Editorial

Pan-peroxisome proliferator-activated receptor agonist lanifibranor as a dominant candidate pharmacological therapy for nonalcoholic fatty liver disease

Masato Yoneda, Takashi Kobayashi, Nogami Asako, Michihiro Iwaki, Satoru Saito, Atsushi Nakajima

Department of Gastroenterology and Hepatology, Yokohama City University Hospital, Kanazawa-ku, Yokohama, Japan

Correspondence to: Masato Yoneda, MD, PhD. Department of Gastroenterology and Hepatology, Yokohama City University Hospital, 3-9 Fuku-ura, Kanazawa-ku, Yokohama, Japan. Email: yoneda-ycu@umin.ac.jp.

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As obesity incidence increases worldwide, nonalcoholic fatty liver disease (NAFLD) has become the most common form of liver disease, with a reported global prevalence of 25.2% (1). Nonalcoholic steatohepatitis (NASH) is a severe form of NAFLD. However, the precise natural history of NAFLD/NASH remains unclear. NASH is rapidly becoming the leading cause of end-stage liver disorders and liver transplants and is associated with increased cardiovascular disease risk (2). As a result, it poses critical health issues globally from both medical and socioeconomic perspectives.

Lifestyle interventions such as caloric restriction and exercise therapy play a central role in the treatment of NAFLD/NASH. However, lifestyle improvements can be difficult to achieve and maintain, which emphasizes the dire need for pharmacotherapy. Yet, to date, no pharmacotherapy has been approved by the European Medicines Agency or the United States Food and Drug Administration for NAFLD and NASH (3-5). Lanifibranor is a pan-peroxisome proliferator-activated receptor (PPAR) agonist that modulates key metabolic, inflammatory, and hepatic fibrotic pathways in the pathogenesis of NASH (6). In a phase 2b, double-blind, randomized, placebo-controlled trial, patients with active NASH without cirrhosis were randomized 1:1:1 to receive lanifibranor 1,200 mg/day or lanifibranor 800 mg/day or placebo for 24 weeks (7). Of the 247 randomized patients, 103 (42%) had type 2 diabetes mellitus. The proportion of patients with a decrease in the steatosis, activity, and fibrosis (SAF)-A score (the activity part of the SAF scoring system that incorporates scores for ballooning and inflammation) of at least 2 points without the development of hepatic fibrosis was significantly higher in patients who received 1,200 mg lanifibranor than in those who received placebo (55% *vs.* 33% for placebo, P=0.007). Secondary endpoints such as NASH resolution without progression of hepatic fibrosis and improvement of at least one stage of hepatic fibrosis without progression of NASH were favorable in the lanifibranor groups compared with the placebo group. The use of PPARs in the treatment of NASH is one of the most evidence-based treatments. Pioglitazone, a PPARγ agonist, is an anti-diabetic medicine recommended in the treatment guidelines for NASH (3-5) and is thought to improve NAFLD by reducing hypertrophic adipocyte size, improving insulin resistance, and inducing adiponectin expression. Pioglitazone significantly improved serum liver enzymes, histological hepatic steatosis, hepatocyte ballooning, and hepatic inflammation in a large randomized controlled trial of 24 weeks of treatment (8). In a long-term observation of 3 years, histological improvement of NASH was maintained in 58% of patients and disappearance of NASH was achieved in 51% of patients (9).

Another PPAR expected to have a therapeutic effect in the treatment of NASH is PPARα, which is used to treat hypertriglyceridemia (10). Pemafibrate, a selective PPARα modulator, is expected to have a strong and highly selective effect on PPARα transcriptional activation, resulting in fewer adverse events. In a double-blind, placebo-controlled,

randomized multicenter phase 2 trial, serum alanine aminotransferase and low-density-lipoprotein cholesterol levels and liver hardness measured by magnetic resonance elastography were lower in the pemafibrate group than in the placebo group. Adverse events were similar to those observed in the placebo group, and the treatment was well tolerated (11).

Elafibranor, a PPAR α/δ agonist, improved the NAFLD activity score in a phase IIb study of 276 patients with NASH (12). Based on these results, a phase III trial (RESOLVE-IT) was conducted in 2,000 patients with F2-F3 NASH. In an interim analysis at 72 weeks, the primary endpoint of "improvement of NASH without worsening of fibrosis" was not demonstrated in this study (13).

While a number of clinical trials in NASH have failed to achieve the primary endpoint (14), lanifibranor achieved the primary and secondary endpoints because it simultaneously improved multiple mechanisms, including adipogenesis, inflammation, and fibrosis. Because NASH is a complex condition involving many factors, a single target may not be sufficient to achieve therapeutic effects. In addition to abnormalities in glucose and lipid metabolism, NASH is a disease in which multiple factors contribute, including changes in intestinal bacterial flora, immune dysregulation, and genetic predisposition. The weight of each factor may vary among individuals. Therefore, in the future, tailored medicines should be established, and the appropriate drug should be selected for each patient.

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References

1. Younossi ZM, Koenig AB, Abdelatif D, et al. Global epidemiology of nonalcoholic fatty liver disease-Meta-analytic assessment of prevalence, incidence, and outcomes. Hepatology 2016;64:73-84.
2. Yoneda M, Yamamoto T, Honda Y, et al. Risk of cardiovascular disease in patients with fatty liver disease as defined from the metabolic dysfunction associated fatty liver disease or nonalcoholic fatty liver disease point of view: a retrospective nationwide claims database study in Japan. J Gastroenterol 2021;56:1022-32.
3. Chalasani N, Younossi Z, Lavine JE, et al. The diagnosis and management of nonalcoholic fatty liver disease: Practice guidance from the American Association for the Study of Liver Diseases. Hepatology 2018;67:328-57.
4. European Association for the Study of the Liver (EASL); European Association for the Study of Diabetes (EASD); European Association for the Study of Obesity (EASO). EASL-EASD-EASO Clinical Practice Guidelines for the management of non-alcoholic fatty liver disease. J Hepatol 2016;64:1388-402.
5. Tokushige K, Ikejima K, Ono M, et al. Evidence-based clinical practice guidelines for nonalcoholic fatty liver disease/nonalcoholic steatohepatitis 2020. J Gastroenterol 2021;56:951-63.
6. Lefere S, Puengel T, Hundertmark J, et al. Differential effects of selective- and pan-PPAR agonists on experimental steatohepatitis and hepatic macrophages ☆. J Hepatol 2020;73:757-70.
7. Francque SM, Bedossa P, Ratziu V, et al. A Randomized, Controlled Trial of the Pan-PPAR Agonist Lanifibranor in NASH. N Engl J Med 2021;385:1547-58.
8. Belfort R, Harrison SA, Brown K, et al. A placebo-controlled trial of pioglitazone in subjects with nonalcoholic steatohepatitis. N Engl J Med 2006;355:2297-307.
9. Cusi K, Orsak B, Bril F, et al. Long-Term Pioglitazone

Treatment for Patients With Nonalcoholic Steatohepatitis and Prediabetes or Type 2 Diabetes Mellitus: A Randomized Trial. Ann Intern Med 2016;165:305-15.
10. Honda Y, Kessoku T, Ogawa Y, et al. Pemafibrate, a novel selective peroxisome proliferator-activated receptor alpha modulator, improves the pathogenesis in a rodent model of nonalcoholic steatohepatitis. Sci Rep 2017;7:42477.
11. Nakajima A, Eguchi Y, Yoneda M, et al. Randomised clinical trial: Pemafibrate, a novel selective peroxisome proliferator-activated receptor α modulator (SPPARMα), versus placebo in patients with non-alcoholic fatty liver disease. Aliment Pharmacol Ther 2021;54:1263-77.
12. Ratziu V, Harrison SA, Francque S, et al. Elafibranor, an Agonist of the Peroxisome Proliferator-Activated Receptor-α and -δ, Induces Resolution of Nonalcoholic Steatohepatitis Without Fibrosis Worsening. Gastroenterology 2016;150:1147-1159.e5.
13. Harrison SA, Ratziu V, Bedossa P, et al. RESOLVE-IT phase 3 trial of elafibranor in NASH: final results of the week 72 interim surrogate efficacy analysis. Hepatology 2020;72:LP23.
14. Ratziu V, Friedman SL. Why do so many NASH trials fail? Gastroenterology 2020. [Epub ahead of print]. doi: 10.1053/j.gastro.2020.05.046.

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