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Review Article

Pipeline of New Drug Treatment for Non-alcoholic Fatty Liver Disease/Metabolic Dysfunction-associated Steatotic Liver Disease

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Abstract

Given the global prevalence and rising incidence of metabolic dysfunction-associated steatotic liver disease (MASLD), the absence of licensed medications is striking. A deeper understanding of the heterogeneous nature of MASLD has recently contributed to the discovery of novel groups of agents and the potential repurposing of currently available medications. MASLD therapies center on four major pathways. Considering the close relationship between MASLD and type 2 diabetes, the first approach involves antidiabetic medications, including incretins, thiazolidinedione insulin sensitizers, and sodium-glucose cotransporter 2 inhibitors. The second approach targets hepatic lipid accumulation and the resultant metabolic stress. Agents in this group include peroxisome proliferator-activated receptor agonists (e.g., pioglitazone, elafibranor, saroglitazar), bile acid-farnesoid X receptor axis regulators (obeticholic acid), de novo lipogenesis inhibitors (aramchol, NDI-010976), and fibroblast growth factor 21/19 analogs. The third approach focuses on targeting oxidative stress, inflammation, and fibrosis. Agents in this group include antioxidants (vitamin E), tumor necrosis factor α pathway regulators (emricasan, pentoxifylline, ZSP1601), and immune modulators (cenicriviroc, belapectin). The final group targets the gut (IMM-124e, solithromycin). Combination therapies targeting different pathogenetic pathways may provide an alternative to MASLD treatment with higher efficacy and fewer side effects. This review aimed to provide an update on these medications.

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Introduction

In 2020, a group of experts aimed to integrate the understanding of patient heterogeneity and more accurately highlight disease pathogenesis captured under the acronym non-alcoholic fatty liver disease (NAFLD). Consequently, the term metabolic dysfunction-associated fatty liver disease (MAFLD) was introduced as a more appropriate overarching terminology.[1] However, concerns were raised about the stigmatizing term "fatty" and the inclusion of two metabolic risk factors, as well as the allowance of more liberal alcohol use, thus distracting our attention from the natural history of the disease. Under the auspices of the American Association for the Study of Liver Diseases (hereinafter referred to as AASLD) and the European Association for the Study of the Liver (hereinafter referred to as EASL), in collaboration with the Asociación Latinoamericana para el Estudio del Hígado and with the engagement of academic professionals worldwide, metabolic dysfunction–associated steatotic liver disease (MASLD) was voted to be the most appropriate replacement in 2023. MASLD is defined as hepatic steatosis with one cardiometabolic risk factor and without any other discernible cause.[2] Given the >99% overlap between patients meeting the criteria for NAFLD and those identified as having MASLD, we hereafter use MASLD as the standardized nomenclature instead of NAFLD.[3] MASLD is now the most prevalent chronic liver disease in the world, encompassing a continuum of liver abnormalities from MASLD to metabolic dysfunction-associated steatohepatitis (MASH), progressing to cirrhosis and hepatic cancer. MASH is the primary risk factor for progressive hepatic fibrosis and possibly cardiovascular disease and malignancy.[4–6] Moreover, patients with moderate to advanced hepatic fibrosis are at increased risk of cirrhosis,[7,8] which justifies the need for pharmacotherapy in patients with MASH and advanced fibrosis.

According to the AASLD and EASL practice guidelines, the main goal of most lifestyle interventions is 5–10% weight loss in overweight/obese MASLD patients.[3,9,10] In clinical trials, MASLD treatments generally target glucose and lipid metabolism to alleviate inflammation and improve hepatic histology. MASLD treatments targeting the enterohepatic axis and gut microbiota are gradually emerging, and a variety of new metabolism-modulating drugs are also under clinical

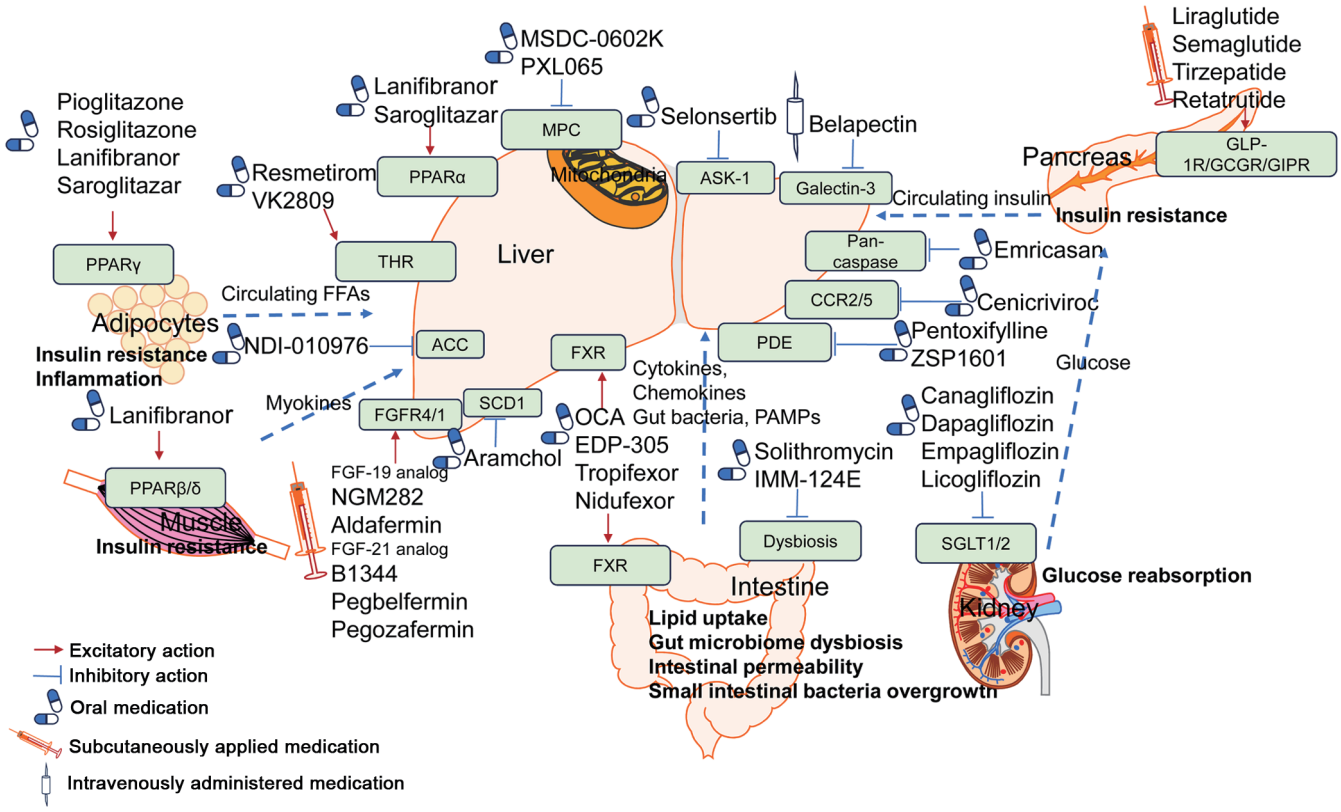

Fig. 1. Potential candidates for MASLD and their mechanisms of action. ACC, Acetyl-CoA Carboxylase; PPAR, peroxisome proliferator–activated receptor; MPC, mitochondrial pyruvate carrier; THR, thyroid hormone receptor; ASK-1, apoptosis signaling kinase-1; GLP-1R, glucagon-like peptide-1 receptor; GCGR, glucagon receptor; GIPR, glucose-dependent insulinotropic polypeptide receptor; PDE, phosphodiesterase; SGLT, sodium–glucose cotransporter; FXR, farnesoid X receptor; SCD1, stearoyl-CoA desaturase 1; FGFR4/1, fibroblast growth factor receptor4/1.

development. Potential medications and targets for MASLD are shown in Figure 1. Here we will explore the latest relevant literature from January 2019 to April 2024 in the database PubMed/MEDLINE, with the results enriched by manual searches and citation mining, and discuss the ongoing therapeutic options for MASLD focused on treating T2DM, insulin resistance, and intermediary metabolism to address the global health burden of these highly relevant diseases. Due to the large number of medications tested only in preclinical models, the review will center on potential medications that have progressed to clinical trials (Table 1).[11–54] Current phase 2 and 3 clinical trials are summarized in Table 2.

Antidiabetic agents

The definition of MASLD includes hepatic steatosis and meets at least one of three criteria: T2DM, obesity, or metabolic disorder.[55] MASLD and T2DM share many common pathophysiological mechanisms. Given that MASLD and T2DM often coexist, various antidiabetic agents have been investigated as potential therapeutics for MASH. Numerous clinical trials are exploring the therapeutic roles of glucagon-like peptide (GLP)-1 modulators, insulin-sensitizing thiazolidinediones, and sodium-glucose cotransporter 2 (SGLT2) inhibitors in patients with MASLD, which will be discussed in this section. Metformin, a biguanide drug and first-line therapy for T2DM, lacks histological benefits in human MASH; therefore, we will not explore it here, despite its potential to inhibit high-fat diet-induced HCC progression.[56]

Incretins: GLP-1R agonist/glucose-dependent insulinotropic polypeptide (GIP) analog/glucagon receptor (GCGR) agonist

Incretins are gut-derived peptide hormones that are promptly induced after a meal, with GIP and GLP-1 being the two major components. GLP-1 is produced through the proteolytic processing of proglucagon, promoting insulin secretion while inhibiting glucagon production. The effects of GLP-1 agonists on MASH may be indirect, resulting from reductions in calorie intake, body weight, and insulin resistance, all of which help decrease liver lipid accumulation and hepatic inflammation.[11,57] Liraglutide, a GLP-1 receptor agonist requiring daily injection, improved MASH histology in a small pilot study.[12] However, the benefits of liraglutide in reducing weight, hepatic steatosis, and hepatocellular apoptosis in obese adults with MASLD were not sustained upon discontinuation, especially when compared to lifestyle modifications (NCT02654665).[13] A phase 2 trial showed that semaglutide, a GLP-1 receptor agonist administered weekly, contributed to significant MASH resolution; however, it did not improve the fibrosis stage (NCT02970942).[14] In cases of MASH-related compensated cirrhosis, semaglutide did not significantly achieve MASH resolution or improve fibrosis (NCT03987451).[15] Dual GLP-1 and GIP agonists are expected to have more profound effects. Statistics from the phase 3 SURMOUNT study, which recruited over 5,000 adults globally, demonstrated a pronounced reduction in body weight in the tirzepatide-treated group compared to placebo (NCT04184622).[16] A sub-study of the SURPASS-3

Table 1. Main agents and their characteristics for treating MASLD

Agents	Mechanisms of action	Positive endpoint (s), Ref	Negative endpoint (s), Ref	Comments
Liraglutide	GLP-1 receptor agonist requiring daily injection	Improved MASH histology in a small pilot study[11]	Decrease in weight, hepatic steatosis, and hepatocellular apoptosis in obese adults with MASLD not sustained if discontinued (NCT02654665).[12]	
Semaglutide	GLP-1 receptor agonist with weekly injection	Contributed to a significant MASH resolution (NCT02970942)[13]	Lacking an improvement in the fibrosis stage (NCT02970942).[13] For MASH-related compensated cirrhosis, did not achieve MASH resolution or improve fibrosis (NCT03987451)[14]	
Tirzepatide	Dual GLP-1 and GIP agonists	Pronounced reduction in body weight (NCT04184622).[15] Decreased liver fat by 8.1% over 52 weeks associated with reduction in ALT, AST, and γ-GT (NCT03882970).[16]	–	
Retatrutide	Novel triple agonist peptide at GCGR, GIPR, and GLP-1R	Significant body weight loss in obese patients (NCT04881760).[17] Reduce plasma ALT and hepatic triglycerides in obese mice.[18]	–	
Pioglitazone and rosiglitazone	PPAR-gamma and the MPC agonist	Long-term pioglitazone treatment is safe and effective in patients with prediabetes or T2DM and MASLD (NCT00994682).[19]	–	The main side effect is weight gain
MSDC-0602K	Preferentially suppress the MPC while minimizing direct binding to PPARγ	The substantial decrease in glucose, insulin, liver enzymes, and NAS effects on patients with biopsy-confirmed MASH and fibrosis (F1-F3).[20]	–	
PXL065	A novel PPARγ agonist	Improve liver fat content, PIIINP, and NAFLD fibrosis score, as well as histological parameters including NAS and fibrosis, with a favorable safety profile.[21]	–	
Canagliflozin, dapagliflozin, empagliflozin ertugliflozin	SGLT2 inhibitors	Improve hepatic lipid content, liver enzymes, and fibrosis.[22–26] Dapagliflozin 10 mg for 12 weeks, significantly reduced intrahepatic lipid contents and ALT in patients with T2DM.[27]	–	Reduce cardiovascular disease risk and improve renal function in T2DM patients
Licogliflozin	Potent SGLT1 and SGLT2 inhibitor	Improve serum ALT in patients with MASH (NCT03205150).[28]	–	

(continued)

Table 1. *(continued)*

Agents	Mechanisms of action	Positive endpoint (s), Ref	Negative endpoint (s), Ref	Comments
OCA	The nuclear FXR agonist	Rapid and sustained improvements in liver enzymes and stiffness with OCA 25 mg qd treatment.[29]	Failed to show OCA's superiority compared to placebo at improving liver fibrosis in patients with compensated MASH-related cirrhosis (NCT03439254).	FDA rejected the application for OCA as a treatment for MASH-related pre-cirrhotic liver fibrosis in June 2023 due to its unfavorable benefit/risk profile.
EDP-305	A novel oral FXR agonist	Reduced ALT level and liver fat content at week 12 (NCT03421431).[30]	–	
Tropifexor (LJN452)	Non-bile acid FXR agonist	Improvement in ALT and hepatic fat fraction was sustained up to 48 weeks of treatment (NCT02855164).[31]	–	Dose-dependent pruritus was also the most common side effect.
Nidufexor (LMB763)	Non-bile acid agent with partial FXR agonistic activity	–	A multicenter study to assess the safety, tolerability, pharmacokinetics, and efficacy of nidufexor in patients with MASH was terminated without results posted (NCT02913105).	
NGM282	FGF19 analog	Twelve weeks contributed to rapid and significant reductions in liver fat content, ALT and AST, and serum markers of fibrogenesis.[32] Improved the histological features of MASH in 12 weeks with significant reductions in NAS and fibrosis scores, accompanied by improvements in noninvasive imaging and serum markers.[33]	–	
Aldafermin	Engineered FGF19 analog	Reduced liver fat and had a trend toward fibrosis improvement.[34]	–	
Efruxifermin	Bivalent Fc-FGF21 analog	Improved hepatic inflammation and fibrosis over 24 weeks in patients with F2 or F3 fibrosis, with acceptable safety (NCT04767529).[35]	–	
Pegbelfermin (BMS-986036)	PEGylated human FGF21 analog	Subcutaneous administration of pegbelfermin consistently for 16 weeks was well tolerated and decreased hepatic fat fraction based on MRI in MASH subjects (NCT02413372).[36]	Once a week for 48 weeks did not achieve a one-stage or greater improvement in the NASH Clinical Research Network fibrosis without NASH worsening (NCT03486912).[37]	

(continued)

Table 1. *(continued)*

Agents	Mechanisms of action	Positive endpoint (s), Ref	Negative endpoint (s), Ref	Comments
Lanifibranor	Pan-PPAR agonist	The percentage of patients who achieved at least a two-point reduction in the SAF-A score without fibrosis progression was higher among those who received the 1,200 mg dose (NCT03008070).[38]	–	
Saroglitazar	PPAR-α/γ agonist	Improved ALT, LFC, insulin resistance, and atherogenic dyslipidemia in patients with MASLD/MASH (NCT03060721)[39]	–	Saroglitazar is an authorized medication for non-cirrhotic MASH in India
NDI-010976	Inhibitor of ACC1 and ACC2	Dose-dependent inhibition of hepatic DNL in overweight male adults	–	
Aramchol	Inhibition of stearoyl-CoA desaturase (SCD) 1	Improve liver fibrosis and ALT level (NCT02279524).[40]	Lacks impact on liver fat fraction (NCT02279524).[40]	
Belapectin	Galectin-3 inhibitor	In a subgroup analysis of patients without esophageal varices, belapectin 2 mg/kg suppressed HVPG and development of varices (NCT02462967).[41]	Lacks favorable effects on HVPG or fibrosis in patients with MASH, cirrhosis, and portal hypertension (NCT02462967).[41]	
Resmetirom (MGL-3196)	liver-targeted THRβ agonist	Produced excellent reductions in hepatic lipid fraction and fibrosis, as well as plasma lipid and enzyme levels in patients with MASH (NCT02912260).[42,43] Significant effects on MASH resolution, fibrosis improvement, and LDL cholesterol reduction (NCT03900429).[44]	–	Potential FDA approval of resmetirom for MASH treatment.
VK2809	THRβ agonist	Reduce liver lipid content in patients with MASLD (NCT02927184).	–	
Vitamin E	Antioxidant	Combination of pioglitazone and vitamin E therapy exerts favorable impact on hepatic inflammation and ballooning.[45]	Lack of efficacy in attenuating hepatic fibrosis in a large randomized controlled trial. A combination of pioglitazone and vitamin EA therapy has no effect on fibrosis.[45]	

(continued)

Table 1. *(continued)*

Agents	Mechanisms of action	Positive endpoint (s), Ref	Negative endpoint (s), Ref	Comments
Emricasan	Pan-caspase inhibitor	Lowered serum ALT in the short-term.[46] Generally safe and well-tolerated in patients with decompensated MASH cirrhosis (NCT03205345).[47]	Did not improve liver histology in MASH-related fibrosis, which may have exacerbated ballooning and fibrosis (NCT02686762). In patients with decompensated MASH cirrhosis, it had no significant effect on the MELD-Na score, international normalized ratio, total serum bilirubin, albumin level, or Child-Pugh score (NCT03205345).[47] Patients with MASH-related cirrhosis and severe portal hypertension could not improve either HVPG or clinical outcomes (NCT02960204).[48]	
Selonsertib	ASK-1 inhibitor	Ameliorated MASH and improved fibrosis in some patients in a short-term clinical trial.[49]	Lack of efficacy in MASH adults with stage 3 (NCT03053050) and stage 4 (NCT03053063) fibrosis.	
CVC	CCR2/CCR5 inhibitor	Reduced 2-year liver fibrosis progression in a clinical trial of MASH (NCT02217475).[50,51]	The treatment of liver fibrosis in adult MASH subjects was terminated early due to lack of efficacy (NCT03028740).	
PTX	Nonspecific PDE inhibitor	Improved hepatic histological features including fibrosis in patients with MASH (NCT00590161).[52]	–	
ZSP1601	Pan-PDE inhibitor	Improved serum liver enzymes, fat content, and Fibroscan parameters in patients with MASLD.[53]	–	
IMM-124e	Product of bovine colostrum enriched in IgG	In biopsy-proven MASH showed a reduction in AST and ALT (NCT02316717).	No change in hepatic fat content in biopsy-proven MASH (NCT02316717).	
AWRK6	Developed on the antimicrobial peptide Dybowskin-2CDYa	Improved lipid and glucose metabolism homeostasis in the mouse model.[54]		novel GLP-1 receptor agonist candidate
Solithromycin	A new generation macrolide antibiotic	Improve NAS and ALT levels in a phase 2 13-week open-label MASH trial (NCT02510599).	–	
Cilofexor and firsocostat	Combine ACC inhibitor and FXR agonist	Well tolerated, improves MASH disease parameters, may improve fibrosis.	–	
PF-06865571 and PF-05221304	Combine DGAT2 inhibitor and ACC1/2 inhibitor	PF-06865571 could mitigate The effect of PF-05221304 on serum triglycerides (NCT03776175).	–	

ALT, alanine aminotransferase; MPC, mitochondrial pyruvate carrier; NAS, non-alcoholic fatty liver disease activity score; PIIINP, procollagen III N-terminal propeptide; FXR, farnesoid X receptor; OCA, obeticholic acid; FGF, factor fibroblast growth factor; AST, aspartate aminotransferase; γ-GT, gamma-glutamyltransferase; HVPG, hepatic venous pressure gradient; OCA, obeticholic acid; ASK-1, apoptosis signaling kinase-1; CCR, C–C motif chemokine receptor; CVC, cenicriviroc; PTX, pentoxifylline; PDE, phosphodiesterase; GCGR, glucagon receptor.

Table 2. Ongoing major clinical trials of pharmacotherapies for the treatment of MASLD

Agent (trial name)	Primary mechanism	Major inclusion criteria	Primary outcome (s)	Estimated completion	Phase	Trial number
Lanifibranor (NATiV3)	pan-PPAR agonist	MASH on biopsy with stage 2 or 3 fibrosis	Resolution of MASH without worsening fibrosis	2026/9/30	3	NCT04849728
MGL-3196 (MAESTRO-NASH)	THR-β agonist	MASH with fibrosis	Resolves MASH and/or reduces fibrosis on liver biopsy and prevents progression to cirrhosis and/or advanced liver disease	2028/1/28	3	NCT03900429
MSDC 0602K	mTOT inhibitor	Subjects with pre-T2D or T2D and evidence of MASLD/MASH	Improved glycemic control and cardiovascular Outcomes	2024/9/1	3	NCT03970031
Pentoxifylline	Phosphodiesterase inhibitor	Patients with MASH	Not specified	2022/10/1	3	NCT05284448
Aramchol (ARMOR)	SCD-1 inhibitor	MASH and fibrosis confirmed by liver histology (F1-F3)	MASH resolution, fibrosis improvement and clinical outcomes related to progression of liver disease.	2027/6/1	3	NCT04104321
Belapectin (NAVIGATE)	Galectin-3 inhibitor	MASH Cirrhosis	Prevention of Esophageal Varices	2024/12/1	2B/3	NCT04365868
VK2809 (VOYAGE)	THR-β agonist	Biopsy proven MASH	Efficacy and Safety	2024/6/1	2B	NCT04173065
PF-05221304 combined with PF-06865571 (MIRNA)	ACC inhibitor and DGAT2 inhibitor	Adult with biopsy-confirmed MASH and fibrosis stage 2 or 3	Resolution of MASH or improvement in liver fibrosis by histology	2024/2/24	2	NCT04321031
Gastric Inhibitory Polypeptide combined with Glucagon Like Peptide-1 Analogue	GIP and GLP-1 agonist	MASH with advanced liver fibrosis and T2DM	Reduction in liver fat and liver stiffness on imaging	2025/2/1	1/2	NCT05751720

MASH, metabolic dysfunction-associated steatohepatitis; MASLD, metabolic dysfunction-associated steatotic liver disease; T2D, type 2 diabete; ACC, Acetyl-CoA Carboxylase; DGAT2, diacylglycerol acyltransferase 2.

trial on overweight/obese patients with T2DM demonstrated that tirzepatide decreased liver fat by 8.1% over 52 weeks, along with significant reductions in serum alanine aminotransferase (ALT), aspartate aminotransferase (AST), and gamma-glutamyltransferase (NCT03882970),[17] indicating that tirzepatide may improve liver steatosis or inflammation. A phase 1/2 clinical trial investigating the effect of a GIP/GLP-1 dual agonist on MASLD with T2DM was recently carried out (NCT05751720). Retatrutide (LY3437943) is a novel triple agonist peptide targeting the GCGR, GIPR, and GLP-1R. *In vitro*, retatrutide exhibits balanced GCGR and GLP-1R activity but higher GIPR activity. GCGR-mediated energy expenditure, combined with GIPR- and GLP-1R-driven calorie intake reduction, contributes to enhanced body weight loss. A phase 2 clinical trial showed that retatrutide treatment for 48 weeks led to significant body weight loss in obese patients (NCT04881760).[18] Retatrutide also improved liver health, as indicated by reductions in plasma ALT and hepatic triglycerides in obese mice.[58] Currently, several phase 3 clinical trials are focused on the effects of retatrutide on obese patients (NCT05929066, NCT05882045, NCT05929079).

Thiazolidinedione insulin sensitizers

Pioglitazone and rosiglitazone are older thiazolidinediones, characterized by their thiazolidinedione ring, used to treat T2DM by improving insulin sensitivity. They are potent activators of the nuclear receptor peroxisome proliferator-activated receptor (PPAR)γ, which is most enriched in adipose tissue and plays a critical role in adipocyte differentiation, lipid and glucose metabolism, and anti-inflammation.[19] The therapeutic effects of pioglitazone on MASLD have been well studied[20]; however, these benefits are compromised by PPARγ-mediated side effects, primarily weight gain. Pioglitazone has lower PPARγ agonism compared with rosiglitazone but has more profound effects on MASH, potentially mediated by the mitochondrial target of thiazolidinediones, specifically the mitochondrial pyruvate carrier. MSDC-0602K is a second-generation thiazolidinedione designed to preferentially suppress the mitochondrial pyruvate carrier while minimizing direct binding to PPARγ. MSDC-0602K has shown substantial decreases in glucose, insulin, liver enzymes, and the non-alcoholic fatty liver disease activity score (NAS) in patients with biopsy-confirmed MASH and fibrosis (F1-F3) with minimal side effects,[21] prompting a phase 3 study to assess the benefits of MSDC-0602K on glycemic control and cardiovascular outcomes in patients with pre-T2D or T2D and MASLD/MASH (NCT03970031). PXL065 is another novel oral agent. Results from a phase 2 study support that PXL065 improves liver fat content, procollagen III N-terminal propeptide, and NAFLD fibrosis score, as well as histological parameters, including NAS and fibrosis, with a favorable safety profile.[22] These findings indicate that PXL065 warrants further clinical testing in pivotal MASH trials.

SGLT2 inhibitors

SGLT2 inhibitors (canagliflozin, dapagliflozin, empagliflozin, and ertugliflozin) increase urinary glucose excretion and are approved anti-hyperglycemic treatments for T2DM. This drug class offers significant benefits in reducing cardiovascular disease risk and improving renal function in T2DM patients. Patients treated with SGLT2i also demonstrate improvements in hepatic lipid content, liver enzymes, and fibrosis.[23–26,59] The efficacy of SGLT2i in reducing body weight and hepatic lipid content has been extensively studied.[26,59,60] SGLT2i has the potential to treat MASH through four main mechanisms: decreasing hepatic de novo lipogenesis by lowering insulin levels, increasing fatty acid β-oxidation by stimulating glucagon secretion, suppressing glucose-induced oxidative stress, and inhibiting liver fibrosis by lowering transforming growth factor-beta levels.[27] Dapagliflozin (10 mg for 12 weeks) significantly reduced intrahepatic lipid content and ALT in patients with T2DM.[28] Licogliflozin, a potent SGLT1 and SGLT2 inhibitor, blocks glucose absorption in the intestine (mediated by SGLT1) and reabsorption in the kidney (90% mediated by SGLT2 and to a lesser extent by SGLT1). Treatment with licogliflozin (150 mg for 12 weeks) resulted in significant improvement in serum ALT levels in patients with MASH (NCT03205150).[61] Overall, SGLT2 are effective in controlling glycemic levels and lowering hepatic lipid content, but histological analyses are necessary to evaluate their effects on MASH.

Targeting intermediary metabolism

Farnesoid X receptor (FXR) agonists

The nuclear FXR agonists may treat MASLD through various mechanisms, including alleviating insulin resistance and exerting direct anti-inflammatory and antifibrotic effects on MASH in both mouse models and human tissues.[62,63] Intestinal FXR mediates suppression of lipid absorption, while hepatic FXR inhibits lipid synthesis.[29] The prototype for this class of compounds is obeticholic acid (OCA), which has been extensively investigated and shown to significantly improve the histological features of MASH, although it can cause side effects such as pruritus and increased low-density lipoprotein (LDL) cholesterol. Although OCA was the first medication to enter phase 3 clinical trials for MASH treatment, the U.S. Food and Drug Administration (hereinafter referred to as FDA) issued a complete response letter to Intercept, rejecting the company's new drug application for OCA as a treatment for MASH-related pre-cirrhotic liver fibrosis in June 2023 due to an unfavorable benefit/risk profile. However, the phase 3 global study (REGENERATE) interim analysis at 18 months reported rapid and sustained improvements in liver enzymes and stiffness with OCA (25 mg qd) treatment.[30] Another phase 3 study (REVERSE) failed to demonstrate OCA's superiority over placebo in improving liver fibrosis in patients with compensated MASH-related cirrhosis (NCT03439254). EDP-305 is a novel oral FXR agonist under development for the treatment of MASH. A phase 2 study revealed that EDP-305 reduced ALT levels and liver fat content at week 12. The most common adverse event (≥ 5%) associated with EDP-305 was also pruritus (NCT03421431).[31] In contrast, several small-molecule FXR agonists without a bile acid structural backbone may not worsen LDL cholesterol or cause pruritus, although this remains unproven. Tropifexor (LJN452) is the most potent non-bile acid FXR agonist currently in clinical studies. The safety and efficacy of tropifexor in patients with MASH (FLIGHT-FXR) were investigated. Improvements in ALT and hepatic fat fraction were sustained up to 48 weeks of treatment with tropifexor, but dose-dependent pruritus was also the most common side effect (NCT02855164).[64] Nidufexor (LMB763) is another non-bile acid agent with partial FXR agonistic activity *in vitro* and FXR-dependent gene regulation *in vivo*.[65] However, a controlled, randomized, double-blind, multicenter study assessing the safety, tolerability, pharmacokinetics, and efficacy of nidufexor in patients with MASH was terminated without results posted (NCT02913105).

Another potential pathway that enhances FXR activity involves the release of the growth factor fibroblast growth factor (FGF) 19 from the intestine upon bile acid binding to FXR,[66] which has shown beneficial effects on MASH in animal models, although results are conflicting.[32,67] Several recom-

binant analogs have been developed to preserve the favorable metabolic effects of FGF19 while avoiding its detrimental proliferative and protumorigenic effects. The FGF19 analog resulted in a substantial reduction in hepatic fat and enzymes in patients with biopsy-confirmed MASH, as shown in a phase 2A study.[33] In a randomized, double-blind, placebo-controlled trial involving patients with MASH, treatment with NGM282 (an engineered FGF19 analog) for 12 weeks led to rapid and significant reductions in liver fat content, ALT, AST, and serum markers of fibrogenesis.[33] In a phase 2 open-label study, NGM282 improved the histological features of MASH within 12 weeks, demonstrating significant reductions in NAS and fibrosis scores, along with improvements in non-invasive imaging and serum markers.[34] In another phase 2 trial of patients with MASH, aldafermin (an engineered FGF19 analog) reduced liver fat and showed a trend toward fibrosis improvement.[68] FGF21 is another member of the FGF family that preserves insulin-sensitizing and antifibrotic properties without mitogenic effects.[35] It has improved steatosis, insulin resistance, and liver stiffness in short-term trials and is actively under clinical investigation as a treatment for MASH. A phase 2B clinical trial (HARMONY) revealed that efruxifermin, a bivalent Fc-FGF21 analog, improved hepatic inflammation and fibrosis over 24 weeks in patients with F2 or F3 fibrosis, with an acceptable safety profile, warranting further investigation in phase 3 trials (NCT04767529).[69] Pegozafermin, a long-acting glycopegylated FGF21 analog, demonstrated improvement in liver fibrosis in MASH as shown in a 24-week phase 2B clinical trial (NCT04929483).[36] Pegbelfermin (BMS-986036), a PEGylated human FGF21 analog, has been suggested to ameliorate metabolic parameters and liver fibrosis in obese patients with T2DM. Subcutaneous administration of pegbelfermin over 16 weeks was generally well tolerated and significantly decreased hepatic fat fraction based on MRI in MASH subjects during a phase 2 study (NCT02413372).[37] However, pegbelfermin administered weekly for 48 weeks did not achieve a one-stage or greater improvement in the NASH Clinical Research Network fibrosis score without worsening NASH, as assessed via biopsy in the phase 2B FALCON 2 study (NCT03486912).[70] B1344, a novel FGF21 analog was under phase 1 study for MASH (NCT05655221).

Experimental PPAR agonists

PPARs are nuclear receptors that modulate key regulatory pathways in metabolism, inflammation, and fibrogenesis.[38,71] Lanifibranor is a pan-PPAR agonist. In a phase 2B study of lanifibranor, the percentage of patients who achieved at least a two-point reduction in the SAF-A score without fibrosis progression was significantly higher among those receiving the 1,200-mg dose compared to placebo (1,200-mg dose vs. placebo: 55% vs. 33%, $P = 0.007$). However, this was not the case for those receiving the 800-mg dose (800-mg dose vs. placebo: 48% vs. 33%, $P = 0.07$) (NCT03008070).[39] Therefore, a phase 3 study examining the efficacy and safety of lanifibranor in adult patients with MASH and fibrosis stages F2 and F3 (NATiV3) is currently underway (NCT04849728). Saroglitazar, a PPAR-α/γ agonist, at a dosage of 4 mg qd significantly improved ALT, liver fat content (LFC), insulin resistance, and atherogenic dyslipidemia in patients with MASLD/MASH (NCT03061721).[72] Currently, saroglitazar is an authorized medication for non-cirrhotic MASH in India.[73]

Target lipid homeostasis and fibrogenesis

Allosteric inhibitors of acetyl-coenzyme A carboxylases (ACC) ACC1 and ACC2 were suggested to inhibit hepatic *de novo* lipogenesis and improve steatosis, inflammation, and fibrosis. NDI-010976 is an inhibitor of both ACC1 and ACC2, which was well tolerated and resulted in profound dose-dependent inhibition of hepatic de novo lipogenesis in overweight male adults in a randomized, controlled crossover trial.[40]

Inhibition of stearoyl-CoA desaturase 1 expression in hepatocytes enhances AMPK activity and lipophagy, as well as attenuates lipid deposition. Aramchol is a stearoyl-CoA desaturase 1 modulator. A phase 2B trial (NCT02279524) showed that although aramchol 600 mg had no impact on liver fat fraction, it provided favorable outcomes in liver fibrosis and ALT levels, suggesting it may be a promising therapy for MASH with fibrosis. This effect is currently being investigated in a phase 3 clinical trial (NCT04104321).[41]

Galectin-3 has been implicated in the pathophysiology of hepatic inflammation and fibrosis through both intracellular effects (such as antiapoptotic activity and macrophage differentiation) and extracellular functions (acting as a chemokinetic/chemotactic factor). Belapectin, a galectin-3 inhibitor, was well tolerated in a year-long biweekly infusion but showed no significant effects on hepatic venous pressure gradient (HVPG) or fibrosis in a phase 2B study involving 162 patients with MASH, cirrhosis, and portal hypertension. However, in a subgroup analysis of patients without esophageal varices, belapectin at 2 mg/kg did suppress HVPG and the development of varices (NCT02462967).[74] Consequently, a clinical trial evaluating the efficacy and safety of belapectin for the prevention of esophageal varices due to MASH-related cirrhosis (NAVIGATE) is currently underway (NCT04365868).

Thyroid hormone receptor (THR) β agonists

The THR is a nuclear receptor that regulates pivotal pathways for cell growth and metabolism. The two isoforms of THR, THRα, and THRβ, are encoded by the genes THRA and THRB, respectively.[75] While excessive activation of THRα may lead to cardiac abnormalities,[42] specific THRβ activators primarily target the liver, inducing hepatic fatty acid oxidation and reducing steatosis and hyperlipidemia in rats and mice with genetically or diet-induced T2DM. The liver-targeted THRβ agonist resmetirom (MGL-3196) demonstrated significant reductions in hepatic lipid fraction and fibrosis, as well as plasma lipid and enzyme levels in patients with MASH, without affecting blood glucose or insulin levels (NCT02912260).[43,76] The results of the 52-week MAESTRO-NAFLD-1 trial supported the efficacy and safety of resmetirom at doses of 80 mg and 100 mg qd (NCT04197479), which are being applied in the ongoing phase 3 MASH study, MAESTRO-NASH.[44] The 52-week data from 966 patients with MASH and F1B, F2, or F3 fibrosis in the MAESTRO-NASH trial revealed significant effects of resmetirom on MASH resolution, fibrosis improvement, and LDL cholesterol reduction (NCT03900429),[77] forming the basis for potential FDA approval of resmetirom for MASH treatment.

VK2809, another THRβ agonist, reduced hepatic steatosis in mice[45] and liver lipid content in patients with MASLD (NCT02927184). The additional potential of THRβ agonists to improve cardiometabolic outcomes has warranted further investigation through an ongoing phase 2B clinical trial (NCT04173065) for MASH lasting 52 weeks.

Medications affecting oxidative stress and inflammation

Cell stress and apoptosis

Oxidative stress and activation of the unfolded protein response are two well-recognized cell stress pathways that cause cell death in MASH. Vitamin E is a prototypic antioxidant and has the most profound anti-steatohepatitic effect of

any drug studied to date.[78] However, its appeal is limited by its lack of efficacy in attenuating hepatic fibrosis in a large randomized controlled trial.[78] Combining pioglitazone with vitamin E therapy has a more favorable impact on hepatic inflammation and ballooning than vitamin E alone, but unfortunately, it has no effect on fibrosis.

Apoptosis induces tissue injury and fibrosis in MASH and many other chronic liver injuries,[79] establishing a rationale for inhibiting apoptosis as a therapeutic strategy. Emricasan, a pan-caspase inhibitor, reduces apoptosis and can attenuate inflammation and fibrosis.[46] However, a phase 2B clinical trial (NCT02686762) revealed that emricasan treatment did not improve liver histology in patients with MASH-related fibrosis and may have exacerbated ballooning and fibrosis. Caspase inhibition lowered serum ALT in the short term but may have redirected cells to alternative mechanisms of cell death, resulting in more hepatocyte ballooning and liver fibrosis.[47] A phase 2 trial revealed that emricasan was generally safe and well-tolerated in patients with decompensated MASH cirrhosis; however, it had no significant effect on MELD-Na score, international normalized ratio, total serum bilirubin, albumin level, or Child-Pugh score (NCT03205345).[48] In patients with MASH-related cirrhosis and severe portal hypertension, emricasan could not improve either HVPG or clinical outcomes (NCT02960204).[49]

Immune targets

Inflammatory cells and cytokines are involved in MASH pathogenesis. Compared with adaptive immune systems, most studies focus on the innate immune system for the pathogenesis of MASH. Pro-inflammatory pathways, including apoptosis signaling kinase-1 (ASK-1)-JNK, MAP kinases, extracellular signal-regulated kinase, and Nuclear Factor-kappa B, are potent mediators of inflammation and thus potential targets for MASLD therapy. The ubiquitous expression of pro-inflammatory pathways in all cells and their critical role in maintaining defenses against tissue injury raise concerns about 'off-target' effects. Fortunately, clinical trials in MASH have not revealed any such effects to date. In particular, the inhibition of ASK-1 ameliorated MASH and improved fibrosis in some patients in a short-term clinical trial.[50] However, two phase 3 trials of selonsertib (an ASK-1 inhibitor) were terminated early due to a lack of efficacy in MASH adults with stage 3 (NCT03053050) and stage 4 (NCT03053063) fibrosis.

Activation of the C–C motif chemokine receptor (CCR) 2–CCR5 chemokine axis exaggerates the liver's innate immune response, activates hepatic stellate cells, and leads to fibrogenesis. Usage of the CCR2/CCR5 inhibitor cenicriviroc was shown to reduce two-year liver fibrosis progression in a clinical trial of MASH (NCT02217475).[51,52] However, a phase 3 study of cenicriviroc for the treatment of liver fibrosis in adult MASH subjects was terminated early due to a lack of efficacy (NCT03028740).

Pentoxifylline (PTX) is a nonspecific phosphodiesterase (PDE) inhibitor that can regulate cyclic AMP levels and suppress TNF-α gene transcription, which are vital mechanisms for inflammation and hepatocellular damage in the progression of MASLD. A phase 2 trial showed that PTX improved hepatic histological features, including fibrosis, in patients with MASH (NCT00590161).[80] A phase 3 study investigating the effect of PTX on MASH is underway (NCT05284448). ZSP1601 is a first-in-class pan-phosphodiesterase (pan-PDE) inhibitor specially designed for MASH by Guangdong Raynovent Biotech Co., Ltd (Guangdong, Guangzhou, China). ZSP1601 suppresses inflammatory responses in MASH, with its maximum inhibitory effect occurring on PDE2 as shown by both *in vitro* and *in vivo* studies.[53,81] A randomized, double-blinded, placebo-controlled, multiple-dose phase 1B/2A trial revealed ZSP1601 improved serum liver enzymes, fat content, and Fibroscan parameters in patients with MASLD.[54] ZSP1601 could be a potential novel agent used in the treatment of MASLD.

Gut microbiome

Gut microbiome dysbiosis renders the gut more permeable, thereby exposing hepatocytes to endotoxins that can eventually result in hepatocyte inflammation and scarring. IMM-124e is a product of bovine colostrum enriched in IgG obtained from cows immunized against LPS. A phase 2 study evaluating the effects of 24 weeks of IMM-124e in patients with biopsy-proven MASH showed a reduction in AST and ALT but no change in hepatic fat content (NCT02316717). A synthetic peptide, AWRK6, developed based on the antimicrobial peptide Dybowskin-2CDYa, was reported to attenuate hyperglycemia as a novel GLP-1 receptor agonist candidate. AWRK6 ameliorates MASLD by improving lipid and glucose metabolism homeostasis, which may be mediated by the PI3K/AKT/AMPK/ACC signaling pathway in the mouse model.[82] Solithromycin, a new-generation macrolide antibiotic, was suggested to improve the NAS and ALT level in a phase 2, 13-week open-label MASH trial (NCT02510599).[83] The application of gut microbiome-based therapy for MASLD seems to have a long way to go.

Combination therapies

Besides the combination therapies described above, in patients with bridging fibrosis and cirrhosis, combining cilofexor (ACC inhibitor) and firsocostat (FXR agonist) for 48 weeks was well tolerated, showed beneficial effects on MASH disease parameters, and might improve fibrosis. This combination offers potential for fibrosis regression in patients with MASH and subsequent advanced fibrosis (NCT03449446).[84]

ACC inhibitors reduce hepatic steatosis in patients with MASLD, but they also increase serum triglycerides.[85] A phase 2A trial showed that PF-06865571 (a DGAT2 inhibitor) could mitigate the effect of PF-05221304 (a novel ACC1/2 inhibitor) on serum triglycerides (NCT03776175).[85] As a result, a phase 2 study specifically aimed to compare the effects of various doses of DGAT2i alone, and in combination with ACCi, on the resolution of MASH or anti-fibrosis via biopsy is underway (NCT04321031).

Conclusions

Recently, remarkable progress has been made in unveiling the pathogenesis of MASLD/MASH, and consequently, in developing drugs to effectively treat the disease. The heterogeneous nature of MASLD means it cannot be investigated or managed as a single condition with a "one size fits all" approach to therapy. Considering the high heterogeneity of MASLD, precisely defining the natural history of its phenotypes and appropriately selecting subjects for clinical trials will help demonstrate significant benefits. Additionally, comparing or pooling results from meaningful trials will aid in discovering effective therapies.[1] The current medications for MASLD are mainly focused on its pathogenic factors, critical links of pathogenesis, and relevant metabolic diseases. Due to the close association between MASLD and T2DM, many agents prescribed for hyperglycemia contribute to the improvement of some MASLD disease parameters, but their application for MASLD treatment warrants further validation by phase 3 trials. The overall benefit of metabolic-targeted therapies for MASLD is appealing, as these agents might also

reduce other cardiometabolic risk factors that contribute to cardiovascular disease, which is the leading cause of death in patients with MASLD. However, medications targeting aspects of intermediary metabolism may have to overcome high rates of adverse effects before being approved for MASLD treatment. Standardization of clinical trial designs and validation of noninvasive procedures will greatly accelerate the pace of discovering effective therapies. The possibility of drug combinations as a therapeutic option is highly likely due to superior efficacy and safety compared to a single approach. For instance, the benefits of agents targeting metabolic pathways may be enhanced by adding drugs with anti-inflammatory and anti-fibrotic effects.[11] Combined therapy from long-term, controlled clinical trials is highly needed. In the coming years, the availability of therapeutic options for MASLD will hopefully curb the rising incidence of MASLD-related diseases.

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Conflict of interest

JGF has been an Associate Editor of *Journal of Clinical and Translational Hepatology* since 2013. The other authors have no conflict of interests related to this publication.

Author contributions

Writing and revising the manuscript (YH), assisting with the writing of the manuscript (CS, YC, YDL), supervising and revising the manuscript (JGF). All authors have approved the final version and publication of the manuscript.

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