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Hot Topic Commentary

THR-β Agonist for Nonalcoholic Steatohepatitis Treatment: Challenges of a Promising Drug

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Introduction

The incidence of nonalcoholic steatohepatitis (NASH) is increasing. Resmetirom, a thyroid hormone receptor β (THR-β) agonist, has demonstrated a good safety profile in published phase 2 and phase 3 studies, meeting the U.S. Food and Drug Administration (FDA)-required histological endpoint for efficacy. Consequently, on March 14, 2024, resmetirom became the first drug to receive FDA approval for the treatment of NASH patients with fibrosis, marking a significant milestone in the field of hepatology. However, there are still some challenges in the clinical application of resmetirom.

NASH: a huge unmet treatment need

Nonalcoholic fatty liver disease (NAFLD), now termed metabolic dysfunction-associated steatotic liver disease, is the most common cause of liver disease, with a global prevalence of up to 29.8%.[1] NAFLD ranges from simple steatosis to NASH, which is associated with an increased risk of cirrhosis, end-stage liver failure, and hepatocellular carcinoma. NAFLD is also associated with higher all-cause mortality, cardiovascular disease, and extrahepatic malignancies.[2]

Lifestyle intervention is the foundation of NAFLD/NASH therapy. A weight loss of 5% improves steatosis, but improving NASH and fibrosis usually requires a weight loss of more than 10%. Achieving and sustaining weight loss is a daunting challenge.[3] The American Association for the Study of Liver Diseases practice guidance states that semaglutide, pioglitazone, and vitamin E can be considered for specific NASH populations, but these drugs still lack anti-fibrotic effects. There is currently a significant unmet treatment need for NASH.

THR-β agonist: A new potential

The expression of the two thyroid hormone receptor (THR) subtypes differs, with THR-α being mainly expressed in the heart, skeletal muscles, and brain, while THR-β is the main subtype in the liver.[4] Resmetirom is an oral, liver-directed, THR-β agonist that exhibits approximately 28-fold selectivity for THR-β compared to THR-α.[5] This allows for targeted modulation of thyroid hormone action in the liver, potentially providing metabolic benefits while minimizing systemic side effects commonly associated with excess thyroid hormone activity in other tissues, such as the heart and bone. One of the mechanisms of action of resmetirom is the increased expression of carnitine palmitoyl-transferase 1, which in turn increases mitochondrial fatty acid oxidation, beta-oxidation, and mitochondrial biogenesis (Fig. 1a).[6] To date, three peer-reviewed randomized controlled trials have assessed the safety and effectiveness of resmetirom in NAFLD/NASH, including one phase 2 clinical trial and two phase 3 clinical trials.[7–9] In the phase 2 study, after 12 weeks of treatment, the reduction in liver fat content was significantly greater in the resmetirom treatment group compared to the placebo group (−32.9% vs −10.4%). After 36 weeks of treatment, the rate of NASH resolution in the resmetirom group and the placebo group were 24.7% and 6.5%, respectively, while the fibrosis response rates were 28.8% and 23.5%, respectively.[7] The MAESTRO-NAFLD-1 study showed that resmetirom was safe and well-tolerated at 52 weeks in NAFLD and presumed NASH populations.[8] The results of a 52-week biopsy show that MAESTRO-NASH is the first phase 3 clinical trial to meet two primary endpoints proposed by the FDA in patients with NASH. The rate of NASH resolution with no worsening of fibrosis was 25.9% to 29.9% in the resmetirom treatment group and 9.7% in the placebo group, and the rate of fibrosis improvement by at least one stage with no worsening of the NAFLD activity score was 24.2–25.9% and 14.2%, respectively.[9] On March 14, 2024, the FDA approved resmetirom for the treatment of patients with NASH with fibrosis.[10]

Challenges of THR-β agonist in clinical practice

Despite its favorable safety, tolerability, and efficacy in clinical trials, the practical implementation of resmetirom in clinical settings remains challenging (Fig. 1b).

Firstly, accurate non-invasive testing of NASH and evaluation of treatment effectiveness are urgently needed. The FDA and the drug label indicate that resmetirom is indicated for NASH with stage 2–3 fibrosis but do not specify whether a liver biopsy is required. It is unclear whether liver biopsy assessments are necessary before prescribing and to moni-

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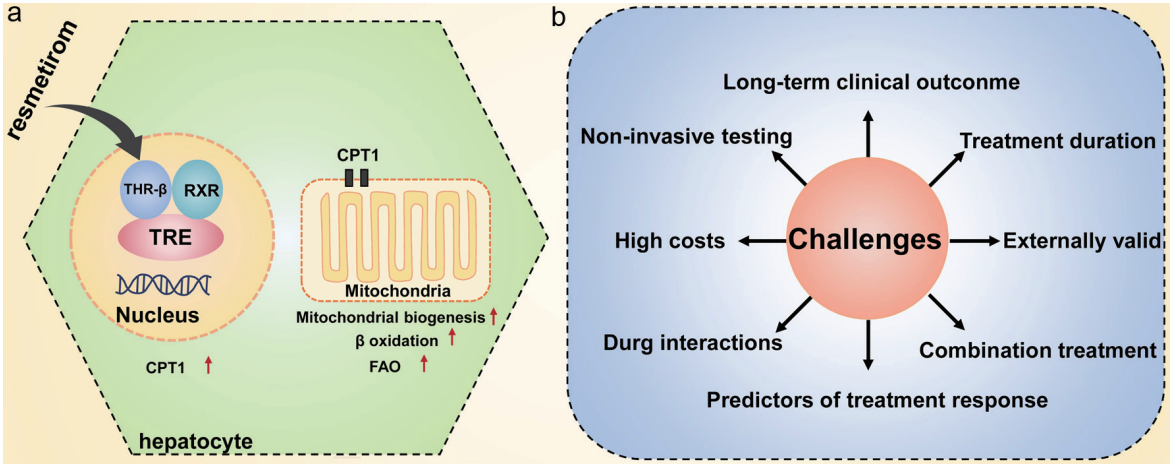

Fig. 1. Resmetirom's mechanisms in regulating hepatic lipid metabolism (a) and clinical challenges (b). RXR, retinoid X receptor; TRE, tetracycline-responsive element; THR-β, thyroid hormone receptor β; CPT1, carnitine palmitoyltransferase I; FAO, fatty acid oxidation; FFA, free fatty acid; LDL, low-density lipoprotein; LDL-R, low-density lipoprotein receptor.

tor the therapeutic response in clinical practice. Liver biopsy has limitations. The consistency of MRI-proton-density-fat-fraction (MRI-PDFF), which is non-invasive, precise, quantitative, and repeatable, with histopathological analysis has been evaluated across several clinical trials. A reduction of 30% in hepatic fat, as measured by MRI-PDFF, seemed to correlate with biopsy outcomes.[7,9] In addition, vibration-controlled transient elastography-based scores are highly accurate in predicting liver-related events in patients with metabolic dysfunction-associated steatotic liver disease.[11] The use of MRI-PDFF and vibration-controlled transient elastography as valid evaluation criteria in clinical practice needs to be assessed in larger clinical trials.

Secondly, the duration of treatment is indeterminate. The current 52-week histological endpoints were used to assess the efficacy of resmetirom in clinical trials. Neither the FDA nor the drug label provides specific recommendations regarding the duration of treatment. In clinical practice, is the treatment duration also 52 weeks? It is noteworthy that the histological response rate is approximately 30% after 52 weeks of therapy. However, it remains uncertain whether a longer duration of treatment would increase the histological response rate. Additionally, close monitoring of endocrine disorders associated with the thyroid, gonads, or bones is required, although 52 weeks of treatment was deemed safe in the phase 3 study.

Thirdly, predictors of treatment response at baseline are lacking. Whether patients with NASH with hypercholesterolemia respond well to resmetirom treatment remains unclear, given that the histological response rate was less than one-third in the MAESTRO-NASH trial.[9] Thyroid hormones play an important role in lipid metabolism. In a phase 2 study, resmetirom significantly improved blood lipid indicators such as LDL-C, triglycerides, lipoprotein (a), and apolipoprotein B.[7] 12 weeks of resmetirom treatment significantly reduced LDL-C, triglycerides, apolipoprotein B, and lipoprotein(a) levels in patients with heterozygous familial hypercholesterolemia.[12] After 12 weeks of resmetirom treatment, liver fat content decreased by 32.9%. In contrast, the liver fat content reduction in the three dose groups of VK2809 exceeded 50% in individuals with NAFLD and hypercholesterolemia.[13] Whether the efficacy of THR-β agonists is more significant in NAFLD/NASH patients with hypercholesterolemia remains to be further explored. Additionally, resmetirom may reduce long-term cardiovascular outcomes in patients with NAFLD/NASH through the dual effect of lowering LDL-C and improving NASH, potentially benefiting NAFLD/NASH patients with hypercholesterolemia.

Fourth, the histological endpoint is a surrogate endpoint, and the effectiveness of resmetirom on long-term clinical outcomes in hepatic and cardiovascular events is undefined. The progression of NASH is typically a chronic process spanning multiple years. The currently published data for resmetirom covers 52 weeks of safety and efficacy, evaluating treatment effects through histopathological assessment. The MAESTRO-NASH study (ClinicalTrials.gov ID: NCT03900429) with a 54-month long-term follow-up will provide evidence for the long-term efficacy of resmetirom.

Fifth, the observed therapeutic effects and safety may not be externally valid. Published studies show that about 90% of the subjects in the resmetirom treatment group are Caucasian, and more evidence is needed for the safety and efficacy of this drug in other ethnic populations. Significant differences in lifestyle habits among different races and regions lead to disparities in liver and mortality outcomes related to NAFLD. Several other THR-β agonists are in phase 2/3 clinical trials. The THR-β agonists ASC41 (ClinicalTrials.gov ID: NCT05118360) and HSK31679 (ClinicalTrials.gov ID: NCT06168383) are currently undergoing phase 2 clinical trials, which will provide safety and efficacy data for THR-β agonists in the Asian population.

Sixth, drug-drug interactions deserve attention. A significant proportion of patients with NAFLD/NASH suffer from comorbidities such as hypertension, hyperlipidemia, type 2 diabetes mellitus, and obesity.[3] These patients often require medications to manage their blood pressure, lipid levels, blood glucose, and body weight. Close monitoring of the interactions between these drugs and resmetirom is crucial, especially when considering the combined use of lipid-lowering agents like statins and ezetimibe with resmetirom and its impact on lipid profiles. Additionally, resmetirom is a CYP2C8 substrate, so more frequent monitoring is needed when used concomitantly with CYP2C8 inhibitors.

Seventh, high costs are a potential barrier to the use of resmetirom. Studies have shown that NAFLD treatment costs more than $12,000 a year, and even with favorable efficacy, it may not provide reasonable value.[14] According to online news sources, the annual wholesale price for resmetirom is

$47,874.[15] High drug prices may exacerbate NASH health inequities in different countries. Additionally, high costs raise challenges for potential combination therapy in the future. Therefore, cost-effectiveness needs to be evaluated in real-world studies and varied socioeconomic contexts. Obviously, the cost will go down when new agents for NASH are approved.

Eighth, combination treatment needs to be explored. The histological response rate of resmetirom monotherapy for NASH is less than one-third. Several potential drugs, such as GLP-1 receptor agonists, GLP-1/glucagon receptor co-agonists, FGF21 analogues, FGF19 analogues, and RNA interference, are undergoing clinical trials. Given the complex pathogenesis of NASH, the combination therapy of resmetirom and the above drugs is worth exploring.

Summary

In summary, the first FDA-approved drug for the treatment of NASH with moderate and advanced fibrosis has emerged. However, it still faces challenges in clinical practice, requiring more clinical trial results and real-world data in the coming years to provide evidence-based medical guidance.

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Conflict of interest

LW has been an Executive Associate Editor of *Journal of Clinical and Translational Hepatology* since 2013. FX has no conflict of interests related to this publication.

Author contributions

Conceptualization (LW, FX), writing-original draft preparation (FX), writing-review and editing (LW). All authors made significant contributions to the study and approved the final manuscript.

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