Update on Clinical Trials for Nonalcoholic Steatohepatitis

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Abstract: Tremendous effort has been put forth over the past 2 decades in understanding the pathophysiology of nonalcoholic fatty liver disease/nonalcoholic steatohepatitis (NAFLD/NASH). Although multiple potential targets for drug development exist, there have been no approved therapies for NAFLD/NASH. Lipotoxicity, owing to increased delivery of fatty acids to the liver, and hepatic de novo lipogenesis are key drivers of disease pathogenesis. Moreover, genetics, environmental factors, and comorbid conditions converge to determine disease progression in individual patients. Given the complexity and heterogeneity of disease pathogenesis, numerous therapeutic targets have emerged and have been tested in clinical trials. Early trial failures have provided key lessons and foundational insights to move the field forward. Current ongoing phase 3 trials and emerging phase 2 trials are reasons for optimism, and 2 drugs, obeticholic acid and resmetirom, are being evaluated for accelerated approval by the US Food and Drug Administration this year. This article highlights key features of NASH pathophysiology and drug targets, the lessons learned from completed trials, and the current landscape of phase 2 and 3 clinical trials in NASH.

Keywords
Nonalcoholic steatohepatitis, nonalcoholic fatty liver disease, therapeutics, clinical trials

Nonalcoholic fatty liver disease (NAFLD) is the most common cause of chronic liver disease worldwide, affecting 25% of the population, and is the leading indication for liver transplant in women and second overall in the United States.[1,2] It is characterized by excess fat deposition in the liver, defined as the presence of steatosis in greater than 5% of hepatocytes without secondary contributing factors such as significant alcohol use, viral infections, or steatogenic drugs.[3] NAFLD is a clinical spectrum with progressive severity from simple steatosis to nonalcoholic steatohepatitis (NASH), which is characterized by hepatocyte ballooning and lobular inflammation with or without varying degrees of fibrosis. Hepatic fibrosis can lead to liver decompensation and hepatocellular carcinoma (HCC), which are causes of liver-related mortality, with the fibrosis stage being the strongest predictor of adverse liver-related outcomes.[4]

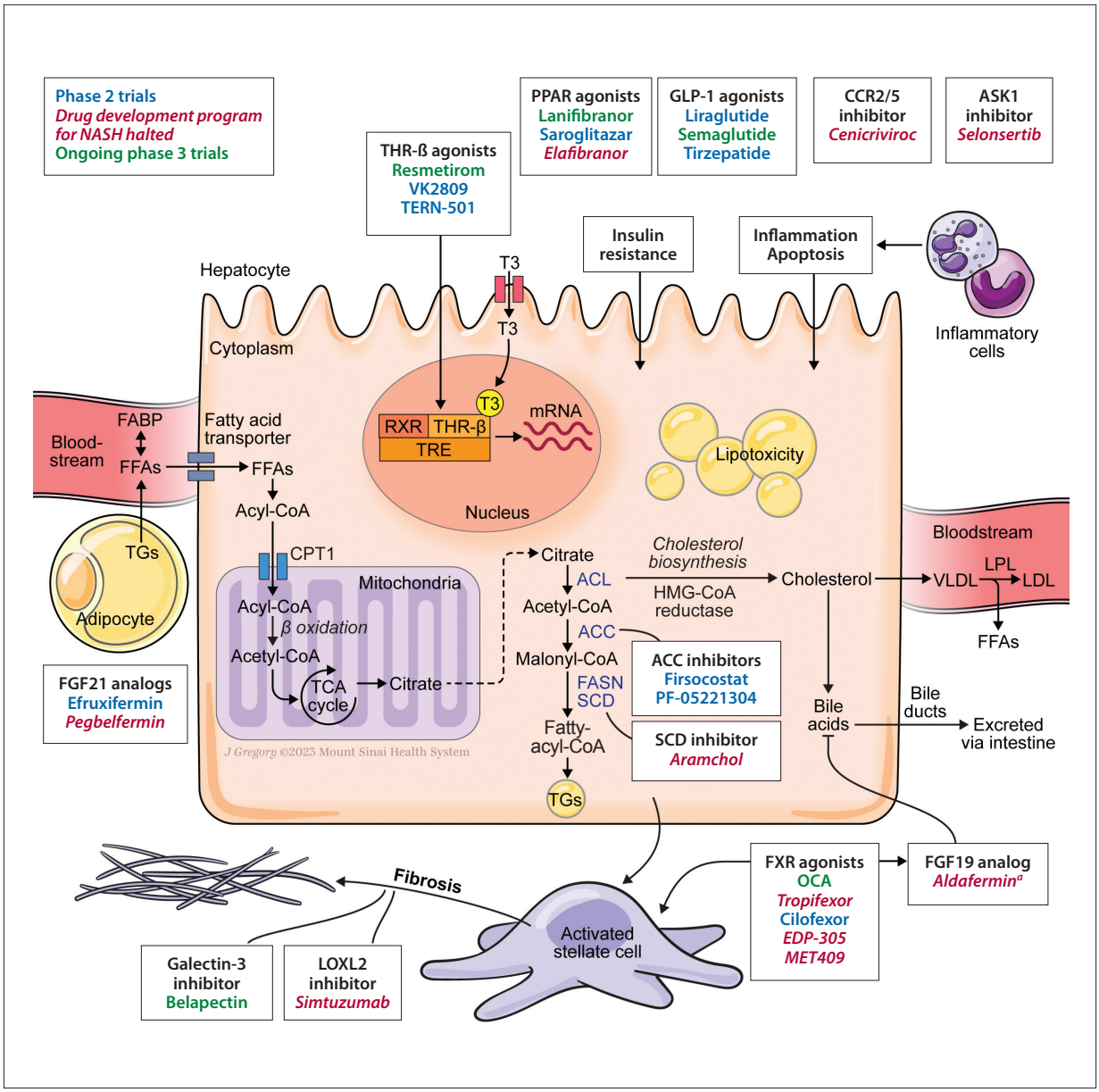

Figure. NASH targets being studied or in phase 2/3 development. Individual drugs target multiple pathways in the pathogenesis of NASH, including metabolic pathways (improved insulin sensitivity, inhibition of de novo lipogenesis, improved mitochondrial utilization of fatty acids), the inflammatory cascade, the gut-liver axis, and hepatic fibrosis. For simplicity, drugs are arranged around the hepatocyte based upon presumed primary mechanisms of action, although most drugs have multiple pleiotropic effects. Ultimately, effects on hepatocyte injury will decrease downstream stellate cell activation, and some drugs have presumed direct effects on stellate cells and fibrogenesis. Drugs are color-coded to indicate whether they are currently in phase 2 or 3 trials or whether the developmental program has been halted.

ACC, acetyl-CoA carboxylase; ACL, ATP citrate lyase; ASK1, apoptosis signal-regulating kinase 1; CCR2/5, chemokine receptors 2 and 5; CoA, coenzyme A; CPT1, carnitine palmitoyl transferase 1; FABP, fatty acid–binding protein; FASN, fatty acid synthase; FFAs, free fatty acids; FGF, fibroblast growth factor; FXR, farnesoid X receptor; GLP-1, glucagon-like peptide-1; HMG-CoA: β-hydroxy β-methylglutaryl-CoA; LDL, low-density lipoprotein; LOXL2, lysyl oxidase homolog 2; LPL, lipoprotein lipase; NASH, nonalcoholic steatohepatitis; OCA, obeticholic acid; PPAR, peroxisome proliferator–activated receptor; RXR, retinoid X receptor; SCD, stearoyl-CoA desaturase; TCA, tricarboxylic acid; TGs, triglycerides; THR, thyroid hormone receptor; TRE, thyroid hormone response element; T3, triiodothyronine; VLDL, very low-density lipoprotein.

[a]Aldafermin is currently being studied in a phase 2b trial in patients with compensated NASH cirrhosis.

Lifestyle modifications such as weight loss, exercise, and a healthy diet remain the cornerstone of therapy. Although weight loss is effective, it may be difficult to achieve and maintain.[5] This has led to the development of several pharmacologic agents in the past decade that are currently being evaluated in clinical trials. This article discusses the road to advances in NASH treatment, focusing on key features of NASH pathophysiology and drug targets, lessons learned from completed trials, and an overview of the current and emerging landscape of NASH therapeutic agents in phase 2/3 clinical trials.

Nonalcoholic Fatty Liver Disease/ Nonalcoholic Steatohepatitis Pathophysiology

NAFLD is a complex disease driven by insulin resistance, lipotoxicity, and activation of inflammatory pathways.[6] Moreover, genetics, environmental factors, social determinants of health, and comorbidities converge to lead to variable disease progression. As fibrosis is the most important predictor of clinical outcomes, fibrosis regression or lack of progression is ultimately critical to any therapeutic intervention's success. Given the complexity of the pathophysiology of NAFLD/NASH, multiple potential targets are available for drug development.[7] Metabolic targets lead to improved insulin sensitivity, inhibition of de novo lipogenesis, and improved mitochondrial utilization of fatty acids. Targets of the inflammatory pathways result in reduced cell stress and apoptosis. The gut-liver axis is a target for some drugs to alter the gut microbiota and modulate enterohepatic circulation, whereas other drugs target fibrosis pathways either by decreasing fibrogenesis or increasing fibrinolysis. Many drugs in development work on multiple pathways to varying degrees.[7] An overview of drugs that have either been studied or are being studied, along with their presumed primary targets in the pathophysiology of NAFLD/NASH, is provided in the Figure.

Select Completed Clinical Trials and Lessons Learned

The path for NASH therapeutics has been long and expensive, although lessons learned along the way have brought the field valuable insights. The first pivotal clinical trial, PIVENS, was a phase 3 clinical trial evaluating the efficacy of naturally occurring vitamin E vs pioglitazone vs placebo in the primary outcome of NASH and fibrosis improvement in patients with NASH without type 2 diabetes mellitus (DM2). Vitamin E was superior to placebo in achieving the primary outcome, but pioglitazone, a peroxisome proliferator–activated receptor (PPAR)-γ agonist (and, to a lesser extent, PPAR-α agonist), was not. However, pioglitazone was associated with significant reductions in steatosis, inflammation, and hepatocellular ballooning, and improvements in insulin resistance and liver enzyme levels.[8] Several additional studies have shown that the antioxidant vitamin E is associated with improved histologic and clinical outcomes in patients with NASH.[9,10] Despite these modest benefits, the use of these drugs has been limited by concern of increased hemorrhagic stroke risk and prostate cancer with long-term synthetic vitamin E use, and weight gain, small bone fracture risk, and, rarely, hypoglycemia with pioglitazone, highlighting the need for a long-term NASH therapeutic agent to have an exceptional safety profile.

Elafibranor (Genfit) is a PPAR-α/δ dual agonist and is not associated with the side effects of PPAR-γ activation such as weight gain and edema seen with pioglitazone. In a large phase 2b clinical trial (GOLDEN), elafibranor initially failed to meet its primary outcome of NASH resolution without worsening of fibrosis,[11] mainly owing to the high placebo response rate of 57%. The critical issue was that the study included patients with a NAFLD Activity Score (NAS) of at least 3. In a modified intention-to-treat analysis including only patients with a NAS of at least 4, the placebo response rate dropped to 12%, and a statistically significant difference was observed. Following these results, the RESOLVE-IT trial (NCT02704403) was launched to assess the safety and efficacy of elafibranor vs placebo; however, owing to the inability to meet the primary endpoint of NASH improvement without fibrosis worsening, this study was terminated. Clinical trials now include patients with a higher NAS at baseline to evaluate study participants with more severe NASH and help mitigate high placebo response rates.

Cenicriviroc (Allergan) is a dual antagonist of chemokine receptors 2 and 5, both of which have been shown to play a role in activating hepatic stellate cells (HSCs) and promote the recruitment of monocytes to the liver as well as activation of hepatic macrophages.[12] The CENTAUR trial was a phase 2b placebo-controlled clinical trial in which cenicriviroc failed to meet its primary efficacy endpoint of histologic improvement in NASH without worsening of fibrosis at year 1; however, there was significant reduction in at least 1 fibrosis stage without worsening of NASH.[13] This finding implied a decoupling of inflammation and fibrosis and suggested that cenicriviroc may be specifically targeting HSCs. The finding also led to virtually every trial adding either a primary or secondary outcome for improvement in fibrosis greater than or equal to 1 stage without worsening of NASH. Although additional antifibrotic benefit was not observed at year 2, exploratory analyses pointed to the durability of the benefit that was seen, as twice the proportion of

Table. Ongoing Phase 3 Clinical Trials for NASH

Drug name	Indication	Name of trial (ClinicalTrials.gov identifier)	Number of participants	Time to endpoint	Primary endpoints
FXR agonist					
Obeticholic acid	NASH F2-F3 by NASH CRN	REGENERATE (NCT02548351)	~2500	18 months	• At least 1 stage of liver fibrosis improvement with no worsening of NASH or • NASH resolution with no worsening of liver fibrosis
Selective THR-β agonist					
Resmetirom	NASH F2-F3 by NASH CRN	MAESTRO-NASH (NCT03900429)	966	52 weeks	• Resolution of NASH (ballooning 0, inflammation 0-1) associated with at least 2-point reduction in NAS without worsening of fibrosis stage or • Proportion with at least 1-stage improvement in fibrosis with no worsening of NAS
			~1700	54 months	• Composite clinical outcome is composed of all-cause mortality, liver transplant, and significant hepatic events (including hepatic decompensation events [ascites, hepatic encephalopathy, or variceal hemorrhage], histologic progression to cirrhosis, and a confirmed increase of MELD score from <12 to ≥15)
	NAFLD/NASH diagnosed by NITs or prior biopsy	MAESTRO-NAFLD1 (NCT04197479)	~1400	52 weeks	• The effect of once-daily, oral administration of 80 or 100 mg of resmetirom vs placebo on the incidence of adverse events
	Participation and completion of MAESTRO-NAFLD1	MAESTRO-NAFLD-OLE (NCT04951219)	~1400	52 weeks	• The effect of once-daily, oral administration of 80 or 100 mg of resmetirom vs placebo on the incidence of adverse events
	NASH diagnosed by NITs or prior biopsy	MAESTRO-NASH-OUTCOMES (NCT05500222)	~700	52 weeks	• Any event of all-cause mortality, liver transplant, ascites, hepatic encephalopathy, variceal hemorrhage, and confirmed increase of MELD score from <12 to ≥15 owing to liver disease
GLP-1 analog					
Semaglutide	NASH F2-F3 by NASH CRN	ESSENCE (NCT04822181)	~1200	72 weeks	• Improvement of steatohepatitis and no worsening of liver fibrosis
				72 weeks	• Improvement in liver fibrosis and no worsening of steatohepatitis
				240 weeks	• Time to first liver-related clinical event (composite endpoint)
PPAR-α, -γ, and -δ agonist					
Lanifibranor	NASH F2-F3 by SAF score	NATiV3 (NCT04849728)	~1000	72 weeks	• Part A: Resolution of NASH and improvement of fibrosis at week 72, defined by NASH CRN scores for ballooning of 0 and inflammation of 0-1, and fibrosis score ≥1 stage decrease compared with baseline
				120 weeks	• Part B: To assess the safety of lanifibranor for 48 weeks after completion of Part A

CRN, Clinical Research Network; FXR, farnesoid X receptor; GLP-1, glucagon-like peptide-1; MELD, Model for End-Stage Liver Disease; NAFLD, nonalcoholic fatty liver disease; NAS, NAFLD Activity Score; NASH, nonalcoholic steatohepatitis; NITs, noninvasive tests; PPAR, peroxisome proliferator–activated receptor; SAF, Steatosis, Activity, and Fibrosis; THR, thyroid hormone receptor.

cenicriviroc-treated patients who had achieved the prespecified fibrosis response at 12 months maintained the benefit at 24 months. This led to the phase 3 AURORA clinical trial (NCT03028740), which was subsequently conducted in approximately 2000 patients with biopsy-confirmed NASH and fibrosis F2 to F3. This study, however, failed to meet its primary endpoint of improvement of at least 1 fibrosis stage without worsening of NASH, leading to its termination.[14] These results underscore the heterogeneity of NASH pathophysiology, the need for robust phase 2b efficacy data, and potential need to concomitantly address upstream drivers of NASH along with antifibrotic approaches.

Selonsertib (Gilead) is an apoptosis signal-regulating kinase 1 (ASK1) inhibitor. The ASK1 pathway is upregulated in patients with NASH and correlates with the stage of liver fibrosis.[15] Improvement in fibrosis stage with selonsertib was demonstrated in a phase 2 clinical trial[16] in which simtuzumab (Gilead), a lysyl oxidase homolog 2 (LOXL2) inhibitor, was equated to placebo owing to lack of efficacy. This led to the inception of 2 large phase 3 clinical trials, one in patients with NASH and bridging fibrosis (F3) (STELLAR-3, NCT03053050) and one in NASH and compensated cirrhosis (STELLAR-4, NCT03053063). However, neither of these trials met their primary endpoint of improvement in at least 1 stage of fibrosis without worsening of NASH at 48 weeks of treatment.[17,18] The failure of these large trials underscores the need for robust phase 2b data with a clear placebo arm before proceeding to phase 3.

The LOXL2 inhibitor simtuzumab was studied in patients with bridging fibrosis (F3) and patients with cirrhosis (F4). The premise was that by inhibiting the enzyme lysyl oxidase, there would be less collagen cross-linking, making the collagen more easily degradable by restorative macrophages. Cirrhosis is the longest phase of fibrosis. Therefore, patients who just transitioned to cirrhosis vs those who have been cirrhotic for many years have immensely different prospects for cirrhosis regression. Although this study failed to meet its primary endpoint, much was learned about the natural progression of F3 and F4 disease.[19] After a median follow-up of 24.9 months, approximately 25% of patients with NASH and bridging fibrosis progressed to cirrhosis. As this was a highly selected advanced population and depended upon biopsy for assessment, this progression rate is an overestimate but helpful for trial design. After a median follow-up of 26.7 months, approximately 20% of cirrhotic patients had liver-related events. Interestingly, the study found no predictive value of baseline NAS or its change over time.[20] Fibrosis stage continues to remain the most important predictor of clinical outcomes. Failure of several additional trials in cirrhotic patients[21,22] underscores the need for better substratification of cirrhotic patients based upon more advanced artificial intelligence (AI)-assisted histologic assessments.

Drugs Currently in Phase 3 Clinical Trials

Obeticholic Acid

Obeticholic acid (OCA) (Ocaliva, Intercept Pharmaceuticals) is a semi-synthetic bile acid derivative. OCA works by binding to the farnesoid X receptor (FXR), a nuclear receptor that regulates multiple processes in the liver, such as inflammation, fibrosis, and metabolism of bile acids and glucose.[23] The FLINT trial, a phase 2b, multicenter, randomized controlled trial (RCT), showed that treatment with OCA in patients with NASH improved liver histology, including fibrosis, but with increased incidence of pruritus and mild low-density lipoprotein (LDL) cholesterol elevation.[24,25] An international, multicenter, phase 3 clinical trial, REGENERATE, is now underway (Table). Interim analysis at 18 months, which included a more recent repeat consensus methodology analysis for histologic review, demonstrated that patients with NASH F2 to F3 fibrosis had a statistically significant improvement in liver fibrosis without worsening of NASH, thereby meeting one of the primary endpoints of this study.[26] A subsequent analysis of these results also demonstrated that an improvement in liver fibrosis on histology corresponded with improvement in fibrosis scores using various noninvasive tests (NITs),[27] strengthening the idea that NITs may be used as primary endpoints for antifibrotic drug trials in the future. The REVERSE trial (NCT03439254) was a phase 3 clinical trial conducted in patients with NASH and compensated cirrhosis that did not meet its primary endpoint of improvement in liver fibrosis without worsening of NASH at 18 months; thus, it was halted. This failure was likely due to the lack of cirrhosis substratification, similar to the issue with other trials in cirrhotic patients. Additional AI-based pathologic analyses may allow for a more nuanced assessment of efficacy.

Resmetirom

Resmetirom (Madrigal Pharmaceuticals) is a selective thyroid hormone receptor–beta (THR-β) agonist that regulates multiple processes in hepatic triglyceride and cholesterol metabolism leading to decreased intrahepatic lipid content.[28] In a phase 2 clinical trial, patients treated with resmetirom had significant reductions in liver fat content at 12 and 36 weeks compared with patients treated with placebo. Resmetirom responders with at least 30% magnetic resonance imaging–proton density fat fraction (MRI-PDFF) reduction at week 12 had higher rates of NASH resolution (37%) on week 36 liver

biopsy compared with nonresponders (4%), suggesting that early MRI-PDFF response could predict future histologic improvement.[29] Resmetirom also positively affected patients' lipid profiles by reducing blood levels of atherogenic lipids. Thus, it may reduce the incidence of cardiovascular disease, which is the leading cause of mortality in patients with NASH.[30] At the end of the 36-week phase 2 study, a 36-week, active treatment, open-label extension (OLE) study was conducted in 31 patients with persistently mild to markedly elevated enzymes. Although all OLE study endpoints were exploratory, patients taking resmetirom displayed significantly decreased alanine aminotransferase (ALT), gamma-glutamyl transferase, serum markers of fibrogenesis, and liver stiffness by vibration-controlled transient elastography.[31] Overall, the positive phase 2 results for resmetirom have led to four phase 3 clinical trials: MAESTRO-NASH, MAESTRO-NAFLD1, MAESTRO-NAFLD-OLE, and MAESTRO-NASH-OUTCOMES (Table).

The MAESTRO-NASH study (NCT03900429) included more than 950 patients, primarily with NASH F2 to F3. In a recent press release,[32] the manufacturer released topline clinical data showing that resmetirom was effective in meeting both its primary biopsy endpoints of proportion of patients with improvement in at least 1 stage of fibrosis without worsening of NAS and proportion of patients with NASH resolution with at least a 2-point reduction in NAS (with a ballooning score of 0 and inflammation score 0-1) and no worsening of fibrosis at 52 weeks. Key secondary endpoints such as significant reductions of liver enzymes and atherogenic lipids from baseline were achieved. Resmetirom was noted to have a favorable safety profile, with the most common adverse effect being mild and transient diarrhea.

MAESTRO-NAFLD1 (NCT04197479) is a 52-week, double-blind, phase 3 clinical trial of around 1400 patients with 3 metabolic risk factors documented with NASH or NAFLD by historical liver biopsy or noninvasive techniques (no biopsy data). Patients were randomized 1:1:1:1 to receive once-daily resmetirom 80 mg, resmetirom 100 mg, placebo in double-blind arms, or resmetirom 100 mg in an open-label arm. The study met its primary safety endpoint and multiple secondary endpoints involving atherogenic lipids and liver fat by MRI-PDFF.[33] MAESTRO-NAFLD-OLE (NCT04951219) is an open-label extension of the MAESTRO-NAFLD1 study to assess safety outcomes.

Initiated in August 2022, MAESTRO-NASH-OUTCOMES (NCT05500222) is a phase 3 trial in patients with probable early NASH cirrhosis (diagnosed by prior biopsy or NITs). Patients will be monitored for progression to a composite clinical outcome of all-cause mortality and liver decompensation events.

Semaglutide

Semaglutide (Ozempic, Novo Nordisk) is a glucagon-like peptide-1 (GLP-1) receptor agonist that is approved for the treatment of DM2. Apart from its effects on weight loss, improved glycemic control in patients with DM2 and obesity, and its cardioprotective effects, it has also been shown to reduce liver enzymes and markers of inflammation.[34-36]

Results from a phase 2 clinical trial of 320 patients with NASH showed that semaglutide met the primary endpoint of improvement in NASH without worsening of fibrosis in patients who received semaglutide 0.4 mg compared with placebo. The trial did not, however, meet its secondary endpoint of improvement in fibrosis without worsening of NASH, although researchers saw a very high placebo response rate of 33%, making the demonstration of efficacy more challenging. Consistent with its mechanism of action, gastrointestinal symptoms and a dose-dependent decrease in weight were most commonly observed.[37]

The phase 3 clinical trial ESSENCE is currently underway (NCT04822181) (Table). The study, which began in 2021, plans to enroll approximately 1200 patients with NASH and aims to assess the effectiveness of a 2.4-mg weekly subcutaneous injection of semaglutide in these patients. The primary endpoint of this study's first part (follow-up of 72 weeks) is an improvement in NASH without worsening of fibrosis and an improvement in fibrosis without worsening of NASH. The primary endpoint of the study's second part (follow-up of 240 weeks) is the time to a composite clinical event.

Lanifibranor

Lanifibranor (Inventiva) is a pan-PPAR agonist activating PPAR-α, -δ, and -γ. It affects the inflammatory, fibrotic, and metabolic pathways in the pathogenesis of NASH.[38,39] In the NATIVE study, a phase 2b double-blind RCT, lanifibranor met its primary endpoint of improvement in Steatosis, Activity, and Fibrosis score on histology with the 1200-mg dose at the end of 24 weeks. This effect was not significant with the lower (800-mg) dose. The study also met its secondary endpoints of improvement in NASH without worsening of fibrosis, improvement in fibrosis by at least 1 stage without worsening of NASH, and improvement in both NASH as well as fibrosis by at least 1 stage at both doses of lanifibranor (1200 mg and 800 mg) compared with placebo. Lanifibranor was also associated with higher frequency of adverse events such as weight gain, peripheral edema, nausea, and diarrhea.[40] Given the dose-dependent increase in weight gain with lanifibranor, with an average 2.7-kg increase with the 1200-mg dose, and the need for long-term therapy, this will need to be closely followed in the phase 3 study.

The phase 3 NATiV3 clinical trial (NCT04849728) is being conducted to assess the efficacy of lanifibranor in patients with NASH and fibrosis F2 to F3 (Table). The study aims to enroll approximately 1000 patients and assess the primary endpoint of NASH resolution without worsening of fibrosis or fibrosis improvement without worsening of NASH in part 1 (72-week follow-up). Part 2 of the trial will assess the safety profile of lanifibranor and will be conducted for 48 weeks after the completion of part 1 of the study. A parallel phase 3 trial is being planned to study the effect of lanifibranor vs placebo in patients with compensated NASH cirrhosis. This study is expected to enroll almost 800 patients who will be followed for approximately 3 years. The developer of the drug also plans to enroll approximately 200 patients not eligible for part 1 of the study (owing to screening failures) into a placebo-controlled exploratory cohort. The researchers hope this will generate additional results using NITs and contribute to the safety profile required for fast-track approval.

Drugs Currently in Phase 2 Clinical Trials

Peroxisome Proliferator–Activated Receptor Agonists

Although the trial for elafibranor was terminated because it did not meet its primary endpoints, and trials for lanifibranor are still ongoing in phase 3, several other PPAR agonists are in development. Saroglitazar (Zydus Therapeutics) is a PPAR agonist that acts on PPAR-α, with moderate PPAR-γ activity. A phase 2 clinical trial in overweight (body mass index ≥25) patients with NAFLD/NASH showed that over 16 weeks, saroglitazar had a dose-dependent reduction in ALT. There was also a significant reduction in liver fat content, adiponectin, homeostatic model assessment of insulin resistance, and triglycerides in the 4-mg (highest-dose) saroglitazar group compared with placebo.[41] These promising results led to the approval of saroglitazar for the treatment of noncirrhotic NASH in India.

Fibroblast Growth Factor Analogs

Endocrine fibroblast growth factor (FGF) analogs have emerged as promising NASH therapeutic agents, not only because of their ability to act directly on the liver, but their ability to shift to an overall healthier metabolic state.[42] Although gut-secreted FGF19 and liver-secreted FGF21 belong to the FGF19 subfamily[43] and share some physiologic roles, such as regulation of glucose and lipid metabolism, there are clear differences based upon their contrasting agonist profiles. Specifically, whereas the FGF19/β-klotho (KLB) receptor complex is able to bind to and activate FGFR1c, FGFR2c, FGFR3c, and FGFR4, the FGF21/KLB receptor complex only signals through FGFR1c, FGFR2c, and FGFR3c.[44]

FGF19 has been shown to have antisteatotic, anti-inflammatory, and antifibrotic activities in preclinical models and promotes hepatocyte proliferation.[45,46] FGF19 modulates hepatic fat metabolism by several mechanisms, including the acceleration of lipid oxidation and inhibition of de novo lipogenesis. It also inhibits bile acid synthesis, thereby reducing potential hepatocyte toxicity of bile acids and stellate cell activation.

Aldafermin (NGM Bio) is an engineered nontumorigenic analog of FGF19 that acts on 2 receptor complexes, FGFR1c-KLB and FGFR4-KLB. Activation of the FGFR1c-KLB receptor is thought to lead to a reduction in liver steatosis and improvement in insulin sensitivity, whereas activation of FGFR4-KLB reduces bile acid synthesis.[47] The ALPINE 2/3 study, conducted in 171 patients with biopsy-confirmed fibrotic NASH (F2-F3), failed to achieve its primary endpoint of an improvement in liver fibrosis by at least 1 stage with no worsening of NASH at week 24. However, compared with placebo, statistically significant NASH resolution was observed along with a dose-dependent reduction in liver fat content and noninvasive assessments of liver injury (ALT, aspartate aminotransferase) and fibrosis (propeptide of type 3 collagen, Enhanced Liver Fibrosis [ELF] test). Aldafermin was also associated with increased LDL cholesterol levels, consistent with its role in inhibiting bile acid synthesis, raising a theoretical concern for its atherogenic potential like OCA.[48] The ALPINE 4 study (NCT04210245) evaluating the safety and efficacy of aldafermin in patients with NASH and compensated cirrhosis is underway.

Unlike FGF19, FGF21 has effects on multiple target organs and is reviewed extensively elsewhere.[42] Briefly, in the liver, it is thought to promote fatty acid oxidation, decrease de novo lipogenesis, increase triglyceride clearance, and increase gluconeogenesis. Moreover, FGF21 improves peripheral insulin sensitivity and promotes uptake of energy by adipose tissue and skeletal muscle.[43] Depending upon their structure, FGF21 analogs have variable tissue penetration and thus clinical benefit in NASH.[42]

The first FGF21 analog studied in NASH was pegbelfermin (PGBF) (Bristol Myers Squibb). The drug was well tolerated and significantly reduced hepatic fat fraction, measured by MRI-PDFF, in patients with NASH.[49] The FALCON 1 trial (NCT03486899) was conducted to assess the efficacy and safety of PGBF in patients with NASH F3. However, data presented at the 2021 annual meeting of the American Association for the Study of Liver Diseases showed that PGBF failed to reach its primary endpoint of improvement in fibrosis without worsening of NASH or NASH resolution without worsening of fibrosis.[50] Subsequently, the FALCON 2 trial (NCT03486912), which evaluated the safety and efficacy

of PGBF in patients with compensated NASH cirrhosis (F4), did not meet the primary endpoint of improvement in fibrosis by at least 1 stage without worsening of NASH[51]; therefore, the program has been halted.

Despite this setback, this class of drugs may still hold promise owing to differences in their chemical structure that lead to improved tissue penetration and target engagement. Efruxifermin (Akero Therapeutics) was studied in a phase 2a clinical trial of 80 patients with NASH and achieved its primary endpoint of a significant improvement in hepatic fat content, measured by MRI-PDFF, compared with baseline. The drug was most associated with gastrointestinal side effects.[52] The manufacturer released topline data[53] from the phase 2b HARMONY study, which included 128 patients (F2/F3) who received once-weekly subcutaneous dosing for 24 weeks. Both the 50-mg dose (41%) and 28-mg dose (39%) demonstrated at least 1-stage improvement in fibrosis without worsening of NASH at 24 weeks compared with placebo (20%). The 50-mg dose (76%) and 28-mg dose (47%) showed NASH resolution without worsening of fibrosis compared with placebo (15%). Perhaps most importantly, a subset of patients receiving 50 mg (41%) and 28 mg (29%) demonstrated both fibrosis improvement and NASH resolution compared with placebo (5%). The SYMMETRY trial (NCT05039450), which is assessing the safety and efficacy of efruxifermin in patients with biopsy-proven compensated NASH cirrhosis, is fully enrolled, with results expected in late 2023.

Glucagon-Like Peptide-1 Analogs

The LEAN study was a phase 2 clinical study evaluating the efficacy and safety of liraglutide (Victoza, Novo Nordisk), a GLP-1 receptor agonist, in patients with NASH. Compared with placebo, there was a statistically significant rate of NASH resolution in patients treated with liraglutide. However, 2 of 26 patients treated with liraglutide experienced fibrosis progression, although this rate was lower than in patients on placebo.[54]

Tirzepatide (Mounjaro, Lilly) is a GLP-1–glucose-dependent insulinotropic polypeptide co-agonist that has been associated with significant weight loss in obese patients.[55] The SYNERGY-NASH trial (NCT04166773), which is comparing the efficacy of tirzepatide with placebo in NASH resolution without worsening of fibrosis, is currently underway.

Thyroid Hormone Receptor–β Agonist

As with resmetirom, VK2809 (Viking Therapeutics) is a THR-β agonist with promising early results. In a 12-week, phase 2a, placebo-controlled clinical trial, VK2809 was associated with a significant reduction in atherogenic lipids such as LDL cholesterol and hepatic fat content by imaging.[56] A 52-week, phase 2b study assessing the safety and efficacy of VK2809 in NASH F1 to F3, compared with placebo, is expected to be completed in 2023.

Fatty Acid Synthesis Inhibitors

Firsocostat (Gilead) is an acetyl–coenzyme A carboxylase (ACC) inhibitor. ACC inhibition has been shown to reduce hepatic steatosis, improve insulin sensitivity, and modulate dyslipidemia in preclinical models.[57] In a phase 2 placebo-controlled RCT, firsocostat at a dose of 20 mg showed a statistically significant reduction in hepatic fat content and tissue inhibitor of metalloproteinase 1, a serum marker associated with liver fibrosis. Firsocostat was subsequently tested alone and in combination with selonsertib and cilofexor as part of the ATLAS trial, as discussed in a later section, and with semaglutide and cilofexor in a small open-label phase 2 study with some potential benefit, warranting a larger double-blind placebo-controlled trial.[58]

Denifanstat (Sagimet Biosciences) is a selective, potent, reversible inhibitor of fatty acid synthase (FASN). In preclinical studies, FASN inhibition has been shown to reduce intrahepatic fat and inhibit diet-induced inflammation and insulin resistance in mouse models.[59] In FASCINATE-1 (NCT03938246), a phase 2 placebo-controlled trial, denifanstat showed a significant dose-dependent reduction in liver fat and improved biochemical, inflammatory, and fibrotic biomarkers after 12 weeks.[60]

PXL065 (Poxel) is a deuterium-stabilized R-enantiomer of pioglitazone that lacks PPAR-γ activity, which causes weight gain, but retains nongenomic target activities (mitochondrial pyruvate carrier and acyl–coenzyme A synthetase 4 inhibition). Recently, results from DESTINY-1, a phase 2, placebo-controlled, dose-ranging, efficacy clinical trial, demonstrated that PXL065 was associated with a significant reduction in hepatic fat content at 36 weeks at all doses of PXL065 (primary endpoint). In addition, among the 92 patients in the study, at least 1-stage fibrosis improvement on histology occurred in 40% (with 7.5 mg), 50% (with 15 mg; P=.06), and 35% (with 22.5 mg) vs 17% for placebo. Up to 50% of PXL065-treated patients achieved at least a 2-point NAS improvement without fibrosis worsening vs 30% with placebo. In addition, favorable trends in noninvasive assessments of liver fibrosis and metabolic parameters were observed without significant adverse effects such as weight gain and edema as seen with pioglitazone.[61]

Antifibrotic Agents

Galectins are carbohydrate-binding proteins that are increased in inflammation, fibrosis, and cancer.[62,63] Galectin-3, which is secreted mainly by macrophages, binds

carbohydrates on the surface of cells and exerts both intracellular (anti-apoptotic, macrophage differentiation) and extracellular (chemokinetic/chemotactic factors) effects that are important in liver fibrosis.[64] Increased galectin-3 expression also activates myofibroblasts. Belapectin (Galectin Therapeutics) is a galectin-3 inhibitor that was safe and well tolerated in mice models and led to significant reductions in liver fibrosis and portal hypertension.[65] In a phase 2b clinical study, biweekly infusions of belapectin were not associated with significant reductions in portal hypertension or liver fibrosis but did prevent the development of esophageal varices in a subgroup of patients without esophageal varices at baseline.[21] The phase 2b/3 clinical study NAVIGATE (NCT04365868) is currently being performed to evaluate the efficacy of belapectin in the prevention of esophageal varices in patients with NASH cirrhosis.

Combination Therapies

Given the heterogeneity of NASH with potentially multiple drivers of disease pathogenesis, 2 or more drugs may be needed to synergistically increase the efficacy of individual therapies. In addition, combination therapies can be leveraged to offset and/or reduce side effects.

Combinations for Improving Efficacy

The ATLAS phase 2b trial assessed the safety and tolerability of firsocostat, selonsertib, and cilofexor (an FXR agonist), administered alone or in combination, in patients with NASH and bridging fibrosis or compensated cirrhosis (F3 or F4 fibrosis). The primary endpoints included the proportion of patients with at least 1-stage improvement in fibrosis without worsening of NASH at 48 weeks based upon liver biopsy as well as the rate of adverse events and laboratory abnormalities. Although there was a trend toward reduced fibrosis with the combination of firsocostat and cilofexor, it did not meet statistical significance. Post hoc machine learning–based pathologic assessment suggests some fibrosis regression. This combination also resulted in a higher proportion of patients with a greater than 1-point reduction in NAS, improved liver enzymes, decreased ELF score, and decreased liver stiffness (via vibration-controlled transient elastography). An increase in both LDL cholesterol and triglycerides was seen, consistent with the mechanisms of action of cilofexor and firsocostat, respectively.[22]

The TANDEM study, a phase 2b clinical trial evaluating the safety and efficacy of tropifexor and cenicriviroc, is currently underway in patients with NASH and fibrosis (F2-F3).[66]

Other ongoing studies evaluating combination therapy include the ELIVATE study, which is evaluating tropifexor with licogliflozin (a sodium-glucose cotransporter 2 inhibitor) (NCT04065841), as well as a phase 2 study on semaglutide, cilofexor, and firsocostat (NCT03987074). Similarly, the DUET study is being conducted to evaluate the efficacy of the THR-β agonist TERN-501 alone and in combination with the FXR agonist TERN-101 to reduce hepatic fat content, as measured by MRI-PDFF, in patients with noncirrhotic NASH (NCT05415722).

Combinations for Reducing Side Effects

LDL cholesterol elevation is a common adverse effect associated with FXR agonists such as OCA and FGF19 analogs, as FGF19 is downstream of FXR agonism. Given that the leading cause of death in patients with NASH is cardiovascular disease, this has raised some theoretical long-term concerns. After 4 weeks of treatment with OCA, the addition of atorvastatin reduced LDL cholesterol below baseline values in the CONTROL study.[67] Similarly, ACC inhibitors have been associated with hypertriglyceridemia.[68] In a phase 2 study, the administration of fenofibrate 2 weeks before the addition of firsocostat in patients with advanced fibrosis owing to NASH prevented increase in triglycerides and improved hepatic fat and liver biochemistry.[69]

Conclusion

The burden of NAFLD/NASH continues to increase and NASH is a leading cause of liver transplant and HCC in the United States. Despite this growing health care issue, no drugs have yet been approved by the US Food and Drug Administration (FDA) for NASH. However, several drugs are currently being studied in phase 2/3 clinical trials. Owing to its complex and heterogenous nature, there are multiple aspects of the pathogenic pathway of NAFLD/NASH that drugs can attempt to target. This article provides an overview of drugs that have failed but led to important insights and lessons learned, ongoing phase 2 and 3 clinical trials, and preliminary results where available. While recent news from the FDA advisory committee on the accelerated approval of OCA was disappointing, we await a final decision from the FDA. *[Editor's Note: As we were going to press, the FDA rejected accelerated approval for OCA.]* Optimism remains for resmetirom given its favorable safety profile and efficacy on fibrosis improvement. The approval of at least 1 NASH therapeutic will be a critical advance for the field, as the bar will be set and provide a road map for additional therapies. Given NASH heterogeneity, no one drug will work for all patients, so having a rich pipeline will allow for a personalized approach and optimal patient care.

Disclosures

Dr Nathani has no relevant conflicts of interest to disclose. Dr Bansal serves/served as a consultant for The Kinetix Group, Madrigal Pharmaceuticals, Pfizer, Myovant, Theratechnologies, Fibronostics, Intercept Pharmaceuticals, and Novo Nordisk. She receives grant funding from the National Institutes of Health, National Institute for Occupational Safety and Health/Centers for Disease Control and Prevention, Pfizer, The Kinetix Group, and HistoIndex.

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