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Ocaliva Improves Liver Fibrosis in People With NASH

About a quarter of people taking a higher dose of Ocaliva saw an improvement in liver fibrosis.

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Ocaliva (obeticholic acid) significantly improved liver fibrosis related to non-alcoholic steatohepatitis (NASH), though it did not lead to NASH resolution, according to a recently published study. The medication is scheduled for a Food and Drug Administration (FDA) review in April 2020.

Zobair Younossi, MD, PhD, of Inova Fairfax Medical Campus in Falls Church, Virginia, and colleagues conducted the Phase III REGENERATE trial to evaluate Ocaliva, being developed by Intercept Pharmaceuticals, as a treatment for NASH. Interim results were published in The Lancet in December and presented at the 2019 International Liver Congress last April

"This study is a pivotal step for the development of drugs to treat NASH and is likely to be the first to receive regulatory approval," wrote the authors of an editorial accompanying the study.

Non-alcoholic fatty liver disease (NAFLD) and its more severe form, NASH, are responsible for a growing proportion of advanced liver disease. The buildup of fat in the liver triggers inflammation, which over time can lead to the development of scar tissue (fibrosis), cirrhosis (severe scarring) and liver cancer; NASH is expected to soon become the leading reason for liver transplants. With no effective approved medical therapies—and several candidates recently missing the mark—management relies on lifestyle changes, such as weight loss and exercise.

Ocaliva is a farnesoid X receptor (FXR) agonist that activates receptors that regulate glucose and lipid metabolism and inflammation. Early studies showed that FXR agonists improve insulin sensitivity and reduce liver fibrosis. Ocaliva is currently FDA-approved for primary biliary cholangitis, a disease of the bile ducts.

REGENERATE has now enrolled nearly 2,500 people at more than 300 centers worldwide, Intercept recently announced. Participants have diagnosed NASH and mild to advanced fibrosis (Stage F1 to F3). People with hepatitis B or C, heavy alcohol consumption and other causes of chronic liver disease were excluded, as were those who had already developed cirrhosis (Stage F4).

The participants were randomly assigned to receive 10 or 25 milligrams of Ocaliva or a placebo

once daily. Liver biopsies were done at the start of the study and 18 months later.

This planned interim analysis of the ongoing study included 931 participants with Stage F2 or F3 fibrosis who received at least one dose of treatment. Nearly 60% were women, around 90% were white and about 18% were Latino; the average age was 55.

The study's dual primary endpoints were improvement of fibrosis by at least one stage with no worsening of NASH or NASH resolution with no worsening of fibrosis.

At the 18-month mark, 23% of participants in the 25 mg Ocaliva group, 18% in the 10 mg group and 12% in the placebo group experienced fibrosis improvement without worsening of NASH. The differences between both Ocaliva groups and the placebo group were statistically significant, meaning they were probably not driven by chance.

However, the NASH resolution endpoint was not achieved significantly more often in the Ocaliva groups compared with the placebo group (12%, 11% and 8%, respectively).

Treatment was generally safe and well tolerated. The most common side effect was itching (pruritus), reported by 51% in the Ocaliva 25 mg group, 28% in the 10 mg group and 19% in the placebo group. This was usually mild to moderate, but 9% of patients in the higher-dose Ocaliva group stopped treatment for this reason. The frequency of serious adverse events was similar across treatment groups (14%, 11% and 11%, respectively).

As noted in the accompanying editorial, Ocaliva recipients saw about a 20% increase in harmful LDL cholesterol levels, which could have implications for cardiovascular risk. However, this rise was generally transient and could be controlled with statins.

The study authors concluded that the 25 mg dose of Ocaliva significantly improved fibrosis and key components of NASH disease activity in this 18-month interim analysis.

"The robust antifibrotic effect of obeticholic acid was dose dependent and consistent across different patient populations and subgroups and was further supported by fibrosis-related secondary endpoints, including an improvement in fibrosis of at least two stages," they wrote. "In addition to consistent improvements in multiple histological parameters, improvement in liver health was also evident based on clinically meaningful, dose- dependent improvements in markers of liver injury (ALT and AST) and oxidative stress (GGT)."

Follow-up will continue over an extended period in order to evaluate all-cause mortality and liver-related clinical outcomes, as well as long-term safety.

"The first positive Phase III study results in NASH represent a real watershed moment for the hepatology field," Younossi said in an Intercept press release. "The antifibrotic efficacy observed with just 18 months of [Ocaliva] treatment in REGENERATE is particularly meaningful because fibrosis is the most important histological predictor of liver failure and death in patients with NASH."

Intercept submitted an application for FDA approval of Ocaliva for NASH in September. A decision was expected in March 2020, but the company recently announced that this date will be pushed back because the agency has scheduled an advisory committee hearing for April 22. The delay is thought to be related to logistics rather than any concern about the medication.

Click here to read the study abstract.

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