Two Experimental Therapies Show Promise for NASH

VK2809 and pegozafermin are among several medications coming through the pipeline for fatty liver disease

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Two different types of medication for non-alcoholic steatohepatitis (NASH) have recently demonstrated good activity in Phase II clinical trials, raising hopes that effective treatments could become available in the next few years.

Viking Therapeutics announced this week that its thyroid hormone receptor agonist, VK2809, reduced liver content and blood lipid levels and demonstrated "encouraging" safety and tolerability. In March, 89bio reported that its fibroblast growth factor analog, pegozafermin, improved liver fibrosis and NASH.

Non-alcoholic fatty liver disease (NAFLD) and NASH, its more severe form, are responsible for a growing burden of advanced liver disease worldwide. Over time, the buildup of fat in the liver can lead to fibrosis, cirrhosis and liver cancer. Linked to obesity and diabetes, fatty liver disease is increasingly recognized as a metabolic disorder. With no effective approved therapies, management depends on lifestyle changes such as diet, exercise and weight loss.

Several treatment approaches aim to improve liver health by targeting metabolic abnormalities. For example, thyroid hormone receptor agonists activate hormones that play a role in fat metabolism. Fibroblast growth factor analogs mimic a hormone that regulates bile acid metabolism and fat storage in the liver. Farnesoid X receptor (FXR) agonists regulate bile acid synthesis and play a role in lipid and glucose metabolism. Glucagon-like peptide-1 (GLP-1) agonists, such as the popular diabetes and weight-loss drug semaglutide (Ozempic or Wegovy), mimic a hormone that stimulates insulin production and regulates appetite.

But developing effective NASH treatments has proved challenging. Several drugs that appeared promising in early studies did not show significant benefits in larger clinical trials. The Food and Drug Administration (FDA) dual benchmark of NASH improvement without worsening of fibrosis and fibrosis improvement without worsening of NASH has been difficult to achieve. What's more, several otherwise promising candidates can cause difficult side effects.

VK2809

The Phase IIb VOYAGE trial compared VK2809, a liver-selective thyroid hormone receptor beta agonist in people with biopsy-confirmed NASH and fibrosis. The drug previously showed promise in a Phase IIa trial of people with NAFLD.

The analysis included 246 participants with at least 8% liver fat content as assessed by magnetic resonance imaging–proton density fat fraction (MRI-PDFF) at baseline. They had either moderate to advanced fibrosis (Stage F2 or F3) or mild fibrosis (F1) plus additional risk factors, such as diabetes or obesity. They were randomly assigned to receive one of four oral doses of VK2809 (1, 2.5, 5 or 10 milligrams) or a placebo.

The study achieved its primary endpoint, showing that VK2809 led to a significantly greater reduction in liver fat content at week 12. Liver fat declined by an average of 17% to 52%, depending on the dose, compared with just 4% in the placebo group. Up to 85% of participants experienced at least a 30% relative reduction in liver fat, the level associated with NASH improvement on liver biopsies.

The company believes these findings "represent the largest reductions reported for an oral agent at this stage of development," Viking CEO Brian Lian, PhD, said in a company press release.

People treated with VK2809 also experienced significant reductions in blood lipids, including low-density lipoprotein (bad cholesterol) and triglycerides. The frequency of adverse events, including gastrointestinal side effects, were similar in the VK2809 and placebo groups, according to Viking. Liver enzyme (ALT and AST) and thyroid hormone levels were also comparable.

These findings have not yet been published or presented at a medical conference. The company said it expects to submit the results for presentation at a future meeting, possibly the EASL Congress in late June or the AASLD Liver Meeting in November.

Pegozafermin

The Phase IIb ENLIVEN trial evaluated the safety and efficacy of pegozafermin, an engineered analog of fibroblast growth factor 21 (FGF21). The analysis included 192 people with NASH and Stage 2 or 3 fibrosis who were randomized to receive one of three pegozafermin regimens (44 mg administered by subcutaneous injection every two weeks, 30 mg once weekly or 15 mg once weekly) or a placebo. The study also included 14 people with cirrhosis (Stage F4) who were not part of the main analysis.

Repeat biopsies from people with moderate to advanced fibrosis at 24 weeks showed that participants in both the 44 mg biweekly and 30 mg weekly groups experienced at least a one-stage improvement in fibrosis with no worsening of NASH (27% and 26%, respectively), compared with 7% in the placebo group, as well as NASH resolution without worsening of fibrosis (26%, 23% and 2%, respectively). What's more, 11 of the 12 treated patients with cirrhosis saw fibrosis improvement without worsening NASH. Noninvasive tests of liver fat, inflammation, blood glucose and blood lipid levels also showed improvements.

“I was especially encouraged by the significant improvement in fibrosis relative to placebo, as fibrosis is a key driver of NASH disease progression which can lead to cirrhosis and other negative clinical outcomes,” Arun Sanyal, MD, of Virginia Commonwealth University, said in a 89bio press release.

The treatment was generally safe and well tolerated. The most common adverse effects were diarrhea, nausea and increased appetite, mostly mid to moderate. Five pegozafermin recipients discontinued treatment for this reason. One person receiving the highest dose developed transient pancreatitis. Side effects occurred less often with every-other-week versus weekly dosing.

“These data are amongst one of the most consistent data sets for drugs in clinical development for NASH with a parallel improvement in both MRI-PDFF and ALT and bodes well for the likelihood of success in the upcoming Phase III program,” said lead investigator Rohit Loomba, MD, of the University of California San Diego. “Given NASH is a chronic and often asymptomatic disease, I am excited to see the strong efficacy and tolerability results observed with every-two-week dosing, as this would provide clinicians and patients multiple advantages.

Other Candidates
A few other candidates are farther ahead in the race to be the first approved treatment for NASH.

Intercept’s obeticholic acid (OCA or Ocaliva), an FXR agonist, is undergoing FDA review, a second attempt after the agency declined approval in June 2020. The company resubmitted its application with additional data last December, and a decision is expected in June.

Madrigal’s resmetirom, another selective thyroid hormone receptor agonist, is also in the running. In December, the company announced that the drug reduced liver fat and improved fibrosis in a Phase III clinical trial that compared liver biopsies before and after treatment. In April, the FDA gave resmetirom a breakthrough therapy designation, putting it on the fast track, and the company expects to file for approval this quarter.

Given the number of different biological processes that play a role in the development of NAFLD and NASH, many experts think optimal treatment may require combining therapies with different mechanisms of action.

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