Systematic Review / Meta-analysis

ANNALS OF MEDICINE & SURGERY

OPEN

Efficacy and safety of resmetirom among patients with non-alcoholic steatohepatitis: a systematic review and meta-analysis

Saad Mazhar, MBBS[a], Aima Azhar, MBBS[b], Ariba Khan, MBBS[c], Gulrukh Shakil, MBBS[d], Sapna Kumari, MBBS[e], Deepa Devi, MBBS[e], Sayed Jawad, MBBS[f,*]

Background: Non-alcoholic steatohepatitis (NASH) is a severe medical illness that has few available therapeutic options. Resmetirom, a liver-targeting agonist of the thyroid hormone receptor (THR), has recently been licenced by the FDA. We assess the effectiveness and safety of resmetirom in patients with NASH.

Methods: PubMed, SCOPUS and Cochrane Central were searched till March 2024 to find potential articles. Outcomes assessed included MRI-proton density fat fraction (MRI-PDFF), Fat Reduction, and NASH Resolution Without Fibrosis, changes in aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma-glutamyl transpeptidase (GGT), low-density lipoprotein (LDL), and triglyceride (TG) levels, along with diarrhoea, nausea, urinary tract infection (UTI), and headache. Subgroup analysis was performed between outcomes before and after 6 months. Outcomes were analyzed with a random-effects model and results presented as mean difference (MD) for continuous outcomes and odds ratios (OR) for safety analysis, along with their 95% confidence intervals. A risk of bias assessment was performed using Cochrane Risk of Bias tool.

Results: Four randomized controlled trials (RCTs) were included in our analysis. Resmetirom shown a substantial improvement in MRI-PDFF with a MD of – 19.23 ($P < 0.00001$). Additionally, it resulted in a 30% reduction in fat (OR: 3.54, $P = 0.004$) and resolution of NASH without fibrosis (OR: 2.41, $P = 0.04$). There was no notable enhancement observed in AST levels, with a mean difference of – 0.87 and a P value of 0.73. The usage of resmetirom resulted in significant improvement in ALT levels (MD: – 4.36, P value: 0.32), GGT levels (MD: – 17.87, P value: <0.00001), TG levels (MD: – 23.48, P value: <0.00001), LDL levels (mean difference: – 12.80, P value: <0.00001), and rT3 levels (MD: -2.08, P value: <0.00001). The use of Resmetirom was associated with a higher likelihood of experiencing diarrhoea (OR: 2.07, $P < 0.0001$) and nausea (OR: 1.81, $P = 0.0003$). However, there was no significant difference observed in the occurrence of UTI (OR: 1.04, $P = 0.85$) or headaches (OR: 0.79, $P = 0.48$).

Conclusion: Resmetirom demonstrates efficacy in enhancing MRI-PDFF score, diminishing adipose tissue, resolving NASH without fibrosis, reducing GGT, TG, LDL, reverse triiodothyronine (rT3) levels in NASH patients. Nevertheless, there is also an observed heightened susceptibility to experiencing diarrhoea and nausea. Additional trials are necessary to further examine the efficacy and safety of this medication.

Keywords: meta-analysis, NAFLD, NASH, placebo, resmetirom

[a]Department of Medicine, King Edward Medical University, [b]Department of Medicine, Fatima Jinnah Medical University, [c]Department of Medicine, Services Institute of Medical Sciences, Lahore, [d]Department of Medicine, Ziauddin Medical College, [e]Department of Medicine, Ziauddin University, Karachi, Pakistan and [f]Department of Medicine, Kabul University of Medical Sciences, Kabul, Afghanistan

Sponsorships or competing interests that may be relevant to content are disclosed at the end of this article.

*Corresponding author. Address: Department of Medicine, Kabul University of Health Sciences, Kabul 1001, Afghanistan. Tel.: +93 (0) 20 250 0326. E-mail: sayedjawad12345@gmail.com (S. Jawad).

Annals of Medicine & Surgery (2024) 86:5447–5454

Received 28 March 2024; Accepted 14 June 2024

Supplemental Digital Content is available for this article. Direct URL citations are provided in the HTML and PDF versions of this article on the journal's website, www.lww.com/annals-of-medicine-and-surgery.

Published online 15 July 2024

http://dx.doi.org/10.1097/MS9.0000000000002314

Introduction

Non-alcoholic fatty liver disease (NAFLD) is a diagnosis of exclusion and is defined as evidence of hepatic steatosis (HS) without secondary causes of hepatic fat accumulation, particularly, excessive alcohol consumption[1]. Overall, the prevalence of NAFLD is estimated to be 1 in 4 adults and is projected to increase in future with the rising prevalence of obesity[2]. NAFLD is a spectrum of disease states, that begins with simple steatohepatitis known as non-alcoholic fatty liver (NAFL) and can progress to non-alcoholic steatohepatitis (NASH)[1]. Around 25% of individuals with NAFLD have NASH[3], also known as metabolic dysfunction-associated steatohepatitis (MASH)[4], which is defined as HS with inflammation and hepatocyte injury (e.g. ballooning), with or without fibrosis[2]. Liver biopsy is considered to be the gold standard for confirming the diagnosis of NASH[1].

NAFLD, including NASH, is associated with a constellation of comorbid conditions that include metabolic syndrome (obesity, diabetes mellitus type 2, hypertension and dyslipidaemia) and hypothyroidism, and is associated with increased cardiovascular risk[2]. Patients with more advanced NASH fibrosis, stage F2 and

F3 on a scale from F0 (no fibrosis) to F4 (cirrhosis)[4], have increased morbidity and mortality from both cardiovascular disease and from the progression of their liver disease to cirrhosis, liver failure, and hepatocellular carcinoma[2]. In NASH, THR-β function in the liver is impaired, which leads to a reduction in mitochondrial function and β-oxidation of fatty acids in association with an increase in fibrosis[4]. Based on 2004–2016 data from the United Network for Organ Sharing/Organ Procurement and Transplantation Network database, NASH was the second leading cause of liver transplant overall[5].

Previously, there was no recognized treatment for NASH, but some patients were evaluated for treatment with bile analogues such as obeticholic acid, which activates farnesoid X receptors[2], pioglitazone (to address insulin resistance) and vitamin E (to address stress). These medications are still undergoing trials[6]. The FDA's approval of the drug "Resmetirom" in March 2024 has effectively addressed the previously unmet need.

The approval of this drug is expected to be a game changer for healthcare providers, the research community and most importantly for the patients who had to rely on lifetime modifications, unapproved therapies and on liver transplant for severe forms of NASH.

In this article we aim to systematically review and thoroughly analyze the published results by performing a meta-analysis of the randomized controlled trials (RCTs) to pool the outcomes in one study. This to our knowledge, is the first meta-analysis on the use of this drug for NASH, which will help healthcare providers make better clinical decisions by providing them with further data on the pharmacological safety and efficacy of the resmetirom.

HIGHLIGHTS

- Resmetirom shows promising efficacy in treating non-alcoholic steatohepatitis (NASH) based on systematic review and meta-analysis.
- Significant reduction in liver fat content observed among patients treated with resmetirom.
- Resmetirom demonstrates favourable safety profile, with minimal adverse effects reported.
- Improvement in liver histology, including a reduction in inflammation and fibrosis, noted with resmetirom therapy.
- Resmetirom holds potential as a therapeutic option for NASH patients, pending further clinical validation.

Methods

The Preferred Reporting Items for Systematic review and Meta-Analyses (PRISMA, Supplemental Digital Content 1, http://links.lww.com/MS9/A553) guidelines and the Risk of Bias in Systematic reviews and assessment of multiple systematic reviews (AMSTAR, Supplemental Digital Content 2, http://links.lww.com/MS9/A554) 2 were both followed when doing this meta-analysis[7,8].

Data sources and search strategy

PUBMED, MEDLINE, EMBASE and Cochrane CENTRAL were comprehensively searched from inception through March 2024 by two independent reviewers, AA and SM. We extracted studies based on abstracts and titles. A full-text appraisal was sought when required. MeSH phrases and keywords were used to find keywords for "Resmetirom", "NASH", "Nonalcoholic steatohepatitis", "NAFLD", and "Non-alcoholic Fatty Liver Disease".

Study selection

Data extraction and assessment of study quality

We included studies if they were: (1) RCTs or analysis of RCTs that determined the impact of Resmetirom in different interventional arms, (2) reported either MRI-proton density fat fraction (MRI-PDFF), hepatic fat reduction, or NASH resolution without fibrosis as one of their outcomes (3) included results on the following parameters: aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma-glutamyl transpeptidase (GGT), triglycerides (TG), low-density lipoprotein (LDL) and reverse triiodothyronine (rT3). A third investigator D.D. was consulted in case of any disagreement regarding study selection. All articles were then uploaded to Endnote Reference Library (Version X7.5; Clarivate Analytics) software to remove any duplicates.

Two reviewers A.A. and S.M. independently extracted from the selected studies the characteristics of the studies, patient demographics, summary events, number of events, sample sizes and treatment type. Summary events were also extracted for outcomes of interest, and mean difference (MD) with standard deviation (SD) from baseline.

The risk of bias in RCTs was assessed using the Cochrane Risk of Bias tool (Figure S1, Supplemental Digital Content 3, http://links.lww.com/MS9/A555)[9].

Statistical analysis

RevMan (version 5.4.1; Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration) was used to conduct the meta-analysis. The outcomes of interest were provided as risk ratios with 95% CIs and were aggregated using an inverse variance weighted random-effects model. Forest plots were used to graphically display the pooled analyses. Continuous outcomes of interest were presented as MDs with 95% CIs and were pooled using an inverse variance weighted random-effects model. When the mean was not available, we used the median for analysis. When the change from the baseline was not reported, we calculated the difference in means between the baseline and the post-treatment measurements. Its standard deviation was derived from the baseline and the follow-up by assuming their correlations were 0.5. The Higgins I^2 was utilized to assess heterogeneity between trials. A 25–50% number was regarded as low, 50–75% moderate, and more than 75% serious. In all cases, a *P* value less than 0.05 was considered significant.

Outcome measures

From the finalized trials, the following outcomes were extracted, MRI-PDFF, 30% fat reduction, NASH resolution without fibrosis, liver markers like AST levels, ALT levels, GGT levels, LDL levels, TG Levels and rT3.

Results

Search results and baseline characteristics

The PRISMA flowchart below summarizes the search and study selection process (Fig. 1). Initial search yielded a total of 61

results. After screening and removal of duplicates, 58 articles were assessed for eligibility. Among those, 17 did not have full-text available, nine did not report complete data, and 5 assessed different outcomes. A total of 4 RCTs were included in the final analysis.[2,3,4,6]

A total of 1444 participants were included in our study amongst which 750 were randomized to resmetirom group while 694 participants were grouped into placebo group. Table 1 summarizes the baseline characteristics of included studies.

Outcomes

MRI-proton density fat fraction

A total of four studies reported MRI-PDFF as an outcome. A subgroup analysis was performed to compare MRI-PDFF before and after 6 months. A significant difference was reported in MRI-PDFF in resmetirom versus placebo group [MD – 19.23, 95% CI (– 23.67, – 14.79), $P < 0.00001$, $I^2 = 100\%$] (Fig. 2).

30% fat reduction

Two studies reported at least 30% fat reduction as an outcome. A subgroup analysis was performed to compare 30% fat reduction before 6 months and after 6 months. Our analysis showed a significant difference in 30% fat reduction in resmetirom group compared to the placebo group [odds ratio (OR) 3.54, 95% CI (1.49, 8.38), $P = 0.004$, $I^2 = 48\%$] (Fig. 3).

NASH resolution without fibrosis

Two studies compared the NASH resolution without fibrosis in patients taking resmetirom compared to the placebo group. Our analysis showed a significant difference in NASH resolution without fibrosis between the resmetirom group versus placebo group [OR 2.41, 95% CI (1.06, 5.47), $P = 0.04$, $I^2 = 57\%$] (Fig. 4).

AST levels

Three studies reported changes in AST levels from baseline. A subgroup analysis was performed in levels of AST before 6 months and after 6 months. No significant difference in AST levels was found between the resmetirom group versus the placebo group [MD – 0.87, 95% CI (– 5.83, 4.08), $P = 0.73$, $I^2 = 99\%$] (Fig. 5).

ALT levels

Three studies reported changes in ALT levels from baseline. A subgroup analysis was performed in levels of ALT before 6 months and after 6 months. No significant difference was found in ALT levels between the resmetirom group versus the placebo group [MD – 4.36, 95% CI (– 12.89, 4.16), $P = 0.32$, $I^2 = 99\%$] (Fig. 6).

Gamma-glutamyl transpeptidase

Three studies reported changes in GGT levels from baseline. A subgroup analysis was performed in levels of GGT before 6 months and after 6 months. Our meta-analysis yielded a significant difference in GGT levels between the resmetirom group versus the placebo group [MD – 17.87, 95% CI (– 30.81, – 4.93), $P < 0.00001$, $I^2 = 100\%$] (Fig. 7).

Triglycerides levels

Three studies reported changes in TG levels. A subgroup analysis was performed in levels of triglycerides before 6 months and after 6 months. Our meta-analysis showed a significant difference in triglycerides levels between the resmetirom group versus the placebo group [MD – 23.48, 95% CI (– 28.63, – 18.34), $P < 0.00001$, $I^2 = 99\%$] (Fig. 8).

LDL levels

Three studies reported changes in LDL levels. A subgroup analysis was performed in levels of LDL before 6 months and after 6 months. Our meta-analysis showed a significant difference in LDL levels between the resmetirom group versus the placebo group [MD – 12.80, 95% CI (– 15.23, – 10.37), $P < 0.00001$, $I^2 = 99\%$] (Fig. 9).

Discussion

The findings of this meta-analysis provide compelling evidence supporting the efficacy of Resmetirom in the treatment of NASH. These results align with previous preclinical and clinical studies demonstrating the potential of THR agonists in ameliorating HS and associated metabolic abnormalities[10]. Notably, the liver-directed action of Resmetirom offers a targeted approach to addressing the underlying pathophysiology of NASH while minimizing systemic side effects associated with thyroid hormone

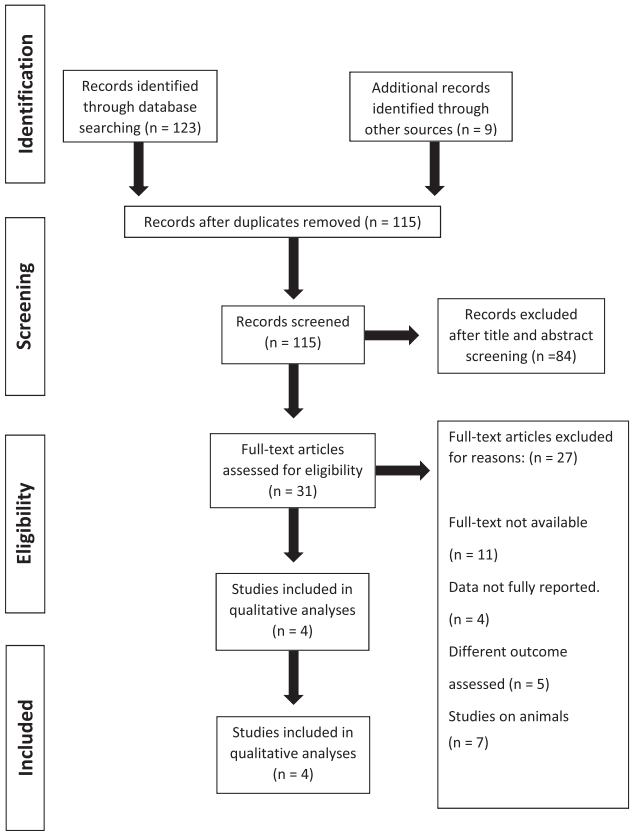

Figure 1. Preferred Reporting Items for Systematic review and Meta-Analyses (PRISMA) flowchart summarizing literature search in detail.

Table 1

Baseline characteristics of included studies.

Author, year, reference number	Country	Study type	Inclusion criteria/diagnostic criteria	Exclusion criteria	Patients (*n*)	Age (year)	Men (%)	MRI-proton density fat fraction, % fat fraction (SD)	Background therapy
Harrisson *et al.*, 2019[6]	USA	RCT	≥ 10% liver fat content on PDFF-MRI; Stage 1–3 fibrosis with a NAFLD activity score (NAS) of 4 or more, including a score of 1 or more in each component according to the NASH clinical research network scoring system	Clinically significant alcohol consumption, use of drugs associated with NAFLD, hypothyroidism, uncontrolled type 2 diabetes, or a requirement for glucagon-like peptide analogue.	125	50.32 (10.9)	49.6	20.0 (7.4)	PPI, Statins, Biguanides, Insulin, ACEi, platelet aggregation inhibitors.
Harrisson, 2021	USA	RCT	≥ 10% liver fat content on PDFF-MRI; Stage 1–3 fibrosis with a NAFLD activity score (NAS) of 4 or more, including a score of 1 or more in each component according to the NASH clinical research network scoring system	Clinically significant alcohol consumption, use of drugs associated with NAFLD, hypothyroidism, uncontrolled type 2 diabetes.	31	48.2 (12.3)	51.6	19.4 (7.1)	NSAIDS; Biguanides; PPI; Statins; ACEi
Harrisson *et al.*, 2023[3]	USA	RCT	NAS = 3, steatosis 1, ballooning 1, inflammation 1, OR NAS = 3, ballooning 0, with F1B, F2 or F3 NAS ≥ 4, at least 1 in all NAS components, F1A or F1C, PRO-C3 ≤ 14 (NASH, but ineligible for MAESTRO-NASH) Compensated NASH cirrhosis based on biopsy at screening of MAESTRO-NASH, including Child Pugh-A (score 5-6), MELD <12, albumin ≥ 3.2, and bilirubin <2	Clinically significant alcohol consumption, diagnosis of HCC, CLD, active autoimmune disease.	645	56.0 (11.9)	45.7	17.7 (6.8)	GLP-1RA; Biguanides; Pioglitazone; SGLT2i; Statin
Harrisson, 2024	USA	RCT	≥ 8% liver fat content on PDFF-MRI; Stage 1–3 fibrosis with a NAFLD activity score (NAS) of 4 or more, including a score of 1 or more in each component according to the NASH clinical research network scoring system	Clinically significant alcohol consumption, use of drugs associated with NAFLD, hypothyroidism, uncontrolled type 2 diabetes, or a requirement for glucagon-like peptide analogue.	643	56.6 (11.0)	44.00%	18.0 (6.8)	NR

CLD, chronic liver disease; HCC, heptatocellular carcinoma; NAFLD, non-alcoholic fatty liver disease; NASH, non-alcoholic steatohepatitis; NR, not reported; NSAIDS, non-steroidal anti-inflammatory drugs; PDFF, proton density fat fraction; RCT, randomized controlled trial.

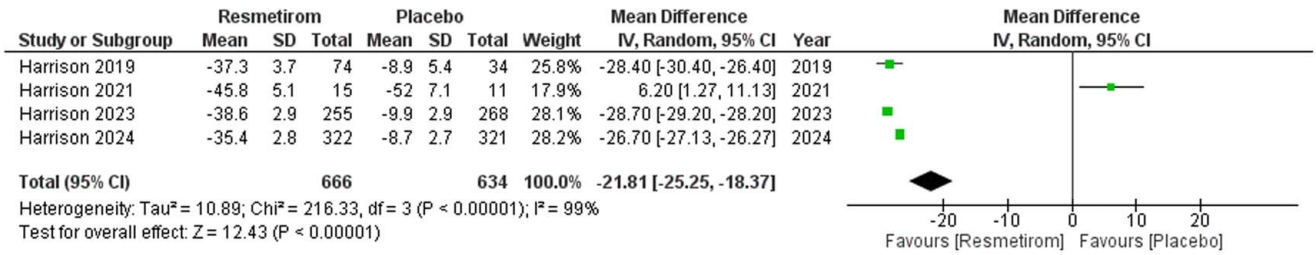

Figure 2. Forest plot comparing MRI-proton density fat fraction among patients taking resmetirom versus placebo.

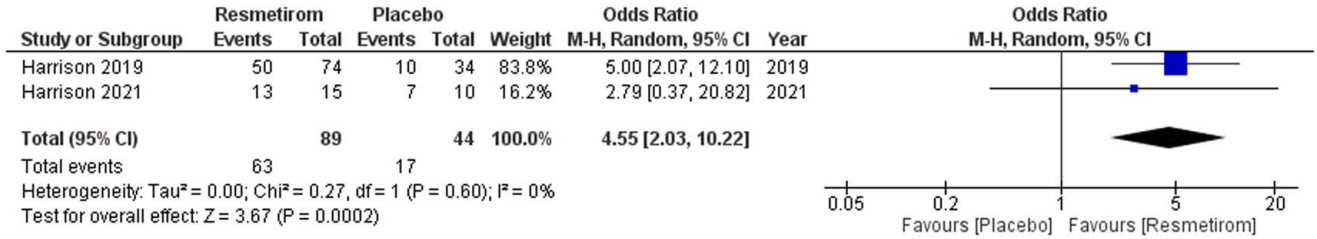

Figure 3. Forest plot comparing 30% fat reduction among patients taking resmetirom versus placebo.

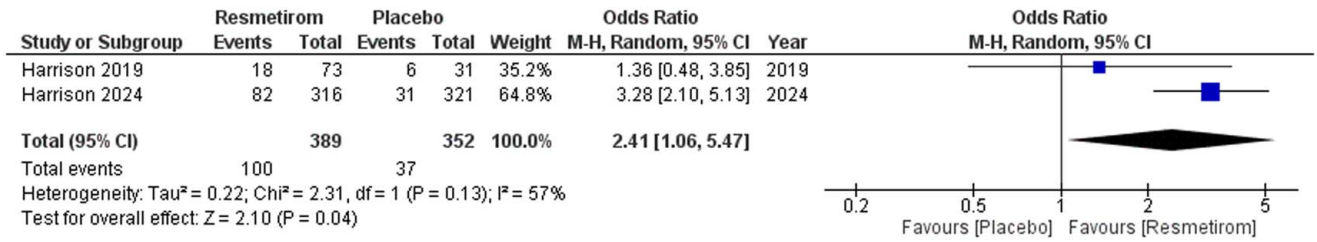

Figure 4. Forest plot comparing non-alcoholic steatohepatitis resolution without fibrosis among patients taking resmetirom versus placebo.

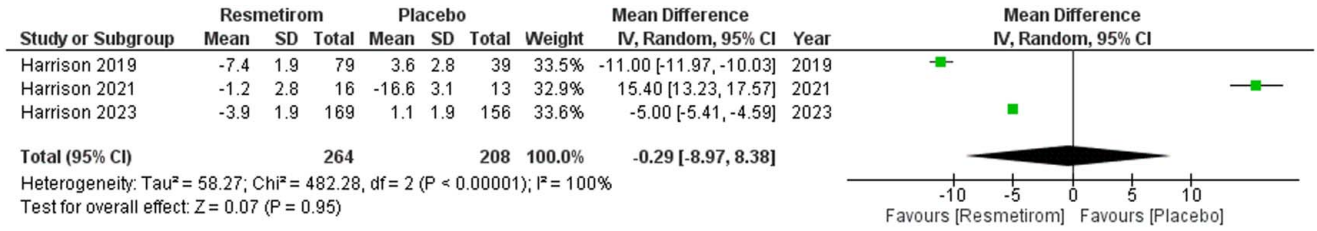

Figure 5. Forest plot comparing aspartate aminotransferase levels among patients taking resmetirom versus placebo.

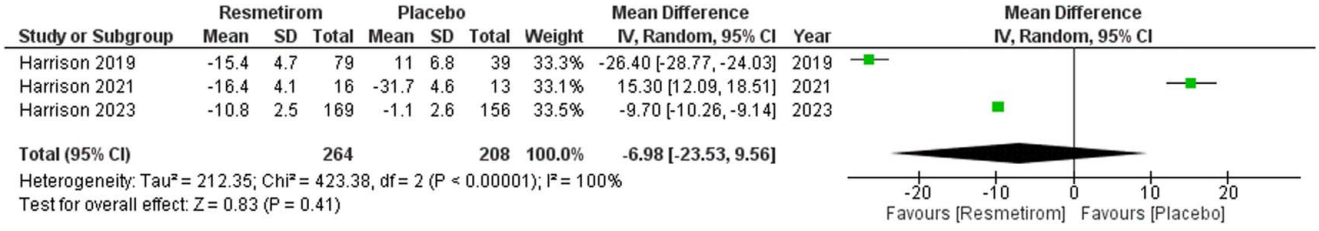

Figure 6. Forest plot comparing alanine aminotransferase levels among patients taking resmetirom versus placebo.

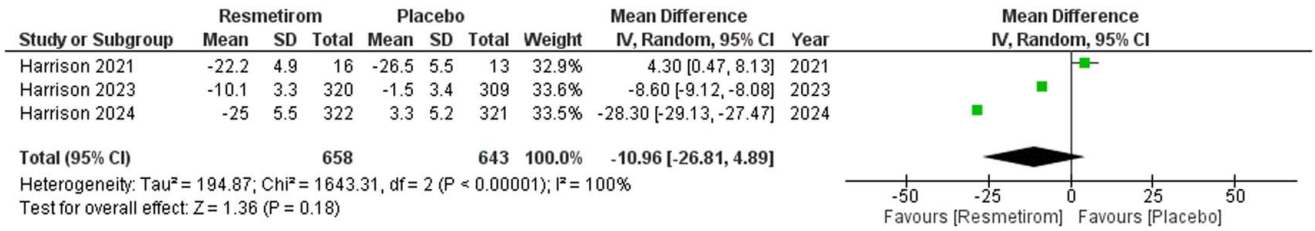

Figure 7. Forest plot comparing gamma-glutamyl transpeptidase among patients taking resmetirom versus placebo.

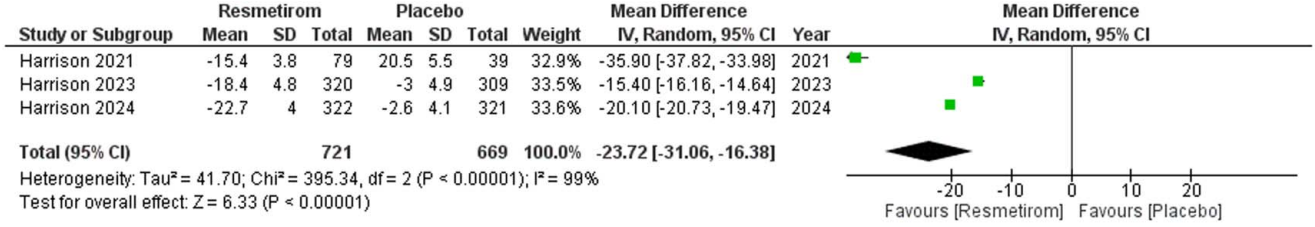

Figure 8. Forest plot comparing triglyceride levels among patients taking resmetirom versus placebo.

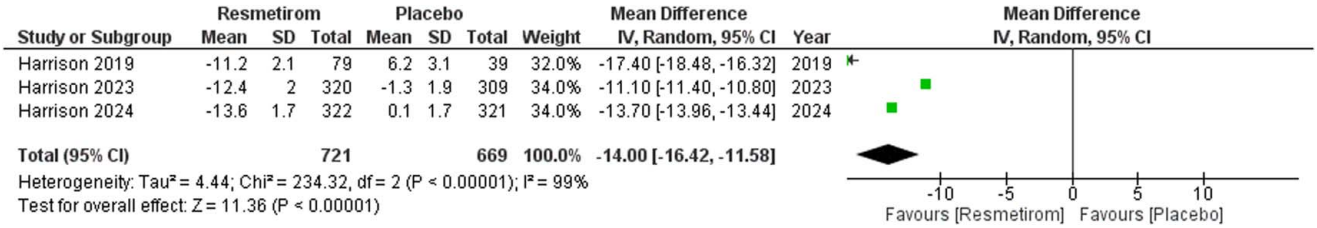

Figure 9. Forest plot comparing low-density lipoprotein levels among patients taking resmetirom versus placebo.

modulation[10,11]. In our analysis, Resmetirom led to a substantial reduction in hepatic fat content, as evidenced by MRI-PDFF, and an increased proportion of patients achieving at least 30% fat reduction. Additionally, Resmetirom exhibited favourable effects on metabolic parameters such as TG, LDL, and rT3 levels. However, the analysis revealed no significant difference in transaminase levels (AST, ALT), except for GGT, which decreased significantly with Resmetirom.

Resmetirom also showed a statistical superiority with respect to a two-point minimum decrease in NASH, demonstrated in a previous network meta-analysis by Kovalic *et al.*[12]. Importantly, Resmetirom also shows promise in promoting NASH resolution without fibrosis, as evidenced by the meta-analysis findings. Similar findings were obtained by Kovalic *et al.*[12]. This outcome is particularly significant given the progressive nature of NASH and the associated risk of liver fibrosis, cirrhosis, and hepatocellular carcinoma[2]. The observed increase in NASH resolution highlights the potential of Resmetirom to halt disease progression and improve long-term outcomes for patients with NASH.

The lack of significant improvements in AST and ALT levels with Resmetirom therapy must be mentioned. While these markers are conventionally used to assess hepatocellular injury and inflammation, their utility as sole indicators of disease progression in NASH is limited, particularly in the absence of significant fibrosis[13]. Additionally, Resmetirom demonstrated significant reductions in GGT levels, indicative of improved hepatic function and reduced cholestasis[14]. Thus, the absence of marked changes in AST and ALT levels should be interpreted cautiously and does not necessarily undermine the overall efficacy of Resmetirom.

The risk for cardiovascular disease and mortality is higher in patients with NASH (a majority of whom also have diabetes)[15,16]. This makes the significant reductions in TG and LDL following Resmetirom treatment, suggesting its ability to ameliorate dyslipidemia and metabolic dysfunction associated with NASH, particularly important. The significant decrease in rT3 levels suggests a restoration of thyroid hormone balance, which may play a role in mitigating metabolic dysregulation[17].

Although resmetirom shows promise effectiveness, its safety profile requires thorough evaluation. The rising occurrence of gastrointestinal side effects, namely diarrhoea and nausea, emphasizes the necessity for careful surveillance and control of these unfavourable incidents in clinical settings. It is important to note that diarrhoea and nausea occurred more frequently in the Resmetirom group compared to the placebo group according to the 2024 RCT by Harrison *et al.*[4]. Notably, this meta-analysis finds no significant difference in the incidence of urinary tract infections (UTIs) or headaches between Resmetirom and placebo groups, indicating a generally favourable safety profile for Resmetirom. The comparatively infrequent occurrence of UTIs and headaches indicates a generally positive safety profile.

However, the gastrointestinal side effects may affect patient compliance and overall therapy efficacy. Future research should prioritize comprehending the mechanisms that cause these side effects and devising methods to alleviate them. This will ensure that the therapeutic advantages of resmetirom can be fully achieved without compromising patient comfort and adherence.

The findings of this meta-analysis have several important implications. From a clinical perspective, the demonstrated efficacy and safety of Resmetirom support its consideration as a first-line treatment option for patients with NASH, particularly those with advanced disease and metabolic comorbidities. Healthcare providers should be aware of Resmetirom's potential benefits and side effect profile when making treatment decisions for patients with NASH. From a policy standpoint, the FDA approval of Resmetirom underscores the importance of continued investment in drug development for NASH and other metabolic liver diseases, highlighting the need for regulatory frameworks that facilitate timely access to innovative therapies. In the past, obeticholic acid, a medication activating the farnesoid X receptor and the initial drug to demonstrate supportive phase 3 histological outcomes for fibrotic NASH, faced FDA rejection due to its limited treatment efficacy and safety concerns, notably including drug-induced liver injury. Similarly, Selonsertib, an apoptosis signal-regulating kinase 1 inhibitor, elafibranor, a PPAR α/δ agonist, and cenicriviroc, a chemokine receptor type 2 and 5 antagonist, all lacked evidence of benefit in their respective phase 3 trials[18]. Future research endeavours should focus on elucidating the long-term efficacy, safety, and cost-effectiveness of Resmetirom in real-world clinical settings, as well as exploring its potential synergies with other therapeutic modalities for NASH. The notable decrease in hepatic fat content (measured by MRI-PDFF) and the higher percentage of patients who achieved a minimum of 30% fat reduction with resmetirom has several clinical implications. This demonstrates the efficacy of resmetirom in alleviating hepatic steatosis, a crucial element in the progression of NASH. Moreover, the potential of resmetirom to address metabolic dysfunctions related to NASH is highlighted by improvements in TG, LDL, and rT3 levels. The absence of fibrosis in NASH resolution indicates that resmetirom not only stops the advancement of the illness but also facilitates regression, potentially enhancing long-term results and diminishing the likelihood of cirrhosis and hepatocellular cancer.

Future research should give higher importance to conducting long-term studies in order to evaluate the enduring effectiveness and safety of resmetirom in a wide range of groups.

Assessing its cost-effectiveness relative to other new medicines for NASH will be essential for making clinical and policy decisions. Examining the possible harmonious effects of resmetirom in conjunction with other treatments, such as lifestyle changes and combination therapy, has the potential to improve results. Furthermore, it will be crucial to investigate the molecular mechanisms underlying the observed side effects and to identify patient subgroups who are more prone to experiencing adverse events.

Despite the promising findings, it is essential to acknowledge certain limitations. Firstly, while RCTs are considered the gold standard for evaluating treatment efficacy, they may not fully capture real-world patient populations and outcomes. The generalizability of findings from RCTs to broader clinical practice settings warrants consideration, particularly regarding the diversity of patient demographics, comorbidities, and treatment adherence. Additionally, the relatively short duration of the included trials may limit the assessment of long-term efficacy and safety outcomes associated with Resmetirom treatment.

The presence of significant heterogeneity across studies also poses a challenge to the interpretation of pooled results. Several factors contribute to this heterogeneity, including the limited number of studies available for analysis and variations in study durations. The lack of uniformity in reporting treatment outcomes at different time points across studies may introduce bias and complicate the synthesis of results. For instance, some studies reported outcomes at 12 and 24 weeks, while others reported outcomes at 28, 36, or 52 weeks post-treatment initiation. Moreover, the inclusion of studies with varying dosing regimens for Resmetirom may also contribute to heterogeneity. While efforts were made to standardize the dosage by selecting 80 mg as the standard dose, variation in dosing of the study, Harrison *et al.* (2024), could influence treatment outcomes and introduce an additional source of heterogeneity[4].

Conclusion

Overall, the findings of this meta-analysis show that resmetirom is a useful treatment for NASH, showing a noteworthy improvement in MRI-PDFF, 30% fat reduction, NASH resolution without fibrosis and in lowering certain liver markers. Resmetirom also has no serious side effects; however, gastrointestinal symptoms like diarrhoea and nausea have been observed in some cases. This demonstrates just how groundbreaking the drug resmetirom can be for patients with NASH. With the recent FDA approval, more thorough recommendations for resmetirom may now be established for future patient populations, which will result in more informed clinical decision-making.

Ethical approval

None to declare.

Consent

Not required because data were publicly available.

Source of funding

None to declare

Author contribution

S.M. and A.A. conceived the idea and designed the study. A.K. collected the data and analyzed it. G.S. drafted the manuscript. D.D. and S.K. conducted literature search and created the illustrations. S.J. revised the manuscript critically.

Conflicts of interest disclosure

The authors declare no conflicts of interest.

Research registration unique identifying number (UIN)

1. Name of the registry: National Institute for Health Research (NIHR) International prospective register of systematic reviews (PROSPERO)
2. Unique Identifying number or registration ID: CRD42024527140
3. Hyperlink to your specific registration (must be publicly accessible and will be checked): https://www.crd.york.ac.uk/PROSPERO/display_record.php?RecordID=527140

Guarantor

Sayed Jawad.

Data availability statement

All the data used in this study are publicly available in the trials, which are referenced in the bibliography.

Provenance and peer review

It was not invited but rather not commissioned and externally peer-reviewed.

References

[1] Guirguis E, Grace Y, Bolson A, *et al*. Emerging therapies for the treatment of nonalcoholic steatohepatitis: a systematic review. Pharmacotherapy J Hum Pharmacol Drug Ther 2021;41:315–28.
[2] Harrison SA, Bashir M, Moussa SE, *et al*. Effects of resmetirom on noninvasive endpoints in a 36-week phase 2 active treatment extension study in patients with NASH. Hepatol Commun 2021;5:573–88.
[3] Harrison SA, Taub R, Neff GW, *et al*. Resmetirom for nonalcoholic fatty liver disease: a randomized, double-blind, placebo-controlled phase 3 trial. Nat Med 2023;29:2919–28.
[4] Harrison SA, Bedossa P, Guy CD, *et al*. A phase 3, randomized, controlled trial of resmetirom in NASH with liver fibrosis. New England Journal of Medicine 2024;390:497–509.
[5] Harrison SA, Ratziu V, Anstee QM, *et al*. Design of the phase 3 <scp> MAESTRO </scp> clinical program to evaluate resmetirom for the treatment of nonalcoholic steatohepatitis. Aliment Pharmacol Ther 2024;59:51–63.
[6] Harrison SA, Bashir MR, Guy CD, *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] Page MJ, McKenzie JE, Bossuyt PM, *et al*. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71; Published online March 29.
[8] Shea BJ, Reeves BC, Wells G, *et al*. AMSTAR 2: a critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both. BMJ 2017;358:j4008.
[9] Higgins JPT, Altman DG, Gøtzsche PC, *et al*. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. BMJ 2011;343:d5928.
[10] Targher G. Editorial: Resmetirom—a promising treatment option for NASH and liver fibrosis. Aliment Pharmacol Ther 2024;59:128–9.
[11] Ray K. Resmetirom safe for nonalcoholic fatty liver disease. Nat Rev Gastroenterol Hepatol 2024;21:2.
[12] Kovalic AJ. Pharmacotherapeutic impact on nonalcoholic steatohepatitis histology: a systematic review and network meta-analysis. J Clin Exp Hepatol 2022;12:1057–68.
[13] Enomoto H, Bando Y, Nakamura H, *et al*. Liver fibrosis markers of nonalcoholic steatohepatitis. World J Gastroenterol 2015;21:7427–35.
[14] Koenig G, Seneff S. Gamma-glutamyltransferase: a predictive biomarker of cellular antioxidant inadequacy and disease risk. Dis Markers 2015;2015:818570.
[15] Angulo P, Kleiner DE, Dam-Larsen S, *et al*. Liver fibrosis, but no other histologic features, is associated with long-term outcomes of patients with nonalcoholic fatty liver disease. Gastroenterology 2015;149:389–97.e10.
[16] Targher G, Day CP, Bonora E. Risk of cardiovascular disease in patients with nonalcoholic fatty liver disease. N Engl J Med 2010;363:1341–50.
[17] Halsall DJ, Oddy S. Clinical and laboratory aspects of 3,3′,5′-triiodothyronine (reverse T3). Ann Clin Biochem Int J Lab Med 2021;58:29–37.
[18] The Lancet Gastroenterology & Hepatology. Resmetirom for NASH: balancing promise and prudence. Lancet Gastroenterol Hepatol 2024;9:273.