EDITORIAL

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Thyroid Hormone Receptor Beta (THRβ) Agonists in Metabolic Dysfunction-Associated Steatohepatitis (MASH): Bridging the Gap Between Promise and Practice

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Metabolic dysfunction-associated steatohepatitis (MASH), formerly known as non-alcoholic steatohepatitis (NASH) [1] is a growing health issue globally. MASH involves a wide range of liver conditions, from simple inflammation to cirrhosis and end-stage liver disease. The condition begins with excess fat buildup in the liver, overwhelming its capacity to metabolize it. This overload triggers a cascade of inflammation, causing injury to liver cells. In an attempt to repair this damage, the liver begins to form scar tissue, which is called fibrosis, that in advanced stages may develop into cirrhosis over the years [2].

Metabolic dysfunction-associated steatohepatitis is expected to become the leading indication for liver transplant in the US soon. The number of MASH cases in the US is expected to increase from 5.8 % to 7.9% by 2050 (from 14.9 million to 23.2 million) [3]. Meanwhile, in Asia, MASH cases are expected to increase from 20% to 35%, while associated hepatocellular carcinoma and decompensated cirrhosis cases are projected to increase at least by 65% before 2030. Additionally, MASH was reported to cause worse health-related quality of life and work productivity. This highlights the need for urgent intervention to decrease the global burden of the disease [4, 5].

Thyroid hormone receptor beta (THRβ) is a protein expressed in the liver that regulates fat metabolism, minimizing the risk of inflammation. Targeting these receptors has shown a role in decreasing hepatic fat and scarring. THRβ agonists stimulate the secretion of high-density lipoprotein (HDL), promote cholesterol conversion to bile acids, inhibit triglyceride synthesis, and increase fatty acid oxidation [6].

A turning point for the treatment of MASH was in March 2024 when the FDA approved resmetirom, providing hope where previously there was only lifestyle change. However, we must temper our excitement with reasonable expectations regarding the true implications of this achievement for clinical practice as we commemorate this milestone [7].

The dual benefit profile of THRβ agonists is what makes them so appealing. Since cardiovascular disease, not liver failure, continues to be the primary cause of mortality for MASH patients, these medications provide significant cardiovascular co-benefits through enhanced lipid metabolism in addition to treating hepatic steatosis and inflammation. Because of their metabolic flexibility, THRβ agonists have the potential to be revolutionary treatments that cure metabolic dysfunction's systemic basis rather than just its hepatic expression [8].

The MAESTRO-NASH results demonstrate that pharmacological intervention can significantly change the course of the disease, even though they are modest in absolute terms (30% MASH resolution vs. 10% placebo). More significantly, the concurrent improvement in fibrosis, which has historically been the hardest part of MASH to reverse, indicates that these medicines might provide true disease change instead just symptomatic relief [8].

Other candidates are VK-2809 and ALG-055009. Theoretically, VK2809's prodrug design surpasses Resmetirom's direct receptor binding strategy. Its CYP3A4-mediated cleavage for liver-specific activation may improve tissue selectivity while reducing systemic exposure, which is crucial for long-term safety. The efficacy signals are more convincing: up to 88% of patients achieve significant fat reduction (≥30%), nearly three times the MASH resolution rate of resmetirom [9].

This raises questions about the optimal approach to constructing THRβ agonists. Is the prodrug strategy used by VK2809 an example of better pharmaceutical engineering, or is it just the result of different trial populations and endpoints? Although the histological endpoints are still the gold standard, the extent of metabolic improvement with VK2809 raises the

possibility that the potency of THRβ agonists is increasing at a generational level.

The field greatly benefits from this competitive dynamic. While VK2809's development holds the possibility of improved efficacy, Resmetirom's approval offers immediate therapeutic utility. Instead of seeing these as rival strategies, we want to think of them as complementary instruments for various clinical situations - VK2809 for individuals who might need more intensive metabolic intervention, and Resmetirom for proven efficacy and safety profile.

There is no published full human article in ALG-055009. ALG-055009-301 is a poster presenting a multi-part, double-blind, randomized, placebo-controlled first-in-human study that demonstrated the administration of ≤1 mg ALG-055009 for 14 days was well tolerated. A generally dose-related decrease in LDL, triglycerides, and Apo-Lipoprotein B was noted, with the maximum reduction occurring on Day 14 [10].

Yet, as with any pioneering therapy, its journey ahead is fraught with challenges. As we have a wide range from MASH, from simple steatosis to advanced cirrhosis. Not all patients are likely to benefit equally; patients diagnosed with biopsy-proven MASH, particularly those with F2-F3 stages, are the prime candidates. However, precise diagnosis with biopsies may not be universally accessible. Thus, validated methods that can detect THRβ agonist responders with readily available diagnostic tools are desperately needed.

Additionally, patients with cardiovascular illness, who are more likely to require THRβ agonist medication in practice, were carefully excluded from clinical trials. How would these medications work in elderly people who have polypharmacy, diabetes, and coronary heart disease? We don't have any predictive biomarkers to help us set expectations, and the efficacy signals can turn out to be very different. Moreover, in clinical practice, trial adherence rates of greater than 90% are not feasible. What occurs if patients experience treatment tiredness, miss doses, or have concurrent illnesses? The tiny efficacy margins we have seen could be significantly impacted by these real-world factors. More studies are needed to establish the full safety profile of cardiac patients and the combination of these drugs in patients with multiple comorbidities.

Metabolic dysfunction-associated steatohepatitis is a chronic disorder that requires lifelong management, so an established long-term safety profile is crucial [11]. Long-term safety is available only for nonselective thyroid hormone analogues. Side effects like loss of bone density, muscle wasting, and affecting cardiac electricity, causing arrhythmias, are involved. While THRβ agonists are liver-selective agents, which decreases concerns, the possible side effects on bones, heart, and thyroid gland can't be excluded without long-term studies. Hence, we need continuous monitoring of liver functions, lipid profile, and other metabolic parameters regularly for long periods. This will help explore the tolerability and the possible downregulation of liver receptors[12].

The big challenge is when it comes to regulatory approval: demonstrating long-term effectiveness in a widely varied patient population. Although it took FDA approval, the way to the European Medicines Agency (EMA) approval is not guaranteed. The European regulators usually demand definitive endpoints such as improved survival, cirrhosis delay, or prevention. Especially with the financial burden, as the drug increases the costs to $66,764 per patient. These challenges are expected to delay the approval and the widespread adaptation, specifically, with competition from other new MASH therapies [13, 14].

The logical combination techniques and strategic drug selection based on patient phenotype are expected to be the future of MASH pharmacotherapy, rather than monotherapy [15]. Although THRβ agonists, GLP-1 receptor agonists, and new anti-fibrotic drugs have complementary processes that point to possible synergistic benefits, the decision between resmetirom and VK2809 may be influenced by the unique characteristics of each patient [16]. VK2809 may be beneficial for patients with significant steatosis and metabolic dysfunction due to its improved fat reduction profile. Resmetirom's established track record gives confidence to patients with established fibrosis who need confirmed histological improvement. However, as the early enthusiasm for FXR agonist combos taught us, we must avoid the temptation to combine medicines too soon without sufficient safety and effectiveness data [17].

Although Resmetirom's approval is a significant step forward, we shouldn't overestimate its immediate impact. Success will depend on our ability to select the right patients, closely monitor safety, and develop logical combination strategies rather than on short-term gains. The real challenge will be transforming regulatory approval into meaningful therapeutic benefits for the millions affected by this increasingly common condition. Our responsibility as we enter this new therapeutic era extends beyond simply writing prescriptions; we must also advance the science that will ultimately determine the effectiveness of MASH treatment while maintaining realistic expectations.

Conflicts of interest: None to declare.

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