under half had type 2 diabetes. The researchers took special note of participants who were using GLP-1 agonist medications, such as semaglutide (Ozempic or Wegovy), to treat diabetes or obesity. About 17% did so, and they had to be on a stable regimen for at least three months at study entry.

The participants were randomly assigned to receive ALG-055009 at doses of 0.3 mg, 0.5 mg, 0.7 or 0.9 mg or a placebo once daily for 12 weeks. Only individuals weighing about 190 pounds or more enrolled in the highest dose group.

Aligos announced topline results from the study in September, and Loomba presented more detailed data at the Liver Meeting. ALG-055009 led to “significant and robust” reductions in liver fat at 12 weeks, he reported. The median placebo-adjusted relative reduction in liver fat by MRI-PDFF was 20%, 24%, 46% and 44% in the successive dose groups. Responses were comparable in men and women.

Among participants taking GLP-1 agonists, those in the two higher ALG-055009 dose groups saw greater reductions in liver fat. Eleven of the 14 people on GLP-1 agonists who were assigned to the study drug experienced liver fat decreases, while all four assigned to the placebo gained liver fat. This suggests that ALG-055009 could potentially be used to augment liver fat reduction in people receiving GLP-1 and related incretin therapy for diabetes or weight loss.

People assigned to ALG-055009 were significantly more likely to experience at least a 30% reduction in liver fat. Here, 28%, 33%, 70% and 59% did so in the successive dose groups, compared with 10% in the placebo group; the difference was statistically significant for the two higher dose groups. People taking ALG-055009 saw greater reductions in LDL cholesterol, lipoprotein(a) and apolipoprotein B compared with the placebo group.

ALG-055009 was also generally safe and well tolerated. Most treatment-emergent adverse events were mild or moderate. Rates of gastrointestinal side effects were similar in the ALG-055009 and placebo groups. There were no serious adverse events among ALG-055009 recipients, and no one developed clinical hypothyroidism or hyperthyroidism

“ALG-055009 has demonstrated robust reductions in liver fat with a favorable tolerability and pharmacokinetic profile and convenient once daily oral dosing,” the researchers concluded, supporting testing of longer treatment durations and evaluation liver histology in Phase IIb.

“This has been an exciting year for the MASH space, which continues with this excellent data from Aligos’s ALG-055009, which has the potential for not only improvement in resolution of MASH, but also fibrosis improvement,” Loomba said in a news release. “In addition, it has potential to improve cardiovascular risk if the noninvasive tests data are confirmed in future trials.”

Click here for more news about fatty liver disease.
Click here for more reports from The Liver Meeting 2024.
