Semaglutide Shows Promise for Fatty Liver Disease

The diabetes medication, alone or in combination regimens, led to improvements in NASH and fibrosis.

January 18, 2021 By Liz Highleyman

Semaglutide, a medication used to treat type 2 diabetes, increased the likelihood of improvement in non-alcoholic steatohepatitis (NASH) without worsening liver fibrosis, according to research presented at the AASLD virtual Liver Meeting. What’s more, combining semaglutide with other drugs led to greater improvements in various measures of fibrosis, metabolism and liver health.

Non-alcoholic fatty liver disease (NAFLD) and its more severe form, NASH, are responsible for a growing burden of advanced liver disease worldwide. Linked to obesity and diabetes, NAFLD and NASH are increasingly recognized as manifestations of metabolic syndrome, a cluster of conditions linked to increased cardiovascular risk. The buildup of fat in the liver triggers cell death and inflammation, which over time can lead to fibrosis, cirrhosis, liver cancer and liver failure.

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.

Semaglutide Monotherapy

Philip Newsome, PhD, of Birmingham Biomedical Research Centre in the United Kingdom, presented results from an international Phase II study of semaglutide for people with NASH. The research was also published in The New England Journal of Medicine.

The study enrolled people with biopsy-confirmed NASH, mild to advanced liver fibrosis and a body mass index indicating overweight or obesity. About 60% were women, nearly 80% were white and the mean age was 55. Nearly two thirds had diabetes, and half had advanced fibrosis.

The trial participants were randomly assigned to receive one of three doses of semaglutide (0.1, 0.2 or 0.4 milligrams) or a placebo administered by injection once daily for 72 weeks. Liver biopsies were performed at the start and the end of the study.

Semaglutide (an injectable formulation sold as Ozempic and an oral version sold as Rybelsus) is a
glucagon-like peptide-1 (GLP-1) receptor agonist that mimics the action of natural GLP-1, which increases insulin secretion and plays a role in appetite regulation and glucose and lipid metabolism.

The primary study endpoint, assessed in the 230 participants with moderate (Stage F2) or advanced (Stage F3) fibrosis, was NASH resolution with no worsening of fibrosis. Improvement in fibrosis with no worsening of NASH was a secondary endpoint. (Some NASH trials look at these endpoints in the reverse order.)

More participants taking any dose of semaglutide experienced NASH resolution (40%, 36% and 59%, respectively, in the 0.1, 0.2, and 0.4 mg dose groups) compared with the placebo arm (17%).

The proportion of people with fibrosis improvement was statistically similar in all groups: 46%, 32%, 43% and 31%, respectively. However, fewer people taking semaglutide experienced liver fibrosis progression (10%, 8% and 5% in the three dose groups) compared with the placebo group (19%).

People who used semaglutide saw greater improvements in fibrosis biomarkers, liver enzyme levels and FibroScan liver stiffness measurements, lost more weight and saw improvements in glucose levels and blood lipid profiles. Harmful cholesterol, triglycerides and free fatty acid levels declined while beneficial HDL cholesterol rose.

Treatment was generally well tolerated and side effects were similar to those seen in people who take semaglutide for diabetes. The most common adverse events were gastrointestinal symptoms, which occurred more often in the highest semaglutide dose group. Treatment-related severe adverse events were rare.

Newsome concluded that semaglutide led to a higher rate of NASH resolution without fibrosis worsening. He suggested that significant improvement in fibrosis could take longer and might become apparent with further follow-up.

Semaglutide Combo Regimens
Given the multiple biological processes that play a role in the development of fatty liver disease, many experts think optimal treatment may require combining therapies with different mechanisms of action.

In another Phase II study, Naim Alkhouri, MD, of Arizona Liver Health, and colleagues compared regimens of semaglutide alone or in combination with Gilead Science’s firsocostat, cilofexor or both.

Firsocostat (GS-0976) is an acetyl-CoA carboxylase inhibitor that blocks an enzyme involved in the conversion of carbohydrates into fatty acids in the liver. Cilofexor (GS-9674) is a nonsteroidal FXR agonist that regulates bile acid synthesis and plays a role in lipid and glucose metabolism.
As previously reported, firsocostat and cilofexor alone or in various two-drug combinations with the ASK1 inhibitor selonsertib (GS-4997) failed to significantly increase the likelihood of fibrosis improvement without worsening NASH. However, findings from the Phase II ATLAS trial, presented at the recent Digital International Liver Congress, showed that some combinations did lead to significant improvements in fibrosis and other measures of liver health.

Alkhouri’s study design was similar to that of ATLAS but substituted semaglutide for selonsertib, which was found to be ineffective in a study presented at last year’s Liver Meeting.

This trial included 108 people with NASH and moderate to advanced fibrosis according to biopsies or noninvasive scans. About 70% were women, a third to a half were Latino (a group more likely to have NASH) and the median age was 54. A majority had overweight or obesity and more than half had diabetes.

Participants were randomly assigned to receive semaglutide alone, semaglutide plus firsocostat, semaglutide plus one of two doses of cilofexor or a combination of all three drugs. Semaglutide was given as a once-weekly injection while firsocostat and cilofexor were taken orally once daily.

All groups lost weight, with percentage losses ranging from -7% to -10%. Liver fat fraction decreased more in all the combination groups compared with the semaglutide monotherapy group, with the greatest loss seen in the triple therapy group.

Liver stiffness also declined in all groups, with the greatest improvement again seen in the triple therapy group. The enhanced liver fibrosis, or ELF, score (a composite index of fibrosis biomarkers) showed similar improvement across all groups. The FAST score (another composite measure) showed greater improvement in the combination groups, especially those that received firsocostat. The combination therapy groups also saw greater improvements in liver enzyme levels, with the largest ALT declines in the groups that used firsocostat.

All treatment groups had similar improvements in glucose and insulin levels. Harmful LDL cholesterol increased in the group taking the higher dose of cilofexor (though it did not change in the lower-dose group), and triglycerides rose in the groups that used firsocostat.

The combination regimens were generally safe and well tolerated. Rates of moderate or worse side effects ranged from 14% to 32%, but few people stopped treatment due to adverse events. Gastrointestinal symptoms were most common, with about two thirds of participants reporting nausea in the triple therapy group. Mild pruritus, or itching, was reported by a small number of people who took cilofexor.

In people with NASH, combining semaglutide with cilofexor or firsocostat may provide additional benefits compared with semaglutide alone, Alkhouri and colleagues concluded.

Click here to learn more about NAFLD and NASH.