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Emerging targets for therapy in ALD: Lessons from NASH

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Abstract

Alcohol-associated liver disease due to harmful alcohol use and NAFLD associated with metabolic syndrome are the 2 most common liver diseases worldwide. Control of respective risk factors is the cornerstone in the long-term management of these diseases. Furthermore, there are no effective therapies. Both diseases are characterized by metabolic derangements; thus, the focus of this review was to broaden our understanding of metabolic targets investigated in NAFLD, and how these can be applied to alcohol-associated liver disease. Conserved pathogenic pathways such as dysregulated lipid metabolism, cell death pathways including apoptosis and activation of innate immune cells, and stellate cells mediate both alcohol and NAFLDs, resulting in histological abnormalities of steatosis, inflammation, fibrosis, and cirrhosis. However, pathways such as gut microbiome changes, glucose metabolism and insulin resistance, inflammatory signaling, and microRNA abnormalities are distinct in these 2 diseases. In this review article, we describe conserved and distinct pathogenic pathways highlighting therapeutic targets that may be of potential in both diseases and those that are unique to each disease.

INTRODUCTION

Hepatic steatosis, or fatty liver, is the most common liver disease worldwide. The 2 most common etiologies of fatty liver are alcohol-associated liver disease (ALD) and NAFLD.[1,2] In the general US population, ~7%–10% engage in harmful alcohol use and 30%–40% are overweight or obese, which is the most common component of metabolic syndrome and the predominant risk factor for NAFLD.[3,4] With the current US population of about 330 million, it is estimated that there are about 10 million overweight or obese individuals with harmful alcohol use.

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CONFLICTS OF INTEREST

Ashwani K. Singal consults for Pleiogenix Pharma. He advises Durect. Vijay H. Shah consults for Durect Corporation, GENFIT, Korro Bio Inc., and Seal Rock Therapeutics Inc. He advises Akaza Bioscience Ltd, AgomAb Therapeutics, Intercept Pharmaceuticals Inc., Mallinckrodt Pharmaceuticals, Resolution Therapeutics Ltd, and Surrozen. Harmeet Malhi has no conflicts to report.

ALD and NAFLD are heterogeneous diseases, with the disease spectrum ranging from steatosis to progressive steatohepatitis, with or without fibrosis, to end-stage liver disease of cirrhosis and its complications. Alcoholic hepatitis (AH) is a unique clinical syndrome in patients with ALD and is characterized by acute onset of severe liver inflammation, potential for high short-term mortality of up to 80% in most severe forms, and acute-on-chronic liver failure with antecedent failure of multiple organs.

The earliest histological and imaging abnormality in either ALD or NAFLD is steatosis. Due to the conserved nature of lipid metabolic pathways, it is not surprising that the pathways that lead to steatosis demonstrate the most overlap between ALD and NAFLD. Nutrient overload mediates metabolic abnormalities and steatosis in NAFLD, whereas in ALD, these abnormalities are mediated by the direct effect of alcohol on the liver tissue or through real or functional deficiencies. In addition, harmful alcohol use mediates direct toxicity to the liver through its metabolism in hepatocytes releasing reactive oxygen species.[5] In NAFLD, direct lipotoxicity of certain lipid species plays a greater role.[6] Liver injury and inflammation are furthered by indirect effects of the gut-liver axis, gut microbiome, intestinal permeability, and innate immune cells.[7] Furthermore, AH is a unique phenotype in ALD and is not seen in patients with NAFLD, where the same pathways mediate the disease pathogenesis, and neutrophils are the major cell type mediating hepatic and systemic inflammation (Figure 1). In contrast, there are distinct changes in the gut microbiome, gut-liver axis, and macrophage-mediated inflammation, which characterize progressive NAFLD (Figure 2).[6,8,9] NAFLD is not a severe illness and is pathophysiologically distinct from AH; therefore, throughout this review, as we extrapolate NAFLD therapies to ALD, the term ALD will be used to refer to the less severe form of alcohol-induced liver disease and exclude AH.

Over the last decade, several therapeutic targets have been identified and tested in phase 2 and 3 studies for both ALD and NAFLD. However, none of these have met endpoints for Food and Drug Administration (FDA) approval for use in routine clinical practice.[10,11] Of several ongoing or completed phase 2 and 3 clinical trials among patients with NASH, several but not all the drugs may have benefit in ALD with the potential of being examined among patients with ALD (Table 1). Throughout this article, we will briefly describe the available preclinical data in an animal model of ALD for the specific target/s, strongly justifying their assessment in clinical trials on patients with ALD. Although FDA-approved surrogate endpoints exist for NAFLD trials, in ALD and AH clinical trials, there is a significant unmet need to develop regulatory endpoints. Past trials in AH have relied on clinical prognostic scores and mortality in severe AH.[34] However, there exists an opportunity to define patient stratification and relevant endpoints in both patients with ALD and those with AH.

PATHOPHYSIOLOGICAL MECHANISMS

Lipid metabolism

Hepatic steatosis—A common and initial pathology in ALD and NAFLD is defined as > 5% of hepatocytes containing fat droplets.[5,35] Hepatic steatosis in NAFLD is multifactorial, arising from increased free fatty acid flux from adipose tissue lipolysis

due to systemic insulin resistance, diet-derived free fatty acids, and *de novo* lipogenesis (Figure 3). In contrast, alcohol mediates hepatic steatosis and abnormalities in lipid metabolism through several pathways: (a) increase in NADH-to-NAD ratio through its metabolism, impairing mitochondrial beta-oxidation of fatty acids; (b) inducing master regulators of *de novo* lipogenesis (SREBP-1c, ChREBP, and PPAR-γ); (c) increased adipose tissue lipolysis, leading to greater delivery and influx of free fatty acids into hepatocytes; (d) increased expression of the fatty acid transporter, CD36; (e) inhibition of AMPK, a regulator of metabolism in cells and inhibitor of lipogenesis; (f) suppression of peroxisome proliferator–activated receptor α (PPARα) activity; (g) impaired assembly and secretion of VLDL particles; and (h) intersection with lipid droplet proteins, variants of which influence susceptibility and progression of ALD.[36,37] Furthermore, alcohol leads to qualitative and quantitative changes in the content of complex lipids in hepatocytes. For example, the activity of sphingomyelinases has been shown to be increased up to 3-fold in humans in response to chronic alcohol use and declined within 1 week of abstinence from alcohol.[38,39] A similar finding of increased sphingomyelinase activity was shown in rodent models after exposure to alcohol,[40] and this effect was blunted in animals pretreated with N-acetylcysteine, suggesting a role of oxidative stress as a mechanism of activation of sphingomyelinase.[41] In another study, sphingomyelinase-knockout mice were resistant to alcohol-mediated fatty liver and apoptosis.[42] Furthermore, alcohol increases the accumulation of ceramides and sphingolipids by increasing the activity of serine palmitoyltransferase, the rate-limiting step in sphingolipid biosynthesis and of ceramide synthase.[43,44] Of the 3 types of ceramide synthases (1, 5, and 6), subtype 6 is the most relevant in the development of alcohol-associated fatty liver, with increased activity in zone 3 hepatocytes in both experimental as well as subjects with alcohol-associated steatosis.[44]

Fatty acids—Hepatocyte fat content is a balance between influx of free fatty acids (import from peripheral tissues due to lipolysis and *de novo* lipogenesis from ingested sugars and proteins) and their use through fatty acid oxidation. *De novo* lipogenesis contributes significantly to hepatic steatosis in both conditions. *De novo* lipogenesis involves 3 key enzymes, acetyl-CoA carboxylase (ACC), which converts acetyl-CoA to malonyl-CoA; fatty acid synthase, which converts malonyl-CoA to long-chain fatty acids; and stearoyl-CoA desaturase 1, which catalyzes the synthesis of monounsaturated fatty acids.[6] Lipogenesis is regulated by SREBP-1c activity with ACC being the rate-limiting enzyme, and fatty acid oxidation is regulated by the nuclear receptors PPAR-α and PPAR-δ, with the mitochondrial carnitine palmitoyltransferase being the rate-limiting enzyme.[36]

Neutral and complex lipids—Fatty acids are stored as simple lipids (ester linkage bond with alcohols like glycerol to form triglyceride) or complex lipids (ester linkage bond with phospholipids or sphingolipids). Present in plasma and cell membranes, sphingolipids comprise 10%–20% of membrane lipids and support specific membrane functions.[45] These complex lipids can be synthesized *de novo* in all cells, starting with the conjugation of amino acid serine and fatty acid palmitoyl CoA. Ceramides, a special class of sphingolipids are generated in the cells from dihydroceramide through the activity of dihydroceramide desaturase 1, from sphingomyelin through hydrolytic activity of sphingomyelinase, or as

a result of acylation of sphingosine through ceramide synthase. The ceramide content is regulated within the cell by its conversion to sphingosine through ceramidases.

Ceramides can directly result in endoplasmic reticulum stress and mitochondrial dysfunction.[46] Phospholipids are also altered in ALD due to choline deficiency and decreased activity of phosphatidylethanolamine methyltransferase, which results in reduced conversion of phosphatidylethanolamine to phosphatidylcholine.[47] Decreased phosphatidylcholine to phosphatidylethanolamine ratio results in decreased export of fatty acids, leading to aggravation of steatosis and steatohepatitis. Phosphatidylcholine administration reduced fibrosis in a baboon model of ALD,[48] and betaine supplementation improved the activity of phosphatidylethanolamine methyltransferase in a mouse model with attenuation of steatosis.[49]

Glucose metabolism and insulin resistance

Insulin resistance is a central pathway in NAFLD, but the data on its role in ALD are scanty and emerging. Apart from inflammation, cell death, and oxidative stress, abnormalities in lipid metabolism and hepatic lipids also mediate insulin resistance (Figure 3). For example, ceramides can result in impaired insulin signaling and beta-oxidation of fatty acids through inhibition of serine-threonine kinase, a critical enzyme for intracellular effects of insulin.[50,51] This is achieved by ceramide-induced activation of protein kinase C, which phosphorylates and inhibits translocation of Akt/PKB, and by activation of protein phosphatase 2A, which is needed for dephosphorylation of Akt/PKB.[52]

Gut-liver axis and bile acid metabolism

Gut microbes include 10^{14} cells, including bacteria, fungi, viruses, archaea, and protozoa. The bacterial microbiome in healthy humans is dominated by beneficial bacterial phyla such as *Bacteroides* and *Firmicutes*, and a smaller proportion consists of *Proteobacteria*, *Actinobacteria*, and *Verrucomicrobia*.[53] The gut bacterial microbiome in patients with liver disease is characterized by dysbiosis, with an increase in harmful and a decrease in beneficial bacteria, and this abnormality worsens with an increase in disease severity and is also associated with liver and patient-related outcomes.[54] Mechanistically, recent studies have identified excess alcohol production by *Klebsiella pneumoniae* as a driver of hepatic steatosis in NAFLD.[55] Generation of shortchain fatty acids, which can serve as a substrate for *de novo* lipogenesis; decrease in expression of tight junction proteins; and regulation of food intake and energy expenditure by endocannabinoid signaling and gut hormones are additional effects of microbial metabolites in NAFLD. Altered bile acid metabolism is also associated with both ALD and NAFLD and has provided therapeutic opportunities.

Farnesoid X receptor (FXR) is a nuclear receptor that regulates cholesterol and bile acid metabolism. FXR can also be activated by FGF family members, especially by FGF-19 (FGF-15 in mice) subfamily.[56] FGF-19, expressed in ileal enterocytes reaches the liver through portal vein to activate the FGF4 membrane receptor, resulting in the inhibition of the rate-limiting enzyme CYP7A1 in the conversion of cholesterol to primary bile acids (cholic acid and chenodeoxycholic acid), with an upregulation of bile acid exporters at the biliary canaliculi and at the basolateral surface of enterocytes (Ost alpha-beta heterodimer).[56]

FGF-21, another member of the FGF-19 subfamily, is synthesized in the liver and other extrahepatic tissues and activates FGF3 membrane receptor, leading to physiological effects of FXR activation.[56]

Hepatic inflammation and cell injury

Lipotoxicity—Mitochondrial dysfunction, endoplasmic reticulum stress, lysosomal membrane permeabilization, hepatocyte injury with apoptosis and other forms of cell death, inflammation, and the recruitment and proinflammatory activation of macrophages, are some of the recognized mechanisms of free fatty acid–induced lipotoxicity.[35] Although, lipotoxicity is well described and studied in NAFLD,[35] it also plays a role in ALD, as free fatty acids are elevated in liver biopsy samples from patients with ALD.[57] For example, preclinical data have shown a shift of intrahepatic fatty acids from saturated to unsaturated fatty acids,[58] with a benefit of saturated fatty acid diet in ameliorating ALD pathology in a mice model of ALD.[59]

Immune cells—Macrophages, neutrophils, and T cells are most studied in the context of NAFLD and ALD as key mediators of the inflammation associated with each disease. Death of resident macrophages (KCs) along with chemokines and cytokines creates an empty niche and a mechanism for the recruitment of monocyte-derived macrophages into the liver. These monocyte-derived macrophages contribute to the infiltration proinflammatory macrophages and restore the KC pool.[60] In AH, there is an increase in circulating neutrophils, which infiltrate the hepatic parenchyma and contribute to inflammation. The role of neutrophils in the pathogenesis of NAFLD remains less well studied, though it has been suggested that neutrophil elastase may be a therapeutic target as it mediates insulin resistance in NAFLD.[61]

Extracellular vesicles and microRNAs (miRs)—Surrounded by a lipid bilayer and containing bioactive cargoes, extracellular vesicles are secreted by hepatocytes into the extracellular space and taken up by surrounding cells, thus mediating cross-talk with adjacent hepatocytes and other liver cells including HSCs.[62–64] Extracellular vesicles may also contain short noncoding RNAs or miRs, which can regulate the expression of genes related to immunity, inflammation, and regeneration. Measurable in serum, distinct EV cargo and miRs have been recognized in ALD and NAFLD.[51,65,66] For example, miRs 34a and 122 are elevated in NAFLD with respective target effects of reducing fatty acid oxidation and fibrogenesis.[36,67] Another miR, let7d, which physiologically regulates fatty acid oxidation is deceased in NAFLD. In contrast, miR-155 is increased in ALD and mainly targets TNF-α, resulting in the induction of LPS sensitization, toll-like receptor-4 activation, and inflammation.[68,69] ALD is also characterized by elevated levels of miR-217, resulting in reduced fatty acid oxidation.[70]

Adipokines—Circulating soluble levels of hormones, especially adiponectin, are increased in ALD, which is the opposite of the observed reduction noted in patients with NAFLD.[35,71,72] Increase in adiponectin levels in ALD is associated with changes in other hormones such as leptin, visfatin, resistin, and omentin, all affecting insulin signaling and steatosis.[72] For example, alcohol induces an increase in leptin levels similar to NAFLD and obesity,

which is also associated with an increase in leptin levels.[72,73] Leptin promotes HSC activation with inflammation of hepatocytes through TNF-α release from KCs and by the release of the chemokine CCL2 from HSCs.[73]

Apoptosis, pyroptosis, and ferroptosis—Cell death in ALD and NAFLD is linked to immune cell activation, and apoptosis is best studied in this regard. For example, a result of inflammatory signaling in ALD and NAFLD is activation of death receptors, leading to apoptosis,[74,75] mediated by death receptors especially TRAIL receptor 2.[76,77] Cross-talk between apoptotic bodies and immune cells leads to the formation of a proinflammatory loop. Other pathways mediating apoptosis are the activation of caspases and apoptosis signal-regulating kinase 1 enzyme, which results in the activation of JNK pathway.[78,79] Caspase 1 is also activated by inflammasomes in hepatocytes and inflammatory cells, mediating sterile inflammation, especially the release of IL-1β.[80,81] Pyroptotic cell death occurs following caspase 1–mediated cleavage of gasdermin, leading to the formation of plasma membrane pores and cell death. Due to its dependence on the inflammasome, which is known to be activated in NASH and ALD, pyroptotic cell death has been suggested to mediate NASH and may also play a role in ALD.[82] Cell-specific activation of the inflammasome, predominantly in KCs in ALD, and within the hepatocytes in NAFLD, may influence efficacy of caspase inhibitors or other drugs targeting this pathway.[36,80] Ferroptosis, iron-dependent cell death, has been implicated in NASH,[83] and may also play a role in alcohol-induced cell death.[84] Thus, many forms of cell death can trigger inflammation in NASH and correspondingly may play a role in ALD.

Hepatic fibrosis

The activation of HSCs is a key step in the development of fibrosis in any liver disease, including ALD and NAFLD.[85] TGF-β is a master regulator of fibrogenesis and is an important therapeutic target.[85] Cross-talk between the extracellular matrix and hepatic cells is a critical step in fibrogenesis. Integrins, which mediate this cross-talk, have attracted the attention as important targets of drug discovery targeting fibrosis. Lysyl oxidase is a family of 4 extracellular enzymes[1–4] that cross-link the collagen fibers and promote liver fibrosis. Other factors, such as sonic hedgehog released from inflamed and ballooned hepatocytes, upregulate the expression of TGF-β in HSCs.[85]

PHARMACOLOGICAL THERAPIES TAGETING METABOLISM

Therapies targeting lipid metabolism

Inhibitors of fatty acid synthesis—The various types of fat within hepatocytes are labile and change in response to intervention. AMP kinase agonists reduce *de novo* lipogenesis through inhibition of SREBP-1c, ChREBP, and ACC phosphorylation. Several AMP kinase agonists are in clinical trials. Resveratol, an agonist of AMP kinase, has shown protection from hepatic steatosis in an alcohol-fed mouse model.[86] Inhibiting ACC using firsocostat (ND-630 or GS-0976) in an animal model showed benefit in reducing hepatic steatosis.[87] In a phase 2b clinical trial, this drug reduced liver fat and levels of tissue inhibitor of metalloprotease-1, without improvement in aminotransferases or liver stiffness measurement.[88] Inhibition of ACC is also associated with enhanced beta-oxidation of fatty

acids, which results in the elevation of serum triglycerides. Similarly, fatty acid synthase can be targeted using its inhibitor TVB-2640.[14] SCD1 can be inhibited by fatty acid/bile acid conjugate 3beta-arachidyl-amido, 7alpha-12alpha-dihydroxy, 5beta-cholan-24-oic acid (aramchol), leading to improved hepatic steatosis and insulin sensitivity.[89] Based on the encouraging data with the use of aramchol in phase 2 studies,[13,90] a phase 3/4 clinical trial is ongoing in patients with NAFLD (NCT 04104321). Fatty acids are stored in the liver and adipose tissue and esterified into triglycerides. The last and committed steps in triglyceride synthesis are mediated by the enzymes acyl-CoA diacylglycerol acyltransferase-1 and 2. Its inhibition in a high-fat diet animal model has been shown to reduce hepatic steatosis.[91] To ameliorate the elevation of serum triglycerides, the inhibition of diacylglycerol acyltransferase-2 is being studied in combination with an ACC inhibitor in an ongoing phase 2 clinical trial (NCT04399538) (Table 2).

PPAR α/δ agonists—In a mouse model, PPAR agonists have shown benefit in reducing the development of steatosis in response to ethanol feeding.[92] PPAR agonists are also in phase 2 and 3 trials in NASH, suggesting that they may be worth investigating in human clinical trials of patients with ALD. Examples include saroglitazar (dual PPAR α/γ), pemafibrate (K-877), seladelpar (MBX-8025), elafibranor (dual PPAR α/δ), and lanifibranor (IVA337, pan-PPAR). In this regard, it is interesting to note that increasing fatty acid oxidation improves NASH, rather than pose oxidative stress, likely by shifting the excess or balance of residual fatty acids. PPARs also regulate immune cell types, which may play a role in the efficacy of these drugs in NASH and ALD.[93]

Thyroid hormone receptor β agonists—Thyroid hormone receptor β is expressed in hepatocytes and regulates lipid metabolism, among its pleiotropic effects. Examples of thyroid hormone receptor β agonists are resmetirom (MGL-3196) and VK2809 (MB07811). Resmetirom administration led to a significant reduction in liver fat in patients with NASH in a phase 2a clinical trial, and there is an ongoing phase 3 clinical trial (Table 1). A phase 2 trial with VK2809 in patients with NASH is ongoing.

Inhibitors of ceramide synthesis—Pharmacological inhibition of synthesis of ceramides improves steatosis and glucose tolerance.[42,94] Of the 3 pathways involved in ceramide biosynthesis, effect on ceramide synthase inhibition and not hydrolysis of sphingomyelin was shown to be most relevant in improving insulin resistance, steatosis, glucose tolerance, and dyslipidemia in an animal model of alcohol-associated steatosis.[44] Inhibition or deletion of dihydroceramide desaturase has also been shown to improve hepatic steatosis in an animal model of NAFLD.[95] Although not yet studied in ALD, this may be an important therapeutic target if the experimental data are encouraging as in NAFLD.[96]

Therapies targeting glucose metabolism

Insulin sensitizers—PPAR-γ agonism with pioglitazone reduced steatosis, inflammation, and fibrosis in patients with NASH.[25,97] Incretin hormones from small bowel mucosa like glucagon-like peptide 1 and gastric inhibitory polypeptide mediate insulin secretion from islet cells of pancreas through binding to their G-protein–coupled receptors. Their agonists like liraglutide, semaglutide, HM15211, and coradudite (MED10382) have been

successfully tried in patients with NASH. Sodium-glucose co-transporter type 2 inhibitors dapagliflozin, epagliflozin, canagliflozin, and licogliflozin reduce reabsorption of glucose across the renal tubules (Table 1).

Although insulin resistance can occur in ALD mediated by the effect of alcohol on liver and on adipose tissue,[94] insulin sensitizers currently do not seem to have a potential in patients with ALD.[36] However, data are emerging on the reprogramming of hepatocyte metabolism of glucose, especially in more severe forms of ALD with severe AH.[98] Reprogramming of hepatocytes leads to impaired use of glucose in generating energy, as glucose is trapped in the cells as glucose-6 phosphate. Hexokinase domain containing 1 is the most activated enzyme in patients with AH and also correlated with disease severity and patient survival. Targeting this enzyme and pathways involved in the transcriptomic and epigenetic reprogramming such as liver-enriched transcription factors especially hepatocyte nuclear factor 4-alpha may be of potential in the treatment of patients with AH.[99] Data are also emerging on the benefit of glucagon-like peptide 1 and gastric inhibitory peptide agonists in the management of alcohol use disorder with a reduction in craving and alcohol consumption.[100] The exact mechanism is unclear, but is thought to be centrally mediated through dopamine signaling.[101] It should be noted that insulin sensitizers will need to be used with caution, and after careful safety testing, in patients with ALD given the added risk of lactic acidosis with metformin in actively drinking patients,[102] and the risk of HCC with PPAR-γ agonists.[103]

Therapies targeting bile acid metabolism

FXR agonists—Obeticholic acid (OCA) is currently ongoing a large phase 3 clinical trial in patients with NASH and significant fibrosis. However, this drug is limited due to its adverse effect profile of an increase in cholesterol levels and potential for severe pruritus.[27] Many second-generation FXR agonists are currently in development in an attempt to overcome the adverse effects of OCA while retaining the histological benefit. These compounds differ in their chemical structure, their propensity for liver accumulation, and their preferential intestinal versus hepatic FXR agonism.[104] For example, EDP-305 in phase 2 clinical trial resulted in improved alanine aminotransferase and reduced intrahepatic fat, with a lower increase in LDL cholesterol.[28] The minimal increase in LDL cholesterol with EDP-305 may obviate the need for the coadministration of statins as needed with use of OCA or an FGF agonist aldafermin (also known as NGM-282).[105] Currently, a clinical trial is also underway examining the benefit of FXR agonist OCA in patients with moderate and severe alcohol-associated hepatitis (NCT02039219). Many other compounds such as tropifexor (LJN452), cilofexor nidufexor (LMB763), non–bile acid FXR agonists like EDP-297 and EDP-305, MET409, and EYP001a are under development for NASH (Table 1) and may have potential for exploring their use in patients with ALD.

FGF analogs—Although FGF activity has been shown to be increased in NAFLD, FGF receptors are resistant to its target effect.[56] In phase 2 randomized placebo-controlled clinical trial, 24-week use of an engineered FGF-19 analog aldafermin resulted in reduced intrahepatic fat and a trend on improvement in fibrosis. The drug was safe and none of the patients had to discontinue the medication due to adverse effects.[106] However,

in another phase 2b study in patients with NASH with stage 2 or 3 fibrosis, use of aldafermin for 24 weeks did not result in meeting the primary endpoint of improvement of fibrosis by one stage without worsening of NASH.[32] Although the drug was well tolerated in both studies, increase in LDL cholesterol between 0.2 and 0.4 mmol/L occurred early at 4 weeks, as among patients treated with OCA. Increase in LDL cholesterol of the same milder magnitude has been observed with cilofexor with a reduced efficacy in lowering hepatic fat and alanine aminotransferase levels.[29,107] Although the role of nuclear receptors such as FGF-19 is not yet determined in patients with ALD, preclinical data in mice have shown that alcohol induces expression of FGF-15/19 or FGF-21 with favorable lipid metabolism and bile acid profiles, resulting in amelioration of alcohol-associated steatohepatitis changes and protection from the development of ALD.[108,109] Other drugs targeting the FGF pathway are being assessed in patients with NASH, such as FGF-21 analogs pegbelfermin (BMS-986036) and efruxifermin (AKR001) and FGF receptor–activating humanized monoclonal antibodies MK-3655 (NGM313) and BFKB8488A (Table 1) and may have the potential for use in patients with ALD. In a mouse model, FGF-21 activity was shown to be activated by alcohol, but this protected from the development of ALD.[110]

Therapies targeting inflammatory and cell death pathways

Of therapies that were assessed targeting this paradigm, several molecules (cenecriviroc, selonsertib, and belapectin) have made it to phase 3 studies in patients with NAFLD and are worthy of investigation in patients with ALD (Table 1). Of these, selonsertib (inhibitor of apoptosis-stimulating kinase 1) examined in a phase 2b study in patients with ALD did not show an efficacy signal and will probably not move further in a phase 3 study. Cenicriviroc, an inhibitor of chemokine ligands type 2 and 5, prevented and treated inflammation and fibrosis in a mouse model of ALD,[111] justifying assessment of this molecule in human studies of patients with ALD. Vitamin E as an antioxidant showed a reduction of hepatic steatosis and inflammation in patients with NASH (PIVENS trial), and is a potential therapeutic target in patients with ALD.[25] Similarly, caspase inhibitor emricasan has been used successfully in patients with NASH.[112] However, a clinical trial in patients with severe AH had to be halted due to issues with pharmacokinetics and drug availability in sick patients with liver failure (NCT01912404). The protein ROCK-1 and sphingolipid, sphingosine-1-phosphate, mediate the release of extracellular vesicles mediating inflammation and can potentially be targeted,[36] to treat patients with ALD.

As the focus of this review is on potential targets gleaned from the NASH world, specific drugs targeting inflammation and hepatic regeneration in ALD such as corticosteroids, granulocyte colony-stimulating factor, IL-22, and DUR-928 will not be discussed here.[5]

Therapies targeting fibrosis

Antagonism of TGF-β can be achieved using monoclonal antibodies (lerdilimumab) or inhibiting its target receptor TGF-β1 receptor. Simtuzumab, a monoclonal antibody that blocks a critical step in laying down of collagen mediated by lysyl oxidase, was ineffective in patients with NASH with bridging fibrosis or compensated cirrhosis.[113] Antibodies to integrins have shown antifibrotic effect in animal models of NASH, and a current

clinical trial is ongoing in patients with NASH with advanced fibrosis.[114] Sonic hedgehog signaling inhibitors such as cyclopamine and vismodegib have been examined in preclinical studies in NASH animal models,[115] and could be of potential in ALD.

Drugs targeting alcohol use and food intake

As the main risk factors for ALD and NAFLD are excess and harmful alcohol use and food intake, respectively, there may be a rationale for therapies targeting pathways controlling alcohol use and food intake. Animal models and functional imaging studies have shown that central pathways in the frontal cortex and midbrain involving neurotransmitters (dopamine, serotonin, GABA, and opioids) mediate addictive behavior to drugs including alcohol, food, or any other activity.[116] Although peripheral pathways and gut-derived hormones (ghrelin, leptin, insulin, and neuropeptide YY) through their interaction with the central pathways are mainly involved to control food intake, data are emerging on the role of glucagon-like peptide 1 in mediating alcohol use behavior in humans.[117,118] Although several pharmacotherapies exist and are in development for alcohol use disorder,[119] the development of therapies targeting food addiction is limited due to their potential risk of adverse effects, especially mood disorders.[116]

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Abbreviations:

ACC	acetyl-CoA carboxylase
AH	alcoholic hepatitis
ALD	alcohol-associated liver disease
ALT	alanine aminotransferase
ASK-1	apoptosis signal-regulating kinase 1
DAMP	damage-associated molecular patterns
DGAT2	diacylglycerol acyltransferase-2
ELF	Enhanced Liver Fibrosis
ER	endoplasmic reticulum
EV	extracellular vesicles
FASN	fatty acid synthase
FDA	Food and Drug Administration
FFA	free fatty acids
FXR	farnesoid X receptor

GIP	gastric inhibitory polypeptide
GLP-1	glucagon-like peptide 1
GNRH	growth hormone–releasing hormone
IRS	insulin receptor substrate
LPS	lipopolysaccharide
MELD	Model For End-stage Liver Disease
miR	microRNA
MRE	magnetic resonance elastography
MR-PDFF	magnetic resonance proton density fat fraction
MRS	magnetic resonance spectroscopy
OCA	obeticholic acid
PPAR	peroxisome proliferator–activated receptor
ROS	reactive oxygen species
SCD1	stearoyl-CoA desaturase 1
SGLT2	sodium-glucose co-transporter type 2
T2DM	type 2 diabetes mellitus
THR-β	thyroid hormone receptor β
TLR-4	oll-like receptor-4

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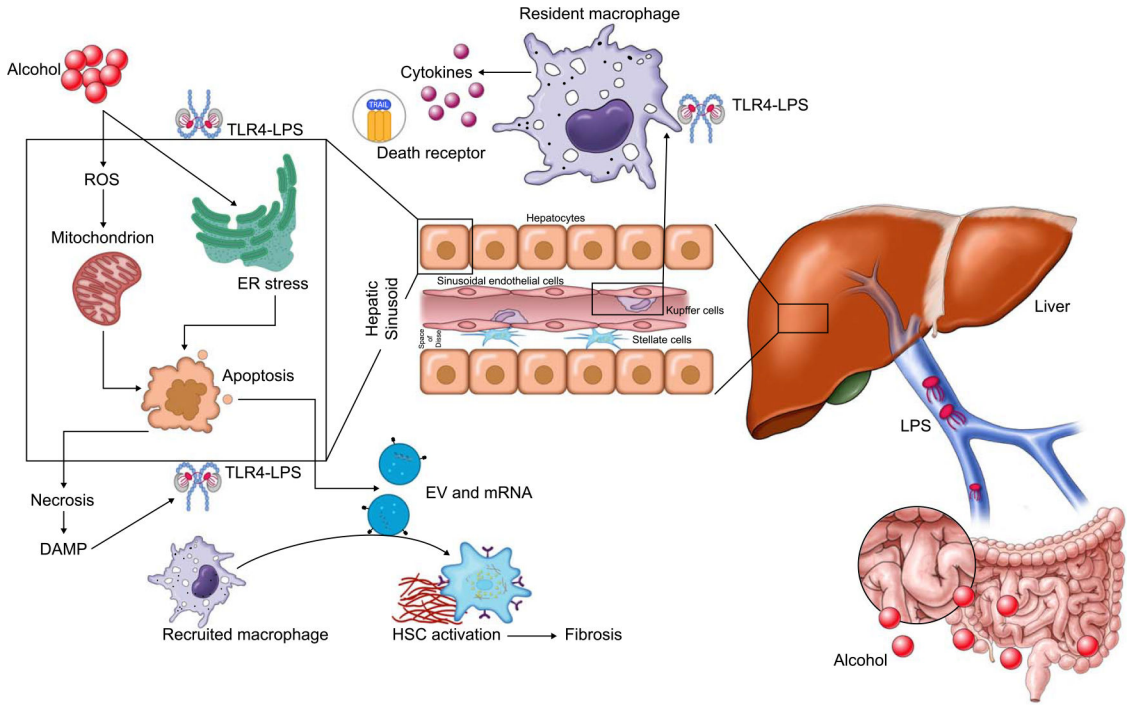

FIGURE 1.

Pathogenesis of alcohol-associated liver disease and alcoholic hepatitis. Abbreviations: DAMP, damage-associated molecular patterns; ER, endoplasmic reticulum; EV, extracellular vesicles; LPS, lipopolysaccharide; ROS, reactive oxygen species; TLR-4, toll-like receptor-4.

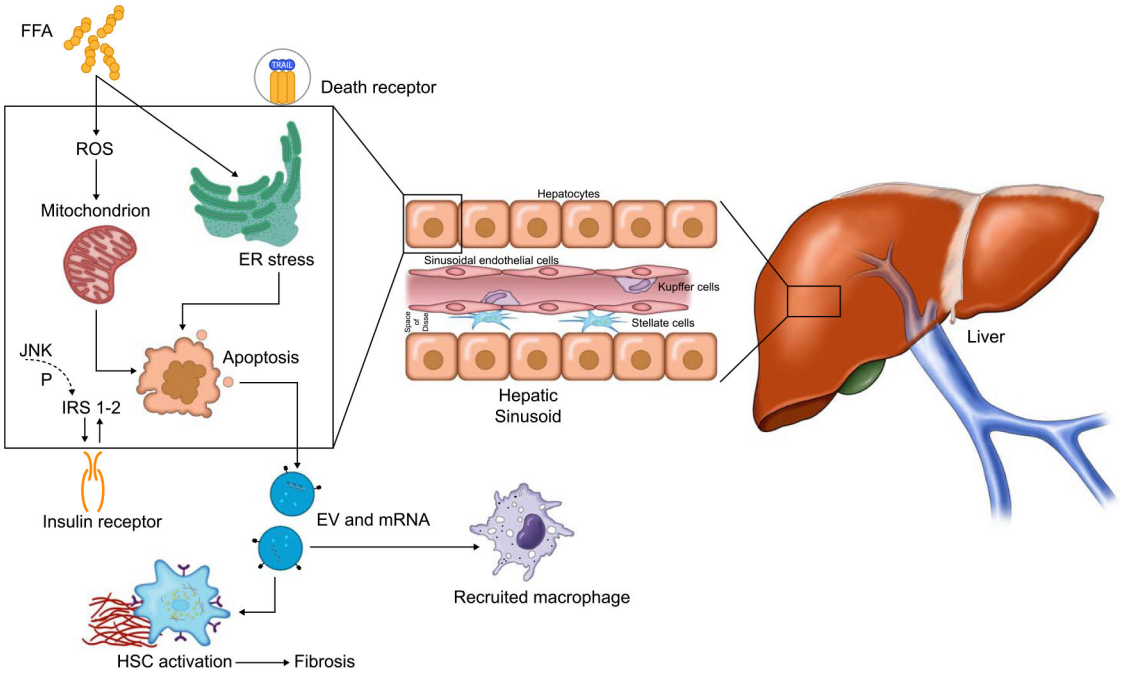

FIGURE 2.

Pathogenesis of NAFLD. Abbreviations: ER, endoplasmic reticulum; EV, extracellular vesicles; FFA, free fatty acids; IRS, insulin receptor substrate; ROS, reactive oxygen species.

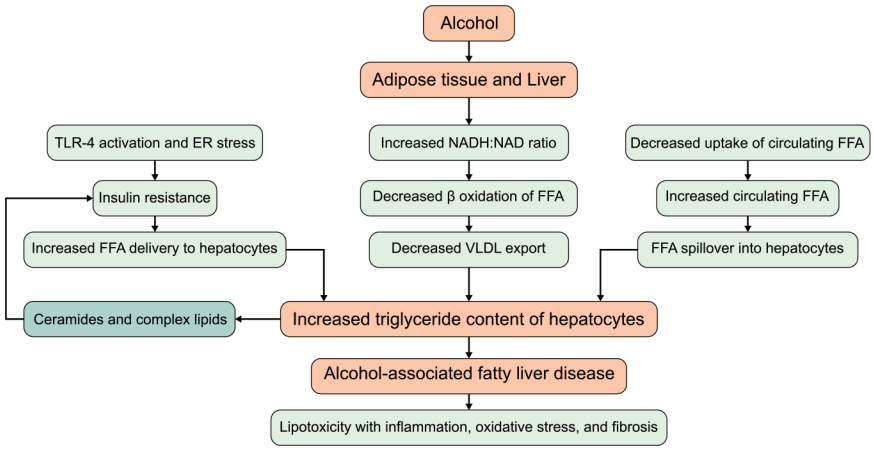

FIGURE 3.

Mechanisms of alcohol induced increased hepatic triglyceride content and steatosis. Abbreviations: ER, endoplasmic reticulum; FFA, free fatty acids; TLR-4, toll-like receptor-4.

TABLE 1

Treatment landscape for compounds targeted to treat NAFLD and NASH

Drug	Target	Indication	Clinical trial name	Primary outcome(s)	Current status	Applicability in ALD
Lipid metabolism						
Firsocostat (GS-0976)[12]	Acetyl-CoA carboxylase inhibition	NASH F1-F3	2-GS-0976	Overall safety (adverse events)	Phase 2: Improved liver fat content, liver chemistry, and serum markers of fibrosis	Yes
Aramchol[13]	SCD1 inhibitor	NASH F0-F3	2-ARREST	Change in liver on MRS	Phase 2b: Reduced liver fat, improved histology, and liver chemistry	Yes
TVB-2640[14]	FASN inhibitor	NASH	FASCINATE-1	Liver fat content	Phase 2a: Improvement in liver fat content	Yes
PXL065[15]	MPC inhibitor	NASH	NCT04321343	Liver fat content	Phase 2: Active not recruiting	
Tesamorelin	GHRH analog	NAFLD	NCT03375788	Liver fat content	Phase 2: Active and recruiting	
Elafibranor (GFT-505)[16]	PPAR-α/δ agonist	NASH F1-F3	2-Golden 3-Resolve-IT	NASH resolution without worsening of fibrosis	Phase 2b: Resolution of NASH without fibrosis worsening No effect on NASH resolution	Yes
Saroglitazar[17]		NAFLD with ALT > 50 IU/L NASH with fibrosis	NCT05011305	ALT and liver fat content NASH resolution without worsening of fibrosis	Phase 2b: Improved ALT, liver fat, and metabolic profile Phase 2: Recruiting	No
Lanifibranor[18]		NASH with fibrosis		Decrease of ≥ 2 points in SAF score without fibrosis worsening	Phase 2b: ≥ 2 points SAF score improvement higher with 1200 mg dose vs. placebo (55% vs. 33%, $p = 0.007$)	Yes
Resmetirom (MGL-3196)[19]	Selective THR-β agonist	NASH F1-F3	2-MGL-3196	Change from baseline in fat fraction on MRI-PDFF Histopathology was the secondary endpoint with paired biopsy at 36 wk	Phase 2: Improved fat fraction and lipid profile, liver chemistry, and NASH histology	No
Resmetirom (MGL-3196)	Selective THR-β agonist	NASH F2-F3	3-MAESTRO (NCT03900429)	NASH resolution on histology All-cause mortality and liver-related events	Phase 3: Active recruiting	No
VK2809	THR-β agonist	NASH F1-F3	NCT04173065	Liver fat content and LDL	Phase 2: Active recruiting	
Glucose metabolism and insulin resistance						
Pioglitazone		T2DM and NASH	NCT04501406	NASH improvement without fibrosis worsening	Phase 2b: Recruiting	No
Liraglutide[20]	GLP-1 analog	NASH F0-F4	2-LEAN	Improvement of NASH	Phase 2: NASH resolution on histology	No but may be of use in alcohol use disorder
Semaglutide[21]	GLP-1 analog	NASH F2-F3	2-Semaglutide	NASH resolution without worsening of fibrosis	Phase 2b: Semaglutide resulted in a higher percentage of patients with	

Drug	Target	Indication	Clinical trial name	Primary outcome(s)	Current status	Applicability in ALD
					NASH resolution without fibrosis worsening	
Semaglutide		NASH F2-F3	NCT04822181	NASH resolution without fibrosis worsening Fibrosis improvement without NASH worsening Time to first liver-related clinical event	Active and recruiting	
Tirzepatide	Dual GIP and GLP-1 agonist	NASH F2-F3	NCT04166773	NASH resolution without fibrosis worsening	Active and recruiting	
Efinopegdutide		NAFLD >10% liver fat content	NCT04944992	Decrease in liver fat content by MR-PDFF Safety	Active and recruiting	
ION224[12]	DGAT2 inhibitor	Type 2 diabetes and NAFLD		Safety Liver fat content by MR-PDFF	Phase 2: Safe and reduced liver fat content	
Dapagliflozin	SGLT2 inhibitor	Type 2 diabetes and NASH	NCT03723252	NASH improvement on histology	Phase 3: Active recruiting	No
Inflammation, apoptosis, and regeneration						
Cenicriviroc[22,23]	Chemokine receptor 2/5 antagonist	NASH F1-F3		Improved NASH without fibrosis worsening Improvement in fibrosis without NASH worsening	Phase 2b: No improvement in NASH, but improved fibrosis without NASH worsening	Yes
Cenicriviroc		NASH F2-F3	NCT03028740	Improvement in fibrosis without NASH worsening Time to first liver-related event	Phase 3: Completed and results awaited	
Selonsertib (GS-4997)[24]	Apoptosis signal-regulating kinase 1 inhibitor	NASH F3	3-STELLAR 3	Fibrosis improvement without worsening of NASH	Phase 3: No benefit in fibrosis improvement	Yes, completed phase 2 clinical trial in severe AH patients
		NASH F4	3-STELLAR 4	Fibrosis improvement without worsening of NASH	Phase 3: No benefit in fibrosis improvement, infection, or survival	
		NASH F2-F3	3-MAESTRO	NASH resolution on histology	No data available	
Vitamin E[25]	Antioxidant	Nondiabetic NASH	PIVENS	Improvement in NASH histology	Vitamin E better than placebo in improving steatosis and NASH but not fibrosis	Yes
Vitamin E[26]	Vitamin E with pioglitazone	Type 2 diabetes and NASH		Improvement in NASH without fibrosis worsening	Combination was better in meeting the primary endpoint	
Tocoretinol	Antioxidant	NASH cirrhosis with MELD 8–17		Change in MELD score	Phase 2: Active and recruiting	
Bile acid metabolism						
Obeticholic acid (INT-747)[27]	FXR agonist	NASH F2-F3	3-REGENERATE	NASH resolution without worsening of fibrosis	Phase 3: histologic improvement in fibrosis without worsening of NASH (interim analysis)	Yes ongoing phase 2 trial

Drug	Target	Indication	Clinical trial name	Primary outcome(s)	Current status	Applicability in ALD
				Fibrosis improvement without worsening of NASH (on histology)		
		NASH F4	2-REVERSE	Fibrosis improvement without worsening of NASH (on histology)	No data available	
EDP-305[28]		NASH F2-F3	NCT04378010	Change in ALT Change in liver fat content	Phase 2 completed with reduction in ALT and liver fat	
MET642		NASH and liver fat ≥ 10%	NCT04773964	Safety and pharmacokinetics	Active but not yet recruiting	
Tropifexor (TXR, LJN452)	Nonsteroidal FXR agonist	NASH F1-F3	2-FLIGHT-FXR (NCT02855164)	Change in transaminases and fat fraction on MRI	Phase 2: Improved liver chemistry and fat content	Yes
Cilofexor (GS-9674)[29]	Nonsteroidal FXR agonist	NASH F1-F3	2-GS-9674	Overall safety	Improved liver chemistry, serum bile acids, and liver fat content	Yes
Efruxifermin[30]	FGF-21	NASH with fibrosis NASH CC		Liver fat by MR-PDFF Safety and tolerability	Phase 2b: Improvement in liver fat content Phase 2a: safely reduced noninvasive markers of injury and fibrosis	Yes
Pegbelfermin	FGF-21	NASH F3 NASH CC	FALCON 1 FALCON 2	Improvement of fibrosis without NASH worsening Improvement in NASH without fibrosis worsening	Phase 2b: Recruiting Phase 2b: Recruiting	Yes
BMS-986036[31]	Pegylated FGF-21	NASH	F1-F3 and fat fraction > 10%	Safety and liver fat by MR- PDFF	Phase 2a: reduced fat fraction on MR-PDFF	Yes
Aldafermin[32]	FGF-19	NASH F2-F3	ALPINE 2/3	Improvement in fibrosis without NASH worsening	Phase 2b: Safe but did not meet primary endpoint	Yes
Aldafermin[32]	FGF-19	NASH CC	ALPINE 4	Safety and improvement in ELF score	Phase 2b: Active not recruiting	Yes
Gut-liver axis						
Fibrogenesis						
Belapectin[33]	Galectin-3 inhibitor	NASH cirrhosis (HVPG > 6 mm Hg)		Reduction in HVPG or fibrosis	Phase 2b: No effect on HVPG or fibrosis. However, reduced variceal development in subgroup without esophageal varices at baseline	

Abbreviations: ALD, alcohol-associated liver disease; ALT, alanine aminotransferase; DGAT2, diacylglycerol acyltransferase-2; ELF, Enhanced Liver Fibrosis; FASN, fatty acid synthase; FXR, farnesoid X receptor; GIP, gastric inhibitory polypeptide; GLP-1, glucagon-like peptide 1; GNRH, growth hormone-releasing hormone; MELD, Model For-End-stage Liver Disease; MRE, magnetic resonance elastography; MR-PDFF, magnetic resonance proton density fat fraction; MRS, magnetic resonance spectroscopy; SAF, steatosis, activity, fibrosis; SCD1, stearoyl-CoA desaturase 1; T2DM, type 2 diabetes mellitus; THR-β, thyroid hormone receptor β.

TABLE 2

Clinical trials with use of combination therapies in patients with NAFLD and NASH

Drugs	Target	Indication	Clinical trial name	Primary outcome(s)	Current status
Saroglitazar+vitamin E	PPAR-γ Antioxidant	NAFLD	NCT04193982	Change in NAFL fibrosis score	Phase 3: Recruiting
PF-06865571+PF-05221304	DGAT2 ACC	NAFLD	NCT04399538	Change in liver fat content	Phase 2: Recruiting
MET-409 +empaglifozin	FXR SGLT2	NASH	NCT04702490	Safety and tolerability of MET-409	Phase 2: Active not yet recruiting
Tropifexor+licoglifozin	FXR SGLT2	ELIVATE NASH F2-F3	NCT04065841	Improvement in fibrosis without worsening of NASH NASH resolution without fibrosis worsening	Phase 2: Recruiting
Semaglutide+cilofexor +firscostat	GLP-1 FXR+ACC	NASH cirrhosis	NCT04971785	Improvement in fibrosis without worsening of NASH NASH resolution without fibrosis worsening	Phase 2: Recruiting
Tropifexor +cenicriviroc	FXR Chemokine receptor 2/5	NASH F2-F3	TANDEM NCT03517540	Safety of combination	Phase 2: Completed and results awaited
Cilofexor+firscostat +selonsertib	FXR ACC+ASK-1	NASH F3-F4	ATLAS NCT03449446	Adverse effects and safety of combination	Phase 2: Completed and results awaited

Abbreviations: ACC, acetyl-CoA carboxylase; ASK-1, apoptosis signal-regulating kinase 1; DGAT2, diacylglycerol acyltransferase-2; FXR, farnesoid X receptor; GLP-1, glucagon-like peptide 1; PPAR, peroxisome proliferator-activated receptor; SGLT2, sodium-glucose co-transporter type 2.