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Review Article

Pharmacological Therapeutics: Current Trends for Metabolic Dysfunction-associated Fatty Liver Disease (MAFLD)

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Abstract

Metabolic dysfunction-associated fatty liver disease (MAFLD) is a new term from nonalcoholic fatty liver disease (NAFLD) and is a positive diagnosis based on histopathology, imaging, or blood biomarkers. MAFLD is one of the common causes of liver dysfunction worldwide, likely due to the increase in metabolic syndrome as well as the high burden of disease and its relationship to other extrahepatic conditions. However, effective pharmacological therapeutic agents are still lacking; current management largely focuses on weight reduction and lifestyle modification. The purpose of this review was to summarize the updated evidence of novel therapies targeting different pathogenetic pathways in MAFLD.

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Introduction

Metabolic dysfunction-associated fatty liver disease (MAFLD) is a new term from nonalcoholic fatty liver disease (NAFLD), which is the positive-criteria diagnosis focusing on metabolic factors and independent of alcohol use.[1] The terminology of MAFLD was defined by evidence of hepatic steatosis based on histopathological examination, imaging, or blood biomarkers in association with one of three criteria, including obesity or overweight status, type 2 diabetes mellitus (T2DM) and evidence of metabolic dysregulation, with at least two metabolic risk factors, including high waist circumference, hypertension, hypertriglyceridemia, low high-density lipoprotein-cholesterolemia, prediabetes, insulin resistance, and high-sensitivity C-reactive protein level. In addition, heterogeneous factors have been found to be associated with MAFLD, including race, sex, diet, genetic predisposition, age, and gut microbiota.[1,2]

To date, MAFLD has become a global health issue, accounting for 25% in Western countries[3] and 25–30% in the Asia Pacific region.[4] MAFLD can progress to cirrhosis and develop complications, such as decompensation and hepatocellular carcinoma, and increases the risk of liver-related mortality. Moreover, the risk of cardiovascular mortality is higher among MAFLD patients.[5] Previous studies have shown higher liver-related mortality among nonalcoholic steatohepatitis (NASH) patients than among those without NASH. As a result, NASH resolution has become one of the main outcomes of clinical studies of MAFLD, apart from liver fibrosis regression.[6]

The most effective therapy for MAFLD is weight reduction; a 10% reduction can lead to resolution of steatohepatitis and improvement of fibrosis by at least one stage. In addition, it will decrease cardiovascular and diabetes risks.[7] Pharmacological interventions are reserved for some MAFLD patients who are not responding to conventional treatment. Through this article, we aimed to review the currently available medications for MAFLD treatment based on the pathophysiology of MAFLD.

Pharmacological therapeutics for MAFLD

To date, the currently available drugs for MAFLD treatment have been studied in many clinical trials. By replacing NAFLD with MAFLD, several aspects of this disease were changed, including terminology, details of the definition, pathogenesis, associated disease, and, crucially, the aspects of research and drug development demonstrated in Table 1.[1,8–11] The major challenges in the research and drug development for "NASH" mainly focus on two outcomes. The first is a resolution of NASH or steatohepatitis, and the second is an improvement

Keywords: Metabolic dysfunction-associated fatty liver disease; Nonalcoholic fatty liver disease; Nonalcoholic steatohepatitis; Pharmacological treatment.
Abbreviations: AASLD, American Association for the Study of Liver Diseases; APASL, Asian Pacific Association for the Study of the Liver; BMI, body mass index; CCR, C-C chemokine receptor; CPGs, clinical practice guidelines; CVD, cardiovascular disease; EASL, European Association for the Study of Diabetes; F, fibrosis; FXR, Farnesoid X receptor; GIP, glucose-dependent insulinotropic polypeptide; GLP, glucagon-like peptide-1; HBV, hepatitis B virus; HCV, hepatitis C virus; HIV, human immunodeficiency virus; HS, hepatic steatosis; LOXL2, lysyl oxidase-like molecule 2; MAFLD, Metabolic dysfunction-associated fatty liver disease; NAFLD, nonalcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis; OCA, obeticholic acid; PPAR, Peroxisome proliferator-activated receptors; RCT, randomized controlled trial; T2DM, type 2 diabetes mellitus; TSH, Thyroid hormone receptor.
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Table 1. Comparison of NAFLD and MAFLD in each domain

Definition and diagnosis	NAFLD	MAFLD
Fatty liver disease	NAFLD: encompasses the entire spectrum of FLD in individuals without significant alcohol consumption. NAFL: presence of ≥5% HS without evidence of hepatocellular injury or fibrosis	MAFLD: histopathology, imaging, or blood biomarker evidence of steatosis involving >5% of hepatocytes, accompanied by obesity or overweight status (BMI >25 kg/m^2 in Whites and >23 kg/m^2 in Asians), T2DM, or evidence of metabolic dysregulation*
Fatty liver with hepatitis	NASH: presence of ≥5% HS with inflammation and hepatocyte injury with or without fibrosis (the traditional dichotomous classification into NASH vs. non-NASH)	MAFLD: single overarching term that replaces the current dichotomous stratification into steatohepatitis and nonsteatohepatitis. Moreover, MAFLD encompasses the full spectrum from simple steatosis without inflammation and fibrosis to stage 4 fibrosis.**
Fatty liver with fibrosis/cirrhosis	NASH cirrhosis: presence of cirrhosis with current or previous histological evidence of steatohepatitis	MAFLD-related cirrhosis: presence of cirrhosis in the absence of typical histology and meets at least one of following criteria: documentation of MAFLD on previous liver biopsy; historical documentation of steatosis by imaging. This term is expected to replace the old term 'cryptogenic cirrhosis' in the majority of patients
Details of definition	Definitive diagnosis requires histology from liver biopsy	Diagnosis based on histology from liver biopsy, imaging, or blood biomarker evidence of fat accumulation (hepatic steatosis)
	Diagnosis by "exclusion" of other causes, especially alcoholic steatohepatitis (overemphasizes the absence of alcohol use while underemphasizing the importance of the metabolic risk factors)	Positive diagnosis, rather than a "none" disease rubric
Pathogenesis	Complex and multifactorial, involving genetic, epigenetic and environmental factors. The term "non" limits consideration of the clinical and pathological attributes of this complex disease and does not highlight the primary role of metabolic dysfunction in its pathogenesis[10]	Defines by the term of metabolic dysfunction as well as reflects the relevant risk factors for liver disease but no established or explained novel pathogenesis
Other common associated liver diseases	"Concurrent disease": Alcoholic FLD; - Drug-induced FLD; HCV-associated FLD; Other†: Hemochromatosis; Autoimmune hepatitis; Celiac disease; Wilson's disease; A-/hypo-, betalipoproteinaemia lipoatrophy; Hypopituitarism, hypothyroidism; Starvation, parenteral nutrition; Inborn errors of metabolism	"Concomitant disease" (dual etiology of FLD): Alcohol-use disorder; Viral infection (HIV, HBV, and HCV); Autoimmune hepatitis; Inherited liver disorders' Drug-induced liver injury; Other known liver diseases
Research and drug development	Current endpoints for NASH drug development are fibrosis improvement and resolution of steatohepatitis	The terminology MAFLD, which eliminates the term "steatohepatitis" as a distinguishing subtype and instead based on grade and stage may interfere with the process of the study in phase 2b and 3 trials in novel drug development because these trials have been designed by using the old term NASH, especially outcomes for NASH resolution and regression of fibrosis[8]

*At least two metabolic risk factors should be present for the definition of metabolic dysregulation: waist circumference ≥102/88 cm in white men and women or ≥90/80 cm in Asian men and women; blood pressure ≥130/85 or specific drug treatment; plasma triglycerides ≥150 mg/dL or specific drug treatment; plasma HDL cholesterol <40 mg/dL (<1.0 mmol/L) for men and <50 mg/dL (<1.3 mmol/L) for women or specific drug treatment; prediabetes (i.e. fasting glucose levels 100–125 mg/dL or 2-h postload glucose levels 140–199 mg/dL or HbA1c 5.7–6.4%; homeostasis model assessment (HOMA) of insulin resistance score ≥2.5; and plasma high-sensitivity C-reactive protein level >2 mg/L.[1] ** From a pathological domain, Brunt *et al*.[11] raised concerns regarding the accuracy of this nomenclature and suggested the term "metabolic syndrome steatohepatitis" (MESH) in 2009. MAFLD, Metabolic dysfunction-associated fatty liver disease; NAFLD, nonalcoholic fatty liver disease; NAFL, nonalcoholic fatty liver; NASH, nonalcoholic steatohepatitis; HS, hepatic steatosis; T2DM, type 2 diabetes mellitus; BMI, body mass index; HCV, hepatitis C virus; HBV, hepatitis B virus; HIV, human immunodeficiency virus.

of fibrosis stage. Thus, changing the name from NAFLD to MAFLD as well as abandoning the term "NASH" might perturb the results of many study trials due to the limitation of MAFLD concerning steatohepatitis and hepatic fibrosis. Nonetheless, pharmacological therapeutic development for MAFLD based on the mechanisms of action, adverse events, and effi-

Table 2. Summary of drug agents and benefit in MAFLD

	Medication	EASL 2016	AASLD 2018	APASL 2020
Potential benefit	Vitamin E	Non-DM, ≥F2 non-cirrhosis (liver biopsy-proven cases)	Non-DM, non-cirrhosis (liver biopsy-proven cases)	Non-DM, non-cirrhosis (liver biopsy-proven cases)
	Pioglitazone	With and without DM, ≥F2 (liver biopsy-proven cases)	With and without DM, ≥F2 (liver biopsy-proven cases)	With and without DM, ≥F2 (liver biopsy-proven cases)
No clear benefit	Statin	CVD indication	CVD indication	CVD indication
	Metformin	None	None	None
	n-3 polyunsaturated fatty acids	None	None	None
	Ursodeoxycholic acid	None	None	None
	Pentoxifylline	None	None	None
Unclear benefit	Liraglutide (GLP1 agonist)	None	Premature to consider	Suggested in T2DM
	OCA	None	Should not be used	Wait for study

DM, diabetes mellitus; F, fibrosis; CVD, cardiovascular disease; GLP, glucagon-like peptide-1; OCA, obeticholic acid.

cacy is reviewed and recommended in clinical practice guidelines (CPGs) issued by the liver international society in the Americas (AASLD),[6] Europe (EASL),[12] and Asia (APASL).[13] Classification of the drugs is based on the benefits of clinical studies (Table 2). Drugs with potential benefits include thiazolidinediones (pioglitazone)[14–16] and vitamin E[16–18] (Table 2), supported by both randomized controlled trials (RCTs) and meta-analyses.[19,20] From the current recommendation, pioglitazone has been established in both diabetic and nondiabetic MAFLD patients with significant fibrosis (≥F2), whereas vitamin E is recommended in nondiabetic MAFLD patients with ≥F2 non-cirrhosis.[21]

To date, many novel therapies have been studied in clinical trials for MAFLD patients (20). Due to the controversial pathogenesis of MAFLD, eight classes of new drugs act against different targets (Fig. 1). A summary of the clinical trials of these new drugs is shown in Table 3.

Farnesoid X receptor (FXR) agonist

There are two generations of FXR agonists, First-generation is obeticholic acid (OCA) (INT-747) and Second-generation is cilofexor (GS-9674) and tropifexor.

FXR, a key nuclear receptor of lipoprotein metabolism in the liver, is activated by bile acids, which are metabolic signaling molecules assisting lipid absorption, facilitating digestion, and regulating lipid metabolism and inflammation.[22] Bile acids activate the FXR receptor, which then inhibits lipogenesis, gluconeogenesis, and the regulation of insulin sensitivity.[23,24]

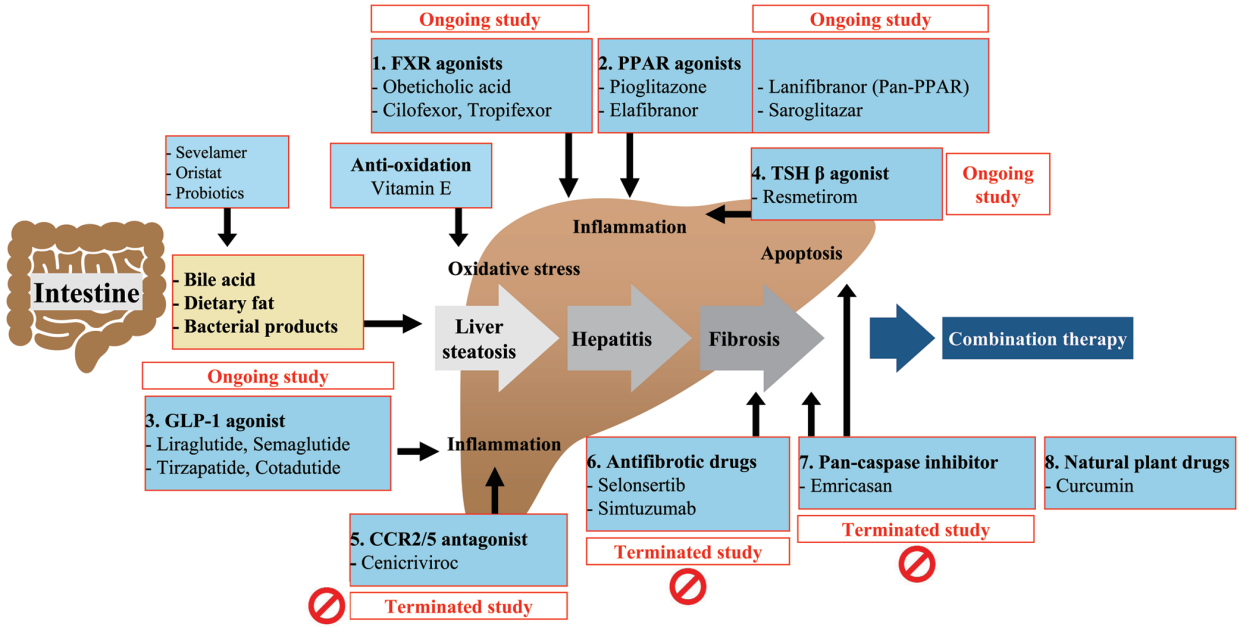

Fig. 1. Pharmacological targets of NASH therapy. FXR, Farnesoid X receptor; PPAR, Peroxisome proliferator-activated receptor; CCR, C-C chemokine receptor; GLP-1, Glucagon-like peptide-1; TSH, Thyroid hormone receptor.

Table 3. Summary of clinical trials of many novel therapies for NASH resolution

Medication	Mechanism of action	Trial	Phase	Trial ID	NASH resolution	Decreased fibrosis
OCA	FXR agonist 1st generation	FLINT study	IIb	NCT01265498	No	Yes
		REGENERATE study (NASH with significant fibrosis)	III	NCT02548351	No	Yes
		REVERSE study (NASH with cirrhosis)	III	NCT03439254	–	–
Cilofexor	FXR agonist 2nd generation	Cilofexor, in patients with noncirrhotic NASH	II	NCT02854605	No	No
Tropifexor	FXR agonist 2nd generation	FLIGHT-FXR study	II	NCT02855164	Yes	–
		TANDEM study	IIb	NCT03517540	–	–
Elafibranor	PPAR α/δ agonist	GOLDEN-505 study	IIb	NCT01694849	Yes	No
		RESOLVE-IT study	III	NCT02704403	No	No
Lanifibranor	Pan-PPAR agonist	NATIVE study	IIb	NCT03008070	Yes	–
Saroglitazar	Dual PPAR-α/γ agonist	EVIDENCE IV study	II	NCT03061721	Yes	No
Liraglutide	GLP-1 receptor agonist	LEAN study	II	NCT01237119	Yes	Yes
Semaglutide	GLP-1 receptor agonist	Subcutaneous semaglutide in NASH	II	NCT02970942	Yes	No
Tirzapatide	GIP and GLP-1 agonist	SYNERGY- NASH study	IIb	NCT04166773		
Cotadutide	Glucagon and GLP-1 agonist	MEDI0382 in overweight and obese individuals with T2DM	II	NCT02548585	–	–
Resmetirom	TSH β agonist	MGL-3196 for NASH	II	NCT02912260	Yes	–
		MAESTRO-NASH study	III	NCT03900429	–	–
Cenicriviroc	CCR2/CCR5 antagonist	CENTAUR study	IIb	NCT02217475	No	Yes
		AURORA study	III	NCT03028740	–	No
Selonsertib	Antifibrotic drugs	STELLAR-3,4 study	III	NCT03053050, NCT03053063	No	No
Simtuzumab	Antifibrotic drugs	GS-6624 for NASH	IIb	NCT01672866, NCT01672879	No	No
Emricasan	Pancaspase inhibitor	ENCORE-NF study	II	NCT02686762	No	No

FXR, Farnesoid X receptor; PPAR, Peroxisome proliferator-activated receptor; GLP-1, Glucagon-like peptide-1; GIP, Glucose-dependent insulinotropic polypeptide; TSH, Thyroid hormone receptor; CCR, C-C chemokine receptor.

A phase IIb RCT including 283 noncirrhotic NASH patients compared OCA and placebo groups for 72 weeks and showed that more patients in the OCA group had improvement in scored liver histology without progression of fibrosis from baseline.[25] The frequent adverse event in the OCA group was pruritus (33 patients, 23%), and only one patient had treatment discontinuation. Another concern was significantly increased cholesterol levels within 12 weeks after OCA treatment, which required concomitant statin therapy and returned to baseline after stopping medication. However, the long-term consequences of CVD outcomes regarding OCA need to be explored. In the interim analysis of a phase III study (REGENERATE trial) at 18 months, 931 NASH patients with stage 2–3 fibrosis were randomly assigned to placebo and showed significant fibrosis improvement without NASH deterioration. However, this study failed to show a benefit of OCA in NASH resolution without fibrosis progression. Pruritus of mild to moderate severity was reported as the most common side effect causing the discontinuation of OCA. Early increases in low-density lipoprotein (LDL)-cholesterol were reported with OCA treatment in the first month; however, levels declined close to baseline by month 18.[26] Statins were initiated in 380 patients in that study and 159 patients in the 25 mg OCA group, but cardiovascular outcomes were not different between the groups.

A recent phase II study using OCA plus atorvastatin therapy initiated at 4 weeks to ameliorate the elevation of LDL cholesterol from OCA (CONTROL) in 84 biopsies confirmed that NASH patients showed no significant elevation in LDL cholesterol at 8 weeks (27). Currently, OCA is not approved by the USA's Food and Drug Administration (FDA) and is not recommended to treat MAFLD patients from CPGs of AASLD, EASL, and APASL.

Second-generation: cilofexor (GS-9674), tropifexor (LJN452)

Cilofexor is a potent, selective, nonsteroidal agonist of FXR that predominantly activates intestinal FXR without involvement of the enterohepatic circulation.[27] A recent phase II study of cilofexor given at doses of 30/day and 100 mg/

day compared with placebo in 140 noncirrhotic NASH patients for 24 weeks showed a significant reduction in hepatic steatosis measured by magnetic resonance imaging-proton density fat fraction and a reduction in serum gamma-glutamyltransferase; however, no significant difference in liver stiffness was reported. The common adverse events were moderate and severe pruritus without significant changes in the lipid profile.[28]

Another second-generation FXR agonist is tropifexor, a nonsteroidal FXR agonist. An interim analysis of a phase II study (FLIGHT-FXR) in biopsy-proven NASH patients with significant fibrosis (defined as stage 2–3 fibrosis) exhibited significant efficacy of tropifexor in hepatic steatosis reduction at 12 weeks after treatment. However, pruritus and increased blood LDL-cholesterol were still the most common adverse events causing discontinuation.[29]

Another double-blinded phase IIb RCT (TANDEM) of the combination therapy of tropifexor and cenicriviroc, an antiretroviral agent inhibiting CCR2 and CCR5 receptors, of 200 biopsy-proven NASH patients evaluated the safety and tolerability accompanied by liver fibrosis improvement over a 48-week period.[30] The results of the study are expected to be announced soon.

Peroxisome proliferator-activated receptor (PPAR) agonists

PPARs agonists are classified into three groups: 1) PPAR α/δ is elafibranor (GFT505), 2) Pan-PPAR agonist (PPAR-α, PPAR-β/δ, and PPAR-γ) is lanifibranor (IVA337), and 3) Dual agonist of PPAR-α/γ is saroglitazar.

PPARs are ligand-activated transcription factors regulating energy homeostasis, especially lipid and glucose metabolisms.[31] The family of PPARs encompasses three subtypes: PPAR-α, PPAR-β/δ, and PPAR-γ. The activation of PPAR-α reduces plasma triglyceride levels. The activation of PPAR-γ promotes insulin sensitization and has a role in lipid storage, whereas the activation of PPAR-β/δ enhances fatty acid metabolism and reveals anti-inflammatory effects by inhibiting inflammatory macrophage phenotypes.[32]

Elafibranor (GFT505) is the first member of the PPAR-α/PPAR-δ agonist family. A recent multicenter international phase II RCT (GOLDEN-505) in noncirrhotic biopsy-proven NASH patients showed an insignificant difference in NASH resolution without fibrosis progression between the elafibranor and placebo groups at 52 weeks of treatment. However, a post hoc analysis of 234 patients with an NAFLD activity score (NAS) of more than 4 at baseline showed the significant resolution of NASH using a modified definition of response (19% in 120 mg elafibranor group and 9% in placebo, p=0.013).[33] An international phase III RCT (RESOLVE-IT, NCT02704403) comparing elafibranor with placebo in NASH patients was terminated early due to insignificant efficacy but without significant adverse events at 72 weeks of treatment.[34]

Lanifibranor (IVA337) is a pan-PPAR agonist of PPAR-α, PPAR-β/δ, and PPAR-γ. Several preclinical studies have shown that lanifibranor has both antifibrotic and positive metabolic effects.[35] A phase IIb study (NATIVE) comparing lanifibranor with placebo in biopsy-proven NASH patients at 24 weeks of treatment demonstrated the efficacy in NASH resolution.[36] Lanifibranor achieved the primary endpoint with a statistically significant reduction in steatohepatitis evaluated by the steatosis activity fibrosis histological score without worsening fibrosis. Lanifibranor is the first drug candidate to achieve statistically significant results on the USA FDA and European Medicine Agency (EMA) primary endpoints.[37] Thus, outcomes relevant for seeking accelerated approval during future phase III RCTs with a longer duration of follow-up are ongoing.

Saroglitazar is a dual agonist of PPAR-α/γ. From real-world clinical studies in India, saroglitazar had a benefit in reducing transaminase levels and improving liver steatosis determined by noninvasive methods in NASH patients as well as improving lipid and glycemic profiles in patients with diabetes and dyslipidemia.[38] A multicenter phase II study (EVIDENCE IV) comparing saroglitazar magnesium with placebo in NASH patients achieved the primary endpoint: improvement of hepatitis from baseline at 16 weeks and improvement of liver fat content measured by magnetic resonance imaging-proton density fat fraction. However, no significant difference in liver stiffness measurement was reported.[39,40]

Glucagon-like peptide-1 (GLP-1) agonists

GLP-1 agonist has three subclasses; 1) GLP-1 receptor agonist: liraglutide, semaglutide, 2) Dual glucose-dependent insulinotropic polypeptide (GIP) and GLP-1 receptor agonist: tirzapatide (LY3298176), and 3) Dual glucagon and GLP-1 receptor agonist: cotadutide (MEDI0382).

GLP-1 is a hormone with an incretin effect that stimulates insulin secretion secreted by intestinal cells after a meal, in addition to glucagon suppression. GLP-1 exerts an effect on weight reduction by activating hypothalamic GLP-1 receptors, enhancing satiety and delaying gastric emptying time.[41]

A multicenter phase II study (LEAN) demonstrated the efficacy of liraglutide (a GLP-1 agonist) in NASH resolution based on the disappearance of hepatocyte ballooning without fibrosis worsening among NASH patients after 48 weeks of treatment. However, this study failed to demonstrate the efficacy of liraglutide in improving lobular inflammation and NAS.[42] The hypothesis of liver histologic improvement from liraglutide is probably based upon the synergistic and multifactorial effects from both directing effects on liver histology and indirect effects on weight reduction.

There were additional nonhepatic benefits of liraglutide in the significant reduction of major cardiovascular events, comprising cardiovascular death, nonfatal myocardial infarction and nonfatal stroke, found in a recent RCT involving diabetic patients.[43]

Semaglutide, another next-generation GLP-1 agonist, has a longer half-life, conferring the advantage of weekly subcutaneous injection. A recent multicenter phase II study in biopsy-proven NASH patients demonstrated that semaglutide had significantly higher efficacy for NASH resolution than placebo. However, there was no significant improvement in fibrosis stage evaluated by liver biopsy at week 72.[44] Phase III RCTs to confirm the benefit of semaglutide in NASH resolution without worsening fibrosis are underway.

Tirzapatide (LY3298176) is a dual GIP and GLP-1 agonist. A phase II RCT showed superior glycemic control and weight reduction in tirzepatide compared with dulaglutide (another GLP-1 agonist) or placebo, with good tolerability and acceptable safety profiles.[45] A combination of GIP and GLP-1 agonists might offer a new therapeutic option in the treatment of T2DM. A phase IIb study of the efficacy and safety of tirzepatide in NASH patients is ongoing (SYNERGY-NASH, NCT04166773).

Cotadutide is a dual glucagon and GLP-1 agonist. A phase IIb RCT in overweight patients with T2DM showed the efficacy of cotadutide in reducing weight and serum transaminases in comparison with placebo (NCT03235050).[46]

Thyroid hormone receptor β agonist: resmetirom (MGL-3196)

Thyroid hormone receptor β agonist, highly expressed in

hepatocytes, regulates many metabolic pathways, including the reduction of triglyceride and cholesterol levels, improvement of insulin sensitivity, promotion of liver regeneration, and reduction of cell apoptosis. Resmetirom (MGL-3196) is a liver-directed, orally active agonist of the thyroid hormone receptor. A multicenter phase IIb RCT in NASH with fibrosis stages 1-3 demonstrated the efficacy of resmetirom in reducing hepatic steatosis at 12 and 36 weeks compared with placebo.[47] The efficacy and safety of resmetirom are currently being studied in a phase III RCT (MAESTRO-NASH) in stage 2–3 fibrosis NASH patients (NCT03900429).

C-C chemokine receptor type 2 (CCR2) and type 5 (CCR5) antagonist: cenicriviroc

CCR2 plays a central role in monocyte and macrophage recruitment and activation at the hepatic injury site. CCR5 promotes the proliferation of collagen-producing activated hepatic stellate cells/myofibroblasts and is associated with fibrosis progression. Cenicriviroc is a dual CCR2/CCR5 antagonist. A recent phase IIb RCT (CENTAUR) showed that cenicriviroc had no efficacy on NASH resolution but improved at least one fibrosis stage at 1 year of treatment but not after 2 years.[48] A recent phase III RCT of cenicriviroc in NASH patients (AURORA) was terminated early, due to a lack of benefit based on the part 1 results.[49] Currently, there are no approved treatments with agents of this class in NASH patients.

Antifibrotic drugs

Selonsertib (GS-4997) is a selective inhibitor of apoptosis signal-regulating kinase 1 (ASK1). Two phase III studies have investigated the efficacy of selonsertib in NASH patients with bridging fibrosis (STELLAR-3) and compensated cirrhosis (STELLAR-4) over a period of 48 weeks. However, both of them failed to show the efficacy of selonsertib in fibrosis reduction.[50]

Simtuzumab (GS-6624) is a humanized monoclonal antibody directed against lysyl oxidase-like molecule 2 (LOXL2). LOXL2 is an enzyme that catalyzes the cross-linkage of extracellular matrix components, such as collagen and elastin. Thus, inhibition of LOXL2 by an anti-LOXL2 monoclonal antibody may lead to a reduction in fibrosis. Phase IIb RCTs failed to show the efficacy of simtuzumab in fibrosis reduction in NASH patients with bridging fibrosis or compensated cirrhosis.[51]

Pancaspase inhibitor: emricasan

Caspases are intracellular proteases regulating apoptotic cell death. Emricasan is an oral irreversible pancaspase inhibitor.[52] A phase II RCT failed to show the efficacy of emricasan in fibrosis reduction in NASH patients with fibrosis stages 1–3.[53]

Natural plant drugs: curcumin

Herbal medicine, formerly whole medicinal plants and unpurified plant extracts, affects several pathogenetic pathways for MAFLD that interfere with hepatic lipogenesis, improving lipid overload, reducing hepatic inflammatory cytokines, and diminishing steatohepatitis. However, some herbal medicines can cause the demotion of hepatocellular endoplasmic reticulum stress as well as enhancement of the insulin signaling pathway.[54] Cucurmin, a potential natural plant drug that shows lipid-modifying, antioxidant, and anti-inflammatory effects, has demonstrated potential benefits for MAFLD. The results of a meta-analysis of RCTs showed that curcumin provided favorable lipid profiles, and a relative advantage in liver pathologic improvement but did not reach statistical significance.[55]

Moreover, many novel monotherapies target different mechanistic approaches, so "combination therapy" is an attractive approach that is currently under investigation. The comprising core drug or ultimate combination will need further studies and outcomes. Because FXR agonists are the most favorable agents, they may be fundamental drugs for combination. Nonetheless, combined possibilities will need additional clinical data composing benefits in NASH as well as safety profiles.

Conclusions

Pharmacological treatment for MAFLD, especially NASH, by definition in clinical trials focuses on NASH resolution and fibrosis improvement. The mainstay treatment for MAFLD remains weight loss through dietary and lifestyle modifications. Regarding current liver-directed pharmacotherapy, CPGs recommend using pioglitazone and vitamin E in select patient groups with significant fibrosis (≥F2 fibrosis) by biopsy-proven cases with or without T2DM. To date, many novel therapies targeting different pathogenetic pathways as well as the combination of different types of targeted pharmacotherapies are currently under investigation. These results provide the hope of effective targeted pharmacology for these patients.

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Conflict of interest

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Author contributions

Conceptualization and study design (TP, PP, ST), data acquisition (TP, ST), initial drafting of the manuscript (TP, ST), critical assessment of the manuscript and provision of intellectual input (TP, PP, ST). All authors approved the final draft.

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