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 pathogenic 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. 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.

To date, MAFLD has become a global health issue, accounting for 25% in Western countries and 25–30% in the Asia Pacific region. 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. 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.

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. 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. 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...
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 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.**

| Definition and diagnosis | 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 |
|-------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Fatty liver disease     | MAFLD: histopathology, imaging, or blood biomarker evidence of steatosis involving >5% of hepatocytes, accompanied by obesity or overweight status (BMI >25 kg/m² in Whites and >23 kg/m² 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) |
| Fatty liver with fibrosis/cirrhosis | 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 |
| Pathogenesis | Diagnosis based on histology from liver biopsy, imaging, or blood biomarker evidence of fat accumulation (hepatic steatosis) |
| Other common associated liver diseases | Positive diagnosis, rather than a "none" disease rubric |
| Research and drug development | 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†: Hemochromatosis; Inherited liver disorders’ Drug-induced FLD; HCV-associated FLD; Other: Alcoholic FLD; Wilson’s disease; A-/hypo betalipoproteinaemia lipoatrophy; Autoimmune hepatitis; Celiac disease; Wilson’s disease; A-/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 |

*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.** 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; 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.
Prasoppokakorn T. et al: Pharmacological therapeutics for MAFLD

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)                         |
|                     | Pioglitazone                                                             | 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                                                            |
|                     | Metformin                                                                | None                                                                      | None                                                                      |
|                     | n-3 polyunsaturated fatty acids                                          | None                                                                      | None                                                                      |
|                     | Ursodeoxycholic acid                                                    | None                                                                      | None                                                                      |
|                     | Pentoxifylline                                                           | None                                                                      | None                                                                      |
| Unclear benefit     | Liraglutide (GLP1 agonist)                                               | Premature to consider                                                    | Suggested in T2DM                                                        |
|                     | OCA                                                                      | Should not be used                                                       | Wait for study                                                            |

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

Pharmacological therapeutics for MAFLD
cacy is reviewed and recommended in clinical practice guidelines (CPGs) issued by the liver international society in the Americas (AASLD), Europe (EASL), and Asia (APASL). Classification of the drugs is based on the benefits of clinical studies (Table 2). Drugs with potential benefits include thiazolidinediones (pioglitazone) and vitamin E, supported by both randomized controlled trials (RCTs) and meta-analyses. 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.

To date, many novel therapies have been studied in clinical trials for MAFLD patients. 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) 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. Bile acids activate the FXR receptor, which then inhibits lipogenesis, gluconeogenesis, and the regulation of insulin sensitivity.

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**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.
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. 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. 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.

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. 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 pruritus and elevated liver transaminases demonstrated the 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 lasofoxifene 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 metabolism.27 The family of PPARs encompasses three subtypes: PPAR-α, PPAR-β/δ, and PPAR-γ. The activation of PPAR-α promotes insulin sensitization and has a role in lipid storage, enhancing satiety and delaying gastric emptying time.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 insulinotrophic polypeptide (GIP) and GLP-1 receptor agonist: tirzepatide (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.

Tirzepatide (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 I/II 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 I/II 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: resmiotrelin (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. 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 a relative advantage in liver pathologic improvement but did not reach statistical significance. 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.

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. 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.

Pancaspase inhibitor: emricasan

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

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. 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.

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

The authors have no conflict of interests related to this publication.

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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