# What's in the Pipeline for NAFLD and NASH?

Optimal treatment for fatty liver disease may involve combining drugs with different mechanisms of action.

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A wide variety of different therapies are being studied for the management of fatty liver disease and its complications. Several experimental drugs, alone or in combination, were highlighted at the recent 2020 Digital International Liver Congress, convened by the European Association for the Study of the Liver (EASL).

Non-alcoholic fatty liver disease (NAFLD) and its more severe form, non-alcoholic steatohepatitis (NASH), are responsible for a growing burden of advanced liver disease worldwide. Over time, the buildup of fat in the liver triggers inflammation, which can lead to fibrosis (scarring), cirrhosis and liver cancer. A study by Zobair Younossi, MD, MPH, of Inova Health System in Falls Church, Virginia, and colleagues found that NAFLD/NASH is responsible for 26% of liver-related deaths in the United States, second only to alcoholic liver disease.

Developing treatments for NAFLD and NASH has proved challenging. Several drugs that appeared promising in early studies did not show significant benefits in larger clinical trials. With no approved therapies, management currently relies on lifestyle changes, such as weight loss and exercise.

Linked to obesity and diabetes, NAFLD/NASH is increasingly recognized as a manifestation of metabolic syndrome, characterized by abdominal obesity, high blood pressure, elevated blood sugar and abnormal cholesterol or triglyceride levels.

Several treatment approaches aim to improve liver health by targeting metabolic abnormalities associated with fatty liver disease.

Treatments under study for NAFLD and NASH include:

- Farnesoid X receptor (FXR) agonists, which regulate bile acid synthesis and play a role in lipid and glucose metabolism

- Glucagon and glucagon-like peptide-1 (GLP-1) agonists, which mimic hormones that regulate appetite and affect glucose and lipid metabolism
- Fibroblast growth factor analogues, which mimic a hormone that regulates bile acid metabolism and fat storage in the liver
- Fatty acid synthase inhibitors, which reduce liver fat production and inflammation
- Thyroid hormone receptor agonists, which activate hormones that play a role in fat metabolism
- Apoptosis signal-regulating kinase 1 (ASK1) inhibitors, which block an enzyme that promotes inflammation and fibrosis
- Acetyl-CoA carboxylase (ACC) inhibitors, which block an enzyme involved in lipogenesis (conversion of carbohydrates into fatty acids in the liver)
- Peroxisome proliferator-activated receptor agonists, which play a role in glucose and lipid metabolism and inflammation
- Immune modulators, which block receptors on immune cells involved in inflammation.

FXR Agonists

Last year, Intercept's FXR agonist Ocaliva (obeticholic acid) was the front-runner in the NASH pack thanks to promising findings from the REGENERATE study. But further results showed that although Ocaliva increased the likelihood of at least a one-stage improvement in fibrosis without worsening of NASH—a common primary endpoint in fatty liver disease trials—it failed to meet the other main endpoint of improvement in NASH without worsening fibrosis.

In June, the Food and Drug Administration (FDA) declined to approve Ocaliva for NASH, suggesting its benefits might not outweigh the risks. Intercept argued that the "totality of data" support the drug's approval. Results presented at the liver congress showed that Ocaliva led to sustained improvement in fibrosis according to newer noninvasive assessments, including the FibroMeter index, FibroMeter plus liver stiffness by transient elastography, and FAST score, which incorporates markers of inflammation.

Also at this year's conference, Vlad Ratziu, MD, PhD, of Pitié-Salpêtrière Hospital in Paris, reported that a novel FXR agonist, Enanta's EDP-305, showed promising results in the Phase IIa ARGON-1 study.

This study included 132 people with NASH-related fibrosis who had not yet progressed to cirrhosis. The mean body mass index (BMI) was in the range for obesity, and three quarters were being treated for type 2 diabetes. They were randomly assigned to receive 1 milligram or 2.5 mg of EDP-305 or a placebo for 12 weeks.

Participants in the high-dose EDP-305 group saw a significantly greater decrease in liver fat content, with 45% having at least a 30% relative reduction. The high dose led to reductions in ALT and GGT liver enzyme levels and C4, a protein involved in the complement immune response. But it also led to a small rise in harmful LDL cholesterol and a significant drop in beneficial HDL cholesterol.

The most common side effect was pruritus, or itching, which was reported by 51% and led to treatment discontinuation in 21% of participants who received the higher dose of EDP-305.

“This trial confirms that FXR agonism is a valuable therapeutic target in NASH with strong antisteatotic effects and the potential to reduce inflammatory injury to the liver,” Ratziu said in an EASL press release.

Another FXR agonist, Novartis’s nudifexor, also showed promising results in a Phase II trial. This study included 121 people with NASH. The average BMI was in the range for obesity. If participants had diabetes, it had to be controlled with medication. The participants were randomized to receive one of two oral doses of nudifexor (50 or 100 mg) or a placebo.

At week 12, body weight decreased by about three pounds in the low-dose nudifexor group and by about four pounds in the high-dose group. The mean relative reduction in liver fat content was 29% in the low-dose group and 32% in the high-dose group. About 50% and 70% in the two groups saw at least a 30% relative reduction in liver fat. ALT declined significantly more in both nudifexor groups compared with the placebo group. LDL and triglyceride levels did not change significantly, but HDL decreased.

Treatment was generally safe, but side effects were common. About a third of people randomized to the high-dose group reduced their dose or discontinued treatment due to adverse events, but this did not occur in the low-dose group. The most common side effect was pruritus, reported by 30% in the low-dose group and 54% in the high-dose group.

Other Drug Classes

Philip Ambery, MD, of AstraZeneca, presented findings from a Phase IIb clinical trial testing cotadutide, a dual receptor agonist that modifies the activity of both glucagon and GLP-1.

This study included 834 people who had overweight or obesity, type 2 diabetes treated with metformin and evidence of fatty liver disease. They were randomly assigned to receive one of three doses of cotadutide (100, 200 or 300 micrograms) via once-daily injection, the diabetes drug liraglutide (a single-action GLP-1 agonist) or a placebo.

After 54 weeks, people taking cotadutide lost more weight and saw greater improvements in metabolic, cardiovascular and liver fibrosis biomarkers. Cotadutide was generally safe, but 41% of people taking the high dose experienced nausea, and 22% stopped treatment due to adverse events.

Ambery said the improvements in fibrosis are “encouraging,” noting that a Phase II study of cotadutide for people with obesity and NASH is underway using a higher dose with an optimized titration schedule in an effort to reduce side effects. (Read the full report here.)

Stephen Harrison, MD, of Pinnacle Clinical Research, in San Antonio, and colleagues evaluated aldafermin (NGM282), a genetically engineered fibroblast growth factor (FGF19) analogue from NGM Biopharmaceuticals. This Phase II trial included 77 people with NASH. They were ramdomized to received aldafermin or a placebo as a daily injection.

Aldafermin significantly reduced liver fat content by week 24, with 66% of participants taking the drug showing at least a 30% relative decrease. What’s more, 38% experienced at least a one-stage improvement in fibrosis without worsening of NASH, while 24% experienced NASH resolution without worsening fibrosis. Nearly a quarter (22%) achieved both endpoints.

Aldafermin was generally well tolerated. No one stopped treatment due to side effects, and rates of gastrointestinal symptoms and pruritus were not higher in the aldafermin group compared with the placebo group. (Read the full report here.)

Rohit Loomba, MD, of the University of California at San Diego, and colleagues evaluated TVB-2640, from Sagimet Biosciences, a first-in-class fatty acid synthase inhibitor.

The Phase IIa FASCINATE-1 trial included 99 people with evidence of NAFLD. They were randomized to receive one of two oral doses of TVB-2640 (25 or 50 mg) or a placebo. Median BMI was in the range for obesity; 76% in the low-dose group, 37% in the high-dose group and 55% in the placebo group had type 2 diabetes.

After 12 weeks of treatment, liver fat content declined significantly more in the high-dose TVB-2640 group compared with the placebo group. In the high- and low-dose groups, 61% and 23%, respectively, experienced at least a 30% relative reduction in liver fat compared to baseline levels.

ALT levels also fell, with 58% in the high-dose group achieving ALT normalization. Both LDL and HDL cholesterol dropped significantly in the high-dose group. This group also saw a 24% rise in levels of adiponectin, a hormone that regulates appetite and glucose and fatty acid metabolism. Finally, TVB-2640 led to reductions in biomarkers of fibrosis.

Treatment was generally well tolerated. Only 3% of people taking either dose of TVB-2640 experienced moderate side effects, and there were no severe adverse events. In particular, no one reported pruritus or elevated triglycerides.

Loomba said these findings warrant further studies to examine whether TVB-2640 will lead to NASH resolution and fibrosis improvement in people with biopsy-proven NASH.

Loomba also presented the latest results from a Phase IIa trial of VK2809, a thyroid receptor beta agonist from Viking Therapeutics. This study included 47 people with NAFLD and elevated LDL and

triglyceride levels. They were randomly assigned to receive one of three oral regimens of VK2809 (5 or 10 mg every day or 10 mg every other day) or a placebo for 12 weeks.

Last year, Loomba reported that people taking VK2809 experienced significantly greater reductions in liver fat content compared with the placebo group. They also saw declines in LDL and ALT levels. Treatment was generally safe with "excellent" gastrointestinal tolerability.

This year, he reported that this effect was maintained four weeks after the end of treatment. Altogether, 70% of those taking VK2809 saw at least a 30% reduction in liver fat at week 16.

"The consistency and durability of efficacy reported with VK2809 in this trial regardless of therapeutic dose, baseline patient characteristics or underlying NASH risk factors is encouraging," Loomba said in a Viking press release. "Particularly noteworthy is that VK2809-treated patients with NASH risk factors, including elevated baseline ALT, obesity and hypertension, experienced reductions in liver fat that were significantly greater than observed among patients receiving placebo."

VK2809 is now being tested for people with biopsy-confirmed NASH and mild to advanced fibrosis in the larger Phase IIb VOYAGE trial.

Combination Treatment

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.

Gilead Sciences' Phase IIb ATLAS trial evaluated three of the company's fatty liver drug candidates alone and in various combinations in people with advanced fibrosis or compensated cirrhosis due to NASH. Selonsertib (GS-4997) is an ASK1 inhibitor, firsocostat (GS-0976) is an ACC inhibitor and cilofexor (GS-9674) is an FXR agonist.

As previously reported, the Phase III STELLAR-3 and STELLAR-4 trials found that selonsertib alone worked no better than a placebo for improving liver fibrosis or reducing the risk of cirrhosis; the selonsertib monotherapy arm of ATLAS was therefore discontinued.

Last December, Gilead announced that neither firsocostat or cilofexor monotherapy nor any of the two-drug combinations significantly increased the likelihood of achieving at least a one-stage improvement in fibrosis without worsening of NASH.

However, Loomba presented data at the recent conference showing that some of the single agents and combinations did lead to significant improvements in fibrosis and other measures of liver health, despite failing to meet the study's primary endpoint.

After 48 weeks of treatment, 21% of participants assigned to receive firsocostat/cilofexor and 19% of those taking selonsertib/cilofexor had at least a one-stage improvement in fibrosis without

worsening of NASH. The likelihood of progression to cirrhosis was lower in all treatment groups compared with the placebo group.

The combination of firsocostat and cilofexor appeared most promising overall, with participants assigned to this regimen seeing improvements in NAFLD activity scores, noninvasive fibrosis tests, ALT and AST levels, insulin levels and body weight. All regimens were generally safe and well tolerated, but 28% of people who used firsocostat/cilofexor reported pruritus. (Read the full report here.)

Another drug that was in the running to be the first approved NASH treatment, Genfit's dual PPAR alpha/gamma agonist elafibranor, was halted in July after it failed to meet the primary endpoint of improving NASH without worsening fibrosis in the Phase III RESOLVE-IT trial.

However, a preclinical study presented at the liver congress showed that combining elafibranor with the GLP-1 diabetes drug semaglutide (Ozempic or Rybelsus) led to improvements in obese mice fed a high-fat diet. Mice that received the combination had decreased NAFLD activity scores, ALT levels and triglycerides in the liver. These effects were not seen when either drug was used alone. About 30% of the mice that received elafibranor showed reduced fibrosis, but this effect was not enhanced by adding semaglutide.

Immune Modulators

Immune-modulating therapies do not directly target metabolic processes involved in the development of fatty liver disease but rather aim to control the inflammation that leads to fibrosis.

Allergan's cenicriviroc, which blocks both CCR2 and CCR5 receptors on immune cells, was previously studied as a treatment for HIV. In the Phase IIb CENTAUR trial, cenicriviroc did not lead to a decrease in liver fat or NAFLD activity scores in people with NASH, but it did reduce liver fibrosis significantly more than a placebo over 48 weeks. Long-term safety results presented at the liver congress showed that cenicriviroc continued to be safe and well tolerated for more than four years.

Another mouse study presented at the conference tested a novel dual CCR2/CCR5 blocker (BMS-687681) plus a fibroblast growth factor (FGF21) analogue (BMS-986171) being developed by Bristol-Myers Squibb. The CCR2/CCR5 blocker reduced inflammation and fibrosis; the FGF analogue reduced body weight, triglycerides and liver fat accumulation; and combining the drugs led to additive or even synergistic benefits.

Cenicriviroc is currently being studied as a treatment for people with NASH and moderate to severe fibrosis in the Phase III AURORA trial. Primary results are expected next year.

Finally, CytoDyn announced in July that it has launched a Phase II trial of its single-action CCR5 blocker leronlimab (PRO14) as a treatment for NASH, following promising preclinical data. The experimental drug is also being evaluated as a treatment for HIV, cancer and COVID-19.

Click here to learn more about NAFLD and NASH.

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