



# Selective Agonists of Thyroid Hormone Receptor Beta: Promising Tools for the Treatment of Nonalcoholic Fatty Liver Disease

Sun Wook Cho

Department of Internal Medicine, Seoul National University Hospital, Seoul National University College of Medicine, Seoul, Korea

Thyroid hormone receptor beta (THR- $\beta$ ) is the primary isoform of the THR found in the liver, and it is primarily responsible for reducing cholesterol levels. Conversely, THR- $\alpha$  is predominantly associated with adverse effects on the heart and bones. Therefore, significant efforts have been made to develop drug candidates with isomer-specific activity, targeting the structure of thyroid hormones to create thyromimetics that selectively target THR- $\beta$  for application in liver disease [1].

Over the past two decades, several THR- $\beta$  selective triiodothyronine (T3) analogs, such as sobetirome (GC-1), eprotirome (KB2115), resmetirom (MGL-3196), and the HepDirect prodrug VK2809 (MB07811), have been developed (Table 1) [2-9]. These compounds have shown promising results by mimicking the beneficial effects of T3 without the adverse side effects. For instance, sobetirome and eprotirome advanced to human clinical trials for dyslipidemia, demonstrating positive outcomes without the typical detrimental effects associated with hyperthyroidism [2-5]. However, phase 2 trials for sobetirome have not been conducted, and a phase 3 trial with eprotirome was halted due to observed harmful effects on cartilage in canines (NCT01410383) [5]. Despite setbacks, the liver and THR- $\beta$  selective agonist VK2809 exhibited positive outcomes in a phase 2 trial involving patients with hypercholesterolemia and nonalcoholic fatty liver

disease (NAFLD) and is currently undergoing evaluation in a phase 2b clinical trial in patients with biopsy-confirmed nonalcoholic steatohepatitis (NASH) (NCT4173065). Moreover, resmetirom (MGL-3196) successfully completed phase 2 trials, significantly reducing liver fat content in patients with NASH over 12 and 36 weeks of treatment without significant side effects [6]. Most recently, the 52-week results of the ongoing phase 3 MAESTRO-NASH trial (NCT03900429) have been presented [7].

NAFLD is a prevalent condition associated with cirrhosis and hepatocellular carcinoma, affecting around 70% of individuals with obesity or type 2 diabetes [10]. Given the lack of approved pharmacotherapies specifically targeting NAFLD, current guidelines recommend addressing NAFLD by targeting obesity or type 2 diabetes [10-12]. This can be achieved through lifestyle interventions for weight loss and the use of glucagon-like peptide-1 receptor agonists, or by treating type 2 diabetes with insulin sensitizers such as pioglitazone. Understanding the role of thyroid hormone in hepatic glucose and lipid metabolism is crucial, although it is challenging to distinguish its contribution to steatohepatitis from those of insulin resistance, obesity, and type 2 diabetes. THR- $\beta$  agonists reverse steatosis through various mechanisms, including promoting the hepatic conversion of thy-

Received: 13 April 2024, Accepted: 16 April 2024

**Corresponding author:** Sun Wook Cho

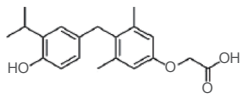
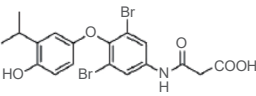
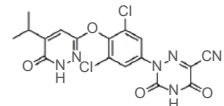
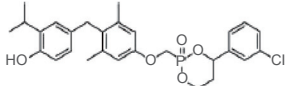
Department of Internal Medicine, Seoul National University Hospital, Seoul National University College of Medicine, 101 Daehak-ro, Jongno-gu, Seoul 03080, Korea

**Tel:** +82-2-2072-4761, **Fax:** +82-2-762-2199, **E-mail:** swchomd@snu.ac.kr

**Copyright © 2024 Korean Endocrine Society**

This is an Open Access article distributed under the terms of the Creative Commons Attribution Non-Commercial License (<https://creativecommons.org/licenses/by-nc/4.0/>) which permits unrestricted non-commercial use, distribution, and reproduction in any medium, provided the original work is properly cited.

**Table 1.** Effects of Thyroid Hormone Receptor Beta-Selective Thyromimetics in Human Trials

Thyromimetic/company	Structure	Beneficial effects	Side effects/clinical trials	Reference
GC-1 (Sobetirome)/QuatRx		<ul style="list-style-type: none"> <li>↓LDL cholesterol</li> <li>↓Serum triglycerides</li> <li>↓Lipoprotein a</li> </ul>	<ul style="list-style-type: none"> <li>No adverse side effects associated with excess thyroid hormone</li> <li>Terminated after phase 1</li> </ul>	[3,4]
Eprotirome (KB2115)/KaroBio		<ul style="list-style-type: none"> <li>↓Total cholesterol</li> <li>↓LDL cholesterol</li> <li>↓Lipoprotein (a)</li> <li>↓Triglycerides</li> </ul>	<ul style="list-style-type: none"> <li>Upregulation of LDL receptors and increased cardiovascular risk</li> <li>Liver toxicity; increase of AST and ALT levels</li> <li>Cartilage defects in dogs</li> <li>Terminated during phase 3</li> </ul>	[2,5]
Resmetirom (MGL-3196)/Madrigal Pharmaceutical		<ul style="list-style-type: none"> <li>↓Hepatic fat in patients with NASH</li> </ul>	<ul style="list-style-type: none"> <li>No adverse side effects after phase 2 clinical trials</li> <li>Phase 3 in progress (NCT03900429)</li> </ul>	[6,7,9]
VK2809 (MB08711)/Viking Therapeutics		<ul style="list-style-type: none"> <li>↓LDL-C</li> <li>↓Liver fat content in patients with NAFLD</li> </ul>	<ul style="list-style-type: none"> <li>Almost negligible side effects reported</li> <li>Phase 2b trial in progress (NCT4173065)</li> </ul>	[8]

LDL, low-density lipoprotein; AST, aspartate aminotransferase; ALT, alanine aminotransferase; NASH, nonalcoholic steatohepatitis; NAFLD, nonalcoholic fatty liver disease.

roxine (T4) to T3 and improving mitochondrial function [13,14].

Harrison et al. [7] presented the 52-week results of the ongoing phase 3 MAESTRO-NASH trial in the *New England Journal of Medicine*. In this study, 966 adults diagnosed with NASH and liver fibrosis were randomly assigned to receive once-daily doses of either 80 or 100 mg of resmetirom, or a placebo. Both doses of resmetirom showed superiority over placebo in achieving the trial's two primary endpoints: resolution of NASH without worsening fibrosis (25.9%–29.9% of patients on resmetirom vs. 9.7% on placebo) and improvement in fibrosis by at least one stage without worsening of the NAFLD activity score (24.2%–25.9% of patients on resmetirom vs. 14.2% on placebo). Additionally, resmetirom improved atherogenic dyslipidemia without significantly affecting body weight, insulin resistance, glycemia, heart rate, or blood pressure. The drug's adverse-event profile was deemed acceptable, although nausea, vomiting, and diarrhea were reported more frequently with resmetirom than with placebo. Notably, no increase was reported in endocrine adverse events. However, attention should be directed toward several changes in the endocrine system in response to resmetirom. In patients with available data, resmetirom led to significant increases in sex hormone-binding globulin, total estradiol, and testosterone levels. While these elevations indicate that resmetirom interacts with THR- $\beta$  and are linked to treatment response, the long-term consequences of these hormonal alterations remain uncertain. Additionally, resmetirom impacted the pituitary-thy-

roid hormone axis, resulting in reductions in free T4 and thyrotropin levels. Although mean plasma free T3 levels remained within the normal range, further exploration of individual cases at the lower end of normal or below-normal range is necessary.

In summary, the MAESTRO-NASH trial's findings mark significant progress in the field. However, it is necessary to remain vigilant about potential adverse effects of the treatment. Close monitoring for endocrine-related adverse events, especially those affecting thyroid, gonadal, or bone health, is crucial. A complete understanding of the long-term safety and effectiveness of resmetirom will only come with the conclusion of the ongoing 54-month trial. The combination of glucagon and T3 as a treatment method, is still in its early stages. However, it offers a promising new approach for diseases that could benefit from T3's specific actions in tissues and isoforms. In the future, this "combinatorial chemistry" technology is expected to be more widely used to maximize benefits and minimize risks compared to using the components separately.

## CONFLICTS OF INTEREST

Sun Wook Cho is the deputy editor of the journal. However, she was not involved in the peer reviewer selection, evaluation, or decision process of this article. No other potential conflicts of interest relevant to this article were reported.

## ORCID

Sun Wook Cho <https://orcid.org/0000-0002-7394-3830>

## REFERENCES

1. Tancevski I, Rudling M, Eller P. Thyromimetics: a journey from bench to bed-side. *Pharmacol Ther* 2011;131:33-9.
2. Berkenstam A, Kristensen J, Mellstrom K, Carlsson B, Malm J, Rehnmark S, et al. The thyroid hormone mimetic compound KB2115 lowers plasma LDL cholesterol and stimulates bile acid synthesis without cardiac effects in humans. *Proc Natl Acad Sci U S A* 2008;105:663-7.
3. Scanlan TS. Sobetirome: a case history of bench-to-clinic drug discovery and development. *Heart Fail Rev* 2010;15:177-82.
4. Hartley MD, Kirkemo LL, Banerji T, Scanlan TS. A thyroid hormone-based strategy for correcting the biochemical abnormality in X-linked adrenoleukodystrophy. *Endocrinology* 2017;158:1328-38.
5. Sjouke B, Langslet G, Ceska R, Nicholls SJ, Nissen SE, Ohlander M, et al. Eprotirome in patients with familial hypercholesterolaemia (the AKKA trial): a randomised, double-blind, placebo-controlled phase 3 study. *Lancet Diabetes Endocrinol* 2014;2:455-63.
6. Harrison SA, Bashir MR, Guy CD, Zhou R, Moylan CA, Frias JP, et al. Resmetirom (MGL-3196) for the treatment of non-alcoholic steatohepatitis: a multicentre, randomised, double-blind, placebo-controlled, phase 2 trial. *Lancet* 2019;394:2012-24.
7. Harrison SA, Bedossa P, Guy CD, Schattenberg JM, Loomba R, Taub R, et al. A phase 3, randomized, controlled trial of resmetirom in NASH with liver fibrosis. *N Engl J Med* 2024;390:497-509.
8. Erion MD, Cable EE, Ito BR, Jiang H, Fujitaki JM, Finn PD, et al. Targeting thyroid hormone receptor-beta agonists to the liver reduces cholesterol and triglycerides and improves the therapeutic index. *Proc Natl Acad Sci U S A* 2007;104:15490-5.
9. Kelly MJ, Pietranico-Cole S, Larigan JD, Haynes NE, Reynolds CH, Scott N, et al. Discovery of 2-[3,5-dichloro-4-(5-isopropyl-6-oxo-1,6-dihydropyridazin-3-yloxy)phenyl]-3,5-dioxo-2,3,4,5-tetrahydro[1,2,4]triazine-6-carbonitrile (MGL-3196), a highly selective thyroid hormone receptor  $\beta$  agonist in clinical trials for the treatment of dyslipidemia. *J Med Chem* 2014;57:3912-23.
10. Cusi K, Isaacs S, Barb D, Basu R, Caprio S, Garvey WT, et al. American Association of Clinical Endocrinology clinical practice guideline for the diagnosis and management of non-alcoholic fatty liver disease in primary care and endocrinology clinical settings: co-sponsored by the American Association for the Study of Liver Diseases (AASLD). *Endocr Pract* 2022;28:528-62.
11. ElSayed NA, Aleppo G, Aroda VR, Bannuru RR, Brown FM, Bruemmer D, et al. Addendum. 4. Comprehensive medical evaluation and assessment of comorbidities: standards of care in diabetes-2023. *Diabetes Care* 2023;46(Suppl. 1):S49-S67. *Diabetes Care* 2023;46:1718-20.
12. Rinella ME, Neuschwander-Tetri BA, Siddiqui MS, Abdelmalek MF, Caldwell S, Barb D, et al. AASLD practice guidance on the clinical assessment and management of nonalcoholic fatty liver disease. *Hepatology* 2023;77:1797-835.
13. Wirth EK, Puengel T, Spranger J, Tacke F. Thyroid hormones as a disease modifier and therapeutic target in nonalcoholic steatohepatitis. *Expert Rev Endocrinol Metab* 2022;17:425-34.
14. Lonardo A, Ballestri S, Mantovani A, Nascimbeni F, Lugari S, Targher G. Pathogenesis of hypothyroidism-induced NAFLD: evidence for a distinct disease entity? *Dig Liver Dis* 2019;51:462-70.