Review Article

Narrative review of current and emerging pharmacological therapies for nonalcoholic steatohepatitis

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Abstract: Nonalcoholic steatohepatitis (NASH) is the most common cause of chronic liver disease today, and it has now emerged as the leading etiology of end-stage liver disease requiring liver transplantation. It is a progressive form of non-alcoholic fatty liver disease which can not only progress to cirrhosis of liver and hepatocellular carcinoma (HCC), but is associated with increased cardiovascular risks too. Despite all the advances in the understanding of the risk factors and the pathogenetic pathways involved in the pathogenesis and progression of NASH, an effective therapy for NASH has not been developed yet. Although lifestyle modifications including dietary modifications and physical activity remain the mainstay of therapy, there is an unmet need to develop a drug or a combination of drugs which can not only reduce the fatty infiltration of the liver, but also arrest the development and progression of fibrosis and advancement to cirrhosis of liver and HCC. The pharmacologic therapies which are being developed target the various components believed to be involved in the pathogenesis of nonalcoholic fatty liver disease (NAFLD)/NASH which includes insulin resistance, lipid metabolism oxidative stress, lipid peroxidation, inflammatory and cell death pathways, and fibrosis. In this review, we summarize the current state of knowledge on pharmacotherapy of NASH, and also highlight the recent developments in the field, for optimizing the management and treatment of NASH.

Keywords: Cirrhosis; fibrosis; nonalcoholic fatty liver disease (NAFLD); nonalcoholic steatohepatitis (NASH); treatment

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Introduction

Nonalcoholic steatohepatitis (NASH) was first described in 1980 by Ludwig and colleagues in young patients with elevated liver enzymes, without a history of alcohol consumption, and a liver biopsy consistent with alcoholic hepatitis (1). NASH, the most common cause of chronic liver disease today, is now the leading etiology of end-stage liver disease requiring liver transplantation (2). The term nonalcoholic fatty liver disease (NAFLD) encompasses a wide spectrum of histological abnormalities including simple triglyceride accumulation in hepatocytes, nonalcoholic fatty liver (NAFL) or steatosis, and NASH which is characterized by the additional presence of inflammation and tissue injury. When diagnosing NAFLD, it is imperative to exclude significant alcohol consumption,

traditionally defined as ethanol intake ≥30 g/day for men and ≥20 g/day for women (3). Other causes of liver injury must also be ruled out.

The original "two-hit" hypothesis for the pathogenesis of NAFLD has been replaced by the "multiple-hit" model (4). This comprehensive model accounts for a multitude of factors and interactions involved in the development of NAFLD including dietary habits, insulin resistance, visceral adiposity, inflammatory states, oxidative stress, alterations in microbiome, and genetic predisposition which are all potential risk factors for disease progression (4,5). The association of NAFLD with metabolic syndrome has been firmly established (6). Peripheral insulin resistance, obesity, dyslipidemia, and altered lipid metabolism synergistically catalyze the accumulation of hepatic triglycerides, lipotoxicity, and inflammation necessary for progression to NASH and cirrhosis (7). Oxidative stress due to alterations in free radical and antioxidant activities leads to the abnormal release of cytokines such as tumor necrosis factor-α (TNF-α), C-reactive protein, and interleukin-6. This pathogenic process contributes to both the progression of NAFLD to steatohepatitis and the development of cardiovascular disease in these patients.

Our increasing understanding of the pathogenic mechanisms involved in NAFLD has led to the development of potential therapeutic agents. An important obstacle in this endeavor is the lack of a reliable, noninvasive endpoint to serve as an accurate surrogate for disease progression and mortality in NASH patients. Obtaining histological samples through a liver biopsy is the most commonly used modality, the disadvantages of sampling error, intra/inter observer variability and risks of complication (8). At this time there are no validated biomarkers available to monitor response to treatment, therefore resolution of NASH and/or improvement of fibrosis on histology are still the currently accepted endpoints. The NAFLD activity score (NAS) quantifies the severity of steatosis, hepatocellular ballooning, and inflammation (9). Improvement in this score is associated with improved clinical outcomes; however, patients may experience a reduction in the severity of these components, especially hepatic steatosis, but continue to progress towards cirrhosis (10).

The American Association for the Study of Liver Diseases (AASLD) guidelines recommend that only biopsy-proven NASH should be considered for pharmacological therapies (11). Unfortunately, there are no medication regimens currently approved by United States Food and Drug Administration (FDA) for treatment in this patient population; however, several therapeutic agents have been investigated with varying degrees of success.

Electronic databases (PubMed Central, OVID Medline, Embase and Clinicaltrials.gov were interrogated from inception until May 2020 for randomized controlled trials, retrospective studies, systematic reviews, meta-analyses and clinical trials. In this comprehensive review, we summarize all pharmacologic treatments for NASH (*Table 1*) including ongoing phase 2 and 3 clinical trials (*Table 2*). We present the following article in accordance with the narrative review reporting checklist (available at http://dx.doi.org/10.21037/tgh-20-247).

Diet and weight loss

Currently, the most effective treatment for NAFLD, including NASH, is weight loss achieved by dietary modifications and physical activity. While some may easily achieve weight loss goals, maintenance of this weight reduction is much more difficult with most patients regaining their lost weight (12). Weight loss should be monitored closely as a loss of greater than 1.6 kilograms (kg) per week may cause a paradoxical increase in the state of inflammation within the liver (13). Bariatric surgery may be considered as a cost-effective option in obese patients with NASH (11). In a study of 109 severely or morbidly obese patients, 85.4% had resolution of NASH on biopsy 1 year after undergoing bariatric surgery. NASH resolution was higher among patient with mild disease compared to moderate to severe NASH (94.2% *vs.* 70%, P=0.007) (14).

A weight loss of 3–5% in patients with simple steatosis and 7–10% in patients with NASH is recommended, with the long-term goal of normalizing body weight (11). A prospective study of 293 patients evaluated the effects of varying degrees of weight loss on NASH-related histological parameters. Of the subjects who achieved ≥10% weight loss, 90% experienced NASH resolution and 45% had fibrosis regression on biopsy (15). Personalized approaches with incorporation of exercise regimens are advised. The mainstay of dietary modification is adhering to a hypocaloric diet with avoidance of certain foods. Interestingly, the benefits of weight loss are independent of the constituents of the hypocaloric diet followed (16). The effects of weight loss were derived from three main studies (17-19). Cognitive-behavioral therapy has also been shown to confer an additive benefit to weight loss when undertaken simultaneously (20).

It has long been established that consumption of more

Table 1 Pharmacological therapies for nonalcoholic steatohepatitis

Drug	Mechanism of action	Dose	Primary outcome	Adverse effects
Rosiglitazone	Selective peroxisome proliferator-activated receptor-γ agonist	8 mg/day	Reduction in steatosis >30% or disappearance of steatosis [FLIRT]	Weight gain, heart failure, bone fracture
Pioglitazone		30 mg/day	Improvement in histologic findings: ≥1 point improvement in hepatocellular ballooning, without worsening fibrosis, and either a decrease in NAS to ≤3 or a ≥2 point decrease in NAS, with ≥1 point decrease in lobular inflammation or steatosis [PIVENS]	
Liraglutide	Glucagon-like peptide-1 analog	1.8 mg/day	NASH resolution without worsening fibrosis [LEAN]	Nausea, vomiting diarrhea
Exenatide		10 mcg twice daily		
Empagliflozin	Inhibits sodium glucose cotransporter 2	25 mg/day	Change/≥1 point improvement in histological parameters; NASH resolution without worsening fibrosis; fibrosis resolution; progression to cirrhosis	Urinary tract infection, mycotic genital infection, nausea
Canagliflozin		100 mg/day	Change in serum ALT level	
Metformin	Increases 5'adenosine monophosphate-activated protein kinase signaling	2,000 mg/day	Change in AST/ALT; change/improvement in histological parameters; change in insulin sensitivity	Diarrhea, nausea, vomiting
Saroglitazar magnesium	Dual peroxisome proliferator-activated receptor α/γ agonist	4 mg/day	% change in ALT [EVIDENCES II, IV]	Well tolerated
Atorvastatin	Inhibits 3-hydroxy-3-methylglutaryl coenzyme A reductase	80 mg/day	Normalization of AST/ALT and/or improvement in liver density	Myalgia
Ezetimibe	Inhibitor of intestinal cholesterol absorption via Niemann-Pick C1-Like1 (NPC1L1) transporter	10 mg/day	Change in liver fat [MOZART]	Diarrhea
Omega-3 polyunsaturated fatty acids	Reduction in the hepatic production of very low-density lipoproteins	2,000–4,000 mg/day	Decrease in liver fat; improvement in liver fibrosis; improvement in AST/ALT	Well tolerated
Elafibranor	Dual peroxisome proliferator–activated receptor-α and -δ agonist	120 mg/day	NASH resolution without worsening fibrosis; composite long-term outcomes: all-cause mortality, cirrhosis, and liver-related outcomes [RESOLVE-IT]	Well tolerated
Obeticholic acid	Farnesoid X receptor agonist	10–25 mg/day	≥1 stage improvement in fibrosis without worsening NASH or NASH resolution without worsening fibrosis; all-cause mortality and liver-related outcomes [REGENERATE]	Pruritus, dyslipidemia
Vitamin E	Anti-oxidant	800 IU/day	Sustained ≥50% reduction in ALT or ALT ≤40 U/L [TONIC]	Hemorrhagic stroke, prostate cancer
Ursodeoxycholic acid	Bile acid homeostasis regulator	28–35 mg/kg/day	Reduction in ALT	Well tolerated
Pentoxifylline	Inhibits tumor necrosis factor-α	1,200 mg/day	Improvement in ALT; change in histological parameters	Well tolerated
Losartan	Inhibits angiotensin II receptor	50 mg/day	Change in hepatic biochemical and histological parameters	Hypotension
Telmisartan		20 mg/day	Improvement in insulin resistance; reduction of cytolysis	Hyperkalemia

ALT, alanine aminotransferase; AST, aspartate aminotransferase; NAS, nonalcoholic fatty liver disease activity score; NAS, nonalcoholic steatohepatitis.

Table 2 Ongoing Clinical Trials without published results for treatment of Nonalcoholic Steatohepatitis

Drug	Mechanism of action	Estimated enrollment	Doses	Primary outcome	ClinicalTrials.gov identifier
NGM282	Fibroblast growth factor 19 analogue	250	5 experimental doses	Change in absolute liver fat content at week 24	NCT02443116
CORT118335	Glucocorticoid receptor modulator/ mineralocorticoid receptor antagonist	120	600 mg	Change in liver fat content at week 12	NCT03823703
Betaine	Increases S-adenosylmethionine levels	26	20 mg	Change in steatosis, necroinflammatory activity, and fibrosis at 1 year	NCT00586911
Tirzepatide	Gastric inhibitory polypeptide/glucagon-like peptide-1 agonist	196	5 mg, 10 mg, 15 mg	Reversal of NASH with no worsening of fibrosis at week 52	NCT04166773
Atorvastatin, L-carnitine	Atorvastatin: inhibits 3-hydroxy-3-methylglutaryl coenzyme A reductase; L-Carnitine: cofactor for β-oxidation	440	Atorvastatin: 20 mg, L-carnitine: 1,000 mg	Improvement in liver stiffness at year 2	NCT01617772
EDP-305	Farnesoid X receptor agonist	134	2 experimental doses	Change in ALT levels at week 12	NCT03421431
TERN-101	Farnesoid X receptor agonist	96	3 experimental doses	Incidence of adverse events	NCT04328077
Solithromycin	Macrolide antibiotic with anti-inflammatory and immunoregulatory properties	10	200 mg	Change in NAS at week 13	NCT02510599
LPCN 1144	Androgen receptor agonist	75	450 mg	Change in hepatic fat fraction at 12 weeks	NCT04134091
Aldafermin	Fibroblast growth factor 19 analogue	152	3 experimental doses	Histologic response at week 24	NCT03912532
GR-MD-02	Galectin-3 inhibitor	162	2 mg/kg, 8 mg/kg	Reduction in hepatic venous pressure gradient at 1 year	NCT02462967

ALT, alanine aminotransferase; NAS, nonalcoholic fatty liver disease activity score; NAS, nonalcoholic steatohepatitis.

than 2–3 alcoholic drinks per day increases the risk of liver cirrhosis, other malignancies, and overall mortality (21). Alternatively, a few studies have demonstrated a potentially beneficial effect of mild alcohol consumption in NAFLD (22-27). However, given that this benefit was observed in cross-sectional studies, mild alcohol consumption cannot be recommended in patients with NASH (28). Alcohol should especially be avoided in obese patients, in whom it has been shown to have a synergistic effect in the development of hepatocellular carcinoma (HCC) (29). Interestingly, coffee consumption may have a protective effect in NAFLD and may prevent progression of disease (30-33).

Anti-diabetic medications

NAFLD is associated with type 2 diabetes mellitus (T2DM) with insulin resistance implicated in the pathogenesis of NAFLD, metabolic syndrome, and atherosclerosis (34). Therefore, many anti-diabetic agents have been studied to evaluate their efficacy in the treatment of NASH.

Thiazolidinediones (TZDs)

TZDs are selective peroxisome proliferator-activated receptor-γ (PPAR-γ) agonists which ameliorate insulin resistance and improve glucose and lipid metabolism in type 2 diabetes (35). The FLIRT trial evaluated the effects of rosiglitazone in patients with biopsy-proven NASH (36). Of the 63 patients included, 32 were treated with rosiglitazone (titrated to 8 mg/day) and 31 received placebo for 1 year. Overall, more patients randomized to rosiglitazone experienced >30% reductions in steatosis (47% *vs.* placebo 16%, P=0.014), but no other histological changes, especially fibrosis were noted. Improvements in steatosis appear to occur early in therapy, as an extension trial failed to demonstrate any further benefit following an additional 2 years of treatment (37). There were also more patients in the rosiglitazone arm with normalization of hepatic aminotransferase levels at the end of treatment (38% rosiglitazone *vs.* 7% placebo, P=0.005). Besides, reductions in aminotransferase levels occurred early and were maintained throughout therapy, but returned to baseline within 4 months of rosiglitazone discontinuation.

Belfort *et al.* studied the effects of another TZD agent, pioglitazone, in 55 NASH patients with impaired glucose tolerance or T2DM (38). Subjects were placed on a hypocaloric diet in addition to either pioglitazone (up to 45 mg/day) or placebo for 6 months. Pioglitazone improved insulin sensitivity which correlated with normalization of aminotransferase levels. Reductions in hepatic fat content were also greater in the pioglitazone group *vs.* placebo (54% *vs.* 0%, respectively, P<0.001). Pioglitazone-treated patients experienced significant improvements in steatosis, ballooning necrosis, and centrilobular inflammation from baseline; however, this medication did not have an effect on hepatic fibrosis.

Pioglitazone was further evaluated in a larger study known as the PIVENS (Pioglitazone, Vitamin E or Placebo for Nonalcoholic Steatohepatitis) trial (10). The investigators included 247 non-diabetic NASH patients who were randomized to one of three arms: pioglitazone 30 mg/day, vitamin E 800 IU/day, or placebo for 96 weeks. Pioglitazone led to resolution of NASH in 47% of patients, but did not reduce fibrosis. When compared to placebo, more patients treated with pioglitazone experienced significant improvements in NASH, defined as improvement in hepatocellular ballooning, without increase in fibrosis, and a decrease in NAS (34% pioglitazone *vs.* 19% placebo, P=0.04). However, this difference did not meet the prespecified 0.025 level of significance possibly because more patients in the pioglitazone group were classified as not having hepatocellular ballooning at baseline. Unfortunately, subjects treated with pioglitazone had a higher mean weight gain of 4.7 kg, which persisted after therapy was completed.

Pioglitazone improves histological features in patients with biopsy-proven NASH, with or without T2DM, and is preferred over rosiglitazone. Weight gain, heart failure, and bone fractures are major adverse effects associated with TZDs that should be considered prior to initiation of therapy. Until further studies have been conducted in NAFLD patients without NASH, the AASLD practice guidelines recommend limiting the use of pioglitazone to only patients with biopsy-proven NASH.

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

GLP-1, a naturally occurring peptide secreted by the L-cells of the small intestine, functions as an incretin and stimulates glucose-mediated insulin production by pancreatic β-cells. Gupta *et al.* reported the presence of GLP-1 receptors in human hepatocytes, and studies have shown that GLP-1 agonists are hepatoprotective and reduce hepatic steatosis (39,40). These medications they also improve lipid metabolism, promote fat redistribution, and reduce insulin resistance. Bernsmeier and colleagues have also shown that

GLP-1 secretion is impaired in patients with NAFLD and NASH (41).

Feng and colleagues randomized 87 patients with NAFLD and T2DM to receive liraglutide (up to 1.8 mg/day), metformin (up to 2,000 mg/day), or gliclazide (up to 120 mg/day) for 24 weeks (42). Subjects in the liraglutide group had the greatest reductions in intrahepatic fat content (baseline 36.7%±3.65% to post-treatment 13.11%±1.84%) which correlated with significant weight loss. Aminotransferase levels also significantly decreased by week 12 of liraglutide therapy.

Another study, the LEAN study was a phase 2 trial conducted in 52 subjects with biopsy-proven NASH, with or without T2DM, and a body mass index (BMI) ≥25 kg/m^2 (43). Patients were randomized to liraglutide (titrated to 1.8 mg/day) or placebo for 48 weeks. More patients treated with liraglutide in the modified intent-to-treat analysis experienced histological improvements, defined as resolution of steatohepatitis without worsening of fibrosis (39% liraglutide *vs.* 9% placebo, relative risk 4.3 (95% CI, 1.0–17.7, P=0.019). Liraglutide also reduced the progression of fibrosis. Patients randomized to liraglutide achieved greater reductions in weight and BMI, with most weight loss occurring within the first 12 weeks of therapy. However, gastrointestinal adverse effects were more common among the liraglutide group, but these symptoms were generally mild-to-moderate in severity.

The efficacy of another GLP-1 receptor agonist, exenatide was studied by Fan *et al.* in diabetic patients with NAFLD and poor glucose control (44). Of the 117 patients enrolled in the study, 49 were treated with exenatide (titrated to 10 mcg twice daily) and 68 who received metformin (up to 2,000 mg/day). All the patients also underwent therapeutic lifestyle interventions. At the end of 12 weeks, the exenatide group had greater reductions in aminotransferase levels, body weight, and BMI when compared to metformin.

Several studies are being conducted currently with newer GLP-1 agonists in the NAFLD population. A phase 2 randomized controlled trial of 320 NASH patients evaluated the efficacy and safety of three doses of subcutaneous semaglutide for 72 weeks (45). However, the results are yet to be published.

The subcutaneous route of administration and expensive costs are potential barriers to use for GLP-1 agonists in patients with NAFLD. Although initial efficacy and safety data are encouraging for this medication class; further larger, long-term studies are necessary to establish its role in the treatment of NAFLD.

Based on the positive outcomes observed with GLP-1 agonists, several new combination agents affecting this pathway are currently under investigation. The dual GLP-1 and glucagon receptor (GCGR) agonist, cotadutide, has been shown to decrease body weight and liver fat content (46). Similarly, treatment with tirzepatide, a dual glucose-dependent insulinotropic polypeptide (GIPR) and GLP-1 agonist, resulted in significant weight loss and decreased NASH-related biomarkers at doses ≥10 mg/week (47,48). The triple combination of GLP-1/GCGR/GIPR agonism was studied in mice with biopsy-proven NASH. This triple incretin combination treatment led to significant reductions in body weight, hepatic steatosis, and NAS scores (49). Although these novel dual/triple therapies still require additional testing within the NASH population, the initial results are promising.

Sodium glucose cotransporter 2 (SGLT2) inhibitors

SGLT2 inhibitors exert antihyperglycemic effects by suppressing glucose reabsorption in the renal tubules. Their beneficial effects have been extensively demonstrated in mice, but large scale human studies are lacking. Empagliflozin was studied in an open-label pilot study involving 9 diabetic patients with biopsy-proven NASH (50). The study subjects were administered empagliflozin 25 mg/day for 24 weeks. Histological features (including steatosis, hepatocyte ballooning, lobular inflammation, and fibrosis) remained unchanged or improved in all patients except one who experienced worsening of hepatocellular ballooning. By the end of treatment, 4 patients experienced resolution of NASH. Another SGLT2 inhibitor, canagliflozin, was found to be potentially useful in the early stages of NASH (51). A single-arm exploratory study evaluated the efficacy of canagliflozin 100 mg/day for 12 weeks in 10 patients with NASH and T2DM. Fibrosis markers, including the fibrosis-4 index (FIB-4) and the FM-fibro index, significantly improved by week 12; however, liver stiffness measurement and controlled attenuation parameter measured by transient elastography did not improve. Canagliflozin also led to reductions in body weight and aminotransferase levels, with greater reductions in alanine aminotransferase (ALT) levels in patients with stage 1 fibrosis at baseline. In conclusion, larger randomized control studies are necessary to confirm the benefits of SGLT2 inhibitors in patients with T2DM and NASH.

Metformin

Metformin, a biguanide, decreases hepatic glucose production and increases skeletal myocyte glucose uptake. This medication improves insulin resistance by increasing 5' adenosine monophosphate (AMP)-activated protein kinase signaling, which in turn, reduces lipid accumulation, glucose output, and TNF-α signaling (52,53). Initial trials evaluating the effects of metformin in patients with biopsy-proven NAFLD found that this medication initially decreased liver enzymes and improved insulin sensitivity, but did not result in histological improvement (54-57). Additional multi-center trials are required to substantiate metformin's beneficial effects on improving liver histology before it can be offered as a standard treatment.

Lipid lowering agents

The liver plays a key role in the lipid metabolism as evidenced by the atherogenic lipid profile observed in NAFLD and NASH. This patient population has elevated triglyceride and low-density lipoprotein levels, in addition to low high-density lipoprotein levels which places them at increased risk for cardiovascular events.

Saroglitazar magnesium

Saroglitazar magnesium, a first in class dual PPARα/γ agonist approved by the Drug Controller General of India for the treatment of NASH in March 2020, improves dyslipidemia and insulin sensitivity (58). Interestingly, saroglitazar differs structurally from thiazolidinediones and therefore, lacks adverse effects such as edema and weight gain (58). The effects of saroglitazar in obese/overweight patients with fatty liver was evaluated in a single center study in India (59). All 64 patients included received saroglitazar 4 mg/day for ≥1 year. Study investigators found that saroglitazar significantly improved lipid parameters, aminotransferase levels, and liver stiffness measurements. Interim analysis data from a different study of 44 patients with NAFLD demonstrated that saroglitazar 4 mg/day significantly reduced steatosis and fibrosis (as measured by transient elastrography) after 6 months (60). The effects of saroglitazar 4 mg on NASH was evaluated in EVIDENCES II, a phase 3, multi-center, placebo-controlled trial of 102 patients (61). After 52 weeks of treatment, significantly more patients in the saroglitazar arm experienced ≥2 point reductions in NAS without worsening of fibrosis. The treatment group experienced significant improvements in hepatocyte ballooning, steatosis, and lobular inflammation. EVIDENCES IV was a phase 2 clinical trial conducted at multiples in the United States that compared the efficacy of 3 different strengths of saroglitazar (1, 2, and 4 mg) to placebo in 106 patients with NAFLD or NASH (62). After 16 weeks of treatment, patients in each saroglitazar group experienced significant decreases in ALT levels when compared to placebo (mean change from baseline: –27.3% in 1 mg, –33.1% in 2 mg, –44.3% in 4 mg). The complete results of both EVIDENCES trials have not yet been published.

A phase 3 clinical trial is planned to further evaluate the effects of saroglitazar with or without vitamin E in patients with NAFLD/NASH (63). This study will have 4 treatment arms: saroglitazar plus vitamin E, saroglitazar monotherapy, vitamin E monotherapy, and behavioral lifestyle changes alone. The primary outcome will be the differences in NAFLD fibrosis score throughout 6 months of treatment. Several studies are also being conducted within the United States evaluating the effects of saroglitazar in various patient populations in an effort to gain FDA approval. As the first drug approved for the treatment of NASH, real world data from its use in India is highly anticipated.

Statins

Statins have been shown to exert anti-oxidant and anti-inflammatory effects beyond their lipid lowering action (64,65). Gomez-Dominguez and colleagues were the first to investigate the use of atorvastatin (up to 80 mg/day) in NAFLD patients (66). Of the 22 patients who completed the study, hepatic aminotransferase levels normalized in 8 patients by month 6. The remaining patients continued atorvastatin therapy through month 12 with 20% having normal transferase levels at the end of treatment.

Another single-arm study evaluated the effect of atorvastatin on histological parameters in patients with biopsy-proven NASH and hyperlipidemia (67). All 31 patients were treated for 24 months with atorvastatin 10 mg/day. In addition they received standard weight loss counseling, and were encourage to maintain a low-fat, low-carbohydrate diet. Among the 17 subjects with follow-up biopsies, atorvastatin significantly improved mean NAS (4.1±0.3 before treatment, 2.9±0.2 after treatment); however, 4 patients experienced progression of fibrosis on treatment. A randomized controlled trial spanning 4 years studied the combined use of atorvastatin 20 mg/day, vitamin

C 1,000 mg/day, and vitamin E 1,000 IU/day for treatment of NAFLD (68). The investigators reported a 71% risk reduction in steatosis. Despite initial concerns of drug-induced hepatotoxicity, recent studies have demonstrated the safety of statins in patients with NAFLD (69).

Ezetimibe

The utilization of ezetimibe, an inhibitor of intestinal cholesterol absorption, in reducing hepatic steatosis has been described in animal models (70,71). The MOZART trial compared ezetimibe 10 mg to placebo in 50 patients with biopsy-proven NASH for 24 weeks (72). Although ezetimibe did reduce liver fat from baseline [as measured by magnetic resonance imaging-derived proton density-fat fraction (MRI-PDFF)], it was not better than placebo. In addition, ezetimibe did not improve histological features. Further studies should be conducted to determine if ezetimibe has any role in the treatment of NAFLD.

Omega-3 polyunsaturated fatty acids (PUFA)

Capanni and colleagues were the first to report improvements in liver steatosis with long-term supplementation of n-3 PUFA in humans (73). A subsequent trial found that n-3 PUFA 2,000 mg/day decreased ALT levels and improved liver echo-texture on ultrasound (74). After 6 months of treatment, 6 of the 18 patients in the PUFA arm had complete regression of steatosis. However, the WELCOME study showed a mild reduction in liver fat but no improvement in fibrosis scores among patients receiving omega-3 fatty acids 4 g/day for 15 to 18 months (75). These studies suggest a potential benefit of n-3 PUFA supplementation in early and mild cases of NASH by reducing oxidative stress; however, additional randomized controlled trials are required to support their use in treating NAFLD.

Elafibranor

Elafibranor (GFT505) is a dual PPAR-α and -δ agonist that has proven to be hepatoprotective in animal models (76). An important distinction between elafibranor and other agents targeting PPARs in NASH is that it does not possess any PPARγ activity; therefore it is devoid of the unwanted side effects commonly associated with PPARγ activation such as weight gain, edema, and fluid retention. This newly developed drug underwent studies for the treatment of NASH and to assess for improvements in cardiometabolic risk profiles. The GOLDEN-505 trial was a randomized, international phase 2b trial comparing elafibranor 80 mg and 120 mg to placebo in 274 NASH subjects (77). After 52 weeks of therapy, significantly more patients in the elafibranor 120 mg group achieved resolution of NASH without worsening fibrosis (19% *vs.* 12% placebo, P=0.045). Resolution of NASH was defined as the disappearance of ballooning and disappearance or persistence of mild lobular inflammation. The RESOLVE-IT phase 3 trial evaluated long-term outcomes of elafibranor 120 mg in patients with NASH and fibrosis (78). The primary endpoints of this study are: reversal of NASH without worsening of fibrosis at week 72 and a composite of all-cause mortality, cirrhosis, and liver-related outcomes after 4 years of therapy. Unfortunately, an interim analysis showed no difference in NASH resolution without worsening fibrosis between groups (19.2% elafibranor *vs.* 14.7% placebo) (79).

Other medication classes

Farnesoid X receptor agonists (FXR)

The FXR is a key regulator of bile acid homeostasis (80). Identified as a receptor for bile acids, FXR has recently been shown to affect lipid metabolism while also modulating glucoregulatory pathways (81,82). Obeticholic acid (OCA) is a potent FXR agonist (83). The FLINT study was a multi-center, randomized controlled trial that compared OCA 25 mg daily to placebo in 283 non-cirrhotic patients with NASH for 72 weeks (84). Nearly half (45%) of the patients in the OCA group experienced histological improvement, defined as ≥2 point improvement in NAS without worsening of fibrosis, and more subjects treated with OCA had improvements in fibrosis (35% OCA *vs.* 19% placebo, P=0.004). However, there was no difference in resolution of NASH between the OCA and placebo arms. Besides, pruritus was identified as a major side effect of OCA requiring the use of antipruritic medications. In addition, OCA also appeared to have a negative effect on lipid profiles.

The REGENERATE trial is an ongoing large, phase 3 study comparing the effects of OCA (10 or 25 mg) to placebo over 6 years in patients with NASH and fibrosis (85). The interim analysis at 18 months reported outcomes in

931 patients. When compared to placebo, OCA improved fibrosis without worsening NASH (18% in OCA 10 mg, 23% in OCA 25 mg, 12% in placebo). However, there were no differences between the groups in resolution of NASH at 18 months.

OCA currently has a black box warning for hepatic decompensation and failure when dosed incorrectly in patients with primary biliary cholangitis (PBC) and Child-Pugh Class B or C or decompensated cirrhosis. A recently published report of 8 patients with PBC or primary sclerosing cholangitis highlighted the risk of hepatoxicity with OCA (86). All patients in this case series developed cholestatic liver injury with modest increases in aminotransferase levels. The onset of injury ranged from 87 to 379 days after the initiation of OCA and half of the patients progressed to liver failure requiring transplantation. Only one patient within this cohort was initiated on an inappropriate dose of OCA based on Child-Pugh score. The FDA recently recommended additional safety analysis from the ongoing REGENERATE study in support of its potential approval for NASH (87). Additional long-term data from this trial is highly anticipated to further assess the potential role of OCA in this patient population.

Vitamin E

Vitamin E (alpha tocopherol) has been studied in numerous trials. Several animal studies have demonstrated that vitamin E decreases TGF-β1, which subsequently improves liver necrosis and fibrosis (88,89). Vitamin E, along with metformin, was evaluated in 173 children and adolescents with biopsy-confirmed NAFLD in the randomized, placebo-controlled, multicenter TONIC trial (90). Patients were randomized to receive either vitamin E 800 IU daily, metformin 1,000 mg/day, or placebo for 96 weeks. There was no significant difference in sustained reduction in ALT levels achieved with vitamin E or metformin when compared to placebo. However, children treated with vitamin E were found to have significant improvements in hepatocellular ballooning and NAS. No significant effects were seen on steatosis, inflammation, or fibrosis. These effects were replicated in adult patients in the PIVENS trial. In this study, treatment with vitamin E 800 IU/day in non-diabetic NASH patients led to a greater degree of histologic resolution at 96 weeks when compared to pioglitazone (43% *vs.* 34%), but did not affect fibrosis (10).

A randomized, double-blinded, placebo-controlled trial of 105 subjects was conducted to evaluate the efficacy of vitamin E in diabetic patients with NASH. Patients were randomized to vitamin E 400 IU twice daily plus pioglitazone 30 mg/day, vitamin E 400 mg IU twice daily, or placebo. A higher number of patients on a combination therapy achieved a two-point reduction in NAS without worsening of fibrosis when compared to those treated with vitamin E monotherapy (54% *vs.* 31%). Steatosis significantly improved in both treatment arms when compared to placebo; however only the combination therapy significantly improved inflammation and ballooning (91).

Long-term outcomes of vitamin E therapy were evaluated in a study of 180 patients with biopsy-proven NASH and bridging fibrosis or cirrhosis. Vitamin E was administered at a dose of 800 IU/day for ≥2 years to 90 patients. This group was propensity-matched to 90 subjects not treated with vitamin E. This study found that patients treated with vitamin E experienced higher adjusted transplant-free survival (78% *vs.* 49%, P<0.01) and lower rates of hepatic decompensation (37% *vs.* 62%, P=0.044). Outcomes were not affected by the presence of diabetes (92).

There are considerable adverse effects associated with long-term use of vitamin E. Interestingly, one meta-analysis found an increased all-cause mortality with high dose vitamin E (≥400 IU/day) (93). This anti-oxidant has also been shown to increase the risk of hemorrhagic stroke and prostate cancer (94,95). Currently, the AASLD and the European Association for the Study of the Liver (EASL) recommend vitamin E 800 IU daily as a short-term option for nondiabetic adults with biopsy-proven NASH (11,96). Further studies are required to determine the long-term safety and efficacy of vitamin E therapy in all NASH patients.

Ursodeoxycholic acid (UDCA)

In recent years, various therapeutic applications of bile acids have been discovered. Nor-ursodeoxycholic acid (NorUDCA), a side-chain of UDCA, led to the development of a new category of drugs used in the treatment of liver disease. NorUDCA has anti-fibrotic and anti-inflammatory properties making it an attractive therapy for NASH (97).

A systematic review of 12 randomized controlled trials demonstrated that UDCA significantly improved liver function and some histological parameters, when utilized concomitantly with other medications (98). A 12 month, multi-center, randomized controlled trial in 126 patients

with biopsy-proven NASH reported significant reductions in mean ALT levels and one fibrosis marker when UDCA was administered at high doses (28–35 mg/kg/day) (99). Despite being written off by various societal guidelines, UDCA still remains a promising option for NAFLD and NASH but requires further larger studies.

Pentoxifylline

TNF-α is a prominent inflammatory marker implicated in the pathogenesis of NASH. Pentoxifylline, an inhibitor of TNF-α, has been shown to be hepatoprotective. Pentoxifylline increases hepatic glutathione synthesis while decreasing the production of free oxygen radicals. Zein *et al.* have demonstrated that pentoxifylline's anti-oxidant effects improved liver histology in NASH (100). In another study of nine patients with histologically-proven NASH and persistently elevated ALT levels, pentoxifylline (400 mg TID) significantly reduced aminotransferase levels at 12 months (101). Over half of the patients included (55%) also experienced reductions in steatosis and lobular inflammation. Six patients experienced a down-grading in Brunt's staging. Van Wagner and colleagues too reported a study on 30 patients treated with pentoxifylline 1,200 mg/day for 12 months, and demonstrated similar findings with a reduction in transaminases and improvement in steatosis and hepatocellular ballooning compared to placebo (102). Pentoxifylline was generally well-tolerated; the common adverse effects reported included headache and abdominal cramping. Unfortunately, since only 4–10% of these patients were diabetics, the beneficial effects of pentoxifylline cannot be extrapolated to patients with diabetes (103). Thus, pentoxifylline may be a reasonable therapeutic option for the treatment of NASH and can improve fibrosis in non-diabetics. Further investigations with large randomized trials are required to determine its appropriate dose and frequency.

A meta-analysis compared currently available drug therapies (vitamin E, TZD, OCA, and pentoxifylline) for the treatment of NASH among 964 patients within nine randomized controlled trials (103). The authors found that pentoxifylline, TZD, and vitamin E improved histological features of NASH. While pentoxifylline and OCA were superior to placebo in improving fibrosis, vitamin E, TZD, and OCA affected ballooning degeneration to a greater extent. Additionally, TZD, pentoxifylline, and OCA were superior to placebo in improving steatosis and lobular inflammation.

Angiotensin II receptor blockers

Various cytokines and adipokines have been implicated in the pathogenesis of NAFLD including the pro-fibrotic agents: transforming growth factor-beta 1 (TGF-β1), platelet-derived growth factor, and angiotensin II (104). Hence, angiotensin II receptor blockers have been explored as a potential treatment option. A small study of 7 patients with NASH and hypertension demonstrated the benefits of losartan 50 mg/day in drastically reducing blood markers of hepatic fibrosis, plasma TGF-β1, and aminotransferase levels (105). At week 48 of therapy, repeat biopsies demonstrated improvements in inflammation in 5 patients and reductions in fibrosis in 4 patients. In another study comparing valsartan 80 mg/day with telmisartan 20 mg/day in NASH patients with mild to moderate hypertension, NAS and fibrosis scores were significantly decreased in the telmisartan arm by month 20 of therapy (106). The investigators suspect that this pronounced effect is due to telmisartan's ability to modulate PPAR-γ. Further placebo-controlled, large-scale trials are necessary to confirm these therapeutic effects and assess the hepatic histological response.

Ongoing trials

Our knowledge and understanding of the underlying mechanisms of this multi-factorial disease is increasing continually with additional research. Thus, numerous clinical trials targeting different pathways in the pathogenesis of NASH and NAFLD are ongoing. Here we will discuss new pharmaceutical agents with ongoing phase 2 and 3 clinical trials in this patient population. Trials without published results have been summarized in *Table 2*.

Cenicriviroc (CVC)

CVC is an orally administered, potent chemokine 2 and 5 receptor antagonist which affects key interactions driving inflammation and fibrosis. In a phase 2 study known as the CENTAUR trial, patients were administered CVC 150 mg or placebo for 2 years (107). The investigators included 289 patients with biopsy-proven NASH and found no difference between groups in histological improvement (≥2 point improvement in NAS without worsening of fibrosis) or NASH resolution. There was, however, a significant reduction in fibrosis without worsening of steatohepatitis in the CVC group (20% *vs.* 10.4% in the

placebo arm, P=0.02). Its effects are being further evaluated in an ongoing global phase 3 study (AURORA), in 1,200 subjects with NASH and stage F2 or F3 fibrosis (108).

Selonsertib

The anti-inflammatory effects of selonsertib, an apoptosis signal-regulating kinase 1 (ASK1) inhibitor, have been demonstrated in animal models and validated in a year-long phase 2 randomized controlled trial. This study compared the effects of selonsertib 6 mg and 18 mg, either alone or in combination with simtuzumab, in patients with NASH and stage F2 or F3 fibrosis (109). Simtuzumab was initially suspected to have anti-fibrotic effects; however, further study results demonstrated that simtuzumab monotherapy did not improve liver fibrosis. Hence, results from both selonsertib monotherapy and selonsertib/simtuzumab groups were combined for analysis. Data from week 24 of therapy showed that 43% of patients in the selonsertib 18 mg group achieved reductions in fibrosis compared to 30% in the selonsertib 6 mg group and 20% in the simtuzumab monotherapy arm. The selonsertib 18 mg group also had the greatest effect in reducing progression to cirrhosis (3%) compared to 7% in the 6 mg group and 20% in the simtuzumab monotherapy group. Two phase 3 studies evaluated the effects of selonsertib in NASH patients with bridging fibrosis (STELLAR-3) and compensated cirrhosis (STELLAR-4) (110). The long-term clinical endpoints were reduction in progression to cirrhosis (STELLAR-3) and fibrosis regression (both) at week 48. The planned treatment duration was 240 weeks in both studies; however, both studies were terminated early due to lack of efficacy at the 48-week analysis.

Berberine

Berberine is an active component of an ancient Chinese herb *Coptischinensis French* which was evaluated in a pilot study by Yin *et al.* (111). Used to treat gastrointestinal infections in China, this herb was found to be an effective anti-diabetic medication. The therapeutic effect of berberine in NAFLD may involve a direct regulation of hepatic lipid metabolism possibly by altering hepatic metabolism-related gene expression (112). A 45-day, open-label trial in 50 patients was conducted in Iran to assess the impact of berberine 6.25 g/day on liver function and metabolic profiles of patients with NAFLD (113). Results have not yet been published. There is also an ongoing phase 4 trial to study the effect of berberine 0.5 g three times daily in NASH patients for 48 weeks, with a primary outcome of improvement in NAS (114).

Acyl Co-A carboxylase inhibitor GS-0976

Acetyl-coenzyme A carboxylase (ACC) is the enzyme required for conversion of acetyl-coenzyme A to malonyl-CoA, which is the rate-limiting step in *de novo* lipogenesis. GS-0976 inhibits both isoforms of ACC: ACC1 and ACC2. In a phase 2 trial in subjects with NASH, this medication was shown to significantly reduce hepatic steatosis (as measured by MRI-PDFF) by ≥30% in nearly half of the patients receiving the 20 mg dose for 12 weeks (115). However, more patients receiving GS-0976 experienced on-treatment hypertriglyceridemia (+14 mg/dL from baseline in the GS-0976 20 mg group *vs.* –6 mg/dL from baseline in placebo group) which responded to treatment with fibrates or fish oil. A multivariate analysis determined that subjects with a baseline triglyceride level ≥250 mg/mL were more likely to develop hypertriglyceridemia on GS-0976. Additional trials utilizing liver biopsies are required to validate its effects on liver histology in patients with NASH.

Emricasan

Emricasan, an oral pan-caspase inhibitor, was investigated in a study of 318 patients with NASH and fibrosis (116). The ENCORE-NF trial randomized subjects to receive either 5 mg BID, 50 mg BID or placebo. After 72 weeks, there was no histological improvement observed with either dose of emricasan. Surprisingly, fewer patients in the placebo arm experienced fibrosis progression (20.4% *vs.* 41.1% emricasan 5 mg and 38.1% emricasan 50 mg). The placebo group also had less patients with worsening of ballooning (11.8% *vs.* 18.9% emricasan 5 mg and 21.6% emricasan 50 mg). Study investigators postulated that emricasan therapy redirected cells from apoptotic cell death to more inflammatory causes of cell death (93).

An early study by Garcia-Tsao *et al.* demonstrated that treatment with emricasan 25 mg BID for 28 days led to clinically significant reductions in hepatic vein pressure gradient (HVPG) in patients with HVPG values ≥12 mmHg, and in those with clinically significant portal hypertension (117). This led to reductions in aminotransferase levels and it was also well-tolerated, with fatigue being the most common side effect. However, in a longer study, the ENCORE-PH trial, a phase 2 multicenter,

double-blind trial of 263 patients with NASH cirrhosis and severe portal hypertension (defined as HVPG ≥12 mmHg), the results did not translate into a positive outcome (118). Patients were randomized to receive emricasan 5 mg BID, 25 mg BID, 50 mg BID, or placebo for 48 weeks. Aminotransferases levels significantly decreased by week 24 with emricasan compared to placebo, but there was no difference in HVPG changes between groups at week 48. The authors concluded that emricasan did not affect HVPG significantly. A small treatment effect was however noted reported in compensated patients with a higher baseline HVPG (≥16 mmHg).

Aramchol

Aramchol targets stearoyl coenzyme A desaturase 1 (SCD1), a key enzyme in the synthesis of monounsaturated fatty acids. Down-regulation of SCD1 decreases adiposity and hepatic lipogenesis, enhances insulin sensitivity, and leads to resistance to obesity (119,120). A phase 2a trial demonstrated that aramchol is safe and effective in reducing liver fat content (121). The ARREST study was a global phase 2b trial in 247 patients biopsy-confirmed NASH and pre-diabetes or T2DM (122). Patients were randomized to one of three study groups: aramchol 400 mg, aramchol 600 mg, or placebo for 1 year. There was a dose-dependent reduction in liver fat content with aramchol. More patients in the aramchol 600 mg arm had NASH reversal without worsening fibrosis (19.2% *vs.* 12.5% aramchol 400 mg *vs.* 7.5% placebo, P=0.046). Similarly, more patients treated with aramchol 600 mg experienced fibrosis improvement without worsening of NASH (29.5% *vs.* 21.3% aramchol 400 mg *vs.* 17.5% placebo). The benefits of aramchol are being further explored in a large phase 3/4 trial (ARMOR) of NASH patients with stage 2 or 3 fibrosis who are overweight or obese and have pre-diabetes of T2DM (123). This clinical trial is still ongoing with a planned enrollment of 2,000 patients.

Pegbelfermin

The pegylated human fibroblast growth factor 21 (FGF21) analogue, pegbelfermin has been effective in decreasing metabolic parameters and improving liver fibrosis in animal models (124). A phase 2a clinical trial enrolled 75 overweight or obese NASH patients who received 16 weeks of either pegbelfermin 10 mg once daily, pegbelfermin 20 mg once weekly, or placebo (125). There was a significant decrease in hepatic fat fraction in both pegbelfermin groups compared to placebo. Diarrhea and nausea were the most commonly reported side effects occurring in a sixth of patients. Further studies of pegbelfermin is warranted in patients with NASH, especially studies that use liver biopsies to assess its effects on liver histology, and also allow appraisal of its safety and efficacy in larger number of patients.

VK2809

The beta isoform of thyroid hormone modulates cholesterol and triglyceride levels; thus VK2809, a liver-selective thyroid hormone receptor beta agonist is being studied for the treatment of metabolic disorders including NASH. VK2809 was shown to improve liver fat content after 12 weeks of therapy in a phase 2 study (126). This novel therapy is currently being evaluated in NASH patients with fibrosis in the phase 2b VOYAGE trial (127). An estimated 337 subjects will be randomized to one of 5 study arms: VK2809 1 mg, 2.5 mg, 5 mg, 10 mg or placebo for 1 year. The investigators will assess histological changes after 52 weeks of therapy, in addition to changes in liver fat content at treatment week 12.

Resmetirom

Another liver-selective thyroid hormone receptor beta agonist, resmetirom (MGL-3196) was studied in a multi-center, randomized, placebo-controlled trial in 125 patients with biopsy-proven NASH (128). Among the 116 patients with MRI-PDFF assessment at week 12, there was a significant reduction in relative hepatic fat fraction in the resmetirom arm *vs.* placebo (–32.9% *vs.* 10.4%, respectively). Based on these results, a phase 3 clinical trial is being conducted to further evaluate the efficacy and safety of resmetirom in patients with NASH and fibrosis with a planned enrollment of 2,000 patients. The primary outcomes are NASH resolution at week 52 in patients with stage 2 or 3 fibrosis and a composite end-point of all-cause mortality, cirrhosis, and other significant liver-related events.

Conclusions

In the setting of the obesity epidemic, the prevalence of NAFLD and NASH continues to increase exponentially. In patients with NASH, liver fibrosis is the strongest predictor

of complications and mortality; therefore multiple treatment regimens are being investigated to determine their effects on the arrest of the disease and fibrosis regression in particular. Until validated biomarkers for fibrosis become available, assessment of therapeutic efficacy requires liver biopsy which has proven to be a major obstacle for clinical trials.

Weight loss through therapeutic lifestyle changes remains the first-line therapy for NASH as there are currently no FDA-approved medications for treatment in this patient population. However, ongoing research to identify potential therapeutic targets have led to several promising drug candidates. Results from phase 2 trials have been quite encouraging; however long-term safety and histological efficacy outcomes need to be studied, before these drugs can be approved. Besides, once approved, this can pave the way for future combination trials to arrest the progression of NASH to cirrhosis and reduce other related complications.

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Footnote

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