Potential Novel Therapies for NASH

Nonalcoholic fatty liver disease (NAFLD) is a general term for a range of conditions characterised by extra fat in the liver that is not caused by alcohol consumption. NAFLD is the fastest growing cause of liver disease worldwide. It is estimated that the prevalence of NAFLD in Europe is 26.9% to 30.9% with a higher prevalence in men than women.

There are two different types of NAFLD; simple fatty liver and nonalcoholic steatohepatitis (NASH). Simple fatty liver is sometimes referred to as nonalcoholic fatty liver (NAFL) and has little or no inflammation of the liver or damage to liver cells and typically does not progress to cause liver damage. NASH is the most severe form of NAFLD and it tends to develop in individuals who are overweight, have diabetes, high cholesterol, or high triglycerides. It typically occurs between 40 and 60 years of age. NASH causes the liver to swell and become damaged. This inflammation and liver damage can cause fibrosis of the liver and may lead to cirrhosis and potentially lead to liver cancer. NASH is becoming an increasing cause of liver transplantation.

The accepted "gold standard" for diagnosis of cirrhosis is liver biopsy. Measurement of the amount of fibrosis is called staging. There are five stages (F0: no scarring (no fibrosis); F1: minimal scarring; F2: scarring has occurred and extends outside the liver area (significant fibrosis); F3: fibrosis spreading and forming bridges with other fibrotic liver areas (severe fibrosis); F4: cirrhosis or advanced scarring). The exact prevalence of NASH remains unclear due to its diagnosis relying on histological examination. Estimates suggest NASH affects anywhere between 1.5% to 6.45% of the general population.

The traditional treatment approach has been weight loss and physical activity. Weight loss can reduce fat, inflammation and fibrosis in the liver. It is generally recommended to gradually lose weight to improve NAFLD. Rapid weight loss and malnutrition may make liver disease worse. Currently, there are no approved drug therapies for NAFLD—either NAFL or NASH - although a number of drugs are in the development stages.

Resmetirom may become the first approved therapy for the treatment of NASH. Resmetirom, from Madrigal Pharmaceuticals, is an oral thyroid hormone receptor-beta agonist that acts by decreasing liver fat and reducing lipotoxicity. In December 2022, Madrigal announced topline results of their Phase 3 trial, MAESTRO-NASH, for the treatment of NASH with liver fibrosis. In this on-going trial, 966 patients with liver biopsy-confirmed NASH were randomised to two different doses of oral resmetirom or placebo. The baseline liver biopsy fibrosis scores were approximately 60% F3, 35% F2 and 5% F1B. The primary efficacy analysis assessed histological response by a second liver biopsy after 52 weeks of treatment through two primary endpoints (NASH resolution with a ≥ 2-point reduction in nonalcoholic fatty liver disease activity score [NAS] and no worsening of fibrosis and ≥ 1 stage improvement in fibrosis with no worsening of NAS).

In the analysis, the primary endpoint of NASH resolution with ≥2-point reduction in NAS and no worsening of fibrosis was achieved by 26%, 30%, and 10% of patients taking 80 mg resmetirom, 100 mg resmetirom, and placebo respectively. The second primary endpoint, a ≥1-point decrease in fibrosis with no worsening of NAS, was achieved in 24%, 26%, and 14% of patients taking 80 mg resmetirom, 100 mg resmetirom, and placebo respectively. Low-density lipoprotein cholesterol (LDL-C) levels at 24 weeks, a secondary outcome measure, were reduced by 12% and 16% for 80 mg and 100 mg resmetirom, respectively, and increased by 1% in the placebo arm. Madrigal also reported that multiple other secondary endpoints were achieved including a statistically significant reduction from baseline in liver enzymes (ALT, AST and GCT),

as well as reductions in atherogenic lipids and lipoproteins, and fibrosis biomarkers in the resmetirom treatment arms as compared to placebo.

Resmetirom was safe and well-tolerated in the trial, showing similarly low rates of serious adverse events to placebo. The rates of study discontinuation were higher in the 100mg resmetirom treatment group as compared to the 80mg and placebo arms (7.7% as compared to 2.8% and 3.7%, respectively). All patients enrolled in MAESTRO-NASH are continuing treatment after the initial 52-week period for up to 54 months to evaluate additional outcomes, including progression to cirrhosis on biopsy, hepatic decompensation events, and all-cause mortality.

There are three additional Phase 3 trials ongoing (MAESTRO-NAFLD-1, MAESTRO-NAFLD-OLD and MAESTRO-NASH-OUTCOMES) to further demonstrate the safety and efficacy of resmetirom for the treatment of NASH. The MAESTRO-NAFLD-1 study does not include a liver biopsy and may more closely resemble clinical practice diagnosis of NASH by non-invasive techniques and adding additional NASH biomarker endpoints. In initial reported results in October 2023, resmetirom showed reductions of over 40% in a measure of liver fat. MAESTRO-NASH-OUTCOMES is focused on early NASH cirrhosis to allow for non-invasive monitoring of progression to liver decomposition events and if this 700-patient study shows positive outcomes, may support the use in well-compensated NASH cirrhosis (F4).

There are a large number of other products in the pipeline for NASH, although only four assets are currently in phase 3 of development. It appears that the potential next products that would likely be approved for NASH would be in 2025. One interesting potential upcoming product is semaglutide. Semaglutide is a glucagon-like peptide-1 (GLP-1) agonist that is currently approved for use in diabetes (Ozempic®, Rybelsus®) and weight loss (Wegovy®). Phase 2 results in patients with stage 4 compensated cirrhosis demonstrated improvements in NASH resolution and triglyceride reduction, along with weight reduction and improvements in A1c in diabetic patients. Other ongoing trials include patients with F2 and F3 NASH as monotherapy and combination therapy with empaglifozin for patients with NASH and type 2 diabetes. Other potential therapies that could be approved in 2025 include azemiglitazone, a thiazolidinedione-like molecule, being studied in pre-type or type 2 diabetes, and belapectin, an IV galectin inhibitor, being studied for NASH cirrhosis.

Given the different mechanisms of action of the upcoming products, combination therapy may be a consideration for physicians in treating this disease and will add to the treatment paradigm and costs. Efficacy has been modest in the available clinical trials and with biopsy being an inclusion criterion, may limit the use until publication of clinical trial results or acceptance by the medical community of non-invasive diagnostic criteria as a surrogate measure.

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