INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES
[ISSN: 0975-4725; CODEN(USA): IJPS00]
Journal Homepage: https://www.ijpsjournal.com

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Review Article

Resmetirom Imapact on Mash: An Overview of Previous Studies

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ARTICLE INFO

Published: 13 Jan 2026
Keywords:
Resmetirom; MASH; Thyroid hormone receptor-β; Pharmacological studies; Analytical studies.
DOI:
10.5281/zenodo.18229578

ABSTRACT

Metabolic dysfunction-associated steatohepatitis (MASH) is a progressive liver disorder .Resmetirom, a selective thyroid hormone receptor-β (THR-β) agonist, has shown results in reducing liver fat and improve metabolic parameters. This review summarizes about pharmacological, clinical, and analytical studies undergone in Resmetirom. The study shows that it lowers hepatic steatosis and improves lipid profiles. From this study, we can see that Resmetirom is a promising therapeutic agent in treatment of MASH.

INTRODUCTION

Metabolic dysfunction-associated steatohepatitis (MASH) is a liver disease which is different from alcoholic liver disease ,as the name implies it is due to metabolic imbalance and hepatic injury which leads to excess fat accumulation in liver, inflammation and progressive fibrosis. It was previously labeled under non-alcoholic fatty liver disease(NAFLD) and non-alcoholic steatohepatitis (NASH)[39].Resmetirom is a selective Thyroid hormone receptor-β(THR-β) agonist.It modulates lipid metabolism in liver by activating THR-β present in the liver, this leads to decrease in hepatic fat content , improve lipid profile and attenuate fibro genesis potentially.Many patients remain undiagnosed until advanced stages because early symptoms are non-specific and limitation of diagnostic tools[41]. Management of MASH remains lifestyle changes like diet and exercise, control of metabolic coexisting conditions(type 2 diabetes and dyslipidaemia), some other extra-hepatic coexistent conditions like cardiovascular disease, chronic kidney disease and sarcopenia.However, some patients still progress disease despite the management.Resmetiromis the first drug emerged as a disease- specific pharmacological agent to treat MASH[2].In this review article, we aim to provide a complete overview of Drug details like

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Relevant conflicts of interest/financial disclosures: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

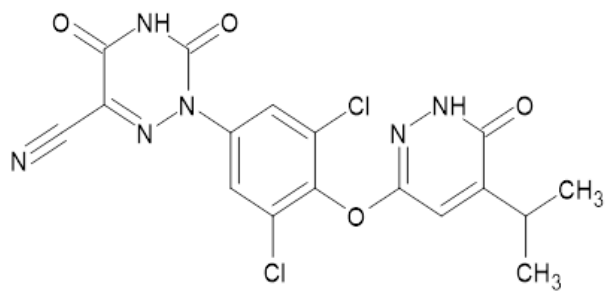
pharmacokinetic and pharmacodynamic characteristics, mechanism of action of Resmetirom and its use in treatment of MASH including its definition, pathophysiology and signs and symptoms. Others drugs or methods used for managing progression of MASH are also mentioned. We also discuss about pharmacological, pre-clinical, clinical trial data of Resmetirom, involving its safety, efficacy, and comparative studies. Analytical studies like HPLC, UV , FTIR, etc… are discussed along with their results.

RESMETIROM:

Resmetirom is an orally administered drug, which is liver targeted agonist that interacts with the thyroid receptor beta (THR- β) and is currently being studied for the treatment of MASH. The FDA has granted approval for its use in managing NASH (now called as MASH), a non-cirrhotic liver disease with moderate to advanced liver fibrosis, along with dietary changes and exercise[26].

The FDA endorsement of this medication marks a significant advancement in the treatment of NASH (non-alcoholic steatohepatitis), particularly following numerous unsuccessful attempt to create effective treatment. On March 14, 2024, The FDA granted conditional approval to Resmetirom, a medication aimed at addressing fibrotic (stage 2or 3) MASH.

RESMETROM STRUCTURE:



- **Synonym :** MGL-3196
- **IUPAC Name :** 2[3,5-dicholo-4-[6-oxo-5-propan-2-yl]1H-pyridazine -3-yl) oxyl]phenyl]-3,5-dooxo-1,2,3-triazine-6-carbonitrile
- **Brand Name :** Rezdiffra
- **Molecular Formula :** $C_{17}H_{12}CL_2N_6O_4$
- **Molecular Weight :** 435.2g / mol
- **Category :** THR β Agonist
- **Dose :** Based on actual body weight: Less than 100kg: 80mg orally a day; 100kg or greater: 100mg orally once a day
- **Solubility :** Limited water solubility at pH level below 6, with increase solubility as pH levels above 7(0.44mg /ml at PH .7.04)
- **Melting point :** 321^0C [35]
- **Storage :** Stored in tightly closed container at room temperature 120^0C -250^0C. Keep away from heat, moisture and from freezing.[29]

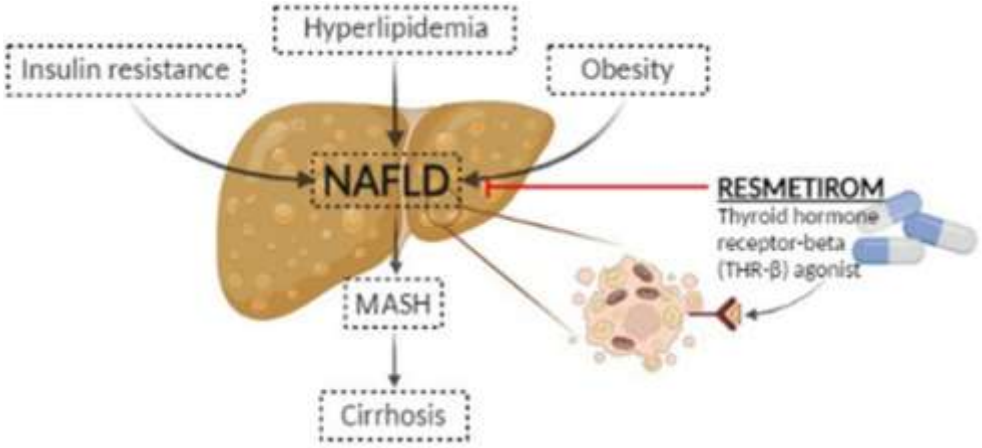
Mechanism of action:

Thyroid hormone receptor are nuclear receptor that oversee the transcription of various genes essential for metabolism functions THR-β mainly found in the liver, where it regulates important metabolic processes such as cholesterol balance, triglyceride metabolism, and hepatic lipogenesis control.By selectively binding to THR-β, Resmetirom imitates the effect of natural thyroid hormone in the liver while avoiding engagement with THR-α, thus reducing unwanted effects on the heart and other peripheral tissues. The activation THR-α can result in adverse side effect like rapid heartbeat, bone loss, and muscle breakdown. The pronounced selectivity of Resmetirom for THR-β results from structural change, which improves its binding affinity to the receptor. Research shows that when the compound binds, its causes a structural alteration in THR-β, which promotes the recruitment of specific coactivators andboosts the transcription of target

genes that enhanced lipid metabolism and decrease hepatic steatosis.

Activation of this receptor results in increased fatty acid oxidation, reduces de novo lipogenesis, and improved cholesterol removal by the liver. It is believed that the combined effects contribute reduce in lipid buildup in hepatocytes, thereby alleviating the pathological characteristics of NASH[43].

Resmetirom
↓
Selectively binds to THR-β (liver-specific receptor)
↓
Induces structural change in THR-β
↓
Recruitment of co-activators
↓
↑ Transcription of lipid-metabolism genes
↓
↑ Fatty acid oxidation
↓ De novo lipogenesis
↑ Cholesterol clearance
↓
↓ Hepatic lipid accumulation
↓
Reduces the MASH



Pharmacokinetics:

Absorption

The median Tmax is roughly four hours after administering multiple doses of Resmetirom at 80 mg or 100mg. Taking the medication with food leads to a 33% decrease in Cmax, an 11% decrease in AUC, and a delay in median Tmax by approximately two hours compared to an under fasted state.

Elimination

The orally administering a 100 mg radio- labeled dose of Resmetirom,nearly 67%of the total radioactive dose was recovered in the feces, primarily as metabolism, and 24%was detected in the urine. Unchanged labeled Resmetirom was found in the feces and it represented only 1%of the dose detected in urine.

Metabolism

Resmetirom is processed by CYP2C8 enzyme. MGL-3623, a significant metabolites, is 28 time less potent for THR-β compared to Resmetirom.

Volume of Distribution

Apparent volume of distribution of Resmetirom (VD/at steady state is (227%)L[30].

Half life

The average terminal plasma half life is 4.5 hours.

Clearance

The apparent clearance steady state (CL/F) is measure as 17.5(56.3%)L/h[28].

Drug Interactions

Resmetirom, when administered with moderate cytochrome P450 2C8 (CYP2C8) inhibitors like clopidogrel and pioglitazone shows increase in AUC and C_{max}. Similarly HMG-CoA reductase inhibitors like simvastatin, pravastatin, atorvastatin also show increase in AUC and $C_{max.}$

Side effects

Most common side effects associated with Resmetirom are diarrhea and nausea. It also causes some serious side effects like hepatotoxicity and gall bladder problems. It may also cause some other effect like dizziness, itching, pain in the stomach and constipation[25].

Uses:

Resmetirom is used along with proper diet and exercise for treatment of MASH. Stage F2 and F3 (moderate to advanced liver fibrosis) are treated with the help of Resmetirom[11].

MASH (METABOLIC DYSFUNCTION ASSOCIATED STEATOHEPATITIS):

Hepatic inflammation and fibrosis affect about 20-3% of individuals with MASLD resulting in a condition known as metabolic dysfunction associated steatohepatitis (MASH). This progression significantly raises the risk of various health issues including liver failure, hepatocellular carcinoma cardiovascular diseases cognitive decline and chronic kidney diseases[15]. The MASH was previously termed as non-alcoholic steatohepatitis (NASH). The MASH is associated with increase the risk of both hepatic and an extra-cellular hepatic complication includes cirrhosis, hepatocellular carcinoma (HCC)[27]. The phrases non alcoholic and fatty are seen as stigmatizing leading to elimination of the former and substitution of fatty with steatosis the NAFLD(Non-alcholic fatty liver disease) was termed as MASLD(Metabolic dysfunction associated steatotic liver disease) it includes individuals who have hepatic steatosis along with cardio metabolic risk such as obesity and type 2 diabetes. NAFLD is characterized by the existence of steatosis over 5% hepatocytes[5]. The livers of both mice and human affected by MASH, elevated levels of free cholesterol are observed in hepatocytes, kuffer cells and HSC's[14]. The primary medication for MASH is Resmetirom which is approved for MASH accompanied by moderate to severe liver fibrosis. Additional medications like semaglutide have also been authorized for MASH especially in patients with moderate to severe fibrosis [3,8,13].

CAUSES:

Factors that increase the risk of MASH and liver damage include obesity, insulin resistance metabolic syndrome[1]. MASLD is linked to cardiovascular risk factors which additionally impact mortality in these individuals complications such as end stage liver cirrhosis and HCC[40]. Non genetic factors include diabetes, hypertension, hyperlipidemia, obstructive sleep apnoea (OSA) gut microbiome smoking, iron overload and alcohol consumption[16]. Genetic risk has linked between genetic polymorphism and the onset of MASH. The only genetic variation found with patatin like phospholipase domain 3 known as PNPLA3. The precise way of PNPLA3 leads to build up of hepatic steatosis remains unclear; it shows that remodelling of lipid droplets in

hepatocytes and secretion of very low density lipoprotein[12].

PATHOPHYSIOLOGY:

Hepatic steatosis refers to accumulation of triglycerides (TG) in hepatocytes is the important factor of MASLD and increased TG accumulation stimulates hepatic inflammation leading to MASH. The excessive lipid deposition in liver cells that exceed the liver's metabolic capacity leads to development of MASLD. The progressive form of MASLD leads to MASH[23]. Day and James proposed a hit model of MASLD pathogenesis in 1998. The first hit is caused by the insulin resistance, which results in accumulation of fat especially TG in hepatocytes resulting in the occurrence of steatosis. The excess carbohydrates contribute for the stimulus for denovo fatty acid synthesis in liver[22]. The 2nd hit is the formation of reactive oxygen species (ROS) that catalyses lipid peroxidation, hepatocytes apotosis, steatohepatitis and fibrosis. The multiple factors such as environment, biochemical and epigenetic factors which is responsible for responsible for pathogenesis of MASLD. During development of disease and progression of MASLD to MASH, there is significant remodelling of the hepatic immune environment. It contains numerous innate immune cells that show the altered function in liver disease includes MASLD and MASH. The innate immune cells include dendritic cells, neutrophil and macrophages. The most important immune cells contributing the pathophysiology of MASH is neutrophil and phagocytic macrophages. The neutrophil involved in chronic inflammatory disorders through ROS, cytokine secretion and neutrophil extracellular traps (NET) [19].

SIGNS AND SYMPTOMS:

Individual with MASH have no clear symptom [21]. The people with MASH shows the pituitary, gonadal disorders, PCOS, and consistent abnormal of liver enzymes. The common symptoms of MASH are tiredness, unexpected weight loss, general weakness and discomfort in the upper abdomen. MASH is most frequently observed in individuals aged between 40 and 60 years. The main complication of MASH is liver cirrhosis. It results in liver failure and rarely leads to hepatic coma development of MASH severity can resemble the symptom of cirrhosis, jaundice, bruising and bleeding spots in the skin, ascities, pedal oedema, enlargement of liver, itching of the pruitis, drowsiness, mental confusion and finally lead to coma[10].

DIAGNOSIS:

Method to diagnosis a MASH is liver tissue biopsy and Non-invasive technique.

1. The liver biopsy is invasive method and most accurate. It involves the collection of liver tissue samples.
2. The Non-invasive techniques are fibrosis 4 index, FAST (Fibroscan AST) which includes age, AST, ALT and platelet count[9]. The routine laboratory test includes test for Alanine aminotransferase (AST), Complete blood count (CBC), Cholesterol (HDL cholesterol, total cholesterol)[34].

TREATMENT:

Resmetirom is a THR-β selective drug (28-fold over THR-α) developed to treat lipid-metabolism disorders. In healthy volunteers, once-daily doses of Resmetiromfor two weeks were well tolerated and produced significant reductions in circulating lipids[33].Patient with MASH and moderate to severe liver fibrosis, administrating semaglutide is a glucagon like peptide-1 receptor agonist at a dose of 2.4mg once a week resulted in enhanced liver histological outcomes[4]. The emergency treatment

for MASH includes the fibroblast growth factor 21 analogues, Aramchol is oral drug that reduce stearoylCoA desaturase-1resulting in a reduced in liver triglycerids and free fatty acid. Dual GLP-1agonists are Survodutide and Trizepatide is an injectable dual GLP agonist. Lanifibranor is an oral Pan- Peroxisome proliferator-activated receptor (PPAR) agonist[6].

ANALYTICAL METHODS PERFORMED IN RESMETIROM AND ITS RESULTS:

Analytical Method	Author Name(s)	Technique Used	Result
Quantitative determination of Resmetirom (pure form)	Shish A. Khan, Sabeeha A. Kamal, Amaan Khan, Megha Pandagale(36)	UV spectroscopy (phosphate buffer: acetonitrile 50:50), λmax-225 nm	Linearity R^2 = 0.9998; intraday precision 0.94% RSD; interday 1.94% RSD; accuracy ~100%; LOQ 0.56 µg/ml; LOD 1.69 µg/ml
		RP-HPLC (Phenomenex Kinetex XB-C18, phosphate buffer:ACN 60:40, 225 nm detection	Retention time 3.41 min; good resolution; validated per ICH parameters
Quantification of Resmetirom in API & prepared tablets	Khushi Dahiya, Sanjay Sharma(20)	RP-HPLC (Kromasil C18, ACN:ammonium acetate 70:30, detected at 298 nm)	R^2 = 0.9951; RSD <2%; accuracy 98–102%; LOD 0.214 µg/ml; LOQ 0.651 µg/ml
Comparative study (anhydrous vs dihydrate forms)	Chen Yang, Ying Luo, Wenxia Sun, Xiangkui Liu, Xueyan Zhu(7)	PXRD, TGA, DSC, FTIR, Raman spectroscopy	PXRD identified polymorphs; dihydrate confirmed by TGA weight loss; Raman showed highest quantitative performance

PHARMACOLOGICAL METHODS PERFORMED IN RESMETIROM AND ITS RESULTS:

- **Systematic Review & PICOT Analysis** –

A comparative study was carried out in 2234 patients. Rayyan software was used for screening and selection of study. It involves comparing patients treated with 80mg Resmetirom and patients treated with Placebo or conventional therapy. It was assessed for efficiency, level of liver enzymes, fat fraction, blood lipids and adverse effects. Cochrane Risk of Bias 2(ROB-2) tool was used for assessing the quality and risk. Resmetirom treated patients showed lowering in LDL-C level and ALT levels than placebo, however fat fraction and AST, GST levels gave non-significant results. Adverse effects like diarrhea, nausea was high in Resmetirom treated than placebo, they are manageable. Quality assessment showed 2 trials of low risk.[17]

- **Clinical Efficacy of Resmetirom in Phase 3 Trials –**

MAESTRO-NASH was a phase 3 trial carried out for 54 months double-blind randomized placebo-controlled trial with 52 weeks of preliminary test[38]. It involves 1:1:1 ratio of placebo, 80mg Resmetirom and 100mg Resmetirom. Separation of group was based on diabetes-2 status and fibrosis stage. MASH with no worsening of fibrosis seen in 25.9% and 29.9% of 80mg and 100mg Resmetirom treated patients respectively as compared to 9.7% of placebo group. Fibrosis improvement was seen in 24.2% and 25.9% of 80mg and 100mg Resmetirom treated patients respectively as compared to 14.2% of placebo group. LDL cholesterol levels and liver enzymes

are reduced in drug treated. 100mg of Resmetirom was more effective[37].

- **Impact of Coffee Consumption on MASH Mechanisms-**

MASH characteristics like inflammation, hepatic steatosis, fibrosis regression have shown improvement of condition on use of black coffee. This is due to certain mechanisms occurring in the body , as we know coffee contains caffeine, this caffeine aids in reducing inflammation, fibrogenesis and enhances lipid metabolism by blocking adenosine receptors. Other bioactive compounds present in coffee helps in cholesterol metabolism by Cyp7b1 activation and support liver generation by lowering CCL2 and increasing IL-6 by regulating inflammatory signals.[18]

- **Phase 2 Clinical Trial: MGL-3196-05 Study Outcomes**

MASH was undergone a 36 week, double blinded placebo controlled phase 2 trial, under MGL-3196-05 study. Hepatic fat content was analyzed at week 12 and week 36 in Resmetirom treated and placebo treated individuals. It was found that Resmetirom treated individual's shows reduction of liver fat content of -32.9% and -37.3% in 12 week and 32 week respectively. The placebo treated group showed -10.4% and -8.5% respectively[32] .

- **Preclinical Assessment of Resmetirom Across Multiple MASH Mouse-**

Gubra-Amylin NASH (GAN) was a diet induced obesity(DIO) induced in 6 mice for 24 weeks, followed by semaglutide and Resmetirom for 4 weeks. Similarly, ob-MASH model was induced by GAN diet in ob-mice for 6 weeks, followed by semaglutide and Resmetirom for 4 weeks and GAN-carbon tetrachloride model was induced by 10 weeks of GAN diet and followed by 4 weeks of carbon tetrachloride in 6 mice, Resmetirom and obeticholic acid(OCA) for last 4 weeks. In GAN DIO-MASH model, both semaglutide and Resmetirom reduces NASH and α-smooth muscle actin (SMA) was reduced in Resmetirom. In ob-MASH model, both drugs reduce NASH and α-SMA expression was reduced by semaglutide. In GAN-carbon tetrachloride model, both Resmetirom and OCA reduces MASH. Resmetirom reduces liver fibrosis and α-SMA expression while, OCA reduces the α-SMA expression only[31].

- **Synergistic Effects of Low-Dose Resmetirom and Metformin in MASH-**

Combination of half dose of Resmetirom and low dose of metformin were studied in vivo and in vitro on treating MASH. Transcriptome and lipidomics are used to assess the efficacy of RM. It was analyzed that RM was comparable to Resmetirom and lesser than metformin on reducing lipid production and accumulation, reducing inflammation and improving fibrosis. RM also aids in cholesterol transformation thereby, managing MASH[42].

- **Evaluation of FCGs from Dianthus superbusin MASLD Models-**

Isolation of four flavones C-glycosides (FCGs) was isolated from Dianthus superbus L. and analyzed its potential for treating MASLD. FCGs modulate various MASLD pathways like lipid metabolism, insulin signaling, inflammation and apotosis. Furthermore, zebra fish model of MASLD induced by egg yolk powder, FCGs administration reduces obesity, hepatic lipid accumulation and liver tissue damage. It also improves lipid metabolism and suppresses inflammation[24].

- **Zebrafish Larvae Study: Developmental Impact and Behavioral Changes-**

This study involves determination of effects caused by Resmetirom on embryo like its growth and development and embryo toxicity. Resmetirom was dissolved in DMSO of 100 µM concentration of stock was prepared. Zebra fish larvae are used for the detection .Solvent control (DMSO), 1, 10, 100 µM of Resmetirom solution in 4ml E3 medium for 6 hr post fertilization to 120 hr post fertilization. Abnormalities, mortality and hatching rates are monitored. It was found that Resmetirom does not affect the early stages of embryo development, but cause development delays and spontaneous behaviors were reduced, no change in neurotransmitter level and activation of metabolic pathway was seen[44].

DISSCUSSION:

Resmetirom represents one of the most promising therapeutic options for the management of metabolic dysfunction–associated steatohepatitis (MASH). Across previous pharmacological studies, the drug has consistently shown significant reductions in liver fat content, improvements in non-invasive biomarkers, and favorable effects on lipid metabolism. Its mechanism as a selective thyroid hormone receptor-β agonist directly targets hepatocellular lipid handling, which addresses the core metabolic dysfunction involved in MASH progression. Although long-term clinical outcome data are still evolving, the available evidence highlights meaningful improvements in fibrosis markers and overall hepatic function.

From an analytical perspective, methods-such as HPLC, UV spectrophotometry, have been developed to support pharmacokinetic, formulation, and quality-control studies of Resmetirom. These analytical tools ensure accurate quantification, purity assessment, and stability profiling, which are crucial for establishing the safety and therapeutic consistency of the drug. However, gaps still remain, particularly in UV method validation and solvent-system optimization, indicating the need for further analytical standardization.Overall, both pharmacological evidence and analytical advancements support the therapeutic value of Resmetirom for MASH. Future studies focusing on long-term outcomes, combination therapy potential, validated analytical protocols, and large-scale clinical evaluation will help in confirming its role as a first-line, targeted treatment for MASH.

ACKNOWLEDGEMENT:

The authors wish to thank Sakthi Arul Thiru Amma and Thirumathi Amma ACMEC Trust, for providing facilities to do the work in successful manner, We are grateful to thank our Dean Research & Director Academic Prof, Dr. T. Vetrichelvan for the kind support and encouraging for the completion of work, We would like to thank all the anonymous individuals who helped with this study.

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HOW TO CITE: Dr. Abirami G, Nanthagopal P, Aishwarya R, Dhivya V, Janani S, Jananipriya B, Resmetirom Imapact on Mash: An Overview of Previous Studies, Int. J. of Pharm. Sci., 2026, Vol 4, Issue 1, 1202-1213. https://doi.org/10.5281/zenodo.18229578