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MINIREVIEWS

- 1 Advances in the treatment of nonalcoholic steatohepatitis

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ABOUT COVER

Peer reviewer of *World Journal of Pharmacology*, Ji Ma is completing a doctorate at China Pharmaceutical University. Having received his Bachelor's degree from the Pharmacy School of China Pharmaceutical University in 2013, he undertook postgraduate training at the university's affiliated Traditional Chinese Pharmacy School and received his Master's degree in 2019. His ongoing research interests involve the establishment of novel animal models of various metabolic diseases, including obesity, hyperlipemia, nonalcoholic fatty liver disease and nonalcoholic steatohepatitis, and the application of these novel *in vivo* systems to study active compounds identified by screening of Traditional Chinese herbal materials. (L-Editor: Filipodia)

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Advances in the treatment of nonalcoholic steatohepatitis

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Abstract

Nonalcoholic steatohepatitis is a subtype of metabolic dysfunction-associated liver disease which has emerged as one of the most common causes of cirrhosis and liver transplantation in the United States and many western countries. The two leading risk factors associated with nonalcoholic steatohepatitis are obesity and insulin resistance with patients often demonstrating features of the metabolic syndrome. Histological improvement including arrest or improvement in fibrosis can occur in patients who are able to modify these risk factors when diagnosed early in the course of their disease. In addition to the development of cirrhosis and its life-threatening complications including hepatocellular carcinoma, variceal bleeding, ascites and hepatic encephalopathy, nonalcoholic steatohepatitis is also associated with coronary artery, carotid artery and peripheral vascular disease with coronary artery disease identified as the most common cause of death. Although multiple clinical trials evaluating a variety of medications targeted at different aspects in the pathogenesis and progression of nonalcoholic steatohepatitis have been completed and are still in progress, there is currently no approved treatment for this disease except for risk factor modification. This article will review the most recent and salient medical advances in the treatment of nonalcoholic steatohepatitis.

Key Words: Nonalcoholic steatohepatitis; Fibrosis; Cirrhosis; Obesity; Insulin resistance; Coronary artery disease

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Core Tip: This review article discusses important advances in the medical treatment of nonalcoholic steatohepatitis. Initially considered to be a disease only affecting western countries, nonalcoholic steatohepatitis and obesity are increasing in prevalence worldwide. This review includes data from the most recent peer-reviewed journals in

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INTRODUCTION

Nonalcoholic steatohepatitis (NASH), a subtype of metabolic dysfunction-associated liver disease (MAFLD), is one of the leading causes of cirrhosis and liver transplantation in many Western countries. However, it is also strongly associated with coronary artery disease which remains the most common cause of death in these patients^[1]. Obesity and insulin resistance, as part of the metabolic syndrome, are the most common risk factors for NASH, and if modified in the early stages of the disease, can lead to reversal of hepatic steatosis and ballooning, inflammation and fibrosis (Table 1). Fibrosis remains the greatest histological predictor of mortality with patients with advanced fibrosis (stage 3 and stage 4 fibrosis) at greatest risk (Table 2). In addition, up to 15% of patients with morbid obesity and normal liver tests have evidence of advanced fibrosis^[2]. However, current guidelines do not recommend further evaluation unless clinically indicated, adding to the complexities of managing this disease^[2]. These risk factors are often unable to be reversed in the vast majority of patients who remain untreated and are at risk of disease progression. For patients who have attempted weight loss and failed treatment of the metabolic syndrome or who are not eligible for bariatric surgery, referral for participation in clinical trials is appropriate^[3].

There are currently multiple clinical trials evaluating medical and occasionally surgical interventions for selected patients with NASH although there is still no approved treatment for NASH. Recently non-invasive tests for steatosis and fibrosis have been utilized for phase 2 studies in lieu of liver biopsies although histology is still essential for phase 3 clinical trials. This article will review the most recent medical advances in this rapidly evolving field which now show promise for patients who suffer from this silent but ubiquitous disease (Table 3).

INSULIN SENSITIZATION

Peroxisome proliferator activated receptors

Peroxisome proliferator activated receptors (PPAR) are nuclear receptors composed of three subtypes: PPAR α , PPAR β/δ and PPAR γ . This family of transcription factors are activated by thiazolidines and play a critical role in intermediary metabolism and inflammation by a myriad of mechanisms including to proliferation of peroxisomes and stellate cell activation^[4]. Each subtype has a specific role in lipid metabolism and as PPAR agonists have multiple targets, they have been extensively studied in NASH. Two placebo-controlled randomized studies of pioglitazone (acting as a PPAR γ agonist) in nondiabetic and patients with insulin resistance with histologically confirmed NASH showed improvement in biochemical and histological endpoints^[5,6]. A larger randomized controlled trial of nondiabetic patients comparing pioglitazone 30 mg per day with placebo and vitamin E with placebo for 96 wk also reported biochemical and histological improvement in patients who received pioglitazone although there was no statistical improvement in the hepatic fibrosis and nonalcoholic fatty liver disease activity score (NAS) compared to placebo^[7]. In an 18 mo prospective trial comparing pioglitazone 45 mg per day *vs* placebo in NASH patients with and without type 2 diabetes, investigators reported resolution of NASH in 48% of patients with type 2 diabetes *vs* non-diabetics^[8]. Furthermore, a significant reduction in fibrosis from baseline was observed only in patients with type 2 diabetes ($P = 0.035$). Expert guidelines have recommended pioglitazone as a treatment for NASH in patients with insulin resistance based on these important studies but prescribers and patients alike have to be cognizant of side effects such as osteopenia, weight gain and a possible

Table 1 Clinical research network non-alcoholic fatty liver disease activity score

Score	Steatosis (%)	Lobular inflammation	Ballooning degeneration
0	< 5	None	None
1	5 to 33	< 2 foci	Few
2	33 to 66	2 to 4 foci	Many
3	> 66	> 4 foci	

Table 2 Fibrosis score in nonalcoholic steatohepatitis

Stage	Histological findings
1a	Mild pericellular fibrosis (only detected on connective tissue stain)
1b	Moderate pericellular fibrosis (detected on hematoxylin and eosin stain)
1c	Portal/periportal fibrosis without pericellular fibrosis
2	Pericellular with portal/periportal fibrosis
3	Bridging fibrosis
4	Cirrhosis

association with congestive heart failure^[9].

Elafibrinor (GFT505) is a dual PPAR α and PPAR γ agonist which acts on multiple pathways in the pathogenesis of NASH to reduce inflammation and fibrosis but also improves insulin sensitivity and lipid metabolism^[10]. In a phase 2, randomized, placebo-controlled trial, patients with histologically confirmed NASH without cirrhosis were randomized to elafibrinor 80 mg ($n = 93$), elafibrinor 120 mg ($n = 91$), or placebo ($n = 92$) each day for 52 wk^[11]. Liver biopsies were repeated at the end of treatment to determine the impact of elafibrinor on the primary end point defined as an improvement in NASH without progression of fibrosis. Although there was no significant difference between elafibrinor and placebo in an intention to treat analysis, a post hoc analysis of the data showed elafibrinor 120 mg per day resolved NASH without worsening fibrosis and was associated with improved lipid and glucose profiles. However, a mild reversible increase in serum creatinine was noted in 2.5% of patients. As approximately 20% of patients had stage 3 fibrosis and 30% with NAS scores between 6 and 8, the impact of elafibrinor is currently being evaluated in a phase 3 trial in patients with advanced disease.

MSDC-0602K is an insulin sensitizer which inhibits the mitochondrial pyruvate carrier but has minimal effect on PPAR activation. Due to its effects on DNL and fatty acid oxidation, it appears to be a promising agent for the treatment of NASH. However, in a randomized double blind 52 wk study comparing placebo with 1 of 3 MSDC-0602K doses in patients with biopsy-confirmed NASH, Harrison *et al*^[12] reported MSDC-0602K did not demonstrate any significant effect improvement in histology or NAS^[12]. As metabolic and non-invasive liver injury markers did improve, further studies were recommended.

Glucagon like peptide 1

Glucagon like peptide 1 (GLP1) is a 30 amino acid incretin hormone secreted from the intestinal epithelial L cells post-prandially and activates multiple genes such as PPAR α that improve insulin sensitivity, hepatic fatty acid oxidation and lipid export from the liver^[13]. GLP1 also has anti-inflammatory, anti-apoptotic, anorectic and lipid lowering effects which has made it attractive in the study of NASH, either directly or by using inhibitors of GLP1 degradation. In a randomized, placebo-controlled phase 2 trial, 52 patients with histologically confirmed NASH were randomized to liraglutide (1.8 mg per day) *vs* placebo for 48 wk with the primary outcome defined as resolution of NASH with no worsening of fibrosis during the treatment period^[14]. In an intention to treat analysis, resolution of NASH and progression of fibrosis was present in 39% and 9% of treated patients, respectively, *vs* 9% and 36% in the placebo arms, respectively. However, gastrointestinal side effects were more common in the treatment arm.

As GLP1 is rapidly metabolized by the enzyme dipeptidyl peptidase IV, dipeptidyl peptidase IV inhibitors such as sitagliptin have recently been studied in patients with

Table 3 Medical treatment of nonalcoholic steatohepatitis

Insulin sensitization	
PPAR receptor agonists	Tropifexor
Glucagon like peptide 1	NGM282
Farnesoid X receptor agonists	
Inhibiting lipogenesis	
Acetyl coenzyme a carboxylase inhibitors	
Aramchol	
Modulating lipid metabolism	
Polyunsaturated fatty acids	
Ezetimibe	
Resmetirom	
Inhibiting oxidative injury	
Vitamin E	
Anti-fibrotics	
Simtuzumab	
Galectin-3 inhibitors	
Anti-inflammatory and anti-apoptotic agents	
Caspase inhibitors	
Chemokine receptor 2 and 5 inhibitors	
Manipulating the intestinal microbiome	
Antibiotics, probiotics, fecal microbiota transplantation	
New and emerging treatments	
Apical sodium dependent bile acid transporter inhibitors	
Apoptosis signal kinase-1 inhibitors	
Protein kinase inhibitors	
Toll-like receptor 4 antagonists	

PPAR: Peroxisome proliferator activated receptors.

MAFLD. In a randomized, double-blind, placebo controlled trial, 50 MAFLD patients with prediabetes or early diabetes were randomized to sitagliptin 100 mg per day *vs* placebo for 24 wk^[15]. These patients had fatty liver disease diagnosed by exclusion of other liver diseases and by imaging studies and not histology which may have excluded patients with NASH. In addition, liver fat was measured by magnetic resonance imaging derived proton density-fat fraction (MRI-PDFF) and improvement in this variable was the primary outcome of the study. The investigators reported short-term use of sitagliptin had no impact on reducing hepatic steatosis, liver tests such as aspartate aminotransferase, low-density lipoprotein levels, homeostatic model assessment insulin resistance or liver stiffness by magnetic resonance elastography. Important limitations of this study include the absence of histology which may have excluded patients with NASH and the truncated treatment duration. However, non-invasive imaging and markers of fibrosis are likely to gain popularity given the increasing prevalence of NASH and reluctance of most patients to undergo serial liver biopsies, a pre-requisite in phase 3 clinical trials for determining the impact of an intervention on NASH.

Farnesoid X receptor agonists

Activation of the farnesoid X nuclear receptor (FXR) leads to multiple effects which include enhancing insulin resistance and reducing triglyceride synthesis, influencing the milieu of the intestinal microbiome and anti-inflammatory and anti-fibrotic

properties^[16]. The multiple effects of FXR activation have led to exploration of this pathway as a possible therapeutic option for NASH. Obetacholic acid (OCA), a semi-synthetic derivative of chenodeoxycholic acid, is an active ligand of FXR and decreases insulin resistance and hepatic steatosis in animal models. OCA was also approved by the United States Food and Drug Administration (FDA) for the treatment of primary biliary cholangitis in 2016.

In a proof of concept phase 2 study, patients with type 2 diabetes mellitus and MAFLD were randomized to placebo, OCA 25 mg per day or 50 mg per day for 6 wk. Both doses of OCA were associated with improved insulin sensitivity and weight loss in parallel with reduced serum markers of hepatic inflammation and fibrosis^[17]. These encouraging findings led to a phase 2b randomized, placebo-controlled trial of 283 patients with biopsy proven NASH treated with OCA 25 mg per day for 72 wk^[18]. The interim analysis demonstrated OCA 25 mg per day produced a decrease in NAS by at least 2 points compared to placebo. A significant reduction in fibrosis was also noted in these patients compared to placebo, possibly due to an indirect effect of OCA as FXR expression is low in hepatic stellate cells and myofibroblasts^[19]. However, OCA treatment was associated with elevations in total serum cholesterol and LDL cholesterol but a reduction in HDL cholesterol. These findings have raised concern as NASH alone is an independent risk factor for cardiovascular disease and it remains unclear if these patients may require dose adjustment of OCA or concomitant statin therapy^[20]. OCA was also associated with pruritus in 20% of patients which may affect compliance.

The long-term safety OCA and its impact on liver-related outcomes and all-cause mortality is currently being evaluated in an international phase 3 trial (REGENERATE) comparing placebo with OCA 10 mg per day and OCA 25 mg per day over a 6 year period in patients with NASH without cirrhosis. Interim results published in 2020 reported fibrosis improvement endpoint was achieved by 37 (12%) patients in the placebo group, 55 (18%) in the OCA 10 mg group ($P = 0.045$), and 71 (23%) in the OCA 25 mg group ($P = 0.0002$)^[21]. Pruritus was the most common side effect which appeared to be dose-related, occurring in 123 patients (19%) in the placebo group, 183 (28%) in the OCA 10 mg group and 336 (51%) in the OCA 25 mg group. In view of the significant improvement in fibrosis scores and NASH disease activity, it is expected this study will continue until completion. A major benefit of the REGENERATE study is its long duration which many investigators believe are necessary to fully study the impact of a medical treatment on NASH, a chronic insidious disease which usually takes many years to develop and thus may also require many years of medical treatment to either arrest or reverse the disease process. Although OCA was well-tolerated in this interim analysis, in September 2017, the United States FDA reported 19 patients with primary biliary cholangitis had died after taking OCA. It appeared that improper dosing was the culprit although liver injury occurred in patients with both mild and moderately severe liver disease. Although few studies have included patients with cirrhosis, the REVERSE trial (ClinicalTrials.gov Identifier: NCT03439254) is a phase 3, multicenter trial comparing placebo with OCA 10 mg per day and OCA 25 mg per day over two years in patients with histologically confirmed cirrhosis from NASH. Although study recruitment has stopped, interim results have yet to be published.

Tropifexor (LJN-45) is a non, bile-acid agonist which induces target genes without Takeda G protein receptor 5 activation. It has shown to be effective in animal studies and well tolerated in phase 1 trials and is currently being evaluated in a 48 wk phase 2 study. Interim results have reported a decrease in liver chemistries liver fat content by MRI-PDFF compared to placebo. However, a dose-related increase in LDL, decrease in HDL together with pruritus were observed in patients who received study drug and it seemed tropifexor was least effective in the most obese patients^[22].

NGM282

Fibroblast growth factor (FGF) 19 is an enteric hormone secreted after FXR activation which inhibits gluconeogenesis, activates glycogen synthesis and regulates bile acid metabolism *via* CYP 7A1. Animal studies have reported an increase in metabolic rate and decrease in adiposity and insulin resistance, thus making it attractive as a potential treatment for NASH. However, concern remains with the association between FGF exposure and development of hepatic carcinogenesis in animal models^[23]. NGM282 is a bioengineered nontumorigenic derivative of FGF 19 which was recently evaluated in a randomized, double-blind controlled study of NASH patients with NAS scores of at least 4, fibrosis stages 1-3 and at least 8% liver fat content. Patients were stratified based on the presence of diabetes mellitus to receive placebo *vs* 3 mg or 6 mg of subcutaneous NGM282 for 12 wk^[24]. This study was

unique as serial liver biopsies were performed after only 12 wk of treatment. At conclusion of the study, 20 (74%) patients in the 3 mg dose group and 22 (79%) in the 6 mg dose group achieved at least a 5% reduction in absolute liver fat content from baseline *vs* two (7%) in the placebo group. No major adverse events were noted except for hypercholesterolemia in patients who received the study medication. Due to the rapid reduction in histology and fat content with an acceptable side effect profile, NGM282 is being evaluated in additional studies with rosuvastatin added for patients who develop hypercholesterolemia.

INHIBITING LIPOGENESIS

Acetyl coenzyme A carboxylase inhibitors

Acetyl coenzyme A carboxylase (ACC) isoenzymes 1 and 2 play a critical role in de novo lipogenesis DNL (the synthesis of fatty acids from carbohydrate and amino acid precursors) and fatty acid oxidation in MAFLD and NASH, respectively^[25]. ACC carboxylates acetyl coenzyme A to form malonyl- coenzyme A which in turn inhibits fatty acid oxidation by allosteric inhibition of carnitine palmitoyl transferase. ACC inhibition may therefore lead to reduced DNL while simultaneously promoting fatty acid oxidation. NDI-010976 is an allosteric inhibitor of ACC 1 and 2 and its effect on DNL was recently studied in obese but otherwise healthy adult males^[26]. In this randomized, double-blind, placebo-controlled crossover trial, a single oral dose of NDI-010976 20 mg, 50 mg or 200 mg was well tolerated and associated with significant inhibition of 70%, 85% and 104% of fructose stimulated DNL, respectively, compared to placebo. Greater than 90% inhibition of DNL was associated with plasma concentration of NDI-010976 greater than 4 ng/mL. Future studies will likely incorporate both clinical and histological end points in subjects with NASH.

In a 12 wk pilot study, firsocostat (GS-0976), an inhibitor of ACC1 and 2, showed improvement in steatosis on MRI-PDFF and liver injury markers^[27]. This led to a 12 wk phase 2 study in patients with NASH stages 1-3. 48% of patients receiving firsocostat 20 mg per day had at least a 30% improvement in MRI-PDFF compared to baseline together with improvement in liver tests and non-invasive markers of fibrosis^[28]. These improvements were also noted in 23% of patients receiving firsocostat 5 mg per day and 15% of patients in the placebo arm. In view of these encouraging findings, phase 2 studies of firsocostat in combination with FXR agonists are currently underway.

Aramchol

Aramchol is a synthetic lipid molecule composed of cholic acid conjugated *via* a stable amide group with arachidonic acid (a saturated fatty acid) which influences fatty acid metabolism by multiple mechanisms from *in vitro* and animal studies. By inhibiting stearoyl coenzyme A desaturase 1 activity, a key hepatic enzyme involved in fatty acid metabolism, aramchol decreases both triglyceride synthesis and promotes β oxidation of fatty acids^[29]. Aramchol also catalyzes cholesterol efflux by activating the adenosine triphosphate-binding cassette transporter A1, a pan-cellular cholesterol export pump, which may lead to reduction in hepatic steatosis and atherosclerosis^[30]. In a phase 2 randomized double-blind, placebo-controlled trial to determine the impact of aramchol on hepatic lipid fat content using magnetic resonance spectroscopy and metabolic parameters, 60 patients with histologically proven MAFLD (of whom 6 had NASH) were randomized to aramchol 100 mg or 300 mg per day *vs* placebo for 3 mo^[31]. The investigators reported aramchol was safe and significantly reduced hepatic steatosis in a dose-dependent fashion and was also associated with an improvement in adiponectin levels and endothelial function although these changes did not reach statistical significance.

MODULATING LIPID METABOLISM

Polyunsaturated fatty acids can influence glucose and lipid metabolism and also have anti-inflammatory effects due to its inhibitory action on sterol regulatory element binding protein 1c. This has led to exploration of polyunsaturated fatty acids as a possible treatment for NASH. However, 2 recent randomized, placebo-controlled trials in patients with NASH and MAFLD did not show any significant impact on liver enzymes, insulin resistance or histology^[32,33]. Ezetimibe (a Niemann-Pick C1-like 1 inhibitor which mediates intestinal cholesterol absorption) was studied in a

randomized, placebo controlled study of 50 patients with MAFLD diagnosed by MRE and demonstrated significant improvement in serum aminotransferases, histological biomarkers and hepatic stiffness compared to placebo^[34]. Further studies are required to investigate the impact of newer lipid modulating agents such as proprotein convertase subtilisin/kexin type 9 inhibitors on NASH.

Resmetiron (MGL-3196)

Thyroid hormone receptor beta (THR β) is highly expressed in hepatocytes and its activation leads to multiple changes in intermediary metabolism in animal studies such as a reduction in hepatic steatosis, promotion of cholesterol export in bile and improvement insulin resistance^[35]. Resmetiron (MGL-3196) is a selective THR β agonist which was recently evaluated in a 36 wk double-blind, randomized, placebo-controlled phase 2 study in NASH patients with fibrosis stages 1-3 and at least 10% steatosis by MRI-PDFF^[36]. The primary end point was a reduction in hepatic steatosis by MRI-PDFF at 12 wk although post-treatment liver biopsy was also required at 36 wk. Although there was an improvement in MRI-PDFF values at the end of treatment, (37.3% *vs* 8.9%) and resolution of NASH compared to placebo, (27% *vs* 6%), respectively, there was no difference in fibrosis regression between the two groups. The most common side effects were nausea and diarrhea which were mild and self-limited. Based on these findings, a phase 3 study incorporating NASH resolution histologically as the new primary end point is underway.

INHIBITING OXIDATIVE INJURY

Insulin resistance alone is insufficient to cause NASH and oxidative injury is the pathway which leads to inflammation, hepatocytes injury and progressive fibrosis. Although a variety of anti-oxidants have been evaluated for treatment of NASH, vitamin E has shown the most promise although side effects remain a concern with long-term use. This was illustrated in the PIVENS study in which 247 nondiabetic patients with NASH were randomized to vitamin E 800 mg international units per day, pioglitazone or placebo for 96 wk^[7,37]. End of treatment liver biopsies demonstrated improved steatosis and inflammation but not fibrosis and side effects were comparable to placebo. After vitamin E was discontinued, aminotransferase levels returned to the same level as placebo, suggesting vitamin E therapy needs to be prolonged or indefinite. However, long-term use of vitamin E has been associated with an increase in cardiovascular disease and genitourinary cancers in two meta-analyses, questioning the use of vitamin E for NASH^[38,39]. Due to the limitations of meta-analyses, no firm conclusions can be made although patients need to be warned of these potential risks with long-term vitamin E.

ANTI-FIBROTIC AGENTS

Simtuzumab is a monoclonal antibody directed against lysyl oxidase-like-2 which in turn promotes cross-linking of collagen I and fibrosis. Due to encouraging results in animal studies and a recent pilot study in patients coinfecting with human immunodeficiency virus and hepatitis C where modulation of TGF- β 3 and IL-10 pathways was demonstrated, two phase 2 randomized, placebo-controlled studies are currently evaluating simtuzumab in patients with stage 3 and stage 4 fibrosis^[40].

Galectins are proteins which bind to β -galactoside sugars present on cell surface proteins and the extracellular matrix. Galectin-3 is highly expressed in macrophages and is involved in multiple cellular processes such as cell migration, inflammation and hepatic fibrosis^[41]. Elevated levels of galectin 3 are associated with NASH and animal studies of galectin-3 inhibitors have demonstrated improvement in hepatocyte ballooning, steatosis, inflammation and fibrosis and are now being evaluated in phase 2 studies in patients with cirrhosis from NASH after an encouraging safety profile from a phase 1 study^[34]. Chalasani *et al*^[42] recently reported the results of a randomized, double-blind phase 2b trial of weekly infusions of GR-MD-02 in patients with cirrhosis from NASH. The primary end point was a change in hepatic venous pressure gradient (HVPG)^[42]. At 52 wk, there was no reduction in HVPG between the 2 groups although the infusions were safe and a sub-analysis reported reduction in HVPG in cirrhotic patients without esophageal varices.

ANTI-INFLAMMATORY AND ANTI-APOPTOTIC MOLECULES

There is strong interest in evaluating modulators of the inflammatory and apoptotic pathways in NASH, particularly caspase inhibitors activated by tumor necrosis factor (TNF) and chemokine receptor antagonists induced by reactive oxygen species. GS-9450 is a caspase inhibitor with activity against caspases 1, 8 and 9, of which caspase 8 plays a key initiating role in apoptosis when activated by the death receptors Fas, TNF-R1 and TNF related apoptosis inducing ligand receptors 1 and 2. In a phase 2, randomized, double-blind placebo-controlled study of 124 patients with biopsy proven NASH, GS-9450 was administered at 1, 5, 10 or 40 mg a day for 4 wk^[43]. Caspase 3 cleaved cytokeratin 18 fragments were decreased in the 10 mg and 40 mg groups but were not statistically significant. Although adverse events did not occur more often than placebo, the trial was terminated early as a larger study of GS-9450 in HCV patients was associated with new onset liver injury.

Activation of chemokine receptors (CCR) 2 and 5 leads to inflammation in adipose and hepatic tissue and leads to hepatic fibrosis. As fibrosis stage is the only histological feature of NASH independently associated with liver-related and all-cause mortality, arresting or reversing fibrosis would expect to improve long-term outcomes in these patients^[44]. Cenicriviroc (CVC) is a dual antagonist of CCR 2 and CCR 5 which is expected to mitigate migration and activation of pro-inflammatory cells and also impair activation of hepatic myofibroblasts^[45]. Due to encouraging studies in animal models and extensive experience in patients with chronic liver disease, CVC was recently evaluated in patients with NASH^[37]. The CENTAUR study was a randomized, double-blind phase 2 study of 289 patients with biopsy proven NASH (stage 1-3 fibrosis, NAS activity score ≥ 4) comparing CVC 150 mg per day *vs* placebo for 1 year^[46]. The primary end points of greater than two point improvement in NAS was similar between treatment arm and placebo but the no worsening of fibrosis end point was achieved by more CVC patients than placebo (20% *vs* 10%; $P = 0.02$) at end of treatment. This was the first clinical trial which demonstrated that an improvement in fibrosis could occur independent of any improvement in steatohepatitis. In view of these results and the findings that patients who benefitted most had higher NAS scores and fibrosis stage at baseline, phase 3 studies in patients with stage 2-3 disease were conducted with 2 year results recently published^[47]. Participants in Arms A and C received CVC 150 mg or placebo, respectively, for 2 year while patients in Arm B received placebo in Year 1 and were switched to CVC in Year 2. Liver biopsy was performed at baseline, Year 1, and Year 2. The investigators reported that at year 2, 24% of patients in Arm B and 17% in Arm C ≥ 1 -stage fibrosis improvement with no worsening of NASH ($P = 0.37$). Twice the proportion of patients in arm A who achieved a fibrosis response at year 1 maintained benefit at year 2 compared to Arm C (60% *vs* 30%, respectively) including 86% in Arm A with stage 3 fibrosis at baseline. The investigators concluded CVC was not only well-tolerated but had an antifibrotic effect that was maintained if patients responded at year 1 and this observation was greatest in patients with more advanced fibrosis at baseline.

INTESTINAL MICROBIOME MANIPULATION

Since the first report of regression of hepatic steatosis with metronidazole in patients with gastric bypass and bacterial overgrowth, increased attention has been directed at the role of the intestinal microbiome in the pathogenesis of NASH and as a target for treatment^[48]. Derangements in the intestinal microbiome and its by-products together with dietary changes may contribute to fatty liver disease by a variety of mechanisms including impaired gut permeability, synthesis of pro-inflammatory molecules, production of ethanol and alterations in bile acids composition and activity^[49]. The role of probiotics and its effect on NASH was explored by a longitudinal study which measured liver tests, fasting glucose intrahepatic triglyceride content, liver stiffness and microbiota analyses of stool samples in NASH patients treated with probiotics for 6 mo *vs* supportive care^[50]. Improved liver tests, reduction in intrahepatic triglyceride content and an increase in the Bacteroidetes: Firmicutes ratio of stool samples were noted in the probiotic group while other parameters did not change compared to placebo. This has led to renewed interest in the role of antibiotics, probiotics and fecal microbiota transplantation and their impact on the intestinal microbiome as possible tools for the treatment of NAFLD in children and adults^[51].

NEW AND EMERGING THERAPIES

Several drugs targeted at different steps in the pathogenesis of NASH and fibrosis are currently being investigated. These include but are not limited to apical sodium-dependent bile acid transporter inhibitors, apoptosis signal kinase-1 inhibitors or mitogen-activated protein kinase 5 inhibitors and toll-like receptor 4 antagonists^[52,53].

CONCLUSION

NASH is a global epidemic with no approved treatment except for modification of its most common risk factors, insulin resistance and obesity, which can reverse disease progression and prevent cirrhosis. However, weight loss has often been unsuccessfully attempted for several years by afflicted patients and although bariatric surgery may play an important role in selected patients with NASH, non-surgical treatment is urgently required given the prevalence of this disease in both the obese and non-obese population^[54]. Several clinical trials over the last decade have reported encouraging studies with a variety of medications targeted at different steps in the pathogenetic pathway of NASH but due to limitations in study design, adverse events or ineffectiveness, no treatment is currently approved for the treatment of NASH.

A major advance was reached in 2015 when the FDA recognized the following therapeutic histological end points for clinical trials of NASH: Reversal or resolution of NASH, defined as the disappearance of necroinflammatory features of hepatocyte ballooning and portal inflammation together with absence of progressive fibrosis in phase 2b and 3 trials^[55]. Despite this mile-stone, many patients are reluctant to participate in studies which require one let alone serial biopsies, which brings attention to the growing importance and popularity of non-invasive serological and radiological markers for this condition/fatty liver disease and fibrosis^[56,57].

The complex pathogenesis of NASH remains a double-edged sword-on the one hand it opens a world of discovery for drug and development and treatment but on the other, treatment may necessitate multiple drugs directed at different phases in the evolution of NASH which may affect compliance. In addition, patients with underlying metabolic syndrome who received treatment(s) for NASH and their physicians need to be reminded about life-long risk factor modification, particularly if therapy for NASH has no impact on insulin resistance or obesity. In other words, although fibrosis progression may be retarded in such patients risk factor medication needs to continue in parallel.

The ideal clinical trial in NASH should have real world applicability-patients will be diagnosed using non-invasive tests, treatment will be of duration sufficient to determine the impact of treatment on reversing an insidious disease using the FDA recognized end points substituting histology with non-invasive tests. If multiple oral medications are required, consolidation into 1 or 2 capsules should be attempted. Although this may appear a herculean/formidable task at present, prescient scientists achieved this against hepatitis C, a target which seemed unattainable until recently.

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