Review Article

Resmetirom in the Treatment of Noncirrhotic Non-Alcoholic Steatohepatitis: An In-Depth Review

ABSTRACT:

Background: Non-alcoholic steatohepatitis (NASH) is emerging as a significant global health challenge, closely linked to obesity and metabolic disorders. Despite its increasing prevalence, effective pharmacotherapy remains limited. Resmetirom, a selective thyroid hormone receptor beta agonist, offers a promising therapeutic approach for NASH, particularly in patients with moderate to advanced liver fibrosis.

Aims: This review aims to comprehensively evaluate resmetirom for its therapeutic efficacy and safety in treating non-alcoholic steatohepatitis (NASH), a severe stage of non-alcoholic fatty liver disease (NAFLD) with a growing global prevalence.

Study design:A narrative literature review was conducted, focusing on the pharmacokinetics, pharmacodynamics, clinical efficacy, and safety of resmetirom in treating NASH.

Methodology:A systematic search was performed across databases, including PubMed and Google Scholar, for English-language articles published between 2010 and 2024. Keywords used included "resmetirom," "thyroid hormone receptor beta agonist," "NASH treatment," and related terms. Articles discussing pharmacology, clinical efficacy, and safety evidence of resmetirom were included. Studies on cost-effectiveness or non-safety-related aspects, non-English articles, or those lacking full-text accessibility were excluded.

Results: Resmetirom, a liver-directed thyroid hormone receptor beta (THR-β) selective agonist, demonstrated significant efficacy in reducing liver fat content, improving liver histology, and reducing LDL cholesterol levels. Phase 3 trials showed improvements in fibrosis without worsening the NAFLD Activity Score. Adverse events were mostly mild to moderate, with gastrointestinal issues like diarrhea and nausea being the most common. Resmetirom exhibited a favourable safety profile, with no systemic hyperthyroidism or hypothyroidism observed. However, careful consideration is needed for drug interactions and specific patient populations.

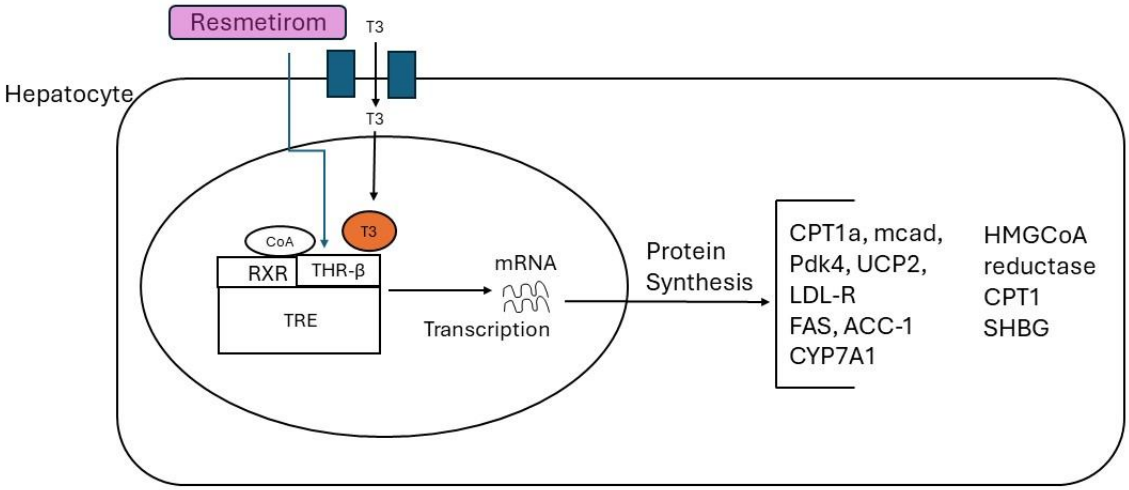
Conclusion: Resmetirom represents a significant advancement in NASH treatment, offering a targeted approach that minimizes systemic thyroid-related side effects. It is the first FDA-approved medication for NASH, showing promise in reducing liver fat and improving histology and metabolic parameters. Further long-term studies are necessary to fully understand its durability and impact on clinical outcomes. Resmetirom provides a promising new option for managing NASH, particularly for patients with moderate to advanced fibrosis.

Keywords: Resmetirom, Non-alcoholic Steatohepatitis, Thyroid Hormone Receptor Beta Agonist, Liver Fibrosis.

1. INTRODUCTION

Non-alcoholic steatohepatitis (NASH) is gaining recognition as a substantial public health issue, with the potential to become a primary driver of liver transplants and liver cancer cases worldwide. It represents an advanced stage of non-alcoholic fatty liver disease (NAFLD), strongly associated with metabolic disorders and obesity. [1] The worldwide occurrence of NAFLD among adults stands at approximately 25–30%. However, this rate differs across countries. The Middle East and North Africa, along with South America, report the highest instances, followed by Asia and North America. Europe and Africa have lower prevalence rates in comparison. [2] The global prevalence of NASH was 33.50% [3] The reported prevalence of adult non-alcoholic fatty liver disease (NAFLD) in India ranges widely from 6.7% to 55.1%, highlighting a significant variation. [4] This substantial range underscores the need for additional, standardised data collection and research to understand better the true prevalence of NAFLD in diverse populations across India. NAFLD is closely linked with metabolic syndrome (MetS), forming a detrimental cycle where each condition exacerbates the other. While not all individuals with MetS develop NAFLD, and not all with NAFLD progress to more severe stages like NASH or cirrhosis, the interconnection is significant. NAFLD is the most prevalent chronic liver disease globally, heavily influenced by obesity and Type 2 diabetes mellitus (T2DM). [5] The pathogenesis of NASH involves multiple factors, with lipotoxicity within hepatocytes and immune-driven inflammation playing critical roles. [6] The “multiple hit” hypothesis suggests that various insults simultaneously affect genetically predisposed individuals to trigger NAFLD, offering a more precise explanation of the disease's pathogenesis. [7] Such hits encompass variations, insulin resistance, and intestinal microbiota, which contribute to the advancement of NASH. Hepatic steatosis, inflammation, and fibrosis are the results of these hits, which also cause adipokine release, endoplasmic reticulum (ER), and oxidative stress. Notably, oxidative stress is a pivotal factor in transitioning from simple fatty liver to NASH.[8] Genetic variations, insulin resistance, and alterations in intestinal microbiota contribute to the progression of NASH through various molecular pathways, including oxidative stress, NOD-like receptors, and Toll-like receptors. [9,10] The significant impact of environmental pollutants like air particulates or polychlorinated compounds on liver metabolism and human well-being is currently being substantially underestimated. (Figure 2) [11]

Thyroid hormone receptor beta (TRβ) plays a crucial role in hepatic lipid metabolism. Predominantly expressed in the liver, TRβ facilitates the transcriptional regulation of genes involved in cholesterol and bile acid synthesis, transport, and clearance. It does so by binding to thyroid hormones (particularly T3, which is more potent and actively converted from T4 in the liver and other tissues) and their response elements in gene promoters. Activation of TRβ leads to altered expression of genes that govern lipid processing pathways, potentially impacting overall lipid profiles and contributing to metabolic responses such as the reduction of cholesterol levels. (Figure 1) [12]



RXR = retinoid X receptor, TRE= tetracycline-responsive element, CoA= coenzyme A, CPT1 = carnitine palmitoyl transferase, mcad = medium-chain acyl-coenzyme A dehydrogenase, Pdk4 = pyruvate dehydrogenase kinase 4, UCP2= uncoupling protein 2, LDL-R = low-density lipoprotein receptor, FAS = fatty acid synthase, ACC1 = acetyl coenzyme A carboxylase 1, CYP7A1 = cholesterol 7 alpha- hydroxylase, HMGCOA =3-hydroxy-3-methyl-glutaryl-coenzyme A reductase, CPT1 = carnitine palmitoyl transferase I, SHPG = sex hormone binding globulin.

Figure 1. Proposed hepatocyte pathways activated by thyroid hormone receptor-β agonists in relation to non-alcoholic steatohepatitis.[13] (Adapted from Karim G, et al.)

Dyslipidemia, insulin resistance, and inflammation are central to NASH progression, leading to hepatocyte injury and the development of hepatic steatosis, inflammation, and fibrosis. Despite these insights into its pathogenesis, effective pharmacotherapy for NASH remains elusive. (6,7)

Vitamin E and pioglitazone have displayed the potential to improve steatosis and inflammation in NASH, but they have limited effectiveness in addressing fibrosis. Concerns about their long-term safety and adverse effects complicate their use. Omega-3 fatty acids have shown promise in reducing oxidative stress and inflammation but have not proven effective in treating NAFLD/NASH definitively. Metformin was initially thought to improve insulin resistance and hepatic steatosis but has not consistently shown benefits in meta-analyses.

Pentoxifylline (PTX) has demonstrated effectiveness in preclinical studies but conflicting results in human trials. With no FDA-approved drugs available, there's a need for novel therapeutic approaches. [15] While weight loss and lifestyle changes stand as the primary treatment for NASH due to the lack of approved medications, they might not suffice for those with advanced fibrosis or cirrhosis. This underscores the pressing necessity for effective pharmaceutical interventions. [16]

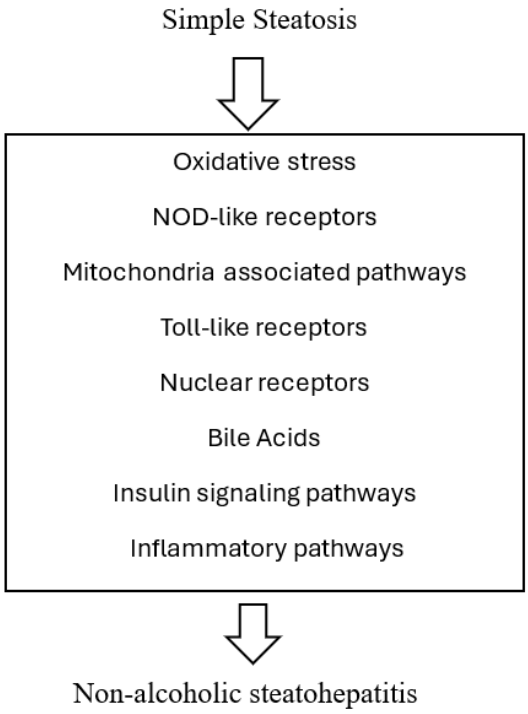


Figure 2. Key molecular pathways involved in the advancement of NASH. [9,17,18]

Resmetirom

Resmetirom is an oral, liver-directed, thyroid hormone receptor beta (THR-β)–selective agonist in clinical development for the treatment of NASH. [13] It has been approved by the FDA for NASH, Noncirrhotic with moderate to advanced liver fibrosis, in conjunction with diet and exercise.

This review aims to comprehensively evaluate resmetirom for its therapeutic efficacy and safety in treating NASH. It will delve into the pharmacokinetic/pharmacodynamic (PK/PD) characteristics, clinical data of resmetirom, and its relevance amidst increasing antibiotic resistance rates and evolving understanding of NASH pathophysiology. The article draws insights from existing studies and does not involve any research with human participants or animals conducted by the authors.

2. METHODOLOGY

We conducted a narrative literature review to gather relevant information on resmetirom. A systematic search was performed across databases, including PUBMED and Google Scholar, encompassing English-language articles published between 2010 and 2024. Keywords employed in the search strategy included "resmetirom," "thyroid hormone receptor beta agonist," "THR-β agonist," "NASH treatment," "resmetirom pharmacology," "resmetirom pharmacokinetics," "resmetirom clinical efficacy," and "resmetirom safety." The inclusion criteria focused on articles that elucidated the pharmacology, pharmacokinetics, clinical efficacy, and safety evidence of resmetirom. Studies addressing cost-effectiveness or non-safety-related aspects, as well as those not available in English or lacking full-text accessibility, were excluded from the review.

3.Pharmacodynamic Properties of Resmetirom

Resmetirom exhibited efficacy in reducing liver fat content, as assessed by magnetic resonance imaging-proton density fat fraction (MRI-PDFF) or FibroScan controlled attenuation parameter (CAP). Decreases in liver fat content, as measured by MRI-PDFF, were noted at 16 weeks (the initial assessment) and sustained through 52 weeks of treatment. Reductions in liver fat content, as evaluated by CAP, were observed after 52 weeks of treatment. Additionally, resmetirom demonstrated the ability to decrease concentrations of pro-hormone FT4, as evidenced at the 4-week mark of treatment and throughout the course of therapy. However, concentrations of sex hormone binding globulin (SHBG) notably increased during the 4-week assessment and over longer durations of treatment. The clinical implications of this change remain uncertain. Furthermore, investigations into cardiac electrophysiology revealed that even at the double the maximum recommended dose, resmetirom did not induce clinically significant prolongation of the QT interval. [19]

4. Pharmacokinetic Properties of Resmetirom

Resmetirom, administered at doses of either 80 mg or 100 mg, achieves its median time to maximum plasma concentration (Tmax) in approximately 4 hours, indicating a relatively rapid onset of action. The influence of food on resmetirom's pharmacokinetics was explored, revealing no clinically significant changes when administered with a high-fat meal. However, concurrent food intake resulted in a notable decrease in maximum plasma concentration (Cmax) by 33%, a reduction in area under the curve (AUC) by 11%, and a delay in median Tmax by around 2 hours compared to fasting conditions. In terms of distribution, resmetirom demonstrates a large apparent volume of distribution (Vd/F) of 68 (227%) L at steady-state, with over 99% of the drug being protein-bound. Regarding elimination, resmetirom exhibits a median terminal plasma half-life (t½) of 4.5 hours and a steady-state apparent clearance (CL/F) of 17.5 (56.3%) L/h, indicating moderate clearance from the body. [19]Resmetirom is metabolized by CYP2C8 and is not metabolized by other CYP enzymes in vitro. MGL-3623, a major metabolite, has 28 times lower potency for THR-β compared to resmetirom. At steady state, following daily administration of 100 mg, MGL-3623 constitutes 33% to 51% of the resmetirom AUC.[19] Whereas one study showed that resmetirom treatment markedly reduced cytochrome P450 8B1 (CYP8B1) expression in both NASH mouse models.[20] In terms of excretion, a significant amount of the administered dose of resmetirom is eliminated through faeces as metabolites, with only a small portion excreted unchanged in the urine. This underscores the crucial role of hepatic metabolism in removing resmetirom from the body. [19]

5.Therapeutic Efficacy of Resmetirom

All the trials taken into consideration for the review are given below (Table 1)

Table 1: Clinical Trials Investigating Resmetirom in NASH Patients and Healthy Subjects

Reference	Study Design	Patients	N	Intervention
Harrison S et al., 2024	Phase-3 Randomized controlled trial	Patients with biopsy-confirmed NASH and fibrosis stages F1B, F2, or F3	966	322 patients received 80 mg Resmetirom. 323 patients received 100 mg resmetirom. 321 patients received a placebo.
Younossi Z et al., 2022	Open-label extension	Patients who complete the main 36-week study (had ALT or AST levels that had not fully	31	80/100 mg of resmetirom daily 36 weeks

		normalized during weeks 16-30 of the main study)		
Harrison S et al., 2021	Phase 2, multicenter, double-blind, randomized, placebo-controlled study	Patients with biopsy-proven non-cirrhotic NASH with hepatic fat fraction of ≥10%	125	84 patients received 80 mg of resmetirom daily. 41 patients received a placebo
Harrison S et al., 2019	Randomised, double-blind, placebo-controlled study	Adults with biopsy-confirmed NASH (fibrosis stages 1-3) and a hepatic fat fraction of at least 10% at baseline	125	84 patients received 80mg resmetirom. 41 patients received a placebo for 36 weeks
Taub R et al., 2013	Randomized, double-blind, placebo-controlled clinical trial. (Single-dose study)	Healthy Subjects	72	54 subjects received Placebo. 18 subjects received MGL-3196 (0.25 to 200 mg of MGL-3196)

5.1 Improvements in Liver histology

Harrison S et al., in a Phase 3 randomized controlled trial, showed that the fibrosis improved from baseline. [13] In a Randomised, double-blind, placebo-controlled study by Harrison S et al., patients showed a reduction of hepatic fat at week 12 and week 36. (Table 2) [21]

Table 2: Clinical Trials showing Improvements in Liver histology by Resmetirom.

Reference	Results
Harrison S et al., 2024	Both 80 mg and 100 mg Resmetirom groups led to fibrosis improvement without worsening NAFLD Activity score vs placebo (p<0.001).
Harrison S et al., 2019	Resmetirom led to a Relative reduction of hepatic fat vs placebo at week 12 (p<0.001) and week 36 (p<0.001).

OLE- Open-Label Extension,

5.2 Effects on metabolic parameters

Harrison S et al., in a Phase 3 trial, showed that LDL cholesterol levels significantly reduced. [13] Younossi Z et al.showed that LDL cholesterol levels significantly reduced from baseline. [22] Taub R et al., in a two-week randomized, double-blind, placebo-controlled study, showed that LDL Cholesterol level was significantly reduced. (Table 3) [23]

Table 3 Clinical Trials Showing Effects on Metabolic Parameters

Reference	Results
Harrison S et al., 2024	Both 80 mg and 100 mg resmetirom groups led to reductions in LDL cholesterol levels from baseline, with decreases of -13.6% and -16.3%, respectively, compared to a change of 0.1% in the placebo group (P<0.001).

Younossi Z et al., 2022	Significant reductions from baseline were observed in LDL cholesterol (−26.1%, P<0.0001), apolipoprotein B (−23.8%, P<0.0001), and triglycerides (−19.6%, P = 0.0012; −46.1 mg/dL, P = 0.0031).
Taub R et al., 2013	Doses of 50 to 200 mg significantly reduced LDL cholesterol (up to 30%, P=0.008-0.0004) and showed trends of up to 60% reduction in triglycerides (P=0.13-0.016).

LDL- Low-Density Lipoprotein

5.3 Assessment of biomarkers of liver injury and fibrosis

Younossi Z et al., in an open-label extension study, showed that markers of fibrosis, including liver and type 3 collagen pro-peptide, were reduced. [22] Harrison S et al., in a post hoc analysis of a main 36-week study, showed that markers of fibrosis were reduced. (Table 4) [24]

Table 4 Clinical Trials showing Assessment of biomarkers of liver injury and fibrosis.

Reference	**Results**
Younossi Z et al., 2022	• Markers of liver fibrosis (P = 0.015) and N-terminal type III collagen pro-peptide (PRO-C3) (−9.8 ng/mL, P = 0.0004 for baseline ≥ 10 ng/mL), were reduced. • The marker of net fibrosis formation, PRO-C3/C3M, decreased in resmetirom-treated patients (−0.76, P = 0.0044; −0.68, P < 0.0001)
Harrison S et al., 2021	Fibrosis markers were reduced, including liver stiffness (−2.1 kPa, P = 0.015) and N-terminal type III collagen pro-peptide (PRO-C3) (−9.8 ng/mL, P = 0.0004 for baseline ≥ 10 ng/mL).

6.Safety and Tolerability Profile of Resmetirom

Most of the reported adverse events were of mild to moderate severity. Gastrointestinal issues, particularly diarrhea and nausea, were the most commonly observed side effects. Diarrhea and nausea began when treatment with resmetirom was started.Around half of the diarrhea incidents were characterized as either an exacerbation of pre-existing conditions or as sporadic instances of loose stools; none were severe. The typical duration of diarrhea ranged from 15 to 20 days and was consistent across different doses of resmetirom.[13] Cardiac dysrhythmia had an incidence of less than 5%, occurring more frequently with resmetirom compared to placebo. Similarly, palpitations were reported in less than 5% of patients, with a higher occurrence associated with resmetirom compared to placebo. [19]

In a double-blinded, placebo-controlled study, both the 80 mg and 100 mg daily doses of resmetirom were well tolerated throughout the 52-week period. There were no notable increases in serious TEAEs or significant imbalances in specific serious TEAEs in the resmetirom groups compared to placebo. Resmetirom normalizes thyroid hormone function in the liver, as evidenced by reduced rT3 levels and improved FT3/rT3 ratio. Importantly, resmetirom's liver-targeted action minimises systemic effects on THR-α receptors, ensuring

no adverse impact on thyroid function in other organs like the heart and bone. Clinical observations confirm the absence of systemic hyperthyroidism or hypothyroidism, with no changes in heart rate and modest reductions in blood pressure, indicating a favourable safety profile. (Table 5) [25]

The available search results do not provide direct information on the effects of resmetirom based on ethnic, sex, or age differences. The studies focused on the overall safety and efficacy of resmetirom in NASH patients, without reporting on potential subgroup analyses.[13,21]Further research is needed to explore these aspects and understand how these factors might influence treatment outcomes.

Table 5 Summary of Safety Study

Adverse Events and Observations	Details
Gastrointestinal Issues [13]	
Diarrhea	- Most common side effect. - Began at treatment start. - Duration: 15-20 days, consistent across doses.
Nausea	- Commonly observed. - Began at treatment start.
Cardiac Issues [19]	
Cardiac Dysrhythmia	- Incidence: <5% - More frequent with resmetirom vs placebo.
Palpitations	- Incidence: <5%. - Higher occurrence with resmetirom vs placebo.
Thyroid Function [25]	
Thyroid Hormone Function	- No adverse impact on thyroid function in other organs (heart, bone). - No systemic

TEAEs- Treatment-emergent adverse events

7.Dosage and Administration of Resmetirom

The prescribed dose of Resmetirom depends on the patient's actual body weight. If the patient weighs less than 100 kg, they should take 80 mg orally once a day. For patients weighing 100 kg or more, the recommended dose is 100 mg orally once daily.

Dosage adjustments and considerations are necessary for patients with specific medical conditions or those taking certain medications concurrently with Resmetirom. Patients with mild or moderate renal impairment do not need dosage adjustments when using Resmetirom. However, Resmetirom has not been studied in patients with severe renal impairment. Similarly, for patients with mild hepatic impairment (Child-Pugh Class A), no dosage adjustments are necessary, but Resmetirom should be avoided in those with moderate to severe hepatic impairment (Child-Pugh Class B or C), especially individuals with decompensated cirrhosis. Concomitant use of strong CYP2C8 inhibitors like gemfibrozil is not recommended, while moderate CYP2C8 inhibitors such as clopidogrel may require dosage reduction based on patient weight. For patients experiencing acute gallbladder events, treatment with Resmetirom should be interrupted until the event is resolved. In cases of hepatotoxicity, therapy should be discontinued, and patients should be closely monitored. [19]

7.2Effectiveness and Adverse Effect of a Multimodal Approach With Other Medications

In a Phase 3 trial, common concomitant medications across the four study arms included antidiabetes drugs such as glucagon-like peptide-1 (GLP-1) receptor agonists, metformin, pioglitazone, and sodium/glucose cotransporter-2 (SGLT2) inhibitors, along with dyslipidemia management drugs like statins, which were used by 46% of participants. The open-label (OL) arm had a higher proportion of patients using GLP-1 receptor agonists (11.7%) and SGLT2 inhibitors (10.5%) at baseline compared to the double-blind (DB) arms, where usage rates ranged from 6.0% to 9.3% for GLP-1 RAs and from 4.7% to 9.3% for SGLT2 inhibitors. Despite the diverse range of concomitant medications, no serious adverse events were reported.[25]

8.Place of Resmetirom in the Management of NASH

The FDA has given accelerated approval to resmetirom (Rezdiffra, Madrigal), the first drug approved for the treatment of NASH. This approval specifies that resmetirom should be used together with diet and exercise in adult patients who have noncirrhotic NASH and moderate to advanced liver fibrosis, identified as stages F2 to F3 fibrosis.

9. CONCLUSION

Resmetirom represents a significant advancement in the therapeutic landscape of NASH, addressing a critical unmet medical need. As the first FDA-approved medication for this condition, resmetirom has demonstrated efficacy in reducing liver fat, improving liver histology, and impacting metabolic parameters favorably without causing significant systemic effects. Its mode of action as a thyroid hormone receptor beta (THR-β) selective agonist offers a targeted approach that minimizes systemic thyroid-related side effects. While resmetirom's safety profile is generally favourable, careful consideration of drug interactions and specific patient populations is essential. Further long-term studies will be necessary to fully understand the durability of its therapeutic effects and its impact on clinical outcomes such as liver transplantation and mortality in NASH patients. Overall, resmetirom provides a promising new option for the management of NASH, particularly for those with moderate to advanced fibrosis who are in urgent need of effective treatment options.

Disclaimer (Artificial intelligence)

Author(s) hereby declare that NO generative AI technologies such as Large Language Models (ChatGPT, COPILOT, etc) and text-to-image generators have been used during writing or editing of manuscripts.

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