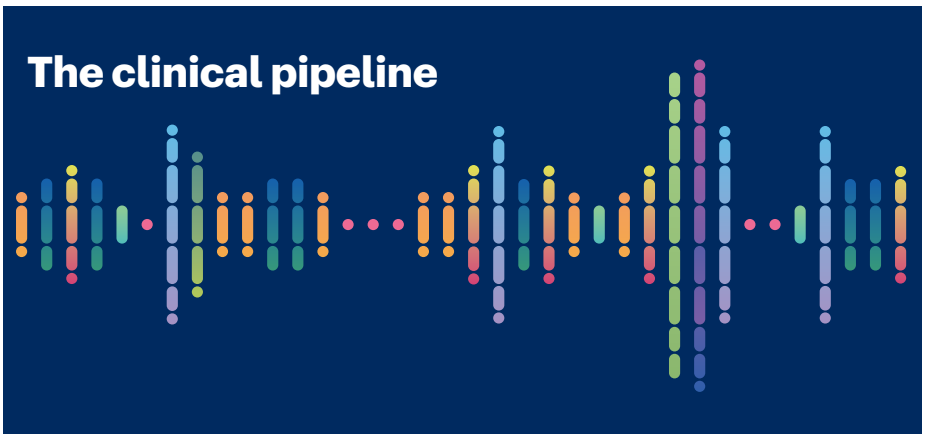
Efruxifermin combined with a GLP-1 receptor agonist reduces liver fat in NASH

Nature Medicine **explores the latest translational and clinical research news, with results from a small expansion cohort of the phase 2b SYMMETRY trial in patients with type 2 diabetes and non-alcoholic steatohepatitis.**



By Thiago Carvalho

Akero Therapeutics has released topline results from a small expansion cohort of the phase 2b SYMMETRY trial of efruxifermin (formerly AKR-001) for nonalcoholic steatohepatitis (NASH). The cohort tested the effects of combining efruxifermin, an agonist for fibroblast growth factor 21 (FGF21), with an agonist for the receptor for glucagon-like peptide-1 (GLP-1) in patients with biopsy-confirmed NASH and type 2 diabetes. The combination therapy showed an acceptable safety profile, with diarrhea, nausea and increased appetite as the most common side effects. Patients who received both efruxifermin and the GLP-1 receptor agonist showed a 65% reduction in liver fat at 12 weeks, compared with a 10% reduction for those treated with the GLP-1 receptor agonist alone.

FGF21 was cloned in 2000 and was considered a promising candidate for the treatment of a range of metabolic disorders. Preclinical work on FGF21 showed that it is an efficient hormonal regulator of sugar and lipid metabolism that can counteract various forms of metabolic syndrome in animal models. Unfortunately, the native FGF21 molecule has a very short half-life, which makes it a poor drug candidate. Amgen designed a much more stable FGF21–immunoglobulin Fc fusion molecule, which was licensed by Akero in 2018 and designated AKR-001.

NASH is the progressive form of nonalcoholic fatty liver disease (NAFLD), which is associated with obesity and diabetes. The World Health Organization estimates that 650 million people are obese. As much as one quarter of all adults worldwide may be suffering from NAFLD. The early, asymptomatic form of NAFLD is characterized by steatosis — excessive fat accumulation in the liver. Over time, the excess fat can perturb hepatocyte homeostasis, causing dysfunction, cell death and inflammation (hepatitis). Patients with NASH are at increased risk for cirrhosis, liver failure and hepatocellular carcinoma — the disease is the second leading indication for liver transplantation in the United States and is growing at a fast clip.

There are no drugs approved specifically for NASH, despite years of effort. Current disease management focuses on weight reduction, which is linked to clinical improvement. The obesity epidemic and concomitant rises in diseases associated with metabolic syndrome mean that NAFLD-related deaths are set to rise by almost 180% by the end of the decade.

Clinical trials for NASH are complicated by the need for histopathological scoring of liver biopsy samples, which are used to diagnose patients and to measure changes in fibrosis, hepatocyte ballooning and inflammation after treatment. Noninvasive liver function tests and imaging can be used to measure efficacy only up to the early phase 2 stage.

GLP-1 receptor agonists, such as Novo Nordisk's semaglutide, are treatments for diabetes that are now known to help patients achieve impressive and sustained weight reduction. However, as single treatments for NASH, they have so far not shown much promise, failing to improve fibrosis in at least two clinical trials.

Akero released positive results on fibrosis in efruxifermin-treated patients with NASH in mid-2020, but the number of patients in the trial was small. The study was conducted during a peak in COVID-19 pandemic restrictions, and the stringent requirements for biopsy samples made the trial design particularly susceptible to disruption. Because efruxifermin is not a native polypeptide, one concern is its immunogenicity. In one study, 41 of 57 subjects developed antibodies to the drug, albeit at low titers, but both fibrosis and weight were reduced. Efruxifermin received fast-track status from the US Food and Drug Administration in 2021 and breakthrough designation the following year.

The GLP-1 receptor and FGF21 pathways have complementary effects on insulin physiology — the former increases insulin production and the latter augments insulin sensitivity. Preliminary work in mice indicates that GLP-1 receptor agonists may cause weight loss by inducing FGF21. A phase 1 trial of efruxifermin in 2020 showed that the drug was safe in patients with type 2 diabetes and was associated with improvements in insulin sensitivity and lipid metabolism.

Patients with NASH are ensnared in a web of comorbidities, which include cardiovascular disease (promising candidate drugs for the treatment of NASH have struggled in the past because they increased levels of low-density lipoprotein in patients, for example) and, of course, type 2 diabetes; NASH promotes the development of type 2 diabetes, and vice versa. The data recently released by Akero on efruxifermin plus GLP-1 receptor agonist combination therapy do not include any histological assessment of liver fibrosis or inflammation, but the safety signals in this small phase 2 expansion cohort are encouraging.

Thiago Carvalho
Lisbon, Portugal.