Therapeutic developments in metabolic dysfunction-associated fatty liver disease

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Abstract

Metabolic dysfunction-associated fatty liver disease (MAFLD) has become one of the most prevalent chronic liver diseases worldwide, bringing risk of multiorgan disfunctions including cardiovascular events, complications of cirrhosis, and even malignance. In terms of health burden management, screening patients with high risk of MAFLD and providing individual comprehensive treatment is critical. Although there are numerous agents entering clinical trials for MAFLD treatment every year, there is still no effective approved drug. The nomenclature of MAFLD highlighted the concomitant metabolic disorders and obesity. MAFLD patients with type 2 diabetes had higher risk of developing liver cirrhosis and cancer, and would benefit from anti-hyperglycemic agents; overweight and obese patients may benefit more from weight loss therapies; for patients with metabolic syndrome, individual comprehensive management is needed to reduce the risk of adverse outcomes. In this review, we introduced the current status and advances of the treatment of MAFLD based on weight loss, improving insulin resistance, and management of cardiometabolic disorders, in order to provide individualized therapy approaches for patients with MAFLD.

Keywords: Metabolic dysfunction-associated fatty liver disease; Nonalcoholic fatty liver disease; Metabolic disorder; Pharmacological targets; Management

From NAFLD to MAFLD

The novel nomenclature of metabolic dysfunction-associated fatty liver disease (MAFLD) was proposed by a panel of experts in attempt toward a more precise and inclusive diagnosis of fatty liver disease in 2020.[1] MAFLD is characterized by hepatic steatosis coupled with one of the following three metabolic features: overweight/obesity, type 2 diabetes mellitus (T2DM), or lean patients with at least two cardiometabolic risk factors.[2] Compared to the former diagnosis of nonalcoholic fatty liver disease (NAFLD), MAFLD reduces the heterogeneity of the NAFLD patients with concomitant metabolic dysfunction, and emphasizes the risk of cardio-metabolic disorders and related adverse outcomes.[3] With the global pandemic of obesity and T2DM, concomitant metabolic disorders become more prevalent in individuals with NAFLD. More than half of the NAFLD patients were obese and around 20% patients had T2DM.[4] Conversely, NAFLD is also highly prevalent in T2DM and obese subjects.[5,6] On the other hand, in lean subjects, the prevalence of NAFLD/MAFLD is also not uncommon. [7] Patients were more likely to be diagnosed as MAFLD than NAFLD when using imaging methods.[8] In addition, the new nomenclature also increases the awareness of policymakers and encourages public and private investments, leading to more efficient and effective therapy development.[9]

Metabolic disorders and NAFLD share common pathogenetic mechanisms. Free fatty acids (FFA) and insulin resistance are central to the pathogenesis of NAFLD and nonalcoholic steatohepatitis (NASH). The increase of FFA in hepatocytes triggers continuous oxidative stress and further aggravates insulin resistance.[10] The progression of MAFLD would in turn be accelerated by various degrees of insulin resistance. Increased fat accumulation in the liver and other organs and associated dysfunction of the visceral adipose tissue also contribute to adverse cardio-metabolic outcomes.[11] The disease burden is particularly huge given the global epidemic of MAFLD. Due to the shared metabolic risk factors, patients with MAFLD had double the risk of dying from cardiovascular disease than death resulting from liver-related disease. However, currently there is still no approved disease-specific medication for the treatment of MAFLD or even steatohepatitis. We are faced with challenges in the

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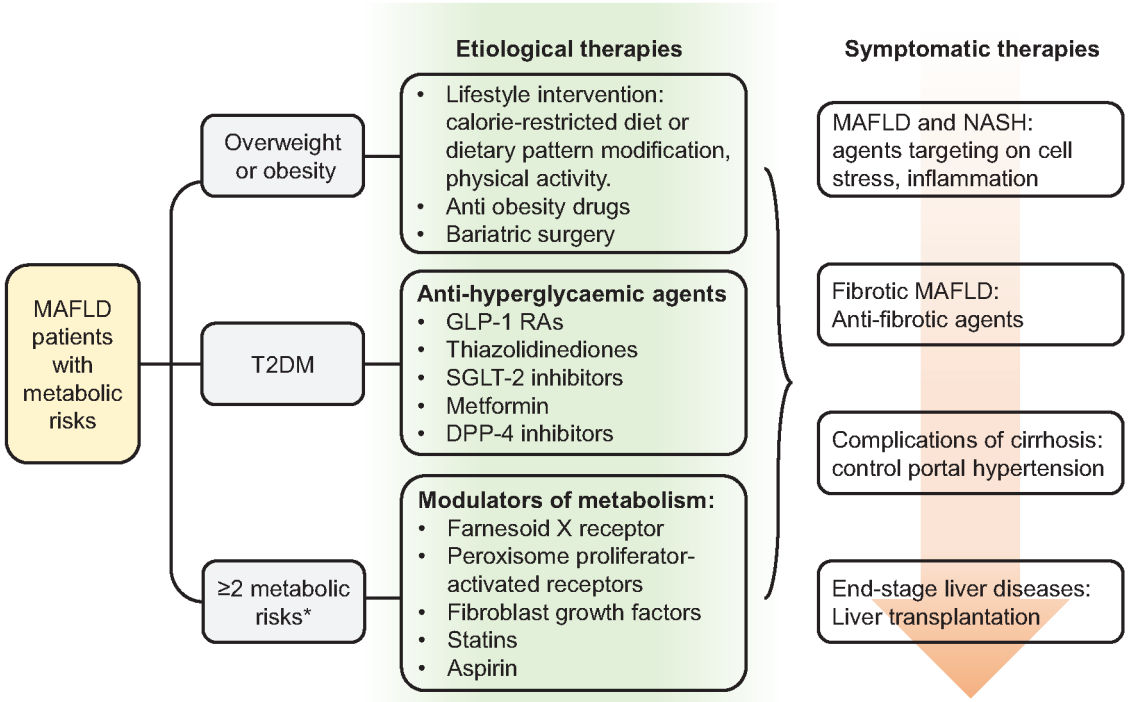

Figure 1: Management of cardiometabolic risk factors in patients with MAFLD. *According to the diagnostic algorithm of MAFLD guidelines, metabolic risks include: abdominal obesity, hypertension, abnormal triglycerides levels, abnormal HDL-cholesterol level, prediabetes, abnormal homeostasis model assessment-insulin resistance (HOMA-IR) levels, and abnormal hs-CRP levels[2] (Eslam M, *et al* Hepatol Int. 2020;14:889-919). HDL: High-density lipoprotein; MAFLD: Metabolic dysfunction-associated fatty liver disease; NASH: Nonalcoholic steatohepatitis; T2DM: Type 2 diabetes mellitus; GLP-1: Glucagon-like peptide-1; DPP-4: Dipeptidyl peptidase 4.

management of MAFLD as well as concomitant metabolic disorders. In this review, we will discuss the current advances and perspective of the treatment of MAFLD [Figure 1].

Weight Loss: Fundamental Treatment of MAFLD

Lifestyle intervention

Lifestyle intervention including diet energy restriction and physical activity is the cornerstone in the management of MAFLD. Available studies have demonstrated that calorie-restricted diet, dietary composition, and the frequency of food intake could have an impact on the intrahepatic triglyceride content.[12,13] In addition, low glycemic food enriched with fruits and vegetables based on a calorie-restricted diet would improve MAFLD-related parameters.[14] Among these, a Mediterranean dietary pattern with restricted cholesterol/saturated fatty acid was recommended for MAFLD patients by major guidelines.[2,15] Cholesterol and saturated fatty acid intake were proved to be associated with the development of advanced fibrosis MAFLD.[16] On the other hand, a Mediterranean dietary could reduce these risks. Recently, ketogenic diets also showed potential efficacy in improving insulin resistance and hepatic steatosis in MAFLD patients and therefore attracted growing interest,[17,18] but the long-term effect and safety of ketogenic diets still need to be evaluated.

Physical activity could enhance the efficacy of diet intervention for MAFLD patients. However, awareness about physical activity in patients with MAFLD still needs to be improved urgently. It is reported that <30% of them met the physical activity recommendations of the guidelines.[19] According to these recommendations, both aerobic and resistance exercise were effective in reducing liver fat content.[20] Compared to aerobic exercise, resistance exercise had similar efficacy at the same level of frequency and duration, but cost less energy. Therefore, resistance exercise may be more feasible for MAFLD patients in those who cannot tolerate aerobic exercise.[21] Recently, sarcopenia/sarcopenic obesity has been recognized as an independent risk factor for the occurrence and development of MAFLD. Physical activity, especially resistance exercise, plays an important role in the management of sarcopenia. On the other hand, for patients with steatohepatitis, the efficacy of physical activity intervention in improving serum aminotransferase levels is still controversial.[22,23]

The primary goal of lifestyle intervention for MAFLD is weight loss, which refers to the reduction of body fat content without decreased lean mass for obese adults, and the reduction of body fat content with increased lean mass for sarcopenic obese adults. Data from the novel drug trials showed that MAFLD patients in the placebo arm could benefit from weight loss during standard care.[24] According to the report by Vilar-Gomez *et al*,[25] greater extent of weight loss led to greater improvement in histologic features of steatohepatitis. Nearly half of the MAFLD patients with weight loss ≥10% could even achieve regression of fibrosis. For non-obese MAFLD patients, less weight reduction is needed to achieve steatosis remission compared to obese patients [Table 1]. Furthermore, they are more likely to maintain the status of improvement after weight reduction in the long term.[26] In addition to physical activity and diet

Table 1: Efficacy of weight loss on MAFLD patients stratified by BMI.

MAFLD patients	Weight loss <5%	5% ≤ Weight loss <7%	7% ≤ Weight loss <10%	Weight loss ≥10%
Overall participants[25]	Steatohepatitis resolution with no fibrosis worsening 10% Steatosis improvement 35%	Steatohepatitis resolution with no fibrosis worsening 26% Steatosis improvement 65%	Steatohepatitis resolution with no fibrosis worsening 64% Steatosis improvement 76%	Steatohepatitis resolution with no fibrosis worsening 90% Steatosis improvement 100%
BMI < 25 kg/m^2 [26]	Remission of MAFLD* 18%	Remission of MAFLD 60%	Remission of MAFLD 75%	Remission of MAFLD 100%
BMI ≥ 25 kg/m^2 [26]	Remission of MAFLD 20%	Remission of MAFLD 40%	Remission of MAFLD 50%	Remission of MAFLD 93%

* Remission of MAFLD is defined as intrahepatic triglyceride content <5% by proton-MRS. BMI: Body mass index; MAFLD: Metabolic dysfunction-associated fatty liver disease; MRS: Magnetic resonance spectroscopy.

intervention, quitting smoking and alcohol consumption are both beneficial in reducing the risk of progression of MAFLD.[27,28] Lifestyle intervention needs long-term persistence, and lifestyle intervention alone is not always enough for patients with advanced fibrosis or morbid obesity. Therefore, the treatment strategy for weight loss often needs anti-obesity drugs to be prescribed and even recommending bariatric surgery.

Anti-obesity drugs

The development of anti-obesity medications is always challenging for technical and societal reasons. Currently, orlistat, naltrexone/bupropion, liraglutide, and semaglutide are approved for the treatment for obesity in the United States and Europe.[29] Although in a previous liver biopsy-proven study orlistat did not improve liver histology in MAFLD patients,[30] orlistat showed decrease in liver fat content (-5.45% *vs.* -1.96% of placebo, $P < 0.001$) assessed by magnetic resonance imagingproton density-fat fraction (MRI-PDFF) in a recent study with larger sample size.[31] The efficacy of orlistat in MAFLD still needs to be investigated. The efficacy of liraglutide and semaglutide on MAFLD will be discussed in the following sections. The efficacy of naltrexone and other anti-obesity medications on MAFLD is still undefined and further studies are needed.[32]

Bariatric surgery: solution for persistent weight loss

Achieving significant weight loss by lifestyle intervention with or without anti-obesity drugs may be especially difficult for morbidly obese patients with MAFLD. It is reported only 50% of the patients were able to achieve 7% weight loss in 1 year of lifestyle intervention.[25] Bariatric surgery could bring massive weight loss accompanied by histological improvement of steatohepatitis and even fibrosis. Since perioperative and long-term complications occur following bariatric surgical procedures, specific criteria were set for bariatric surgery for patients with body mass index (BMI) >40 kg/m^2 or BMI 35 to 40 kg/m^2 with associated comorbid conditions. Current patterns of bariatric surgery consist of Roux-en-Y gastric bypass, sleeve gastrectomy, biliopancreatic diversion with duodenal switch and implantation of devices. More than half of the patients receiving bariatric surgery achieved NASH resolution, and 30% to 40% of the patients had improvement in liver fibrosis.[33,34] A considerable proportion of the MAFLD patients even achieved long-term maintenance of NASH resolution. The fibrosis improvement also continued until 5 years after bariatric surgery.[35] As for MAFLD patients with advanced fibrosis or morbid obesity, bariatric surgery would be more cost-effective in improving quality-adjusted life-years, compared to those without fibrosis or morbid obesity.[36,37] For MAFLD patients, bariatric surgery also had the superiority of maintaining major adverse cardiovascular events.[38]

Notably, the safety of bariatric surgery in cirrhotic patients is still to be evaluated. Meta-analyses reported adverse outcomes and risk of complications in a small percentage of the MAFLD related cirrhotic patients receiving bariatric surgery.[33,39-41] For these patients, consultation should be made with surgeons to weigh the pros and cons of surgery. Compared to pharmaceutical strategies, bariatric surgery could provide the most promising efficacy by far. For morbidly obese patients with MAFLD, especially those who do not respond to lifestyle modifications, bariatric surgery is an attractive and appropriate therapeutic option.

Anti-hyperglycemic agents for MAFLD patients

T2DM are frequently found to coexist with MAFLD and act as the strongest risk factor for disease progression and adverse hepatic or extrahepatic outcomes.[42,43] Developing therapeutics for both MAFLD and metabolic targets might be extremely beneficial for MAFLD patients with T2DM. Since anti-hyperglycemic drugs may address the common pathophysiological mechanisms of MAFLD and T2DM, the main categories of anti-hyperglycemic drugs have been widely tested in MAFLD patients, in order to figure out a shortcut to the development of novel therapeutics. Of these, glucagon-like peptide-1 receptor agonists (GLP-1 RA), thiazolidinediones, and sodium-dependent glucose transporters 2 (SGLT-2) inhibitors showed some promise to improve histological features of steatohepatitis, while metformin and dipeptidyl peptidase 4 (DPP4) inhibitors failed to provide significant efficacy on neither hepatic steatosis nor fibrosis. These drugs are often used in T2DM patients concomitant with MAFLD for initial evaluation, and then tested in clinical trials of NASH patients without T2DM, to assess the histological benefits for steatohepatitis and fibrosis.

Glucagon-like peptide-1 receptor agonists

GLP-1RA and DPP4 inhibitors are both novel agents targeting incretin for the treatment of patients with T2DM. The GLP-1 receptor was proved to be present in human hepatocytes. Compared to placebo group, hepatic GLP-1 receptors in NASH patients were reduced, which indicate that the GLP-1 signal pathway is closely related to the development of MAFLD.[44] Early evidence of GLP-1RA application for MAFLD begins with exenatide studies. In these studies, exenatide showed potent efficacy on weight loss and improvements in liver enzymes in T2DM patients concomitant with MAFLD.[45,46] Liraglutide, a long-acting GLP-1RA, had well-defined positive efficacy on T2DM and cardiovascular outcomes.[47] Liraglutide treatment also led to weight loss, decrease of serum cholesterol and triglyceride levels, and decrease of liver fat content in T2DM patients with MAFLD.[48,49] In the representative study of liraglutide, a 48-week treatment was able to prevent the progression of liver fibrosis.[50] As the first GLP-1RA used for MAFLD, liraglutide gained the attention of guidelines.[28,51]

Semaglutide had higher homology (94%) in humans and needed a less dosing frequency compared to liraglutide. Previous studies have confirmed the efficacy on weight loss, improved glycemic control, and reduced levels of liver enzymes of semaglutide.[52,53] A recent phase 2 trial validated the safety and efficacy of semaglutide in patients with biopsy-proven NASH with fibrosis of stage F1-F3. The 0.4-mg group achieved the highest rate of NASH resolution without worsening of fibrosis. Semaglutide also led to improvement in insulin resistance and persistent weig ht loss.[54] GLP-1RAs shared common adverse effects of gastrointestinal symptoms including nausea, vomiting, and abdominal pain, but these events were dose-dependent and usually transient.[55] Several meta-analyses summarized the studies of GLP-1RAs on MAFLD.[56,57] Although effective for hepatic steatosis and inflammation scores, the potential to reverse fibrosis requires evaluation by further prospective studies with histological endpoints. Recently, the Food and Drug Administration (FDA) of the United States has approved semaglutide 2.4 mg for the treatment of obesity.[58] The oral form of semaglutide also showed improvement in some non-invasive markers of MAFLD, while histological benefits still need to be confirmed.[59]

SGLT-2 inhibitors

SGLT-2 inhibitors reduce glucouria and plasma glucose through inhibition of glucose reabsorption in the proximal tubule of the kidney. SGLT-2 inhibitors also reduce major cardiovascular events and heart failure, and currently are widely used in T2DM patients with risk of cardiovascular diseases.[60] The efficacy of SLGT2 inhibitors in imaging diagnosed MAFLD patients was first described in a 24-week trial, in which dapagliflozin showed the potential to improve hepatic lipid content.[61] In the following studies, luseogliflozin, canagliflozin, ipragliflozin, and empagliflozin all achieved improvement in liver fat content (ranges from 3.9% to 6.9%) among T2DM patients with MAFLD.[62-65] Nevertheless, the meta-analyses of recent studies did not reach agreement, and results based on non-invasive endpoints of NASH still need to be confirmed.[66,67] In a biopsy-proven NASH trial, empagliflozin showed improvements in the histological scores of steatosis, hepatocytes ballooning, and fibrosis in NASH patients with T2DM.[68] Histological benefits of SGLT-2 inhibitors on NASH are still accumulating in studies with larger sample size. The phase 3 trial of dapagliflozin (DEAN study) based on histological endpoints is now recruiting patients (NCT03723252).

Thiazolidinediones

Thiazolidinediones are peroxisome proliferators-activated receptors (PPAR) γ agonists, also known as insulin sensitizers in the treatment of T2DM, and have been extensively evaluated in NASH. Thiazolidinediones reduces plasma FFA, decrease hepatic fat deposition, and improve insulin resistance, mainly by stimulating adipocyte differentiation.[69] In T2DM patients with NASH, pioglitazone showed significant reductions in liver fat content measured by magnetic resonance spectroscopy. Although pioglitazone failed to achieve better improvement in NASH compared to vitamin E in the large phase 3 trial of NASH patients without T2DM[70], current meta-analyses reported that pioglitazone demonstrated significant efficacy in reversing fibrosis in NASH patients.[67,71] Although in the large phase 3 trial of NASH patients without T2DM, pioglitazone failed to achieve better improvement in NASH compared to vitamin E,[70] current meta-analyses reported significant efficacy of reversing fibrosis in NASH patients.[67,71] In addition, patients in the pioglitazone group had an average weight gain of 4.7 kg during treatment, which was still sustained after discontinuation. This would present an additional concern in the long-term use of pioglitazone in obese MAFLD patients.[72]Based on these evidences, pioglitazone was recommended in guidelines[51,73] for patients with biopsy-proven NASH but not simple fatty liver patients. Moreover, the long-term safety of thiazolidinediones in MAFLD patients without T2DM is still to be established. MSDC-0602K is a new generation thiazolidinedione; it selectively binds to the mitochondrial pyruvate carrier (MPC) to regulate the entry of pyruvate into the mitochondria. As a mediator of the nutritional overload signals, MPC deals with dysfunctional lipid metabolism.[74] In a phase 2 trial, MSDC-0602K failed to demonstrate effects on composite histological endpoint, but improved NAFLD activity score (NAS) and insulin resistance in NASH patients.[75] Long-term cardiovascular outcomes are being evaluated in its further phase 3 study (NCT03970031).

Metformin and dipeptidyl peptidase 4 inhibitors

Metformin is a classical agent and well-established for the treatment of T2DM, and is often recommended as the initial pharmacotherapy for most of the T2DM patients at their diagnosis. Metformin was also effective in reducing obesity, and improving heart failure and other related metabolic dysfunctions.[76] Recent meta-analyses summarized the benefits of metformin on insulin resistance, weight loss, and liver enzymes.[77,78] A recent study conducted in MAFLD patients without T2DM showed

improvements in liver stiffness measurement and controlled attenuation parameter during metformin treatment.[79] However, there were a few studies that evaluated the histological improvement of metformin and the endpoints were not achieved.[80] Well-designed randomized controlled trials of metformin are needed. Several observational studies found evidence that metformin treatment might reduce the risk of hepatocellular carcinoma in diabetic patients.[81,82] The mechanism behind the efficacy of metformin in reducing this risk remains remains unclear. Investigators also speculated that metformin reduced liver fat accumulation before the onset of MAFLD, and then delayed the development of inflammation of the adipose tissue, preventing liver tumorigenesis.[83] Hence, we still need more preclinical evidence and observational cohorts to support the use of metformin in MAFLD patients.

DPP-4 inhibitors are also used for T2DM patients as second-line medication options. It was reported that circulating DPP-4 levels were associated with the prevalence of hepatic steatosis and the score of lobular inflammation,[84] but this feature is not related to the efficacy of DPP-4 inhibitors in MAFLD patients. A randomized placebo-controlled study demonstrates that sitagliptin was not effective in improving hepatic steatosis or fibrosis measured by MRI-PDFF and magnetic resonance elastography.[85] A recently published meta-analysis also showed similar findings.[56] In addition, DPP-4 inhibitors have no beneficial effects for cardiovascular events[86] and are therefore not recommended for MAFLD patients.

Modulators of Metabolism Disorders

Triglyceride in hepatocytes is synthesized from fatty acyl CoA, which is determined from the balance between FFA formation and utilization. The treatment goal of MAFLD targets reducing the accumulation of hepatic lipid. Bile acids are produced by hepatocytes and facilitate dietary lipid absorption through emulsification effect on the fat. Therefore, bile acids and derivatives showed therapeutic effects on liver diseases including NASH and primary sclerosing cholangitis. The farnesoid X receptor (FXR) is expressed in the liver and intestines, and is involved in the synthesis and enterohepatic circulation of bile acids. FXR could also be activated by selected bile acids.[87] PPAR are a family of ligand-dependent transcription factors, playing an important role in metabolic processes in the liver and other organs. Different isoforms of PPARs (PPARα, PPARβ/δ, and PPARγ) have different tissue distribution, affinity, and specificity for agonists. All isoforms participate in lipid homeostasis and glucose regulation.[88] Fibroblast growth factors (FGFs) are a large family involved in a myriad of biological functions, among which FGF19 and FGF21 participate in inter-organ endocrine signaling axes including bile acid, glucose, and lipid metabolism. Endocrine FGFs may serve as risk factors, biomarkers, or even treatment targets for MAFLD.[89]

Farnesoid X receptor

Obeticholic acid (OCA) is the first agent of FXR meeting the primary endpoint of improvement in fibrosis of one stage or more without worsening of NASH and with completed phase 3 trial (REGENERATE study).[90,91] Improvement in fibrosis was also observed in non-invasive markers.[92] A total of 23% patients with fibrosis stage F2-F3 in the OCA 25-mg group achieved improvement in fibrosis while only 12% patients achieved NASH resolution. On the other hand, OCA did improve each aspect of the NASH histological features including steatosis, lobular inflammation, and hepatocyte ballooning. However, the FDA delayed conditional approval of OCA in 2020 until more efficacy and safety data are available. One of these concerns may be the adverse events of pruritis, increased serum low-density lipoprotein (LDL) cholesterol, and reduced serum high-density lipoprotein cholesterol levels. Pruritus was mild to moderate and dose dependent, and even caused treatment discontinuation in the 25-mg group. Furthermore, whether OCA related increasing LDL cholesterol would affect the long-term cardiovascular outcome of MAFLD patients need to be further studied. Moreover, further studies are needed to ascertain whether an OCA-related increase in LDL cholesterol can affect the long-term cardiovascular outcome in MAFLD patients. Now the FDA has requested the REGENERATE trial to continue to review the clinical outcome in the future.

EDP-305 and cilofexor (formerly GS-9674) are novel FXR agonists, and both showed improvements in non-invasive endpoints of NASH assessed by MRI-PDFF among non-cirrhotic patients in their recent phase 2 trials. During 12 weeks of treatment, EDP-305 achieved 7.1% reduction in liver fat content in overweight biopsy-proven NASH patients. Similar to OCA, a considerable proportion (50.9%) of the patients in the 2.5-mg group suffered pruritis and >20% patients discontinued treatment due to pruritis.[93] Cilofexor is a small molecule nonsteroidal agonist of FXR, and provided significant reductions in hepatic steatosis and serum alanine transaminase (ALT) level in the current study. Nearly 40% patients in the cilofexor 100-mg group had >30% reduction in liver fat content assessed by MRI-PDFF. Cilofexor was not a bile acid and therefore was expected to have fewer adverse events of pruritus. Only 14% patients in the 100-mg group reported moderate to severe pruritus.[94] These two studies are both designed with short treatment durations, while MAFLD is a slowly progressive disease which evolves over years. Between baseline and week 24, cilofexor did not achieve significant changes in biomarkers of fibrosis, which indicates that further studies need a longer time to observe beneficial effects of treatment.

Peroxisome proliferator-activated receptors (PPARs)

PPARα and PPARβ/δ activation mostly facilitates energy combustion, while PPARγ activation mainly contributes to energy storage. Thiazolidinediones as classic PPARγ ligands are used for treatment of T2DM, as discussed in the previous paragraphs. Lanifibranor is a pan-PPAR agonist, and is reported to be more effective than single or dual PPAR agonists in reducing liver fibrosis and inflammatory gene expression.[95] The phase 2b trial of lanifibranor was conducted in NASH patients for 24 weeks, with the primary endpoint of a decrease of activity score in the steatosis-activity and fibrosis scoring system by least two points without worsening of fibrosis.

Nearly half the patients in the 1200-mg group achieved the primary endpoint, and lanifibranor was well tolerated.[96] Based on these positive results, lanifibranor received FDA breakthrough therapy designation, and the phase 3 trial among NASH patients with stage F2/F3 fibrosis (NATiV3) is now recruiting (NCT04849728).

Saroglitazar (lipaglyn) is a dual PPARα/γ agonist, recently approved for the treatment of NASH by the Drug Controller General of India (DCGI). This makes saroglitazar the first drug for NASH treatment worldwide. According to the recent evidence, saroglitazar decreased liver fat content as well as serum lipid profile.[97] However, the approval of saroglitazar was based on the phase 3 trial (EVIDENCES II), which revealed histological improvement of NASH during 52 weeks of treatment (unpublished data). In the phase 2 trial, saroglitazar achieved reductions of hepatic fat content in MRI-PDFF and in serum ALT levels in obese patients with NASH after 16 weeks of treatment.[98] Our concern is that not all the NASH patients had elevated serum ALT levels. In addition, there were no cut-offs for ALT as a marker to predict NASH or long-term events. More histological evidence should thus be added and released before recommendations for the treatment of NASH can be made available. Elafibranor (formerly GFT-505) is a dual PPARα-PPARδ agonist. In previous studies, elafibranor improved liver enzymes and insulin sensitivity in obese patients with MAFLD.[99] In the phase IIb clinical trial (GOLDEN-505), elafibranor achieved higher NASH resolution rate than placebo after 52 weeks treatment (19% *vs.* 12%, $P = 0.045$).[100] However, the phase 3 trial of elafibranor was terminated due to insufficient improvement in histological NASH endpoints (NCT02704403). In addition, some patients developed elevated serum creatinine levels and renal impairment during elafibranor treatment, which added to the concerns about the safety.

Fibroblast growth factors

Aldafermin (formerly NGM282) is an engineered FGF19 analog. In the phase 2 trial in biopsy-proven NASH patients, 12 weeks' aldafermin treatment resulted in a reduction in absolute liver fat content measured by MRI-PDFF. More than 70% patients receiving aldafermin achieved the endpoint of ≥5% reduction in liver fat content.[101] Although aldafermin did not achieve significant improvement in the NASH resolution without worsening of fibrosis, it did improve every aspect of NAS. In the further study (ALPINE 2/3), aldafermin still did not achieve improvement of fibrosis in NASH patients with stage F2-F3 fibrosis, which was set as the primary endpoint: fibrosis improvement by >1 stage with no worsening of NASH.[102] The phase 2b trial (ALPINE 4) of aldafermin is recruiting to evaluate its efficacy among patients with compensated MAFLD-related cirrhosis (NCT04210245). Efruxifermin and pegbelfermin (formerly BMS-986036) are both FGF 21 analogues, designed to be injected subcutaneously once-weekly for 16 weeks. Both efruxifermin and pegbelfermin showed potent efficacy in reducing liver fat content assessed by MRI-PDFF (−14.1% and −5.2%, respectively) in their phase 2a trial.[103,104] In addition, pegbelfermin showed improvements in liver injury markers and cardiometabolic parameters, while efruxifermin showed improvements in serum lipid metabolism and glycemic control as well as weight loss, which may be more attractive for MAFLD patients. Further studies of efruxifermin on patients with NASH (NCT04767529) and NASH related compensated cirrhosis (NCT05039450) are now moving on to assess the efficacy in histological endpoints.

In addition, the management of other metabolic risks of MAFLD including insulin-resistance, hypertension, dyslipidemia, and systemic inflammation are of similar importance.[2] Although there was no evidence supporting the view that statins can improve NASH and liver fibrosis, statins are safe for MAFLD patients and useful for reducing cardiovascular events and even achieving reduction of incident liver cirrhosis and cancer. In MAFLD patients concomitant with hypertension, insulin resistance accelerated the activation of the inflammatory arm of the renin-angiotensin system. Angiotensin II receptor antagonists are safe in MAFLD patients and showed potential efficacy in reducing serum ALT levels.[28] Among these, telmisartan may be the most promising; it not only blocks the renin-angiotensin system (RAS) but also reduces insulin resistance,[105] and this property could be useful in patients with concomitant arterial hypertension.

Furthermore, except for cardiometabolic targets, agents directly targeting hepatocytes stress, apoptosis, inflammation, and fibrosis are more urgently needed for fibrotic NASH patients. Although several agents (emricasan, simtuzumab, selonsertib, etc.) failed to prove their efficacy in fibrotic NASH in clinical trials, more emerging agents target are being evaluated.[106]

Summary

MAFLD is an umbrella term, and it represents a heterogeneous disease with different clinical characteristics, natural histories, and outcomes. Obesity, metabolic syndrome, and T2DM increase the risk of developing MAFLD and related liver cirrhosis and cancer and add to the burden of management. In current investigational studies, only 20% to 40% patients respond to pharmaceutical treatment, reflecting the importance of heterogeneity of MAFLD. In order to provide an appropriate therapeutic approach, it is important to identify and stratify MAFLD patients at greatest risk of disease progression. The definition of MAFLD stratifies patients according to the presence of coexisting metabolic features into subgroups with different risks. The perspective of precision medicine may be required in the treatment strategy for these patients in key subgroups. Similarly, the American Gastroenterological Association identified three subgroups known to be at higher risk of MAFLD related fibrosis: patients with T2DM, patients with two or more metabolic risk factors, and patients with incidental finding of hepatic steatosis or elevated aminotransferases, according to the guidelines released recently.[107]

Considering the lack of approved potent agents for MAFLD treatment, lifestyle intervention based on diet and physical activity is now the fundamental method of managing

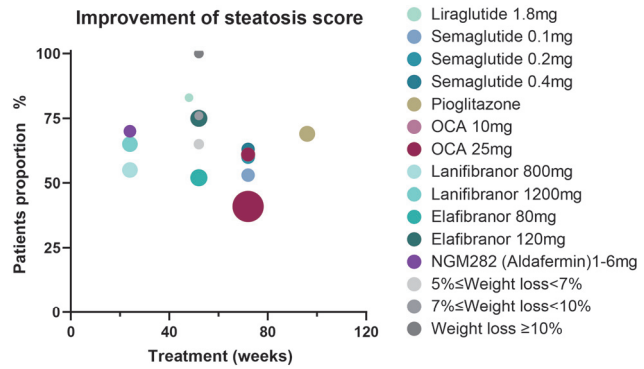

Figure 2: Efficacy of current therapies on histological improvement of steatosis in patients with MAFLD. Steatosis improvement is defined as improving ≥1 score in steatosis score according to NASH-CRN or SAF-FLIP scoring system. MAFLD: Metabolic dysfunction-associated fatty liver disease; NASH: Nonalcoholic steatohepatitis; NASH-CRN: NASH Clinical Research Network; SAF-FLIP: steatosis, activity, and fibrosis (SAF) score and fatty liver inhibition of progression (FLIP) algorithm; OCA: Obeticholic acid.

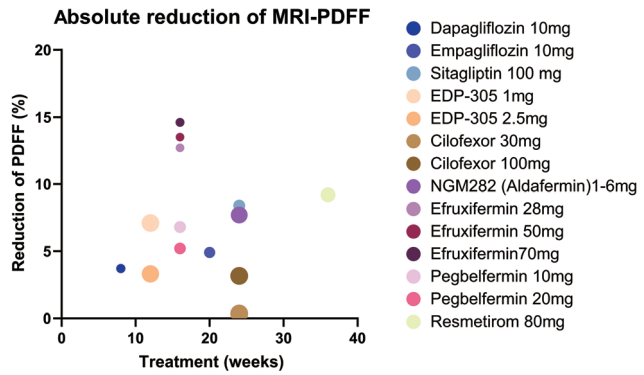

Figure 3: Efficacy of current therapies on reduction of hepatic lipid content in patients with MAFLD. The hepatic lipid content reduction is measured by MRI-PDFF. The reduction of hepatic lipid content is defined as absolute changes from baseline. MAFLD: Metabolic dysfunction-associated fatty liver disease; MRI-PDFF: Magnetic resonance imaging-proton density-fat fraction.

MAFLD. Weight loss through bariatric surgery may be an effective approach to achieve significant improvement for morbidly obese patients with MAFLD. Drug development targeting MAFLD and underlying cardiometabolic risk factors have been quickly progressing over the past decades. Anti-hyperglycaemic agents provided a shortcut for MAFLD drug agents' development, but not all the traditional drugs were effective for MAFLD. Novel modulators of glucolipid metabolism showed their promise in improving MAFLD [Figures 2–4]. Last but not least, numerous ongoing clinical trials are expected to identify novel agents capable of achieving improvements in the efficacy of the clinical outcomes of MAFLD.

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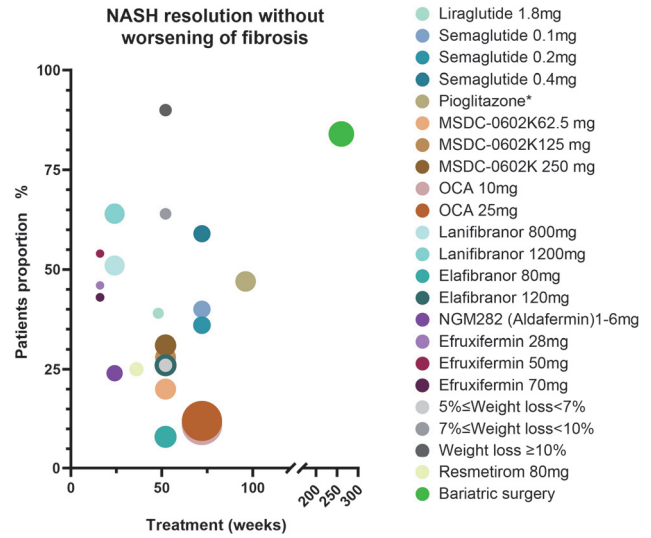

Figure 4: Efficacy of current therapies on steatohepatitis resolution in patients with MAFLD. NASH resolution is defined as no more than mildly inflammatory (score 0–1) and no hepatocyte ballooning (score 0) with no worsening of liver fibrosis. *Data of pioglitazone refers to NASH resolution (without assessment of fibrosis) since the study was published earlier. MAFLD: Metabolic dysfunction-associated fatty liver disease; NASH: Nonalcoholic steatohepatitis; OCA: Obeticholic acid.

Conflicts of interest

None.

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