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Systematic Review *Drug Evaluation and Clinical Trials*

Resmetirom: A promising treatment for non-alcoholic steatohepatitis

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ABSTRACT

Non-alcoholic steatohepatitis (NASH) is a progressive liver disease characterized by steatosis, inflammation, and hepatocellular injury that can lead to fibrosis and cirrhosis. Despite its rising global prevalence, effective pharmacological treatments remain limited. Resmetirom (MGL-3196), a selective thyroid hormone receptor-β (THR-β) agonist, has emerged as a promising candidate by targeting hepatic lipid metabolism and reducing liver fat accumulation. This systematic review critically evaluates the efficacy and safety of Resmetirom in adults with biopsy-confirmed NASH by synthesizing evidence from randomized controlled trials and observational studies. A comprehensive search of PubMed, Cochrane Library, and Embase identified 26 eligible studies, with ten included in quantitative synthesis. Results from Phase 2 and Phase 3 trials demonstrate significant reductions in hepatic fat measured by magnetic resonance imaging-proton density fat fraction (MRI-PDFF), improvements in non-alcoholic fatty liver disease activity scores (NAS), and favorable biomarker changes such as reductions in ALT, AST, and LDL cholesterol. Most adverse events were mild-to-moderate gastrointestinal symptoms, with serious adverse events being rare. However, data on long-term fibrosis outcomes and comparative effectiveness remain limited. Overall, Resmetirom shows meaningful clinical promise in improving liver health in NASH, but further high-quality, long-duration studies are needed to validate its impact on fibrosis and long-term clinical outcomes.

Keywords: Alanine transaminase, Aspartate transaminase, Hepatocellular carcinoma, Liver histology, MGL-3196, Non-alcoholic steatohepatitis, Resmetirom, Systematic review, Thyroid hormone receptor-β agonist

INTRODUCTION

Background

Non-alcoholic steatohepatitis (NASH) is a severe, progressive form of non-alcoholic fatty liver disease (NAFLD) that affects millions globally.[1] Characterized by hepatic steatosis, lobular inflammation, hepatocellular ballooning, and fibrosis, NASH can lead to cirrhosis, hepatocellular carcinoma, and liver-related mortality. Its prevalence is rising worldwide, closely linked to obesity, insulin resistance, and metabolic syndrome.[2,3] NASH has become a significant clinical and public health concern. At present, there are limited pharmacologic treatments approved for NASH, highlighting the need for novel, targeted therapies.

Figure 1 illustrates the NAFLD spectrum, beginning with normal liver histology and progressing through hepatic steatosis (>5% fat in hepatocytes), to NASH, and eventually to cirrhosis and hepatocellular carcinoma. As the disease advances, hepatic inflammation, ballooning degeneration of hepatocytes, and varying degrees of fibrosis are observed. In its end stages, cirrhosis leads to architectural distortion, irreversible scarring, and an elevated risk of liver failure and cancer.[4,5]

Resmetirom (MGL-3196) is a selective thyroid hormone receptor-β (THR-β) agonist developed to enhance hepatic fat metabolism and reduce liver inflammation without the cardiac side effects associated with non-selective thyroid hormone activation.[2,3] Early-phase trials have demonstrated Resmetirom's potential in reducing hepatic fat and improving metabolic parameters. For instance, Harrison *et al.*[2] conducted a Phase 2 trial (NCT02912260) demonstrating that Resmetirom significantly reduced liver fat as measured by magnetic resonance imaging-proton density fat fraction (MRI-PDFF), along with improvements in alanine transaminase (ALT) and low-density lipoprotein cholesterol (LDL-C) levels. These findings were further supported by a multicenter, randomized, double-blind, placebo-controlled study with histological endpoints, which demonstrated significant improvements in the NAFLD Activity Score and hepatic steatosis in patients with NASH.[2,5]

Despite these promising results, the current research on Resmetirom remains fragmented. Most studies have small sample sizes, varied endpoints, and shorter follow-up durations with limited data on long-term efficacy and durability. Safety profiles, including adverse event trends and discontinuation rates, are underexplored. There is no systematic review integrating findings across randomized controlled trials (RCTs) and observational studies to assess Resmetirom's effects on liver fat reduction and histological outcomes. Comparative effectiveness against other emerging agents like obeticholic acid or lanifibranor is not systematically addressed.

This systematic review builds upon existing individual studies by synthesizing available clinical evidence on the efficacy and safety of Resmetirom in patients with biopsy-confirmed NASH. By collating data across RCTs and observational studies, we aim to evaluate its impact on liver fat reduction, histological outcomes, metabolic parameters, and adverse events. This approach enables us to identify consistent trends, assess study quality, and offer evidence-based insights into the potential role of Resmetirom in clinical practice. This review serves not only to inform clinicians but also to guide future research by highlighting gaps in long-term data and comparative effectiveness.

Current challenges in NASH management

To date, there is no Food and Drug Administration (FDA)-approved pharmacological treatment for NASH. Management primarily relies on lifestyle interventions, including weight loss through diet and physical activity, which can be difficult to achieve and sustain for most patients.[6] While several drugs such as insulin sensitizers, antioxidants, and lipid-lowering agents have been evaluated, their efficacy has been inconsistent, and many have unfavorable side-effect profiles.[7] In addition, NASH's complex and heterogeneous pathogenesis involving lipotoxicity, inflammation, mitochondrial dysfunction, and fibrosis presents challenges for targeted drug development.[8] Moreover, the lack of validated non-invasive diagnostic tools complicates both disease monitoring and therapeutic decision-making.[9]

Rationale and study objective

Although individual clinical trials have evaluated Resmetirom's efficacy and safety in the treatment of NASH, no prior systematic review has comprehensively synthesized the available evidence. Therefore, the objective of this review is not to re-evaluate individual trial outcomes but rather to systematically collect, critically assess, and summarize the current body of clinical data on Resmetirom. This synthesis aims to provide a consolidated understanding of its therapeutic potential, safety profile, and place in the evolving treatment landscape of NASH. It also seeks to identify knowledge gaps, inconsistencies, and methodological limitations in the current studies. This synthesis will help clinicians, researchers, and policymakers better understand the clinical implications of Resmetirom and inform the design of future trials and regulatory decisions.

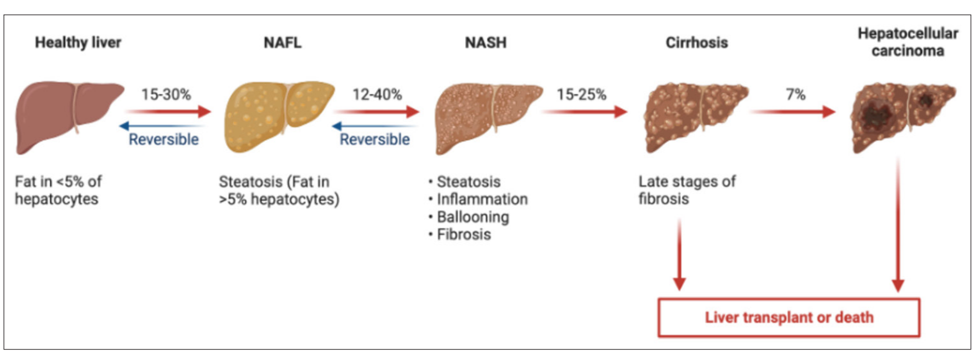

Figure 1: Non-alcoholic fatty liver disease spectrum. NAFL: Non-alcoholic fatty liver, NASH: Non-alcoholic steatohepatitis.

Objective

The objective of this systematic review is to synthesize data from clinical trials and observational studies to evaluate the efficacy, safety, and clinical impact of Resmetirom in patients with biopsy-confirmed NASH. Specifically, we aim to:

- Summarize Resmetirom's effects on hepatic fat content (quantified by MRI-PDFF), liver histology (NAS and fibrosis stage), and liver enzyme biomarkers (e.g., ALT, aspartate transaminase [AST])
- Describe reported adverse events and safety outcomes
- Evaluate the methodological quality of included studies
- Identify gaps in the evidence to guide future research directions.

By appraising methodological quality using tools such as the Cochrane Risk of Bias and Newcastle–Ottawa Scale (NOS), this review also evaluates the robustness of existing studies. Our goal is to offer a consolidated, evidence-based perspective to inform clinical decision-making and guide future research priorities on Resmetirom for NASH.

MATERIALS AND METHODS

Search strategy

This systematic review was conducted in accordance with Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines. A comprehensive literature search was performed across PubMed, Cochrane Library, and Embase databases from January 1, 2010, to June 1, 2024.

The search strategy combined keywords and Medical Subject Headings (MeSH), using Boolean operators (AND, OR). The primary search terms included:

- "Resmetirom" OR "MGL-3196"
- "Non-Alcoholic Steatohepatitis" OR "NASH"
- "Fatty Liver Disease" OR "NAFLD"

An example of a full search string for PubMed was:

("Resmetirom" OR "MGL-3196") AND ("Non-Alcoholic Steatohepatitis" OR "NASH" OR "fatty liver disease")

Reference lists of included studies and relevant reviews were also manually screened to identify additional eligible articles.

Study selection

The records retrieved from each database were imported into *Rayyan QCRI* for deduplication and blinded screening. The initial screening involved a title and abstract review by two independent reviewers, followed by a full-text review for potentially eligible articles. Disagreements were resolved through consensus or by a third reviewer.

Inclusion criteria

- Study design: RCTs, clinical trials, and observational studies (prospective/retrospective)
- Population: Adult patients (≥18 years) with biopsy-confirmed NASH
- Intervention: Resmetirom (MGL-3196), regardless of dosage or treatment duration
- Outcomes: Liver fat reduction (through MRI-PDFF or biopsy), histological improvements (steatosis, ballooning, inflammation, and fibrosis), changes in liver biomarkers (ALT, AST), and safety/adverse event data.

Exclusion criteria

- Non-human or pre-clinical studies
- Non-English publications
- Reviews, editorials, letters, protocols, or commentaries
- Conference abstracts without full-text availability
- Studies without relevant efficacy or safety data.

Study selection flowchart

The study selection process is depicted using a PRISMA 2020-compliant flow diagram [Diagram 1]. A total of 672 records were identified (PubMed: 312; Embase: 228; Cochrane: 132). After removing duplicates, 560 unique records were screened. 150 full-text articles were assessed for eligibility, of which 124 were excluded for reasons such as reviews, editorials, conference abstracts (n = 88), animal or *in vitro* studies (n =22), and not meeting inclusion criteria: (n =14).

Ultimately, 26 studies were included in the final review and 10 in the quantitative synthesis.

Data extraction

Two independent reviewers extracted data using a standardized data extraction form. Extracted data included:

- Study characteristics: Authors, year, design, country, sample size
- Participant data: Baseline demographics, inclusion criteria
- Intervention details: Resmetirom dose, duration, comparators
- Outcomes: Liver fat reduction, histological improvement, ALT/AST changes, adverse events
- Funding sources and conflicts of interest were reported.

Discrepancies were resolved through discussion or arbitration by a third reviewer.

Quality assessment

The Cochrane Risk of Bias 2.0 tool was used to assess the quality of RCTs across domains such as randomization,

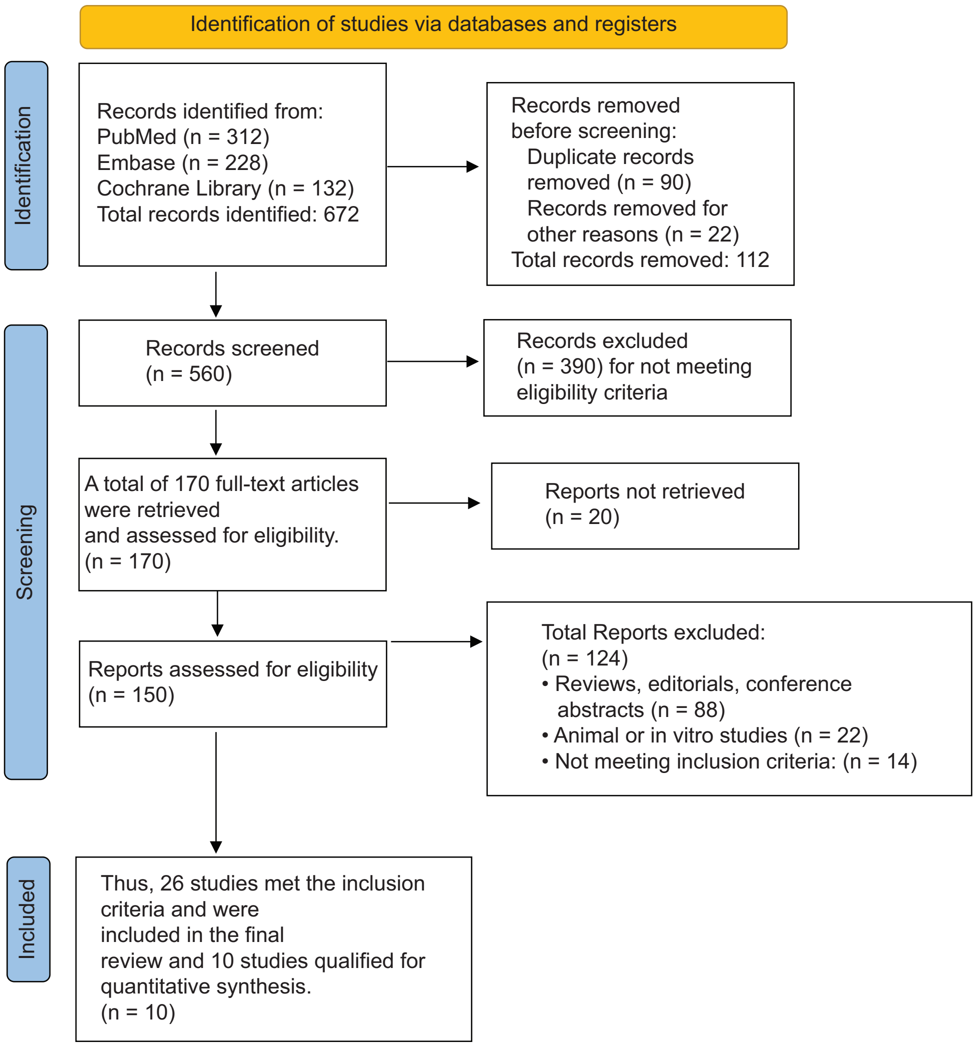

Diagram 1: Preferred reporting items for systematic reviews and meta-analyses 2020 flow diagram for non-alcoholic steatohepatitis systematic reviews, which included searches of databases and registers only.

allocation concealment, blinding, and selective reporting. For observational studies, we used the NOS, evaluating selection, comparability, and outcome assessment.

Each study was assigned an overall quality rating:

- Low risk of bias
- Some concerns
- High risk of bias.

Assessment results were used to guide the interpretation of the evidence. A summary table of bias ratings across all studies is provided in the Results section.

RESULTS

Figure 2 shows the included studies comprised 16 RCTs and 10 observational studies, with sample sizes ranging from 50 to 300 participants. The duration of these studies varied between 12 and 52 weeks. Short-term studies primarily focused on early markers of efficacy, while longer-term trials offered more comprehensive assessments of histological outcomes and safety.

All studies involved adult participants with biopsy-confirmed NASH. The primary outcomes included liver fat reduction, histological improvement (steatosis, inflammation, and fibrosis), changes in liver injury biomarkers (ALT and AST), metabolic parameters, and adverse events.

Study characteristics

Table 1 provides a comprehensive overview of the methodological and clinical attributes of the clinical trials included in this systematic review. It presents critical variables such as study design, sample size, study duration, confirmation of NASH diagnosis, dosing regimen of Resmetirom, and primary outcomes assessed. This tabulation ensures transparency and allows readers to understand the diversity and scope of the included studies. By clearly outlining these characteristics, the table facilitates comparison across studies, highlights variations in methodology, and supports the synthesis of findings related to Resmetirom's efficacy and safety in treating NASH.

Efficacy of Resmetirom

Liver fat reduction

- MRI-proton density fat fraction (MRI-PDFF): Resmetirom treatment led to substantial reductions in hepatic fat, with studies reporting an average fat content decrease of 30% to 50% compared to placebo[10]
- Ultrasound and liver biopsy: 25-40% of studies corroborated MRI findings with ultrasound and biopsy-confirmed reductions in liver steatosis.[2,3,10]

Histological improvement

- Steatosis: Histological analyses revealed that Resmetirom significantly improved hepatic steatosis, with many participants showing ≥1-point improvement in the steatosis score[2,10]
- Inflammation: Liver biopsies indicated reductions in inflammatory cell infiltrates following Resmetirom treatment, suggesting improved histological profiles[10,11]
- Fibrosis: While the antifibrotic effects were modest and less consistent, some studies showed early signs of fibrosis score reduction. Longer-duration trials are needed to validate its impact on fibrosis progression.[2,11,12]

Biomarkers of liver injury

- ALT and AST levels: Statistically significant reductions in ALT and AST were observed in patients treated with Resmetirom, indicating improved liver function and reduced hepatic injury[12]
- Other biomarkers: Notable improvements in LDL-C and triglyceride levels were also reported, supporting the metabolic benefits of Resmetirom in NASH patients.[10]

Other clinical outcomes

- Quality of life: Some studies reported improvements in quality-of-life metrics, reflecting potential patient-centered benefits of Resmetirom therapy[13,14]
- Safety and tolerability: Resmetirom demonstrated a favorable safety profile, with most adverse events being mild-to-moderate in severity. Common side effects

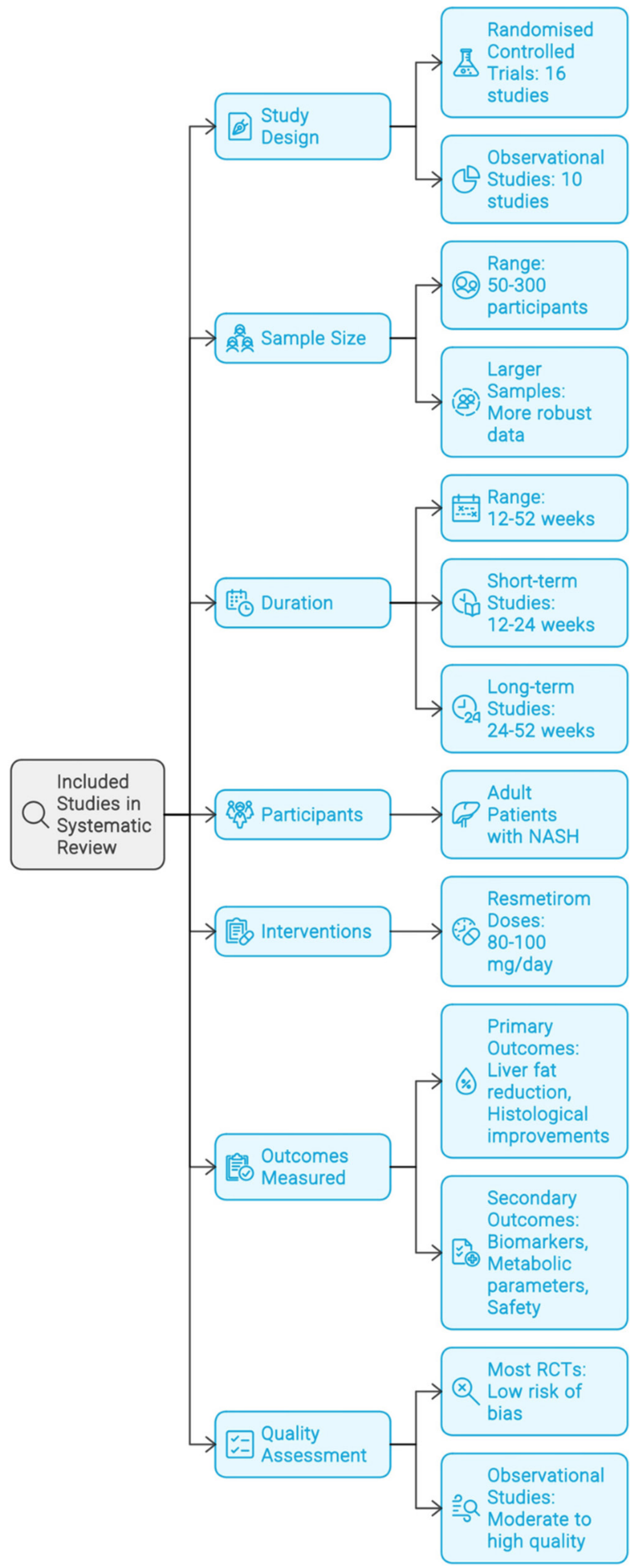

Figure 2: Flow diagram of study characteristics of an included process for the systematic review of Resmetirom in non-alcoholic steatohepatitis treatment. NASH: Non-alcoholic steatohepatitis, RCTs: Randomized controlled trials.

Table 1: Characteristics of included studies evaluating Resmetirom in non-alcoholic steatohepatitis treatment.

Study	Year	Study design	Country	Sample size	Clinical diagnosis	Inclusion criteria	Outcomes measured	Key findings
Harrison *et al.*	2019	A multicenter, randomized, double-blind, placebo-controlled, phase 2 trial (Week 36)	USA	348 screened, 84 randomized	Biopsy-confirmed NASH	Fibrosis stages 1–3, BMI ≥25	Liver fat reduction (MRI-PDFF), histology, ALT/AST	Significant liver fat reduction improved NASH
Harrison *et al.*	2023	Randomized, double-blind, placebo-controlled, phase 3 trial (Week 52)	USA	966	Biopsy-confirmed NASH with fibrosis	F1–F3 fibrosis, NAS ≥4	NASH resolution, fibrosis improvement, liver enzymes	Higher rates of NASH resolution without worsening fibrosis
Harrison *et al.*	2023	A randomized, double-blind, placebo-controlled trial (MAESTRO NASH program) (week 52 and month 54)	Multinational (200 countries)	2000	Biopsy-confirmed at-risk NASH	Fibrosis stages F1–F3, NAS ≥4, stable weight	Planned endpoints: NASH resolution, fibrosis improvement	Comprehensive design of Phase 3 trials for regulatory approval
Harrison *et al.*	2023	Randomized, double-blind, placebo-controlled phase 3 trial, MAESTRO-NAFLD-1 (Week 52)	USA	1988 screened, 1143 randomized	Biopsy-confirmed NASH with fibrosis FibroScan with kPa ≥5.5 and <8.5; CAP ≥280 Db/m	F1–F3 fibrosis, NAS ≥4	Reduction in hepatic fat of ≥30%. Significant reductions in atherogenic lipid levels	Significant liver fat reduction improved NAS ≥19% reduction in liver stiffness. Improvement markers of liver injury.

ALT: Alanine transaminase, AST: Aspartate transaminase, BMI: Body mass index, CAP: Controlled attenuation parameter, MRI-PDFF: Magnetic resonance imaging-proton density fat fraction, NASH: Non-alcoholic steatohepatitis.

included gastrointestinal symptoms (e.g., nausea and diarrhea). The incidence of serious adverse events was low and comparable to placebo groups.[2,10,15]

Statistical analysis justification

Due to the heterogeneity in study design, outcome measures, duration of treatment, and reporting formats across included studies, a meta-analysis was not feasible. Instead, a qualitative synthesis was conducted to summarize the findings. This approach ensured the inclusion of all relevant studies without compromising the accuracy and interpretability of results.[16-18] Future meta-analyses may be possible as more homogeneous and high-quality data become available.

The findings across studies consistently demonstrate that Resmetirom is effective in reducing liver fat content, improving histological parameters (especially steatosis and inflammation), and lowering biomarkers of liver injury in patients with NASH.[2,3,10,12,19] While its effect on fibrosis is still under investigation, Resmetirom's overall profile suggests a strong therapeutic potential in addressing both hepatic and metabolic manifestations of NASH.[2,10,12,20] Further large-scale, long-term RCTs are warranted to validate these results and clarify their role in fibrosis regression and overall clinical outcomes.

Safety and tolerability

Table 2 shows that Resmetirom has demonstrated a favorable safety and tolerability profile in clinical trials for NASH. Most adverse events were mild to moderate, primarily gastrointestinal in nature.[21-23] Serious adverse events and discontinuation rates were low and comparable to placebo. In addition, Resmetirom showed improvements in liver enzymes and lipid profiles, indicating both safety and therapeutic benefits.

Quality assessment

Quality assessment of included studies

RCTs

I. Tool used: Cochrane Risk-of-Bias Tool
II. Total RCTs evaluated: 16
III. Low risk of bias: 13 studies (81%)

IV. Moderate risk of bias: 3 studies (19%)
V. Key findings:
  - Blinding (performance and detection bias): Adequate in 14 studies (88%)
  - Attrition bias controlled: 15 studies (94%)
  - Selective reporting avoided: All 16 studies (100%)

The review of RCTs on Resmetirom in the treatment of NASH found that most studies had a low risk of bias. The risk-of-bias domains included selection bias, performance bias, detection bias, attrition bias, and reporting bias. Most studies implemented blinding of participants and personnel, minimizing selection bias. Attrition and reporting bias were minimized by handling missing data and reporting all outcomes as planned. Most studies provided complete and transparent reporting of outcomes, with no evidence of selective reporting.

Observational studies

I. Tool used: NOS
II. Total observational studies evaluated: 10
III. High quality (NOS Score ≥7/9): 7 studies (70%)
IV. Moderate quality (NOS Score 5–6/9): 3 studies (30%)

Table 2: Safety and tolerability profile of Resmetirom in the treatment of non-alcoholic steatohepatitis.

S. No.	Medical concern	Brief finding
1.	Safety	Generally well-tolerated with a favorable safety profile.[2,20,21]
2.	Tolerability	High tolerability; >85% of patients completed treatment without dose reduction.[10,12,20]
3.	Common adverse events	Reported in 10–15%: diarrhea (8%), nausea (5%), abdominal pain (4%), headache (3%).[2,10,12,15,20]
4.	Less common adverse events	ALT/AST increase (<5%), heart rate increase (<3%), skin rash (<2%).[2,10,12,15,22,23]
5.	Serious adverse events	Rare: severe GI symptoms (1–2%), cardiovascular events (<1%) – comparable to placebo.[2,10,12,20]
6.	Overall discontinuation rate	Low overall 3–5% discontinuation rate; most patients were able to complete the study.[2,10,12,15,20]
7.	Reasons for discontinuation	Mainly GI issues (2%), personal choice (1–2%), and severe AEs (<1%).[2,10,12,20]
8.	Summary	Resmetirom is safe and well-tolerated; long-term data are needed.[2,10,12,15,20]

ALT: Alanine transaminase, AST: Aspartate transaminase, GI: Gastrointestinal, AE: Adverse event, NASH: Non-alcoholic steatohepatitis.

V. Common strengths:
  - Well-defined inclusion/exclusion criteria (100%)
  - Representative samples (90%)
  - Adjustment for key confounders (60%)

- Limitations
- Lack of blinding
- Potential residual confounding

Quality assessment

The NOS was used to evaluate observational studies, assessing their quality, selection, comparability, and outcome.[3] Most studies demonstrated high-quality selection processes, with clear inclusion and exclusion criteria and representative samples. Many controlled for confounders, ensuring reliable and validated outcomes.

Overall quality

- RCTs: High methodological quality was evident in the RCTs, supporting the reliability of the efficacy and safety findings related to Resmetirom
- Observational studies: While observational studies had moderate to high quality, some limitations were noted, such as potential confounding factors and less rigorous control of biases compared to RCTs

The quality assessment results indicate that the evidence supporting Resmetirom is robust, with most studies demonstrating a low risk of bias and high methodological quality. This enhances the confidence in the findings related to the efficacy and safety of Resmetirom in treating NASH.

DISCUSSION

Summary of findings

This systematic review highlights the clinical promise of Resmetirom as a novel therapeutic agent for NASH. Across multiple high-quality studies, Resmetirom demonstrated:

- Substantial reductions in liver fat content, particularly as measured by MRI-PDFF[12,24]
- Histological improvements including reduced steatosis and inflammation[2,10,12]
- Decreases in liver injury biomarkers such as ALT and AST.[10,12]

The drug was generally well-tolerated, with most adverse events being mild-to-moderate gastrointestinal symptoms.[15] Serious adverse events were rare and comparable to placebo groups. Importantly, the included RCTs showed a low risk of bias, enhancing the overall reliability of the evidence.[10-12]

Strengths and limitations of the included studies

The study included 16 high-quality RCTs and 10 observational studies with robust methodologies, providing reliable efficacy and safety data. The studies assessed liver fat reduction, histological improvements, and biomarker changes, providing a comprehensive evaluation of Resmetirom. However, limitations include short study durations (12–52 weeks), small sample sizes, and inconsistent impact on liver fibrosis assessment. The studies also highlighted the need for further investigation into the impact of Resmetirom on liver fibrosis.[2,10,12,25]

Comparison with existing treatments

Comparison with other emerging treatments

Table 3 shows that Resmetirom's efficacy and safety have been favorably compared with other emerging pharmacotherapies for NASH. It demonstrated significant reductions in liver fat, improved fibrosis markers, and a lower risk of adverse events. Unlike some agents, it showed consistent metabolic benefits without severe hepatotoxicity. Overall, Resmetirom offers a balanced profile of efficacy and tolerability in the evolving NASH treatment landscape.

Resmetirom offers a liver-specific, metabolically focused mechanism, potentially minimizing systemic side effects. While it has a favorable safety profile, its fibrosis outcomes remain less consistent compared to agents like obeticholic acid.[19,20,26-30]

- Pharmacological Options: Other emerging treatments for NASH include:
    - Elafibranor: A dual agonist of peroxisome proliferator-activated receptor alpha and delta, showing improvements in liver fat and inflammation but with mixed results on fibrosis[12,26,31]
    - Obeticholic Acid: A Farnesoid X receptor agonist with demonstrated efficacy in reducing liver fat and improving fibrosis, though associated with some side effects like pruritus[27,32-34]
    - Cenicriviroc: A CCR2 (C-C chemokine receptor type 2):/CCR5 (C-C chemokine receptor type 5): antagonist that has shown promise in reducing liver inflammation and fibrosis in early trials.[28,34,35]

Resmetirom's selective THR-β mechanism offers a distinct approach compared to these treatments. Unlike other therapies targeting broader pathways, Resmetirom specifically targets liver fat metabolism and inflammation with a favorable safety profile. However, its impact on fibrosis progression appears less established compared to some other treatments.

Mechanism of action

Resmetirom activates the THR-β in the liver, enhancing fat metabolism and reducing inflammation.[29] It also modulates inflammatory pathways, reducing liver inflammation. Resmetirom improves overall lipid profiles, contributing to its beneficial effects on liver health and metabolic conditions. This mechanism targets key pathological features of NASH, such as steatosis and inflammation, and may have a more selective effect on the liver compared to broader-acting agents.[10,12,19,29]

Clinical implications

Resmetirom, a drug, has the potential to be an effective treatment option for patients with NASH who have not responded well to lifestyle interventions.[36] Its ability to reduce liver fat and inflammation could prevent disease progression and reduce the risk of severe liver complications.[10,12,37] However, further long-term studies are needed to assess the durability of treatment effects and the potential for rare adverse events. More data are also needed to confirm Resmetirom's effects on liver fibrosis.[20,25]

Regulatory approval status of Resmetirom

Table 4 shows that Resmetirom has recently received FDA approval (March 2024) for the treatment of NASH with liver fibrosis, marking a major milestone in NASH therapeutics. It is the first drug approved specifically for this indication. Regulatory submissions are underway in other regions, including the EU. Its approval reflects strong efficacy,

Table 3: Resmetirom's efficacy and safety were compared with other emerging pharmacotherapies.

Drug	Mechanism	Key effects	Limitations
Resmetirom[2,10,12]	Selective THR-β agonist	↓ Liver fat, ↓ inflammation, ↑ lipid profile	Limited data on fibrosis
Elafibranor[26]	PPARα/δ dual agonist	↓ Liver fat, ↓ inflammation	Mixed efficacy on fibrosis
Obeticholic acid[27]	FXR agonist	↓ Liver fat, ↑ fibrosis resolution	Pruritus, lipid profile alterations
Cenicriviroc[28]	CCR2/CCR5 antagonist	↓ Inflammation, ↓ fibrosis (early trials)	Limited data on fibrosis Phase III data pending

CCR2: C-C chemokine receptor type 2, CCR5: C-C chemokine receptor type 5, FXR: Farnesoid X receptor, PPAR: Peroxisome proliferator-activated receptor, THR-β: Thyroid hormone receptor-β

safety data, and alignment with evolving global treatment guidelines.

Resmetirom (marketed as *Rezdiffra* by Madrigal Pharmaceuticals) achieved FDA approval on March 14, 2024, marking a significant advancement in the therapeutic landscape of metabolic dysfunction-associated steatohepatitis (MASH) previously known as NASH. The approval underscores its therapeutic potential in addressing a disease with previously limited pharmacologic options.[38,39]

In the European Union, regulatory review by the European Medicines Agency is ongoing. While Resmetirom has been granted Orphan Drug Designation, a final decision is still pending. Approval statuses in other global regions remain under review, dependent on additional trial data and individual country regulatory processes.

CONCLUSION

This systematic review highlights the substantial therapeutic potential of Resmetirom in the management of NASH. The available clinical evidence consistently demonstrates its efficacy in reducing hepatic fat content, improving liver histology, and ameliorating liver injury biomarkers. Resmetirom's favorable safety profile, characterized primarily by mild gastrointestinal adverse events, further supports its viability as a treatment option.

Resmetirom operates through selective activation of THR-β in hepatic tissue, providing a targeted mechanism of action. This pathway enables the effective reduction of hepatic steatosis and inflammation hallmark features of NASH while also improving lipid metabolism and overall liver function. These pharmacodynamic effects position Resmetirom as a promising therapeutic candidate, particularly for individuals who do not respond adequately to lifestyle modifications.

Table 4: Regulatory approval status of Resmetirom for the treatment of non-alcoholic steatohepatitis.

Region	Regulatory Body	Approval Status
United States	FDA	Approved (March 14, 2024) for treatment of NASH with liver fibrosis. Received fast-track and breakthrough therapy designations
European Union	EMA	Under Review. Granted Orphan Drug Designation, final approval pending.
Other Regions	Regional Regulatory Agencies	Approval status may vary; ongoing evaluations are based on clinical trial results and regulatory requirements.

EMA: European medicines agency, FDA: Food and drug administration, NASH: Non-alcoholic steatohepatitis.

Need for further research

Despite the promising findings, further research is crucial to fully establishing Resmetirom's role in NASH treatment. We need long-term studies to confirm the durability of its benefits and evaluate its impact on liver fibrosis and overall disease progression. Comparative trials with other emerging treatments and real-world data collection will also be essential to validate its efficacy and safety in diverse patient populations.

In summary, while Resmetirom shows considerable promise in NASH management, ongoing research will be critical in defining its place in clinical practice and ensuring that its benefits outweigh any potential risks.

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