Editorial Commentary

Tropifexor, a selective non-acid farnesoid X receptor agonist, improved nonalcoholic steatohepatitis in a phase 2 trial, but several issues remain to be resolved

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As obesity continues to escalate worldwide, nonalcoholic fatty liver disease (NAFLD) has emerged as the most prevalent form of liver disease, with a reported global prevalence of 30.1% (1). The prevalence of NAFLD, which was around 25% in the 1990s, has been increasing year by year in recent years and has exceeded 35% in the past few years (1). The spectrum of disease includes nonalcoholic fatty liver (NAFL), characterized by macrovesicular hepatic steatosis that may be accompanied by mild inflammation, and nonalcoholic steatohepatitis (NASH), which is additionally characterized by the presence of inflammation and cellular injury (2). NASH is rapidly becoming the leading cause of end-stage liver disorders and liver transplants and is associated with increased cardiovascular disease (CVD) risk (3). As a result, it poses critical health issues globally from both medical and socioeconomic perspectives. In recent years, when NASH is diagnosed on liver biopsy, and the fibrosis stage is ≤2, it is defined as "at-risk NASH" and requires aggressive therapeutic intervention (2).

Lifestyle interventions, including caloric restrictions and exercise, are essential in the treatment of NAFLD/NASH (2,4). Weight changes have the greatest impact on the activity of NASH. A weight loss of 7% is required for generalized NASH with obesity and 3–5% for lean NAFLD (4-6). It is important to note, however, that achieving the target weight loss goal is challenging, and studies have reported that only around 20% of patients successfully reached the 7% target for improvement of NASH (5). Therefore, achieving and sustaining lifestyle improvements can indeed be challenging, highlighting the critical need for pharmacotherapy for the treatment of NAFLD/NASH (2,4). However, it is worth noting that currently, neither the European Medicines Agency nor the United States Food and Drug Administration (FDA) has approved any pharmacotherapy specifically for the treatment of NAFLD and NASH.

Tropifexor is a selective non-acid farnesoid X receptor (FXR) agonist, along with obeticholic acid (OCA), cilofexor, nidufexor, and EDO-305. These compounds play a role

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in regulating the transcription of various genes in the liver and intestines, which helps maintain cholesterol/bile acid balance, decrease hepatic gluconeogenesis, and alleviate inflammation (7-10).

In a phase 2, multicenter, double-blind, randomized, placebo-controlled trial with a three-part adaptive design (part A, B, and C), patients diagnosed with NASH and fibrosis stage 2 and 3 (so-called "at-risk NASH") were randomized 1:1:1:1:1 to receive placebos (n=16), tropifexor 10 mg (n=14), 30 mg (n=16), 60 mg (n=16), or 90 mg (n=15) for 12 weeks in part A (total 77 patients), and 5:4:15 to receive placebos (n=30), tropifexor 60 mg (n=21), or 90 mg (n=70) for 12 weeks in part B (total 121 patients). And in part C, a total of 152 patients were randomly assigned in a 1:1:1 ratio to receive either placebos (n=51), tropifexor at a dose of 140 mg (n=50), or 200 mg (n=51) for a duration of 48 weeks (11).

The primary endpoints were changes in aspartate aminotransferase (AST), alanine aminotransferase (ALT), and hepatic fat fraction (HFF) levels assessed using magnetic resonance imaging-proton density fat fraction (MRI-PDFF), the most reliable method for quantifying hepatic steatosis (2,4). The high-dose tropifexor groups (140 and 200 mg) showed a substantial reduction in ALT levels compared to the placebo group, which persisted until week 48 (tropifexor 140 µg: –31.6 U/L; 200 µg: –32.5 U/L; placebo: –8.4 U/L). The mean decrease from baseline in AST levels was not significant for tropifexor compared to the placebo. Relative change in HFF% showed a greater change of –7.48% to –15.04% in the tropifexor 10–90 µg 12 weeks group compared to the placebo group (–6.19%) in part A/B. In part C, the relative change in HFF% of the tropifexor 140 and 200 µg groups at 48 weeks was –31.25% and –39.54%, statistically significant compared to the placebo group (–3.58%) (11).

Due to their ability to modulate bile acid homeostasis, and lipid metabolism and exhibit anti-inflammatory properties, FXR agonists such as tropifexor are currently being investigated in clinical trials for the treatment of NASH (7-12). OCA was the first FDA-approved FXR agonist and was also the first drug to be considered an investigational drug for NASH. The "regenerate study" is currently ongoing as a phase 3 trial for OCA, with an interim analysis of 931 patients in liver fibrosis stages F2–F3 (there were 311 participants in the placebo group, 312 participants in the OCA 10 mg group, and 308 participants in the OCA 25 mg group) reported in 2019 (12). The fibrosis improvement endpoint was achieved in 55 patients in the OCA 10 mg group (18%, P=0.045 *vs.* placebo) and 71 patients in the OCA 25 mg group (23%, P=0.0002 *vs.* placebo), compared to 37 patients in the placebo group (12%). The NASH remission endpoint was achieved in 25 (8%), 35 (11%, P=0.18 *vs.* placebo), and 36 (12%, P=0.13 *vs.* placebo) patients in the placebo, OCA 10 mg, and OCA 25 mg groups, respectively. The preliminary results of a phase 3 trial for OCA indicate consistent positive clinical outcomes in terms of reducing hepatic fibrosis. However, OCA use was associated with side effects such as an increased rate of pruritus and dyslipidemia. The results showed that compared to the placebo group, there was an increase in low-density lipoprotein cholesterol (LDL-C) levels and a decrease in high-density lipoprotein cholesterol (HDL-C) levels. Consequently, in 2020, the FDA evaluated OCA and determined that the predicted benefits of the drug, based on a surrogate histopathologic endpoint, were uncertain. They concluded that the potential risks associated with the medication outweighed its benefits, leading to the decision not to grant accelerated approval for the indication of liver fibrosis due to NASH.

In this tropifexor study by Sanyal, the frequency of pruritus increased in a dose-dependent manner, with 52% of patients receiving 140 µg of tropifexor and 69% receiving 200 µg of tropifexor. The frequency of grade 2 or more severe pruritus also increased at higher doses. The pathogenesis of pruritus is even more cryptic. Recent studies have shown a correlation between interleukin (IL)-31 levels and pruritus in patients with cholestatic disease and NASH. Interestingly, treatment with FXR agonists has been found to increase serum levels of IL-31 in patients with NASH (13). These findings have important therapeutic implications for individuals suffering from liver disease and pruritus, suggesting that targeting the FXR pathway may provide relief from itching.

Increases in LDL-C and decreases in HDL-C levels were also seen as side effects of tropifexor, as well as other FXR agonists (11). LDL-C levels were –4.52, +8.8, and +26.96 mg/dL at 48 weeks in the placebo, tropifexor 140 µg, and 200 µg groups, respectively. The HDL level changes at week 48 were +1.08 mg/dL in the placebo group, –8.55 mg/dL in the 140 µg tropifexor group, and –9.88 mg/dL in the 200 µg group.

CVD has been identified as a leading cause of mortality among patients with (NAFLD) (3). In addition, the accumulation of fat in the liver has been independently associated with the presence of coronary plaques, particularly non-calcified plaques, while both hepatic

steatosis and fibrosis have been significantly linked to diastolic cardiac dysfunction. Numerous studies conducted over the past decade have suggested important associations between NAFLD and CVD outcomes (14,15). However, the relationship between NAFLD and CVD is more intricate than initially understood, and the specific mechanisms linking NAFLD to the development of CVDs remain unclear. Further research is needed to fully elucidate the complex interplay between NAFLD and CVD and understand how NAFLD contributes to the pathogenesis of cardiovascular complications (14,15). There were no discontinuations due to dyslipidemia caused by tropifexor or deaths in this study (11). However, given the mechanism of development of atherosclerotic disease states, the long-term safety of tropifexor must be evaluated.

Many clinical trials on NASH have failed to meet their primary endpoints. In addition, although FXR agonists have shown useful effects, some problems cannot be overlooked. Due to the complexity of NASH, which involves multiple factors, targeting a single factor may not be adequate to achieve therapeutic efficacy. Alongside abnormalities in glucose and lipid metabolism, NASH is influenced by various factors, such as alterations in the gut microbiota, immune system abnormalities, and genetic predispositions. In the case of FXR agonists, side effects such as concomitant use of LDL-lowering agents may also have to be addressed at the same time. The specific weight of each factor varies among individuals. Therefore, in the future, tailor-made therapies should be established, and appropriate medications should be selected for each patient.

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Footnote

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