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Review

Pharmacological advances in the treatment of nonalcoholic fatty liver diseases : focused on global results of randomized controlled trials

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Nonalcoholic fatty liver disease (NAFLD) is the most common cause of liver disease globally, and its prevalence is rapidly increasing. Nonalcoholic steatohepatitis (NASH), a progressive form of NAFLD, is characterized by hepatocellular injury, inflammation, and fibrosis. Patients with NASH or severe fibrosis should be treated according to international NAFLD guidelines. Currently, regulatory agencies have not approved any pharmaceutical treatment for NAFLD. Vitamin E and pioglitazone are efficacious for NASH resolution; however, their benefits must be weighed against the reported risks. In a phase 2 trial, a glucagon-like peptide-1 agonist commonly used for diabetes and obesity was found to improve liver histology in patients with NASH. Furthermore, therapeutic agents targeting NASH pathogenesis, including bile acid signaling, insulin resistance, and lipid metabolism, are in various phases of clinical development. In this article, we review the benefits and drawbacks of current pharmacotherapy and the efficacy of upcoming treatments for NASH. **(Clin Mol Hepatol 2023;29(Suppl):S268-S275)**

Keywords: Nonalcoholic fatty liver disease; Nonalcoholic steatohepatitis; Treatment; Drugs; Clinical trials

INTRODUCTION

Nonalcoholic fatty liver disease (NAFLD) affects approximately one-quarter of the adult population worldwide, making it the most common liver disease.[1] Nonalcoholic steatohepatitis (NASH), the progressive form of NAFLD, is characterized by hepatic triglyceride accumulation, hepatocyte injury, and lobular inflammation.[2] NASH is associated with accelerated fibrosis progression to cirrhosis and increased morbidity and mortality from liver disease.[3] More than 20% of patients with NASH will develop cirrhosis during their lifespan.[4] NASH is the leading indication for liver transplant in the United States,[5] and it is expected to become the most common cause of hepatocellular carcinoma in developed countries.[6]

Patients with NAFLD should be encouraged to lose weight by following a hypocaloric diet and engaging in physical activity.[2,7] In patients with NASH who are overweight or obese, more than 10% of weight loss due to lifestyle modification is associated with NASH resolution and fibrosis regression.[8,9] Weight loss also leads to a reduction of liver fat content in non-obese patients with NAFLD.[10] However, only a small percentage of patients achieve substantial weight loss, and long-term lifestyle changes are difficult to implement.[8,11] Therefore, patients with NASH require a practical therapeutic approach.

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Currently, there are no licensed drugs specifically approved for the treatment of NASH. In clinical practice, vitamin E and pioglitazone are efficacious for biopsy-proven NASH.[12] Furthermore, glucagon-like peptide 1 (GLP-1) agonists, which are commonly prescribed medications for diabetes and obesity, have the potential to ameliorate NASH.[13] The field of NASH treatment is rapidly evolving owing to the rising disease incidence and scarcity of current treatment options. Because the underlying mechanism of NASH is complex, NASH treatments are being developed for a wide range of targets, including oxidative stress, insulin resistance, apoptosis, bile acids, lipid metabolism, and hepatic inflammation and fibrosis. In this article, we review and summarize the efficacy and safety of current treatment options, based primarily on representative data from randomized controlled trials (RCTs), as well as emerging therapies that may enter clinical practice in the future.

CURRENT PHARMACOLOGIC THERAPIES

Vitamin E (alpha-tocopherol)

The imbalance between the reactive oxygen species' production and scavenging capacity causes oxidative stress.[14] Excess hepatic lipid causes reactive oxygen species over-production, accelerating the transition from NAFLD to NASH.[14] Vitamin E shows antioxidant properties by increasing specific enzymes and anti-fibrotic actions by regulating the inflammatory response.[15] In phase 3 PIVENS trial, patients with NASH without diabetes who received high dose vitamin E (800 IU/day; n=84) for 96 weeks showed a more statistically significant histological improvement, defined as ≥2 point reduction in the NAFLD activity score, than the placebo group (n=83) (43% vs. 19%).[12] The proportion of NASH resolution in the vitamin E group was also higher (36% vs. 21%). Recent prospective trials involving patients with NASH and diabetes, found that a combination treatment of vitamin E (800 IU/day) and pioglitazone is more efficacious than a placebo in terms of NASH resolution and steatosis improvement.[16] No prospective randomized studies have reported improved liver fibrosis and reduced liver-related death.[16] The international NAFLD guidelines suggest vitamin E supplementation for patients with NASH without diabetes (Table 1).[2,7,17] Unfortunately, although controversial, long-term administration of vitamin E is likely to raise the incidence of prostate cancer and hemorrhagic stroke.[18]

Pioglitazone

Pioglitazone, a peroxisome proliferator-activated receptor (PPAR)-γ agonist, reduces insulin resistance in the adipose tissue, muscle, and liver. Several prospective trials reported that patients with or without diabetes who received pioglitazone

Table 1. Summary of current NASH medications recommended by international guidelines

Drugs	Mechanism	Population	Guidelines (level of recommendation)
Vitamin E	Anti-oxidant	Non-diabetic patients with biopsy-proven NASH	AASLD 2018* EASL 2016 (B2) KASL 2021 (B1) AACE 2022 (Grade B, high strength of evidence)
Pioglitazone	PPAR-γ agonist	Diabetic patients with biopsy- proven NASH	AASLD 2018* EASL 2016 (B2) KASL 2021 (B1) AACE 2022 (Grade A, high strength of evidence)

NASH, nonalcoholic steatohepatitis; PPAR, peroxisome proliferator-activated receptor; AASLD, American Association for the Study of Liver Diseases; EASL, European Association for the Study of the Liver; KASL, Korean Association for the Study of the Liver; AACE, American Association of Clinical Endocrinology.
*The level and length of recommendations were not presented in the AASLD guidance 2018.

Abbreviations:

NAFLD, nonalcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis; GLP-1, glucagon-like peptide 1; RCTs, randomized controlled trials; PPAR, peroxisome proliferator-activated receptor; SAF, steatosis, activity, fibrosis; THR-β, thyroid hormone receptor beta; MRI, magnetic resonance imaging; ASK1, apoptosis-signal regulating kinase 1; MAPK, mitogen-activated protein kinase

(30 or 45 mg/day) showed more histological improvement in NASH than those who received placebo.[12,19,20] Cusi et al.[21] conducted a single-center study in which patients with prediabetes/diabetes and histologically confirmed NASH were randomly administered either pioglitazone (45 mg/day; n=50) or placebo (n=51). Pioglitazone treatment reduced NAFLD activity score by at least 2 points (58% vs. 17%) and resolved NASH (51% vs. 19%). A meta-analysis of eight RCTs found pioglitazone is efficacious for NASH resolution (odds ratio [OR] 3.22), improvement of advanced fibrosis (OR 3.15), and reversal of fibrosis (OR 1.66).[22] Thus, regardless of the diabetes status, pioglitazone is indicated for biopsy-proven patients with NASH (Table 1).[2,7,17] It is important to note that weight gain, fluid retention, and increased risk of fracture and bladder cancer are side effects of pioglitazone.

GLP-1 agonists

GLP-1 agonists affect glucose regulation by enhancing glucose-dependent insulin release, suppressing postprandial glucagon levels, and slowing gastric emptying. GLP-1 agonist is the mainstay treatment of obesity and diabetes because of their significant therapeutic benefits in weight loss, glycemic control, and improvements in the cardiometabolic system.[23] Although the underlying mechanisms of GLP-1 agonists on NASH have not been fully explained, considerable weight loss induced by GLP-1 agonists may lead to subsequent disease improvement. A phase 2 RCT with 320 biopsy-confirmed patients with NASH found that the semaglutide group (0.4 mg once daily for 72 weeks) had a higher proportion of disease resolution than the placebo group (59% vs. 17%).[24] Even though the treatment group had a lower rate of liver fibrosis progression (4.9% vs. 18.8%), there were no significant differences in the proportion of patients whose fibrosis stage improved. The American Association of Clinical Endocrinology guidelines recommend the use of GLP-1 agonist in patients with histology-proven NASH and diabetes.[17] A phase 3 ESSENCE trial involving 1,200 patients with NASH and F2-F3 fibrosis is currently investigating the efficacy of semaglutide at a dose of 2.4 mg once-weekly for NASH resolution and fibrosis improvement (NCT04822181; Table 2). The most common side effects among patients that receive GLP-1 agonist are gastrointestinal symptoms, such as nausea, vomiting, and diarrhea. GLP-1 agonists may increase the risk of acute pancreatitis, gallbladder disease, and biliary disease. Although GLP-1 agonists are currently used as subcutaneous injections in clinical protocols, oral formulations with improved tolerability are being developed.

Recently, advances have been made in developing glucagon-containing co-agonists to enhance the efficacy of GLP-1 agonists. A glucagon-stimulated increase in energy expenditure augments the effect of GLP-1-induced weight loss.[25] Cotadutide is a dual-receptor agonist with balanced GLP-1 and glucagon action. In phase 2 PROXYMO trial, 74 obese patients with biopsy-proven NASH and F1-F3 fibrosis were randomized to receive once-daily subcutaneous injections of cotadutide (300 μg or 600 μg) or placebo.[26] Cotadutide was associated with dose-dependent reductions in hepatic fat compared to the placebo. In the ongoing phase 3 PROXYMO-ADV trial, cotadutide is expected to show efficacy in treating NASH (Table 2).

FUTURE PHARMACOLOGIC THERAPIES

Obeticholic acid

The farnesoid X receptor is a nuclear receptor activated by bile acids that is abundant in the liver and intestines. It regulates bile synthesis, conjugation, and transport,[27,28] and plays a role in lipid and glucose metabolism.[28] The farnesoid X receptor activation can help reduce hepatic inflammation and fibrosis.[29,30]

Obeticholic acid is a potent and selective farnesoid X receptor agonist. In the interim analysis of phase 3 REGENERATE trial, 931 biopsy-proven patients with NASH and fibrosis stages F2-F3 were randomly assigned to receive obeticholic acid 25 mg daily (n=308), obeticholic acid 10 mg daily (n=312), or placebo (n=311) (Table 2).[31] At 18 months, the obeticholic acid group improved liver fibrosis by at least one stage with no worsening of NASH in a dose-dependent manner (23% vs. 18% vs. 12%, respectively), with no difference in the proportion of NASH resolution (12% vs. 11% vs. 8%, respectively). Indeed, in NASH phase 3 trials, obeticholic acid was the first agent to show a significant improvement in fibrosis. Mild to moderate pruritus was the most common adverse event, affecting up to 51% of patients treated with obeticholic acid 25 mg. Furthermore, nearly 17% of the obeticholic acid group experienced an early increase in low-density lipoprotein cholesterol, which returned to baseline

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Table 2. Current status of emerging drugs from phase 3 clinical trials of nonalcoholic steatohepatitis

Drug	Target	Population	Study name	Status
Obeticholic acid	Farnesoid X receptor agonist	NASH with F2-F3 fibrosis	REGENERATE	Ongoing
Lanifibranor	Pan-PPAR agonist	NASH with F2-F3 fibrosis	NATiV3	Ongoing
Resmetirom	Thyroid hormone receptor-beta agonist	NASH with F1-F3 fibrosis	MAESTRO-NASH	Ongoing
Semaglutide	Glucagon-like peptide-1 (GLP-1) agonist	NASH with F2-F3 fibrosis	ESSENCE	Ongoing
Cotadutide	dual GLP-1 and glucagon receptor agonist	NASH with F2-F3 fibrosis	PROXYMO-ADV	Ongoing
Obeticholic acid	Farnesoid X receptor agonist	NASH with compensated LC	REVERSE	Halted
Elafibranor	PPAR-alpha and -delta agonist	NASH with F1-F3 fibrosis	RESOLVE-IT	Halted
Selonsertib	Apoptosis signal-regulating kinase inhibitor	NASH with F3 fibrosis	STELLAR-3	Halted
Selonsertib	Apoptosis signal-regulating kinase inhibitor	NASH with compensated LC	STELLAR-4	Halted
Cenicriviroc	Inhibitor of CC chemokine receptors 2 and 5	NASH with F2-F3 fibrosis	AURORA	Halted
Aramchol	Fatty acid bile acid conjugate	NASH with F1-F3 fibrosis	ARMOR	Suspended*

PPAR, peroxisome proliferator-activated receptor; NASH, nonalcoholic steatohepatitis; LC, liver cirrhosis.
*Starting the double-blind part of phase 3 trial is delayed due to the formulation of Aramchol Meglumine.

levels at the end of the study. In contrast, in the recent REVERSE trials of 919 randomized patients with compensated NASH cirrhosis, obeticholic acid did not improve fibrosis (11.1% vs. 11.9% vs. 9.9% in obeticholic acid 10 mg vs. obeticholic acid 10 mg titrated to 25 mg vs. placebo, respectively).[32] The US Food and Drug Administration has not yet approved obeticholic acid as a NASH treatment due to its uncertain long-term benefit and safety risks.

pan-PPAR agonist

PPARs are a nuclear receptor family with three isotypes that regulate glucose and lipid metabolism, inflammatory cell activation, and fibrotic processes.[33] Three PPAR isotypes have been identified: PPAR-α, PPAR-β/δ, and PPAR-γ. PPAR-α is an essential regulator of fatty acid oxidation that suppresses inflammation by reducing reactive oxygen species formation. PPAR-β/δ stimulates hepatic glucose utilization and *de novo* lipogenesis. PPAR-γ regulates adipocyte differentiation and insulin sensitization.

Lanifibranor (IVA337), a pan-PPAR agonist, demonstrated higher efficacy in terms of improvement of insulin sensitivity, macrophage activation, and reduction of liver fibrosis than single or dual PPAR agonists.[34,35] In 2021, the results of phase 2b trials comparing lanifibranor 1,200 mg (n=83), lanifibranor 800 mg (n=83), or placebo (n=81) for 24 weeks in patients with biopsy-proven NASH were published.[36] The proportion of patients who met the primary endpoint, a decrease of at least 2 points in the SAF-activity score (the activity component of the Steatosis, Activity, Fibrosis [SAF] scoring system that includes hepatocytes ballooning and inflammation), was higher among those who received lanifibranor 1,200 mg than the placebo group (55% vs. 33%). The outcomes favored lanifibranor 1,200 mg over placebo for improvement in the fibrosis stage of at least one without worsening of NASH (48% vs. 29%). Fewer than 10% of patients in the lanifibranor group reported diarrhea, weight gain, and peripheral edema as common adverse effects. An ongoing phase 3 study of lanifibranor for NASH and F2-F3 fibrosis (NATiV3) is also expected to reveal similar results (Table 2).

In contrast, a phase 3 RCT of the dual PPARα–PPARδ agonist elafibranor (RESOLVE- IT) was halted because it failed to meet the predefined primary surrogate efficacy endpoint, NASH resolution without fibrosis worsening the interim analysis.[37]

Thyroid hormone receptor β-agonist

The thyroid hormone regulates glucose and lipid metabolism, in addition to fatty acids oxidation.[38,39] A selective thyroid hormone receptor beta (THR-β) agonist has been developed to improve liver-specific action while minimizing negative effects on the cardiac and skeletal systems, which are predominantly mediated by THR alpha. Resmetirom, an oral THR-β agonist, was studied in a phase 2 RCT involving 125 overweight or obese adults with biopsy-confirmed NASH

and stages 1–3 fibrosis.[40] Resmetirom treatment for 36 weeks resulted in a significant reduction in hepatic fat measured using magnetic resonance imaging (MRI)-proton density fat fraction compared with placebo (-37% vs. -9%). An ongoing phase 3 MAESTRO-NAFLD1 trial is evaluating the impact of resmetirom on liver histology in patients with NASH and stage 2–3 fibrosis (Table 2). The preliminary results showed that resmetirom was efficacious for hepatic fat assessed using MRI-proton density fat fraction.[41] The most prevalent side effects were mild gastrointestinal symptoms, including diarrhea and nausea.

Selonsertib

Apoptosis-signal regulating kinase 1 (ASK1) is a member of the mitogen-activated protein kinase (MAPK) family.[42] ASK1 is activated in response to oxidative stress and promotes hepatic inflammation and apoptosis, leading to liver fibrogenesis via MAPK downstream signaling. Hence, ASK1 is considered a treatment target for NASH.[43] Selonsertib is a first-in-class small-molecule ASK1 inhibitor with antifibrotic and anti-inflammatory effects. Based on the success in phase 2 trials of selonsertib in patients with NASH and F2-F3 fibrosis,[44] phase 3 RCTs comparing selonsertib 18 mg, selonsertib 6 mg, and placebo were subsequently conducted in patients with NASH and bridging fibrosis (F3, STELLAR-3; n=802) or compensated cirrhosis (F4, STELLAR-4; n=877) (Table 2).[45] The STELLAR-3 trial did not reveal significantly different fibrosis improvement without worsening of NASH between groups (10% vs. 12% vs. 13%, respectively). Moreover, fibrosis improvement was not observed in STELLAR-4 patients with cirrhosis (14% vs. 13% vs. 13%, respectively). In phase 2b ATLAS trial with 392 patients with NASH and F3-F4 fibrosis, selonsertib combination therapy revealed unfavorable outcomes in reversing fibrosis.[46] Although selonsertib is no longer being investigated, ASK1 may still be a viable candidate if more effective inhibitors are discovered.

Other NASH therapies in clinical trials

The novel medications that have entered phase 3 development stage include armachol (a bile acid and fatty acid analog)[47] and cenicriviroc (inhibitor of CC chemokine receptors 2 and 5) (Table 2).[48] Moreover, a large number of additional agents with diverse mechanisms for targeting the pathogenesis of NASH are in phase 2 development.[49]

CONCLUSIONS

Since the PIVENS study with vitamin E and pioglitazone on NASH resolution was successful in 2010, NASH has been extensively investigated to identify optimal medications. Large-scale RCTs have yielded promising results for farnesoid X receptor, GLP-1, and pan-PPAR agonists in improving hepatic inflammation and fibrosis. However, several obstacles must be overcome before they are approved by the US Food and Drug Administration for NASH treatment: 1) while liver biopsy remains the gold standard for diagnosis in clinical trials, further studies are needed to develop easy-to-use panels of serum and imaging-based biomarkers for noninvasive patient selection and treatment response; 2) given the complex pathophysiology of NASH and modest treatment response rates to individual drugs, it is highly likely that a combination treatment will also be required; and 3) the external validity of the RCT results should be confirmed, especially for real-world patients with NASH with more significant comorbidities. We believe that numerous drugs added to the pipeline of novel therapies could increase the chances of successful treatment of NASH and more completely reverse disease progression in affected patients in the future.

Authors' contribution

Study concept and design: Jihyun An and Joo Hyun Sohn; Data analysis and interpretation: Jihyun An and Joo Hyun Sohn; Wrote the paper: Jihyun An and Joo Hyun Sohn; All authors have read and approved the final version of the manuscript.

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Conflicts of Interest

The authors have no conflicts to disclose.

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