Experimental NASH Drugs Improve Fibrosis and Liver Health

The best-performing combo, firsocostat and cilofexor, showed benefits despite missing the main study endpoint.

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A set of experimental drugs from Gilead Sciences led to improvements in fibrosis and other measures of liver health despite failing to meet a study's primary endpoint of significantly reducing liver fibrosis without worsening non-alcoholic steatohepatitis (NASH), according to results presented at the 2020 Digital International Liver Congress.

NASH and its less severe form, non-alcoholic fatty liver disease (NAFLD), are responsible for a growing proportion of advanced liver disease. Linked to obesity and diabetes, NAFLD/NASH is increasingly recognized as a manifestation of metabolic syndrome. The buildup of fat in the liver triggers inflammation, which over time can lead to fibrosis (scarring), cirrhosis and liver cancer. With no approved therapies, management relies on lifestyle changes, such as weight loss and exercise.

Developing treatments for NAFLD and NASH has proved challenging, and several drugs that appeared promising in early studies have not demonstrated significant benefits in larger trials. Part of the difficulty lies in determining which biomarkers will predict clinical benefits. Given the number of different biological processes that play a role in the development of NAFLD/NASH and its complications, many experts think optimal treatment will require combining drugs with different mechanisms of action.

Gilead's Phase IIb ATLAS trial evaluated three of the company's NASH candidates alone and in various combinations.

Selonsertib (formerly GS-4997) is an apoptosis signal-regulating kinase 1 (ASK1) inhibitor, firsocostat (GS-0976) is an acetyl-CoA carboxylase (ACC) inhibitor and cilofexor (GS-9674) is a nonsteroidal farnesoid X receptor (FXR) agonist. ASK1 promotes inflammation and fibrosis, ACC is involved in lipogenesis (conversion of carbohydrates into fatty acids) and FXR regulates bile acid synthesis and plays a role in lipid and glucose metabolism.

ATLAS included 392 participants with biopsy-confirmed advanced fibrosis (Stage F3) or compensated cirrhosis (Stage F4) due to NASH, unexplained cirrhosis with two or more features of

metabolic syndrome (abdominal obesity, elevated blood sugar, abnormal blood lipids and high blood pressure) or noninvasive measures suggesting advanced fibrosis. About 65% were women, and the median age was approximately 60. The average body mass index was in the range for obesity, and nearly three quarters had diabetes. More than half (56%) had cirrhosis at baseline.

Participants were randomly assigned to one of seven arms, receiving selonsertib, firsocostat or cilofexor alone, one of the three dual combinations or a placebo. Liver biopsies were done at the start of the study and at week 48, and scans for liver stiffness and liver fat content were done at baseline and weeks 24 and 48.

At last year's AASLD Liver Meeting, researchers reported that selonsertib alone worked no better than a placebo for improving liver fibrosis or reducing the risk of cirrhosis in the Phase III STELLAR-3 and STELLAR-4 trials. The selonsertib monotherapy arm of ATLAS was halted after those results were reported.

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, often used as the primary endpoint in fatty liver disease studies.

However, as Rohit Loomba, MD of the University of California at San Diego reported at the recent conference, some of the single agents and combinations led to significant improvements in various secondary endpoints.

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 NASH. The corresponding rates were 15% with selonsertib/firsocostat, 12% with either firsocostat or cilofexor monotherapy and 11% in the placebo group. In the STELLAR trials, 10% to 14% of patients taking selonsertib alone achieved this endpoint.

The likelihood of progression to cirrhosis was lower in all treatment groups compared with the placebo group, in which 41% progressed. Selonsertib/cilofexor performed best, with just 8% developing cirrhosis. Progression rates were 15% with firsocostat monotherapy or selonsertib/firsocostat, 20% with cilofexor monotherapy and 23% with firsocostat/cilofexor.

NASH resolution without worsening of fibrosis was uncommon in all treatment groups. No one in the cilofexor monotherapy or placebo groups achieved this endpoint, rising to 1.4% with selonsertib/firsocostat, 1.5% with selonsertib/cilofexor, 3.0% with firsocostat monotherapy and 4.5% with firsocostat/cilofexor.

People assigned to firsocostat/cilofexor or firsocostat monotherapy were most likely to see at least a two-point reduction in their overall NAFLD activity score and the three components of that score: steatosis (fat accumulation), lobular inflammation and ballooning of hepatocytes. Firsocostat/cilofexor performed significantly better than the placebo for all these measures.

When fibrosis and bile duct proliferation were assessed using a machine learning algorithm, firsocostat/cilofexor led to greater improvements overall, although firsocostat and cilofexor monotherapy performed well on some measures.

Fibroscan liver stiffness scores and enhanced liver function (ELF) scores improved most in the firsocostat monotherapy arm. For liver stiffness, 55% of firsocostat recipients, 45% of firsocostat/cilofexor recipients and 38% of cilofexor recipients were classified as responders, compared with 20% in the placebo group. For ELF scores, the corresponding proportions were 44%, 31% and 24% compared with 19%.

Firsocostat/cilofexor led to significant reductions in biomarkers of liver injury, inflammation and liver function, including ALT and AST liver enzymes, bilirubin and bile acids; those taking firsocostat or cilofexor alone saw smaller improvements.

Finally, people who received firsocostat/cilofexor had significantly greater reductions in body weight and insulin levels and a greater improvement in kidney function compared with the placebo group, Loomba reported.

All treatments were generally safe and well tolerated. Severe side effects were uncommon, seen in two people (3%) in the firsocostat/cilofexor arm, one (1%) in the selonsertib/cilofexor arm and none in the other groups. In all groups, 3% to 5% of participants discontinued treatment due to adverse events.

The most common adverse event overall was pruritus, or itching, which can be a symptom of cirrhosis itself. This was most common in the selonsertib/cilofexor and firsocostat/cilofexor groups (29% and 28%, respectively). The pruritus rate was approximately 20% in the other treatment groups and 15% in the placebo group.

Triglyceride levels rose in all treatment groups, but there was no change in the placebo group. The largest increases were seen in the firsocostat/cilofexor and firsocostat monotherapy arms (44 and 42 milligrams per deciliter). None of the groups saw a significant increase in harmful LDL cholesterol. Both pruritus and elevated triglycerides were considered “manageable,” according to the researchers.

Overall, these findings show that although it has been difficult to meet the endpoint of at least a one-stage fibrosis improvement without worsening of NASH, various agents do lead to beneficial changes in other indicators of liver health, especially when used in combination. These results suggest that further studies of combination therapies for advanced fibrosis due to NASH—in particular firsocostat/cilofexor—are warranted, Loomba said.

Click here to learn more about NAFLD and NASH.

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