A Review Of Current And Upcoming Treatment Modalities In Non-Alcoholic Fatty Liver Disease And Non-Alcoholic Steatohepatitis

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Abstract: Non-alcoholic fatty liver disease (NAFLD) is the most common cause of chronic liver disease in the West. Non-alcoholic steatohepatitis (NASH) is the progressive form of NAFLD and can lead to cirrhosis, hepatocellular carcinoma, and is associated with increased cardiovascular risks. Multiple components and risk factors are thought to be involved in the pathogenesis of NAFLD and NASH. Optimal therapy has not yet been found, but many advances have been made with the discovery of potential therapeutic options. In this paper, we aim to provide a comprehensive review of approved, studied, and upcoming treatment options for NAFLD and NASH. Non-pharmacologic therapy (lifestyle modifications and bariatric surgery) and pharmacologic therapy are both reviewed. Pharmacologic therapy target components thought to be involved in the pathogenesis of this disease process including insulin resistance, oxidative stress, inflammation, lipid metabolism, and fibrosis are reviewed in this paper. Results of the emerging treatment targets in phase 2 and 3 clinical trials are also included.
Keywords: NAFLD, NASH, obesity, cirrhosis, treatment

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Introduction

Non-alcoholic fatty liver disease (NAFLD) has become the most common cause of chronic liver disease in the West, affecting up to 30% of the general population.[1,2] NAFLD is a spectrum of diseases ranging from simple steatosis to non-alcoholic steatohepatitis (NASH). NASH is a more progressive form of NAFLD associated with increased cardiovascular and liver-related mortality. NASH has increased risk of progression to cirrhosis, end-stage liver disease, and development of hepatocellular carcinoma (HCC).[3,4]

Previously, the pathogenesis of NAFLD was proposed to be related to the "two-hit" hypothesis with the first hit being hepatic lipid accumulation from risk factors associated with metabolic syndrome leaving the liver susceptible to the second hit, which resulted in activation of inflammation and fibrosis.[5] Recent findings support a "multiple hit" hypothesis in which a number of parallel processes contribute to the development of progression of NAFLD including gut microbiome dysbiosis, insulin resistance, hormone secretion from adipose tissue, obesity, oxidative stress, and imbalance in inflammatory cytokines.[5–7] These concurrent "hits" have been translated to potential therapeutic targets now being studied.

Currently, treatment options for NASH are limited. Lifestyle changes with weight loss being the main goal is the foundation of treatment, but it is hard to

achieve and maintain and is often not enough in morbidly obese patients. There are no current FDA-approved pharmacologic treatment options for NASH emphasizing the need for development of efficacious therapeutic options. However, as the pathogenesis of NASH is further evaluated, targeted treatment options are being studied. Here, we aim to review current and upcoming treatment modalities for the treatment of NAFLD including the progression to NASH.

Non-Pharmacologic Therapy
Diet And Weight Loss

Obesity is an important risk factor in the development of NAFLD and NASH; thus, weight loss is the first-line treatment option for this disease process.[8] Multiple studies have shown the positive effect of weight loss in the improvement of NAFLD.[9–12] These studies demonstrated improvement in NAFLD Activity Score (NAS), liver histology, and/or imaging with weight loss. The amount of weight loss required in the treatment of NAFLD has not yet been established, but evidence suggests weight loss of 5% in NAFLD or 7–10% in NASH is needed for improvement in histology with even greater weight loss (>10%) required in morbidly obese patients.[13–15] Combination of diet and exercise was found to be most effective in improving NAFLD.[14] However, the long-term efficacy of diet and lifestyle management in weight loss has been poor given difficulty with compliance.[16–18]

There are limited data on the specific effects of certain diets on NAFLD/NASH. One randomized control trial (RCT) evaluating the effects of the Mediterranean diet compared to low-fat high-carbohydrate diet in non-diabetic biopsy-proven NAFLD patients demonstrated reduction of hepatic steatosis and improvement of insulin sensitivity with Mediterranean diet despite lack of difference in weight loss between diet types.[19] However, a more recent RCT comparing the Mediterranean diet and low-fat diet found hepatic steatosis and liver enzymes to significantly improve in both groups with no difference in liver fat reduction between groups. As in the previous study, weight loss did not differ between the groups. Unlike the low-fat diet, the Mediterranean diet did improve total cholesterol, serum triglyceride (TG), and glycated hemoglobin (HbA1c), and also had higher adherence rate.[20] Another randomized study of patients with type 2 diabetes compared the effects of mono-unsaturated fatty acid (MUFA) diet and high-carbohydrate/

high-fiber/low glycemic index (CHO/fiber) diet on liver fat content.[21] Results from this study demonstrated a significantly lower liver fat content in MUFA diet compared with the CHO/fiber diet independent of weight loss. There is a lack of consensus in results amongst these studies and they are limited by the small sample sizes as well lack of standardization of study length. Given the historically high rate of long-term non-adherence to lifestyle changes, longer-term studies with a larger sample size are needed.

A review on the effects of different diets on liver fat content and insulin sensitivity demonstrates the multifactorial ways in which macro- and micronutrients contribute to liver fat content. Short-chain fatty acids (SFAs) have been shown to increase liver fat and replacing them with MUFA or N-6 polyunsaturated fatty acids (PUFA) reduces liver fat content.[22] Of note, the Mediterranean diet is also high in MUFA.[22] Fiber is another critical macronutrient that can play a role in the pathogenesis of NAFLD. High-fermentable fibers have shown to improve risk factors associated with NAFLD including body weight and insulin resistance.[23] Low-fermentable fibers have also been shown to decrease risk factors associated with NAFLD including blood glucose and postprandial triglyceride.[23] In addition, high fiber diets like the Mediterranean diet have also been shown to decrease cardiovascular risk.[23,24] There is little research on the benefits of specific micronutrients except for Vitamin E, which is discussed later in this review.[25]

An aspect of weight loss that has yet to be widely studied in NAFLD patients is the effects of pharmacologic weight loss agents in the reduction of liver fat content. These drugs can help patients lose 7–10% of their total body weight, fitting well with the amount of weight loss shown needed to improve liver histology in NASH.[26,27] One of the criteria to be placed on pharmacologic weight loss agents includes a BMI of greater than 27, a criterion in which 85% of the NASH patients qualify. Further, long-term RCTs with assessment of risk factors associated with these agents in patients with NAFLD are required at this time.

Bariatric Surgery

Bariatric surgery is another option for achieving weight loss in NAFLD and NASH patients. Unlike weight loss through diet and exercise, which can be difficult to achieve and sustain, bariatric surgery provides a longer-term option for weight loss. Bariatric surgery improves NAFLD not only through weight loss but also through the metabolic effects on lipid metabolism and inflammatory pathways associated

with NAFLD pathophysiology.[28,29] This procedure is currently indicated in patients with BMI ≥40 kg/m^2 with no comorbidities or a BMI 35 to 39.9 kg/m^2 with at least one serious comorbidity including but not limited to type 2 diabetes, hypertension, obstructive sleep apnea, NAFLD, and NASH.[30,31]

A systematic review of 29 studies in patients undergoing bariatric surgery reported statistically significant improvement in post-operative liver biochemistry (ALT, AST, GGT) and histology.[32] Another systematic review and meta-analysis by Chavez –Tapia et al reported improvement in liver histology (steatosis, steatohepatitis, and fibrosis) with weight loss after bariatric surgery.[33] Laursen et al reviewed 13 cohort studies of patients with NAFLD undergoing bariatric surgery with reports of improvement in NASH histology; however, some of the studies also reported worsening histology after bariatric surgery.[34]

As with any invasive procedures, bariatric surgery is not without risks. A systematic review and meta-analysis of the effectiveness and risks of bariatric surgery conducted by Chang et al reported adjustable gastric banding (AGB) with lower mortality and complication rates but higher reoperation rates as well as less significant weight loss as compared to gastric bypass (GB).[35] Sleeve gastrectomy (SG) was more effective in weight loss than AGB and similar to GB in efficacy.[35] The mortality rate within 30 days of bariatric surgery was reported to be 0.08% in the RCTs and 0.31% after 30 days.[35] The death rates reported in this review were lower than those reported in previous meta-analysis.[35,36] Of note, a nationwide inpatient sample (1998–2007) found the mortality of bariatric surgery to be higher in patients with compensated and decompensated cirrhosis.[32]

A recent Cochrane review of the benefits and risks of bariatric surgery for NASH patients was unable to find conclusive data given the lack of RCTs available.[33] The Longitudinal Assessment of Bariatric Surgery (LABS) consortium reported rare fatal complications following bariatric surgery including sepsis from anastomotic dehiscence, shock secondary to hemorrhage, and cardiopulmonary events.[37] The leading cause of death after bariatric surgery was found to be due to thromboembolic disease with an incidence of 0.34%.[37]

Long-term complications are dependent on the type of bariatric surgery and have been well outlined in a review by le Roux and Heneghan.[38] GB can be associated with stricture formation at anastomosis site leading to partial or full obstruction.[38,39] Internal herniation can complicate both laparoscopic and open bariatric procedures with a rate of 2.5–6.2% for internal herniation.[38,40] Patients who have undergone gastric banding are at risk for band-related complications including band slippage and/or erosion as well as esophageal dysmotility, which all result in re-intervention rates of up to 48%.[38,41] Dietary complications related to bariatric surgery include nutritional deficiencies, dumping syndrome, and postprandial hyperinsulinemic hypoglycemia.[38,42–45]

Large RCTs with longer-term follow-ups are required to better assess the risks and benefits of bariatric surgery in the treatment of NAFLD and NASH.

Pharmacologic Therapy
Insulin Resistance Targets

Insulin resistance has been implicated in the pathogenesis of NAFLD with progression to NASH. Therefore, insulin sensitizers are natural targets for treatment intervention. See Table 1 for a comprehensive overview of specific pharmacotherapy therapy target agents studied in NAFLD/NASH.

Metformin

Metformin, a biguanide, improves insulin resistance by increasing 5′adenosine monophosphate (AMP)-activated protein kinase signaling, in turn, reducing lipid accumulation, glucose output, and TNF-α signaling.[46,47] Clinical trials of metformin in the treatment of NASH have shown improvement in insulin resistance and liver enzymes. The Treatment of NAFLD in Children (TONIC) trial was an RCT studying the effects of Vitamin E (400 IU twice daily), Metformin (500mg twice daily), or placebo (twice daily) in the treatment of NASH for 96 weeks.[48] This study demonstrated some improvement in liver histology with metformin treatment, but histologic improvement has been inconsistent between this and other published clinical trials.[48] Furthermore, a meta-analysis published data from four high-quality RCTs regarding the effect of metformin on NASH and concluded that 6–12 months of metformin along with lifestyle interventions did not improve liver histology aminotransferases in comparison to lifestyle intervention alone.[49] Although the weight loss-promoting and insulin-sensitizing properties of metformin are desirable, there is lack of evidence in the improvement of liver histology in NAFLD or NASH to suggest this as an adequate treatment option at this time. Ongoing multi-center trials are required for definitive data.

Table 1 Therapeutic Targets Studied In NASH

Therapy Target	Mechanism Of Action	Medical Treatment Options	Trial(s)	Study Endpoints	Potential Therapeutic Benefits	Pitfalls
Insulin Resistance	Biguanide: increases 5-AMP activated protein kinase signaling	Metformin	TONIC[48]	-Primary endpoint was sustained reduction in ALT by 50% or less of the baseline level or 40 U/L. -Secondary endpoint was improvement in histologic features of NAFLD and resolution of NASH.	-Improvement in insulin resistance -Weight loss promoting properties	-Inconsistent data on improvement of liver histology and liver enzymes
			Musso et al.[49]	-Primary endpoint was histological improvement. -Secondary endpoint was biochemical and radiological steatosis improvement.		
	SGLT-2 inhibitor	Empagliflozin	E-LIFT[50]	-Primary endpoint was change in liver fat measured by MRI-PDFF. -Secondary endpoint was change in ALT, AST, and GGT levels.	-Reduction of ALT and liver fat assessed by MRI-PDFF[50] -Improvement in histology[51] - Significant improvement in AST, FIB-4 index, and some metabolic parameters including hgbA1c[52]	-Lack of standardization amongst studies -Lack of studies comparing SGLT-2 inhibitors with standard NAFLD treatment - Small studies lacking power (N = 9–50) - Small duration of treatment (20wks–48 wks) - Inconsistent significant improvement in reduction of ALT between studies
			NCT02964715[51]	-Primary endpoint was change in histological outcomes. -Secondary endpoint was change in anthropometric measurements.		
		Canagliflozin	Seko et al.[52]	-Primary endpoint was change in serum ALT. -Secondary endpoints were liver function/fibrosis markers, metabolic parameters, and safety.		
	Thiazolidinedione: selective PPAR-γ agonists	Rosiglitazone	FLIRT[54]	-Primary endpoint was improvement of at least 30% of the histological score of steatosis. -Secondary endpoints were improvement in ALT values, necrosis, and inflammation and fibrosis.	-Improvement of steatosis and transaminase levels with rosiglitazone	-Adverse effect of weight gain in rosiglitazone -Lack of improvement in fibrosis score with pioglitazone
		Pioglitazone	PIVENS[59]	-Primary endpoint was improvement in NAS by 2 or more in at least two NAS features, or a post-treatment NAS of 3 or less, and improvement in hepatocyte ballooning by 1 or more, and no worsening of fibrosis. -Secondary endpoints were the number of patients with improvement in steatosis, lobular inflammation, hepatocellular ballooning, fibrosis, and resolution of NASH.	-Greater improvement of steatosis and inflammation with pioglitazone	-Lack of improvement in primary endpoint of histologic features of NASH with pioglitazone -Worsening liver enzymes after discontinuation of medication in pioglitazone

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Table 1 (Continued).

Therapy Target	Mechanism Of Action	Medical Treatment Options	Trial(s)	Study Endpoints	Potential Therapeutic Benefits	Pitfalls
	GLP-1 agonist	Liraglutide	LEAN[67]	-Primary endpoint was liver histological improvement in 48 weeks. -Secondary endpoints were the NAFLD activity score as well as fibrosis panel, liver function tests, cytokeratin-18, glycemic control, fibroscan, and quality of life.	-Significant resolution of steatohepatitis without worsening fibrosis -Fewer patients progressing to fibrosis	-Lack of significant change in lobular inflammation and NAS -Small sample size -Intrahepatic fat content evaluated by ultrasound vs gold standard, H-MRS
Oxidative Stress	α-tocopherol: antioxidant	Vitamin E	TONIC[48]	-Primary endpoint was sustained reduction in ALT by 50% or less of the baseline level or 40 U/L. -Secondary endpoint was improvement in histologic features of NAFLD and resolution of NASH.	-Hepatocellular ballooning with significant improvement[48]	-No sustained reduction of ALT in pediatric population -Population limited to those with limited fibrosis
			PIVENS[59]	-Primary endpoint was improvement in histologic features of NASH assessed with composite of standardized scores for steatosis, lobular inflammation, hepatocellular ballooning, and fibrosis. -Secondary endpoint was change in ALT/AST levels.	-Improvement of steatosis[59] -Histologic improvement of NASH[59] -Significant improvement in AST/ALT[59]	-No significant improvement in fibrosis at end of study in adult population -Lack of consistent histologic improvement between studies -Unclear risk for all-cause mortality with increased dose[75,76] and prostate cancer[78,79] -Increased risk for hemorrhagic stroke[77]
Anti-Inflammatory/ Hepatoprotective	Bile acid	Ursodeoxycholic Acid	Ratziu et al.[83]	-Primary endpoint was a reduction in ALT levels from baseline in patients treated with HD-UDCA compared to placebo. -Secondary endpoints were the proportion of patients with ALT normalization, relative reduction in the scores of serum markers of fibrosis and hepatic inflammation, and safety and tolerability.	-Sustained reduction in mean ALT -Well tolerated	-Low quality and heterogeneity between studies -Limited data on histologic outcomes

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Table 1 (Continued).

Therapy Target	Mechanism Of Action	Medical Treatment Options	Trial(s)	Study Endpoints	Potential Therapeutic Benefits	Pitfalls
	TNF-a inhibitor	Pentoxifylline	Van Wagner et al.[92]	-Primary endpoint was the number of participants with a 30% Reduction in alanine aminotransferase treated with Pentoxifylline (PTX) or placebo for 12 Months. -Secondary endpoints were the effect of Pentoxifylline on TNF-a, leptin, and adiponectin for 12 months.	-Improvement in liver enzymes and insulin resistance -Reduction in steatosis and lobular inflammation on histology	- Conflicting research on improvement in ballooning and fibrosis - Side effect of nausea limiting use - Small sample sizes of studies -Lack of standardization of dose and frequency between studies
	Dual PPAR-α and -δ agonists	Elafibranor	NCT01694849/ GOLDEN-505[97]	-Primary endpoint was the reversal of NASH without worsening fibrosis at 52 weeks.	- Improvement in hepatic inflammation with post hoc analyses with a modified definition of the primary outcome[97]	-Initial analysis not significant[97] - Longer trial results currently underway[98]
			NCT02704403/ RESOLVE-IT[98]	-Primary endpoint is resolution of NASH without worsening fibrosis at 72 weeks and composite long-term outcome composed of all-cause mortality, cirrhosis, and liver-related clinical outcomes.		
	Toll-Like Receptor (TLR)-4 antagonist	JKB-121	NCT02442687[137]	-Primary endpoint was reduction in liver fat content by MRI-PDFF and/or serum ALT		-Failed to meet primary endpoint -Placebo outperformed treatment group -Small sample size
	Caspase inhibitor	Emricasan	ENCORE-NF/ NCT02686762[141]	-Primary endpoint was fibrosis improvement by at least one stage without worsening of steatohepatitis. -Secondary endpoints were steatohepatitis resolution, improvement in NAS, and/or caspase 3/7 relative light units and ALT improvement.		-Final study results not yet published

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Table 1 (Continued).

Therapy Target	Mechanism Of Action	Medical Treatment Options	Trial(s)	Study Endpoints	Potential Therapeutic Benefits	Pitfalls
	ASK-1 inhibitor	Selonsertib	STELLAR- 3[131]	-Primary endpoint was ≥1-stage improvement in fibrosis without worsening of ballooning or inflammation at 48 weeks. Clinical endpoint was reduction in progression to cirrhosis at 5 years.		- Final study results not yet published
			STELLAR-4[132]	-Primary endpoint was ≥1-stage histologic improvement in fibrosis without worsening of NASH. Clinical endpoint was reduction in hepatic decompensation, hepatocellular carcinoma, transplant and/or death at 5 years.		
Lipid metabolism	3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) inhibitor	Atorvastatin	Gómez-Domínguez et al.[101]	-Primary endpoint was normalization of transaminases and/or improvement in liver density.	-Reduction in aminotransferases and lipid levels[101]	-Insufficient data. Need large blind RCTs comparing statins to current standard of care therapy
			Hyogo et al.[102]	-Primary endpoint was improvement of biochemical and histologic features of disease activity in NASH patients with dyslipidemia with 24 months of treatment.	-Improvement in NAS[102]	-Lack of standardization between studies
			Foster et al.[103]	-Primary endpoint was change in liver to spleen (LS) ratios.	- Reduction in steatosis[103,104]	-Lack of data on other statins in treatment of NAFLD and NASH
			Ekstedt et al.[104]	Primary endpoint was change in histologic outcome in NAFLD patients.	- Appear to be safe for use in NAFLD with added benefit of reduction of cardiovascular events[104-106]	-Worsening fibrosis with treatment[102]
						-Confounding data with combination treatment[103]
	Decreases intestinal cholesterol absorption	Ezetimibe	MOZART[109]	-Primary endpoint was change in liver fat as measured by MRI-PDFF in 24 weeks.	-Improvement of aminotransferases and hepatocyte ballooning	-No significant reduction in hepatic steatosis

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Therapy Target	Mechanism Of Action	Medical Treatment Options	Trial(s)	Study Endpoints	Potential Therapeutic Benefits	Pitfalls
	FXR agonist	Obeticholic Acid	FLINT[113]	-Primary endpoint was histologic improvement after 72 weeks.	-Improvement in fibrosis and all components of NAS[113]	-No significant change in resolution of borderline NASH
			NCT02548351/ REGENERATE[114]	-Primary endpoint is the effect of treatment on liver fibrosis with longer duration of therapy (6 years).		-Increase in total cholesterol, LDL, and decrease in HDL -Longer term study currently underway[114]
		GS-9674	Patel et al.[145]	-Primary endpoint was overall safety as assessed by the percentage of patients experiencing or having treatment emergent adverse events.	-Decrease in hepatic fat as well as improvement in liver biochemistry	-Side effect of pruritus
	ACC inhibitor	GS-0976	NCT02856555/ Loomba et al.[133]	-Primary endpoint was the safety and tolerability of drug as well as reduction in hepatic steatosis and liver stiffness with 12 weeks of treatment.	-Significant improvement of MRI-PDFF and markers of fibrosis	-Data on histologic changes with treatment lacking -Longer duration study needed to adequately assess safety and tolerability
	SCD-1 inhibitor	Aramchol	ARREST[128]	-Primary endpoint was the change in liver triglyceride ratio as measured by MRS.	-Reductions in liver fat and ballooning, NASH resolution, fibrosis improvement, decrease in AST, and better glycemic control in initial findings	-Longer duration study needed to adequately assess safety and tolerability
Fibrosis	Angiotensin Receptor Blocker (ARB)	Losartan	Yokohama et al.[117]	-Primary endpoint was to assess for differences between treatment groups in the improvement of steatosis, hepatocellular inflammation, and fibrosis	-Improvement in serum aminotransferases and histologic outcomes	-No RCT data available at this time -Longer duration studies needed

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Table 1 (Continued).

Therapy Target	Mechanism Of Action	Medical Treatment Options	Trial(s)	Study Endpoints	Potential Therapeutic Benefits	Pitfalls
	CCR2/CCR5 antagonist	Cenicriviroc	NCT02217475/CENTAUR[125]	-Primary endpoint was improvement in NAS without fibrosis worsening.	-Significant improvement in fibrosis	-NAS improvement and resolution of steatohepatitis not statistically significant -Longer term study assessing safety and efficacy currently underway
			NCT03028740/AURORA[126]	-Primary endpoint is to confirm the efficacy and safety of treatment of fibrosis.		
	Thyroid receptor β agonist	VK-2809	Loomba et al.[136]	-Primary endpoint was reduction in LDL-C.	-Reductions in liver fat on imaging	-Studies assessing histologic improvement needed -Longer term studies assessing safety and efficacy needed
		MGL-3196	Harrison et al.[144]	-Primary endpoint was change from baseline in hepatic fat fraction assessed by MRI-PDFF in 12 weeks		
	PEGylated human FGF21 analogue	Pegbelfermin	NCT02413372/Sanyal et al.[135]	-Primary endpoint was to evaluate the safety and efficacy of treatment for 16 weeks.	- Significant decrease in absolute hepatic fat fraction	-Larger study with longer duration of treatment needed for further assessment of efficacy and safety -Studies assessing histologic improvement needed
	Monoclonal antibody to lysyl oxidase-like 2 (LOXL2)	Simtuzumab	Harrison et al.[138] NCT01672879[139] NCT01672866[140]	-Primary endpoints were changes in hepatic collagen assessed via morphometry in patients with bridging fibrosis and change in hepatic venous pressure gradient in patients with cirrhosis.		-Efficacy analysis at week 96 stopped due to lack of results -No significant reduction in primary endpoint compared with placebo
	Galectin-3 inhibitor	GR-MD-02	NASH-CX/NCT02462967[142] Chalasani et al.[143]	-Primary endpoint was the baseline adjusted change in hepatic venous pressure gradient (HVPG) at 1 year.	-Significant improvement of hepatocyte ballooning -Significantly lower number of patients with treatment developed new varices	-No improvement of HVPG or liver fibrosis -Longer term RCTs assessing safety and efficacy needed

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Table I (Continued).

Therapy Target	Mechanism Of Action	Medical Treatment Options	Trial(s)	Study Endpoints	Potential Therapeutic Benefits	Pitfalls
	FGF19 variant	NGM282	Harrison et al.[146]	-Primary endpoint was change in absolute liver fat content measured by MRI at 24 weeks.	-Reduction in liver fat content with an acceptable safety profile	-Larger study with longer duration of treatment needed for further assessment of efficacy and safety -Studies assessing histologic improvement needed

Sodium-Glucose Cotransporter-2 Inhibitors

Another anti-diabetic agent category that has been studied includes the sodium-glucose cotransporter 2 (SGLT-2) inhibitors. SGLT-2 inhibitors have shown promising results in reducing liver fat content in rodent models,[148,149] but the data in humans are limited.

The Effect of Empagliflozin on Liver Fat Content in Patients with Type 2 Diabetes (E-LIFT) trial was an RCT evaluating the effects of Empagliflozin versus the standard treatment of Type 2 diabetes mellitus (T2DM) in the treatment of NAFLD. Liver fat, assessed by MRI proton density fat fraction (MRI-PDFF), was significantly reduced compared to control group with a mean difference in fat change between groups −4%.[50] ALT level was also significantly reduced.[50] Although MRI is non-invasive, there are limitations to its use including the lack of information on inflammation, hepatocyte ballooning, and fibrosis. In addition, patients were using other medications in addition to the treatment medication, which could have led to confounding bias in this study.

Other studies evaluated the effects of Empagliflozin and another SGLT-2 inhibitor, Canagliflozin, in patients with T2DM and NASH and found significant improvement in histology, AST, FIB-4 index, or metabolic parameters.[51,52] However, the effects of these studies are hard to compare given the lack of standardization between studies including the doses of medications, treatment length, and treatment and control options. Further studies with RCTs comparing SGLT-2 inhibitors with standard NAFLD treatment with longer follow-up periods are needed.

Thiazolidinediones (TZDs)

TZDs are selective peroxisome proliferator-activated receptor-γ (PPAR-γ) agonists that improve insulin resistance and promote fat redistribution from liver and muscle to adipose tissue.[53]

The Fatty Liver Improvement with Rosiglitazone Therapy (FLIRT) trial was the largest trial to evaluate the effects of Rosiglitazone, a TZD, in patients with NASH. Patients had improvement with steatosis and transaminase levels,[54] but weight gain was a major adverse effect. The FLIRT 2 trial was an extension of the FLIRT trial by an additional 2 years but did not show further improvement in steatosis.[55]

Pioglitazone has shown promise in the treatment of NASH with improvement in steatosis and inflammation compared to placebo in patients with NASH and T2DM.[56–59] A long term 3-year study of 101 patients

with NASH and pre-diabetes/T2DM confirmed the long-term safety and efficacy of pioglitazone.[58] The PIVENS (Pioglitazone, Vitamin E or Placebo for Nonalcoholic Steatohepatitis (PIVENS) trial was a double-blind, RCT evaluating the efficacy of treatment with Vitamin E, Pioglitazone, or placebo for the treatment of NASH in nondiabetic adults.[59] This trial demonstrated significant improvement of hepatic steatosis and lobular inflammation with pioglitazone use but not with improvement in fibrosis score.[59] In addition, there was no benefit to using pioglitazone over placebo for the primary outcome of improvement in histologic feature of NASH. Furthermore, liver enzymes worsened after discontinuation of this medication indicating the need for long-term use. Data from studies using pioglitazone have been shown greater benefit than the studies using rosiglitazone.[54–56,59]

There were drawbacks, however, to using this class of drugs including weight gain throughout duration of use as well as risk for heart failure.[59,60,61] The data support the use of pioglitazone over rosiglitazone in the treatment of T2DM and NASH.[54–56,58] Pioglitazone improves liver histology in patients with and without T2DM with biopsy-proven NASH. AASLD practice guideline recommend its use to treat these patients.[147] Risks and benefits should be discussed with each patient before starting therapy. However, given the drawbacks and side effects of this class of medications along with lack of improvement in fibrosis, pending further data to support its safety and efficacy, pioglitazone should not be used to treat NAFLD without biopsy-proven NASH.[147]

Glucagon-Like Peptide (GLP)-1 Agonists

GLP-1 agonists are a relatively novel class of antidiabetic medications. They are incretin hormones derived from the gut. Native GLP-1 lowers blood glucose by inducing insulin secretion and reducing glucagon secretion.[62,63] GLP-1 receptors have been found on hepatocytes leading to further evaluation in their role on the liver. Studies have shown that GLP-1 agonists decrease hepatic steatosis, are hepatoprotective against fatty acid-related death, and reduce fatty acid accumulation.[64,65] Furthermore, Bernsmeier et al. suggested that GLP-1 secretion is impaired in patients with NAFLD and NASH.[66]

Of the GLP-1 agonists, Liraglutide is the most widely studied medication. The Liraglutide Efficacy and Action in NASH (LEAN) study assessed the effects of treatment with Liraglutide against placebo in patients with biopsy-proven NASH.[67] The results of this study demonstrated statistically significant resolution of steatohepatitis without worsening fibrosis, which was the primary endpoint. The Liraglutide arm of the study also showed statistically significant fewer patients with progression to fibrosis compared to placebo. However, there was no statistically significant change in lobular inflammation and NAS. The small sample size was a major limitation of this study. Feng et al evaluated treatment with Liraglutide, Metformin, or Gliclazide for 24 weeks in an open-label trial.[68] All three treatment groups showed a significant decrease in intrahepatic fat with Liraglutide having the greatest reduction. In addition, liver function with AST/ALT levels also improved significantly in the Liraglutide and metformin groups. Small sample size was, again, a major limitation of this study. Further limitations included the use of ultrasonography instead of liver biopsy, the gold standard, to evaluate intrahepatic fat content.

Other GLP-1 agonists being evaluated in the treatment of T2DM and NAFLD/NASH include Exenatide and Semaglutide. Efficacy of Exenatide has not yet been evaluated in the histological outcomes in patients with NAFLD and NASH, but it has shown significant improvement in AST, ALT, and GGT as compared to intensive insulin therapy in a 12-week study.[69] Exenatide has also shown to be more effective than metformin in reducing body weight and improving liver enzymes.[70] Semaglutide is undergoing a placebo-controlled RCT of 372 patients evaluating the efficacy and safety of three different dosage levels of subcutaneous Semaglutide in the treatment of NASH.[71]

The data on GLP-1 is promising but lacking validation at this time. Large-scale placebo-controlled RCTs with assessment of histologic outcomes are needed to evaluate the efficacy and safety of GLP-1 in treatment of NAFLD and NASH. Furthermore, their cost and parenteral route of administration limit the use of these medications in certain populations.

Oxidative Stress Target

Oxidative stress and impaired antioxidant defense is one of the proposed pathways in the multiple-hits theory in the pathogenesis and progression of NAFLD.

Vitamin E

Vitamin E (α-tocopherol) is a fat-soluble vitamin that has been extensively studied due to its well-known anti-oxidant properties and role in lipid peroxidation in NASH pathogenesis.[72] Animal models of NASH demonstrated that Vitamin E decreases levels of TGF-β, a pro-fibrogenic cytokine, leading to improvement in liver necrosis and

fibrosis.[73,74] Vitamin E therapy was studied in pediatric population in the aforementioned TONIC trial in which hepatocellular ballooning was the only histologic feature of NASH showing significant improvement after treatment (metformin and vitamin E), but neither treatment demonstrated sustained reduction in ALT (the primary outcome) or improvement in steatosis, lobular inflammation, or fibrosis score.[48] Of note, the patient population included in this study also had only mild fibrosis on histology at the start of treatment. The aforementioned PIVENS trial was similar to the TONIC trial in an adult population demonstrating a higher rate of histologic resolution of NASH at week 96 of treatment with Vitamin E vs pioglitazone (43% vs 19%, p=0.001).[59] There was, however, no significant improvement in fibrosis at week 96.

Miller et al conducted a meta-analysis of 11 randomized controlled trials studying the dose–response relationship of Vitamin E treatment with all-cause mortality.[75] This study suggested an increased all-cause mortality with high-dosage Vitamin E (≥400 IU/day). Of note, the high dose trials were small and included patients with chronic diseases, which could be contributing to confounding bias. Another larger meta-analysis with 57 trials demonstrated no effect on all-cause mortality with Vitamin E doses up to 5500 IU/day.[76] Furthermore, Vitamin E showed increased risk in the incidence of hemorrhagic stroke.[77] Another concern with the use of Vitamin E is the increased risk of prostate cancer. However, that risk is unclear given the mixed results between multiple studies.[78,79]

Currently, the European Association for the Study of the Liver (EASL) and the American Association for the Study of Liver Diseases (AASLD) consider Vitamin E a short-term treatment option for non-diabetic adults with biopsy-proven NASH.[80,147] However, further studies elucidating the long-term safety profile and effectiveness of Vitamin E are required.

Anti-Inflammatory Targets And Hepatoprotectants

Imbalance in the inflammatory pathways causing hepatocellular damage has been implicated as part of the pathogenesis of NAFLD and NASH.

Ursodeoxycholic Acid (UDCA)

UDCA is a bile acid that has been evaluated in the treatment of NAFLD given its anti-inflammatory and anti-apoptotic properties thought to prevent progression of NAFLD.[81] A systematic review of 12 RCTs demonstrated promising results for treatment of NASH with UDCA especially in combination with other drugs including vitamin E.[82] However, the quality of these studies was low and there was significant heterogeneity between results. Ratziu et al performed a 12-month placebo-controlled RCT evaluating the efficacy and safety of high dose UDCA (28–35 mg/kg/day) in biopsy proven NASH with promising results.[83] They reported significant and sustained reduction in mean ALT and was found to be safe and well tolerated. However, the data on UDCA are limited and further well-designed large RCTs with histologic outcomes are needed to make an informed decision regarding its use in the treatment of NAFLD and NASH.

Pentoxifylline (PTX)

The imbalance of inflammatory cytokines, such as TNF-α, can lead to hepatocellular damage.[84] PTX inhibits many pro-inflammatory cytokines include TNF-α, reduces oxidized fatty acids, and is thought to have hepatoprotective properties.[85–89] Small published studies have demonstrated significant improvement of liver enzymes[90–92] and insulin resistance[90] as well as improvement in histology[92–94] with the use of PTX in treatment of NASH. Histologic improvements included significant reduction in steatosis and lobular inflammation.[92–94] However, there was discordance between improvement in ballooning and fibrosis between these studies. Singh et al completed a meta-analysis evaluating pharmacological interventions in treatment of NASH and found that PTX demonstrated significant improvement in fibrosis compared with placebo whereas Vitamin E, TZDs, and Obeticholic acid (OCA) were not superior to placebo in fibrosis improvement.[95] PTX was well tolerated other than the side effect of nausea[91,94] which improved with dose reduction.[94] The small sample size and lack of standardization regarding the dosage amount and frequency of PTX used between the RCTs and pilot studies posed some limitations. Overall, these initial studies of PTX offer initial promise in its role in the treatment of NASH but cannot be recommended as monotherapy without further evaluation.

Elafibranor

PPAR-α increases beta-oxidation and decreases steatosis, while PPAR-δ decreases steatosis and inflammation while increasing insulin sensitivity. Elafibranor is a dual PPAR-α and -δ agonists. Animal models have demonstrated PPAR to be hepatoprotective by decreasing lipid accumulation, inflammation, and fibrosis.[96] An RCT evaluated 80mg or 120mg of Elafibranor vs placebo in NASH patients for 52

weeks and found significant improvement in hepatic inflammation in patients with NAS ≥ with 120 mg dosing.[97] However, the primary endpoint of resolution of NASH without worsening fibrosis was not met. A longer-term phase 3 study of Elafibranor 120 mg daily for 72 weeks vs placebo is currently underway to evaluate its efficacy in improving histologic outcomes.[98]

Lipid Metabolism Targets
NAFLD and NASH are hepatic manifestations of metabolic syndrome. Dyslipidemia and abnormal lipid metabolism are thought to be a part of the pathogenesis of development of NASH.

Lipid-Lowering Agents
Statins are used to treat dyslipidemia and are thought to also have anti-oxidant and anti-inflammatory effects.[99,100] A pilot study with atorvastatin treatment demonstrated significant reduction in serum aminotransferase and lipid levels in patients with NAFLD.[101] However, this study did not evaluate histologic outcomes. An open-label study evaluating atorvastatin in patients with biopsy-proven NASH reported significant improvement in NAS, but 24% of the patients had worsening fibrosis.[102] An RCT evaluating atorvastatin in combination with antioxidants such as Vitamin C and E effectively reduced the risk of steatosis by 71% after 4 years of treatment in patients with NAFLD.[103] Many patients with NAFLD and NASH usually receive statins regardless given their cardiovascular risk factors. Although there have been concerns regarding the safety of statin use in patients with liver disease given the risk of hepatotoxicity, recent studies demonstrated statins to be relatively safe in patients with NAFLD.[104–106]

Ezetimibe is another medication used in the treatment of hypercholesterolemia. It has been found to prevent hepatic steatosis and decrease hepatic insulin resistance in mice model of hepatic steatosis.[107] Nakade et al completed a meta-analysis including 6 studies and reported improvement of serum aminotransferases and hepatocyte ballooning in patients with NAFLD receiving ezetimibe treatment.[108] The Magnetic Resonance Imaging and Elastography in Ezetimibe Versus Placebo for the Assessment of Response to Treatment in NASH (MOZART) trial, however, did not show significant reduction in hepatic steatosis with ezetimibe treatment.[109] However, liver biopsy was not performed and steatosis was measured through MRI-derived proton density fat fraction (MRI-PDFF).

These lipid-lowering agents are not recommended as monotherapy for NAFLD and NASH at this time without further evaluation with large RCT evaluating histologic outcomes.

Farnesoid X Receptor (FXR) Agonists
FXR has been identified as a receptor for bile acids and has been found to regulate lipid metabolism and modulate glucoregulatory pathways.[110,111] This is a relatively novel class of drug target being studied in the treatment of NAFLD and NASH. Obeticholic acid (OCA) is a FXR agonist and bile acid analogue with a 100-fold greater potency on FXR.[112] The Farnesoid X Receptor Ligand Obeticholic Acid in Nash treatment (FLINT) trial was a multicenter RCT that evaluated the histologic improvement with OCA 25mg daily treatment in non-cirrhotic patients with NASH for 72 weeks.[113] Results from this trial demonstrated fibrosis improvement without worsening of steatohepatitis in OCA (43% vs 21% in placebo, p<0.001) as well as improvement in all components of NAS as well as fibrosis. However, OCA group had an increase in total cholesterol and LDL along with a drop in HDL compared with placebo. Further studies evaluating the long-term safety of this medication are required. One such study, the Randomized Global Phase 3 Study to Evaluate the Impact on NASH With Fibrosis of Obeticholic Acid Treatment (REGENERATE) trial, is a current long-term 6-year duration study evaluating the effect of treatment with OCA 10 mg vs 25 mg vs placebo on liver fibrosis.[114] Overall, OCA seems to be another promising agent in the treatment of NASH.

Fibrosis Targets
Targeting the progression of fibrosis is another pharmacologic option in preventing the progression of NAFLD and NASH.

Angiotensin Receptor Blockers (ARBs)
ARBs are a class of medications frequently used in the treatment of hypertension especially in the setting of diabetes. Angiotensin II is thought to promote liver fibrosis by activating transforming growth factor-β (TGF-β) and Toll-like receptor-4 (TLR-4) signaling.[115,116] Uncontrolled trials with Losartan, an ARB, demonstrated significant improvement in serum aminotransferases as well as in histologic outcomes.[117,118] However, an open-label trial evaluating concurrent treatment with Rosiglitazone and Losartan did not show an improvement in histopathology as compared to

treatment with rosiglitazone alone.[119] Another ARB, Telmisartan, was found to significantly reduce serum ALT levels and improve insulin sensitivity as well as steatosis, necroinflammation, and fibrosis with greater efficacy than valsartan.[120] A study involving rats with T2DM demonstrated reduction in hepatic fibrosis and steatosis as well as decreased tissue expression of TNF-α with administration of the ARB, Valsartan (15mg/kg/day), for four months.[121] Further placebo-controlled, large-scale RCTs evaluating of histologic outcomes are required at this time to confirm the therapeutic effects of ARBs in treatment of NAFLD and NASH.

Chemokine Receptor (CCR) Antagonists

CCRs are expressed on immune cells and stimulate hepatic stellate cells promoting fibrosis. Cenicriviroc (CVC) is a CCR2 and CCR5 inhibitor. Animal models of NASH demonstrated decreased fibrosis and inflammation with CVC treatment.[122–124] The CENTAUR trial was a phase 2b randomized double-blind multinational study in patients with NASH undergoing treatment with CVC.[125] Significant improvement in fibrosis was seen in twice as many patients in the treatment arm compared with placebo (20% vs 10%, p=0.02).[125] There was also NAS improvement as well as resolution of steatohepatitis, but these were not statistically significant. Currently, phase 3 (NCT03028740) of this study is underway to confirm the efficacy and safety of CVC in treatment of fibrosis in NASH.[126]

Ongoing Trials

Many new pharmacologic targets are being evaluated currently for the treatment of NAFLD and NASH. Here, we will summarize current ongoing trials of potential therapeutic targets in the treatment of NASH. See Table 1 for comprehensive overview NAFLD/NASH pharmacotherapy target agents including agents currently being studied which have not been discussed in the following text given lack of data at this time.

Aramchol

Stearoyl-CoA desaturase 1 (SCD1) is a key enzyme involved in triglyceride biosynthesis. Aramchol inhibits SCD1 and enhances fatty acid oxidation and has been shown to decrease steatohepatitis and fibrosis in mice models of NASH.[127] Recent Phase 2 one-year results from the RCT ARREST trial evaluated the role of aramchol 600mg, 400mg, or placebo in biopsy-proven NASH and found the 600mg arm of the study with significantly more patients with dose-dependent reduction in liver fat and ballooning, NASH resolution

as well as fibrosis improvement.[128] There was also decrease in serum aminotransferases and better glycemic control. Further testing in phase 3 trial is underway.[129]

Selonsertib

Inhibition of apoptosis signaling-regulating kinase 1 (ASK 1) has been shown to improve inflammation and fibrosis in animal models of NASH. In a 24-week open-label phase 2 RCT, the safety and efficacy of 6mg or 8mg Selonsertib, a selective ASK 1 inhibitor, alone or in combination with Simtuzumab (SIM) or SIM alone in patients with NASH and stage 2 or 3 fibrosis was evaluated.[130] Progression to cirrhosis was lowest in the 18mg treatment group at 3% vs 7% in the 6mg group vs 20% in the SIM group. Phase 3 trials of Selonsertib in patients with NASH and F3 fibrosis (STELLAR-3) and compensated cirrhosis (STELLAR-4) have been completed, but final results have yet to be published.[131,132] In these studies, the efficacy of daily Selonsertib 18mg, 6mg, or placebo was evaluated with the primary endpoint being ≥1 point decrease in fibrosis stage without worsening of ballooning or inflammation at 48 weeks. The clinical endpoint at year 5 was to be the reduction in progression to cirrhosis in STELLAR-3 and hepatic decompensation, hepatocellular carcinoma, transplant, and/or death in STELLAR-4. However, the study was halted prior to the set clinical endpoint due to inefficacy, as both the the studies did not meet the pre-specified week 48 primary endpoint of a ≥ 1-stage histologic improvement in fibrosis without worsening of NASH. The final results have not been published at this time.

Acetyl-Coenzyme Carboxylase (ACC) Inhibitor (GS-0976)

ACC is the rate-limiting step in de novo lipogenesis. The safety and efficacy of GS-0976, an inhibitor of ACC, were evaluated in a phase 2 placebo-controlled RCT. Patients received 20mg, 5mg, or placebo daily for 12 weeks. The 20mg group was found to have significant improvement in MRI-PDFF and markers of fibrosis.[133]

Pegbelfermin (BMS-986036)

Pegbelfermin is a PEGylated human fibroblast growth factor 21 (FGF21) analogue that has been shown to improve markers of metabolism and liver fibrosis in mouse model of NASH.[134] A phase 2 placebo-controlled RCT evaluated the safety and efficacy of subcutaneous injections of placebo daily, 10 mg pegbelfermin daily, or 20mg pegbelfermin once weekly for 16 weeks of total therapy in patients with NASH.[135] Results demonstrated significant decrease in absolute hepatic fat fraction in 10mg treatment group (−6.8% vs −1.3%, p=0.0004)

and in 20mg treatment group (−5.2% vs −1.3%, =0.008) compared with placebo. Further assessment of efficacy in improvement of histologic endpoints in a larger study is warranted.

VK2809

Thyroid hormones, especially the β isoform, regulate lipid metabolism especially via specific hepatic receptor. VK2809 is a novel liver-directed thyroid receptor β receptor agonist whose safety and efficacy were evaluated in a phase 2 RCT where patients with NAFLD were administered oral 5mg daily, 10mg daily, 10mg every other day (QOD), or placebo over a 12-week period.[136] Results demonstrated significant reductions in liver fat content assessed by MRI-PDFF as compared with placebo (53.8% in 5mg QD vs 56.5% in 10mg QOD vs −59.7% 10mg QD vs 9.4% in placebo, p=0.0001 vs 0.0018 vs 0.0004 vs 0.0003). As high as 100% of the patients also demonstrated ≥30% reduction in liver fat at 12 weeks with 5mg QD dosing vs 76.9% with 10mg QOD dosing vs 90.9% in 10mg QD dosing vs 16.7% in placebo (p = 0.0002 vs 0.0048 vs 0.0006). These robust improvements are promising and prompt further evaluation.

Conclusions

There are currently no FDA approved drugs for the treatment of NASH. The current mainstay of therapy is diet and life-style modification. Given the slow rate of progression of hepatic fibrosis in most patients with NASH it is emphasized that treatment be aimed at controlling associated metabolic risk factors rather than pharmacological intervention. Since, weight loss is associated with improvements in serum aminotransferase activities as well as components of metabolic syndrome, this is commonly recommended. Weight loss through bariatric surgery has shown promising results. Patients at risk for fibrosis progression and those who already have advanced disease should be given opportunity to particiapte in clinical trials. In patients included in clinical trials, therapy should not only be aimed at improving the aminotransferses and NAS activity score, but also to halt or reverse fibrosis progression. From a practical stand point, while dealing with such patients in the clinical practice, we would suggest intervention based on the patients associated metabolic risk profile. The gut–liver axis, another pathway in the pathogenesis of NASH has been explored, and this apparoch may lead to many newer therapies in the future targeting gut dysbiosis.

TZDs and Vitamin E seem to have the most abundant promising data but has not shown any benefit in fibrosis improvement which is the key marker of long term outcome in NASH patients. Many of the other drugs reviewed in this paper, including the newer drug targets, have shown very promising results with regards to their safety and efficacy in treating NAFLD/NASH, but an unequivocal proven benefit is yet to be shown. Before progress in treatment can be achieved, additional rigorous research aimed at elucidating the key pathways of its pathogenesis is warranted. Future clinical and preclinical studies on existing and newer agents hopefully will pave the way for treatment of this increasingly prevalent disease.

Author Contributions

Sanjaya K Satapathy, Surosree Ganguli, and Peter DeLeeuw made substantial contributions to conception and design, acquisition of data, and analysis and interpretation of data. All assisted in drafting the article or revising it critically for important intellectual content. They have all given final approval of the version to be published and have agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Disclosure

Dr Sanjaya K Satapathy reports grants from Gilead, Intercept, Shire, Allergan, Bayer, Conatus, Exact Sciences, Dova, Biotest, and Genfit, served on the Speakers Bureau for Alexion, Intercept, and Dova, and served on the Advisory board for Gilead, Bayer, and Dova, outside the submitted work. The authors report no other conflicts of interest in this work.

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