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Resmetirom and beyond: A new era in MASLD therapeutics

Dear Editor,

Metabolic dysfunction-associated steatotic liver disease (MASLD), formerly known as non-alcoholic fatty liver disease (NAFLD), has emerged as the most prevalent chronic liver condition globally, affecting nearly 100 million individuals in the United States alone.[1] The recent reclassification of NAFLD to MASLD and non-alcoholic steatohepatitis (NASH) to metabolic dysfunction-associated steatohepatitis (MASH) reflects a paradigm shift in understanding the metabolic underpinnings of this disease.[2]

The pathogenesis of MASLD is multifactorial, involving insulin resistance, oxidative stress, chronic inflammation, and fibrogenesis.[3] These mechanisms are further modulated by genetic variants such as patatin-like phospholipase domain-containing 3 (*PNPLA3*) and transmembrane 6 superfamily member 2 (*TM6SF2*), which influence disease progression and therapeutic response.[4] Historically, treatment of MASH has relied on lifestyle interventions, but the recent Food and Drug Administration (FDA) approval of resmetirom (Rezdiffra) marks a significant milestone in pharmacologic management.[5]

Resmetirom is a selective thyroid hormone receptor beta (THRβ) agonist that targets hepatic lipid metabolism. By enhancing mitochondrial β-oxidation and reducing lipogenesis, resmetirom significantly decreases hepatic fat content and improves markers of inflammation and fibrosis.[6] Drug development for fibrosis, particularly in conditions like MASH, is closely tied to fibrosis staging, ranging from stage F0 (indicating a healthy liver) to stages F1 through F4, which reflect progressively worsening liver damage, from mild-F1 to severe-F4. In a pivotal phase 3 trial, resmetirom demonstrated histological resolution of MASH and fibrosis improvement in patients with stage F2–F3 fibrosis.[7] Its favorable safety profile, with mostly mild gastrointestinal side effects, further supports its clinical utility.[8]

The approval of resmetirom represents a turning point in MASLD management, offering the first disease-modifying therapy for patients with MASH and fibrosis.[9] However, it is unlikely to be the last. Several other agents are advancing through late-stage clinical trials, targeting diverse pathogenic pathways.

Lanifibranor, a pan-peroxisome proliferator-activated receptor (PPAR) agonist, modulates lipid metabolism, insulin sensitivity, and fibrogenesis. In the NATIVE trial, it improved both liver histology and cardiometabolic parameters, including reductions in triglycerides and systemic inflammation.[10] Common side effects included diarrhea, nausea, peripheral edema, anemia, and weight gain. Semaglutide, a glucagon-like peptide-1 (GLP-1) receptor agonist, has shown promise in resolving MASH and improving fibrosis, particularly in patients with obesity or type 2 diabetes.[11] Semaglutide acts both centrally, by targeting the hypothalamus to regulate appetite, and peripherally, by enhancing insulin secretion and sensitivity as well as slowing gastric emptying. Side effects include gastrointestinal disturbances, while more serious adverse events, though less common, include pancreatitis and a boxed warning for medullary thyroid carcinoma.

Fibroblast growth factor 21 (FGF21) analogs such as efruxifermin and pegozafermin are also in phase 3 trials. These agents enhance fatty acid oxidation, reduce hepatic inflammation, and improve insulin sensitivity.[12] Preliminary data suggest they may offer dual hepatic and metabolic benefits, with once-weekly dosing improving adherence. Liver-to-brain FGF21 signaling is a key mechanistic pathway underlying its action. Common side effects of both agents include gastrointestinal symptoms such as diarrhea and nausea. Pegozafermin is additionally associated with increased appetite, while efruxifermin may cause injection site reactions.

Beyond these agents, the MASLD pipeline includes stearoyl-CoA desaturase 1 (SCD1) inhibitors (*e.g.*, Aramchol), galectin-3 inhibitors (*e.g.*, Belapectin), and dual GLP-1/glucagon receptor agonists (*e.g.*, Survodutide and Pemvidutide).[13] These therapies target distinct mechanisms, from lipid remodeling to portal hypertension and mitochondrial dysfunction.

Given the multifactorial nature of MASLD, combination therapies are likely to become the standard of care. Trials, such as ATLAS (NCT03449446), have already explored the synergistic effects of combining acetyl-CoA carboxylase (ACC) inhibitors with other agents.[14] Future regimens may integrate metabolic, anti-inflammatory, and anti-fibrotic strategies tailored to individual patient profiles.[14]

MASLD drug development is increasingly mechanism-informed, with efforts spanning metabolic, inflammatory, fibrotic, and genetic pathways. Table 1 provides a classification of agents by their principal mechanisms.

Dozens of agents are now progressing through clinical development, targeting inflammation, lipotoxicity, fibrosis, and insulin resistance. These include metabolic modulators, incretin-based therapies, FGF analogs, cyclophilin inhibitors, and RNA-based anti-fibrotics. Table 2 summarizes MASLD therapeutic agents currently in phase 1 to 3 trials.[14]

The rapid evolution of MASLD therapeutics necessitates a shift in clinical practice. While lifestyle modification remains foundational, clinicians must now consider pharmacologic options for patients with progressive fibrosis or high-risk features. Noninvasive tools such as magnetic resonance imaging proton density fat fraction (MRI-PDFF) and transient elastography will be critical for

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Table 1
Mechanism-based classification of MASLD therapeutics.

Mechanism	Representative drugs	Role in MASLD
THRβ agonists	Resmetirom, TERN-501	Stimulate hepatic β-oxidation, reduce liver fat
GLP-1 receptor agonists	Semaglutide	Promote weight loss, reduce hepatic steatosis and inflammation
Pan-PPAR agonists	Lanifibranor	Improve lipid metabolism, reduce inflammation and fibrosis
GLP-1/glucagon receptor dual agonists	Survodutide, Pemvidutide	Promote weight loss, reduce steatosis and inflammation
FGF21 analogs	Efruxifermin, Pegozafermin	Improve insulin sensitivity and lipid homeostasis
Lipogenesis inhibitors	Firsocostat, Denifanstat, Aramchol	Inhibit hepatic fat synthesis
Cyclophilin inhibitors	Rencofilstat	Protect mitochondria, reduce fibrosis
Galectin-3 inhibitors	Belapectin	Inhibit stellate cell activation, reduce portal hypertension
FXR agonists	ASC42	Anti-fibrotic and anti-inflammatory via bile acid signaling
Chemokine/integrin inhibitors	CM-101, PLN-74809	Target immune-fibrotic interface
RNA therapies	BMS-986263, ARO-HSD	Gene silencing for fibrosis/injury regulation
Mitochondrial modulators	HU6	Enhance energy metabolism, reduce liver steatosis

Abbreviations: FGF21, fibroblast growth factor 21; FXR, farnesoid X receptor; GLP-1, glucagon-like peptide-1; MASLD, metabolic dysfunction-associated steatotic liver disease; PPAR, peroxisome proliferator-activated receptor; RNA, ribonucleic acid; THRβ, thyroid hormone receptor beta.

Table 2
MASLD therapeutic drugs in clinical trials (phase 1–3).

Phase	Drug	Mechanism	Trial ID/status	Outcomes
3	Resmetirom	THRβ agonist	Completed (NCT03900429)	Met primary endpoint: Significant reduction in liver fat and NASH resolution
3	Semaglutide	GLP-1 receptor agonist	Ongoing (NCT04822181)	The primary end point: Achieved resolution of steatohepatitis without fibrosis worsening and reduction in fibrosis without steatohepatitis worsening In August 2025, the U.S. FDA granted accelerated approval for semaglutide to treat adults with MASH and moderate-to-advanced liver fibrosis (F2–F3) who do not have cirrhosis.
3	Lanifibranor	Pan-PPAR agonist	Ongoing (NCT04849728)	N/A (Ongoing)
3	Aramchol	SCD1 inhibitor	Completed (NCT04104321)	Did not meet primary endpoint (NASH resolution without fibrosis worsening)
3	Efruxifermin	FGF21 analog	Ongoing (NCT06215716)	N/A (Ongoing)
3	Pegozafermin	PEGylated FGF21 analog	Ongoing (NCT06318169)	N/A (Ongoing)
3	Belapectin	Galectin-3 inhibitor	Cirrhosis (NCT04365868)	The trial ended on September 30, 2025, but data is not yet available; some benefit in patients without varices
2	Survodutide	GLP-1/glucagon receptor dual agonist	Ongoing (NCT04771273)	N/A (Ongoing)
2	Pemvidutide	GLP-1/glucagon receptor dual agonist	Ongoing (NCT05989711)	N/A (Ongoing)
2	Firsocostat	ACC1/2 inhibitor	Completed (NCT02856555)	Reduced hepatic steatosis; combination therapy is more effective.
2	Denifanstat	FASN inhibitor	Ongoing (NCT03938246)	N/A (Ongoing)
2	Rencofilstat	Cyclophilin inhibitor	Ongoing (NCT05402371)	N/A (Ongoing)
2	ALG-055009	Selective THRβ agonist	Ongoing (NCT06342947)	N/A (Ongoing)
2	MSDC-0602K	Insulin sensitizer	Ongoing (NCT02784444)	N/A (Ongoing)
1	HU6	Mitochondrial modulator	Ongoing (NCT05267297)	N/A (Ongoing)
1	TERN-501	THRβ agonist	Completed (NCT05415722)	Reduced liver fat; good safety profile
1	BMS-986263	HSP47 antisense oligonucleotide	Ongoing (NCT04267393)	N/A (Ongoing)
1	ASC42	FXR agonist	Ongoing (NCT05144546)	N/A (Ongoing)
1	CM-101	CCL24 mAb (anti-inflammatory/fibrotic)	Ongoing (NCT05075842)	N/A (Ongoing)
1	PLN-74809	Integrin αVβ1/αVβ6 inhibitor	Ongoing (NCT04480840)	N/A (Ongoing)
1	ARO-HSD	HSD17B13 siRNA	Ongoing (NCT04202354)	N/A (Ongoing)

Abbreviations: ACC, acetyl-CoA carboxylase; CCL24, C–C motif chemokine ligand 24; FASN, fatty acid synthase; FGF21, fibroblast growth factor 21; FXR, farnesoid X receptor; GLP-1, glucagon-like peptide-1; HSD17B13, hydroxysteroid 17-beta dehydrogenase 13; HSP47, heat shock protein 47; MASH, metabolic dysfunction-associated steatohepatitis; MASLD, metabolic dysfunction-associated steatotic liver disease; N/A, not applicable; NASH, non-alcoholic steatohepatitis; PEG, polyethylene glycol; PPAR, peroxisome proliferator-activated receptor; SCD1, stearoyl-CoA desaturase 1; THRβ, thyroid hormone receptor beta.

monitoring treatment response and guiding therapeutic discussion.

Moreover, the integration of genetic and metabolic biomarkers may enable personalized treatment approaches. As our understanding of MASLD pathophysiology deepens, precision medicine strategies will likely emerge, optimizing outcomes while minimizing adverse effects.

Despite these advances, challenges persist. No therapy is currently approved for advanced cirrhosis, and the role of drugs in reversing portal hypertension remains unclear. Further, reliance on liver biopsy as a trial endpoint is increasingly untenable. Enhanced liver fibrosis (ELF) test, fibrogenesis marker PRO-C3, and miRNA panels comprising miR-122, miR-22, miR-132, miR-103/107, etc., are showing promise in reducing biopsy dependency.[15]

Experts now advocate for combination therapy targeting multiple disease axes. For example, pairing a THRβ agonist with an anti-fibrotic or incretin mimetic may improve long-term histologic and metabolic outcomes. Additionally, genetic and biomarker-guided precision medicine is on the horizon, with *PNPLA3*, hydroxysteroid 17-beta dehydrogenase 13 (*HSD17B13*), and *TM6SF2* variants being investigated as stratification tools. Despite these promising

developments, combination therapies introduce new challenges in terms of safety and tolerability. Overlapping or additive adverse effects, such as gastrointestinal disturbances with GLP-1 agonists, thyroid dysfunction with THRβ agonists, or potential hepatotoxicity with certain anti-fibrotics, require careful monitoring and dose optimization. Rigorous clinical trial designs are needed to balance efficacy with long-term safety in combination regimens. Translational studies and preclinical models support synergistic effects from targeting metabolic and fibrotic pathways simultaneously.

The approval of resmetirom heralds a new era in MASLD management, transforming a historically untreatable condition into one with viable therapeutic options. With a robust pipeline of agents targeting diverse pathways, the future of MASLD care is poised to become increasingly personalized and effective. Continued research, patient stratification, and real-world data will be essential to fully realize the potential of these innovations.

Authors' contributions

Tejona Johnson-Moore: Writing – original draft, Conceptualization. **Dasia Simmons:** Writing – original draft, Conceptualization. **Alvina Okafor:** Writing – original draft, Conceptualization. **D'Era Washington:** Writing – original draft, Conceptualization. **Padmamalini Baskaran:** Writing – review & editing, Writing – original draft, Supervision, Investigation, Funding acquisition, Conceptualization.

Declaration of competing interest

The authors declare that they have no conflict of interest.

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