When Will We See Drug Treatments for NASH Fibrosis?

Currently, there are no pharmacological treatments for liver fibrosis related to non-alcoholic steatohepatitis.

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Perhaps as many as one in four people in North America have non-alcoholic fatty liver disease (NAFLD), in which excess fat accumulates in the liver of an individual who drinks little or no alcohol. The disease is tightly linked with metabolic syndrome and insulin resistance and is a top driver of liver disease, including non-alcoholic steatohepatitis (NASH).

NAFLD and NASH often occur with fibrosis (scarring) of the liver, and yet to date no medications have been approved to treat such liver damage in this population. For anyone with NAFLD and fibrosis, the primary recommended treatment is moderate intensity exercise along with a healthy diet to promote weight loss.

In a review article published in Hepatology International, Baltimore-based researchers Joseph J. Alukal, MD, of the Institute of Digestive Health and Liver Diseases at Mercy Medical Center, and Paul J. Thuluvath, MD, of the department of medicine at the University of Maryland School of Medicine, assessed the pipeline for such therapies.

The paper characterizes NAFLD as “a spectrum of liver disease," starting with fatty liver at one end of the spectrum and cirrhosis at the other end.

Some people with NAFLD, the authors write, will see their liver disease progress to NASH, which is characterized by steatosis (in which more than 5% to 10% of the liver’s volume is fat), inflammation of the liver and ballooning of liver cells. They may also experience liver fibrosis, which is graded on a four-stage scale, with F0 signifying no fibrosis, F1 to F3 indicating progressively advanced fibrosis and F4 pointing to severe fibrosis, or cirrhosis.

By the time they are diagnosed with the disease, about 25% of those with NASH already have moderate or severe fibrosis, which raises their risk of further severe health complications, as well as death.

The leading cause of death among those with NASH is cardiovascular disease (CVD), followed by cancer and then cirrhosis of the liver. According to a meta-analysis of five studies that together

included nearly 1,500 people with the disease, those with NASH and early-stage fibrosis have perhaps a 40% increased risk of death compared with their counterparts with no fibrosis, while those with cirrhosis have a more than 40-fold increased risk.

Examining the limited available research detailing the risk of fibrosis progressing among those with NAFLD, the review's authors found rather cloudy answers. In a meta-analysis of 11 studies that included 150 people who had NAFLD and 261 people with NASH, 34% of the study population experienced at least one stage of fibrosis progression during a cumulative 2,145 years of follow-up. On average, those with NAFLD experienced one stage of fibrosis progression after 14 years, while those with NASH did so in half the time.

While there are still no treatments for NASH-related fibrosis, the American Association for the Study of Liver Diseases recommends that people with the disease receive 800 international units of vitamin E daily or the diabetes medication pioglitazone. Each of those therapies has been associated with improvements in various NASH-related factors, although not with fibrosis regression

Note that such high-dose vitamin E is linked to a higher risk of death and, among men, prostate cancer. So a lower dose may be advisable.

Four notable medications that target at least one of the pathways that drive NASH and fibrosis are currently in Phase III trials. (Following the completion of a Phase III trial, a pharmaceutical company may apply for approval from the Food and Drug Administration, or FDA.) They are all trying to achieve the key benchmark of improving fibrosis by one stage without NASH worsening.

Intercept is gearing up to apply to the FDA for approval, in late 2019, of Ocaliva (obeticholic acid, or OCA) after the Phase III REGENERATE study found that the farnesoid X receptor agonist did indeed improve fibrosis without any worsening of NASH. The randomized, double-blind placebo-controlled trial of the drug included 931 people with F2 or F3 fibrosis due to NASH. Participants received 10 milligrams or 25 mg of OCA daily or a placebo and were treated for 18 months.

The Phase III STELLAR-4 trial of Gilead Sciences' apoptosis signal-regulating kinase-1 (ASK-1) inhibitor, selonsertib, on the other hand, has produced disappointing results after one year of treatment among people with compensated cirrhosis (the less severe form of the advanced liver disease) resulting from NASH. The participants were randomized such that 354 received 18 mg of selonsertib daily while 351 received 6 mg of selonsertib and 172 received a placebo. After one year, there was no significant difference in the proportion of each group that experienced a decline of one fibrosis stage without their NASH worsening.

In the placebo-controlled Phase II GOLDEN-505 study of Genfit's PPARalpha/gamma activator, elafibranor, which included 276 people with NASH but no cirrhosis, 52 weeks of treatment led to no improvement of fibrosis. However, when the analysis excluded the 15% of participants with a mild case of NASH, the higher dose of the drug tested (120 mg) was indeed associated with a superior outcome compared with the placebo. Consequently, the Phase III RESOLVE-IT trial is

currently assessing 120 mg of elafibranor versus a placebo among those with moderate to severe NASH. The study should wrap up in late 2021.

Lastly, in the placebo-controlled Phase IIb CENTAUR study, the anti-inflammatory drug cenicriviroc reduced fibrosis among 208 people with NASH and mild to severe fibrosis, with better results among those with worse liver disease at the study's outset. The drug, which is being developed by Allergan, is a dual antagonist of CCR2 and CCR5, meaning it blocks two coreceptors on the surface of immune cells. Cenicriviroc has been advanced to the Phase III AURORA trial, which includes people with NASH and F2 or F3 fibrosis and is expected to complete its primary portion in October 2021.

As for drugs to treat fibrosis in those with NASH that are in earlier stages of development, Conatus Pharmaceuticals'caspase inhibitor emricasan showed a disappointing trend halfway through a 48-week trial that included 263 people with NASH cirrhosis.

The diabetes drug Victoza (liraglutide), a GLP-1 analog, appeared to resolve NASH without worsening fibrosis after 42 weeks in a portion of the study group in a small placebo-controlled Phase II study. A drug in the same class, semaglutide, is currently being assessed in a Phase II trial of people with NASH.

The drug aramchol, a stearoyl-CoA desaturase (SCD-1) inhibitor, also showed promise in resolving NASH and dialing back fibrosis in a Phase II trial. Called ARREST, it included 247 people with NASH, 60% of whom had F2 or F3 fibrosis.

"There exists a critical need to develop effective pharmacotherapy against fibrosis given the magnitude of its clinical implications," the review authors concluded.

"Since the pathogenesis of NASH is complex and involves multiple pathways, a combination of pharmacological agents may be required to tackle the problem rather than a single agent," they continued. "Early results from some Phase II and Phase III trials are encouraging, and we believe that therapeutic agents which can halt or improve fibrosis may be available in the near future."

Editor's note: In a previous version, this article misstated the companies behind cenicriviroc's development. Allergan is the company developing the drug, not Takeda and Tobira Therapeutics as previously stated.
