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Treatment options for alcoholic and non-alcoholic fatty liver disease: A review

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Abstract

Alcoholic liver disease (ALD) and non-alcoholic fatty liver disease (NAFLD) are serious health problems worldwide. These two diseases have similar pathological spectra, ranging from simple steatosis to hepatitis to cirrhosis and hepatocellular carcinoma. Although most people with excessive alcohol or calorie intake display abnormal fat accumulation in the liver (simple steatosis), a small percentage develops progressive liver disease. Despite extensive research on understanding the pathophysiology of both these diseases there are still no targeted therapies available. The treatment for ALD remains as it was 50 years ago: abstinence, nutritional support and corticosteroids (or pentoxifylline as an alternative if steroids are contraindicated). As for NAFLD, the treatment modality is mainly directed toward weight loss and co-morbidity management. Therefore, new pathophysiology directed therapies are urgently needed. However, the involvement of several inter-related pathways in the pathogenesis of these diseases suggests that a single therapeutic agent is unlikely to be an effective treatment strategy. Hence, a combination therapy towards multiple targets would eventually be required. In this review, we delineate the treatment options in ALD and NAFLD, including various new targeted therapies that are currently under investigation. We hope that soon we will be having an effective multi-therapeutic regimen for each disease.

Key words: Alcoholic liver disease; Non-alcoholic fatty

liver disease; Treatment options; Glucocorticoids; Liver transplantation

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Core tip: Alcoholic liver disease (ALD) and non-alcoholic fatty liver disease (NAFLD) are serious health problems worldwide. Despite extensive research on understanding the pathophysiology of both these diseases there are still no targeted therapies available. In this review, we delineate the treatment options in ALD and NAFLD, including various new targeted therapies that are currently under investigation.

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INTRODUCTION

Alcoholic liver disease (ALD) and non-alcoholic fatty liver disease (NAFLD) are serious health issues whose incidences are on the rise with each passing decade. Alcohol is responsible for approximately 4% of all deaths annually and 5% of all disabilities worldwide^[1]. The Centers for Disease Control and Prevention in 2013 have estimated that in the United States acute deaths from alcohol attributable causes have outnumbered deaths from chronic diseases (44000 to 35000) (<http://apps.nccd.cdc.gov/ardi/homepage.aspx>). Motor vehicle accidents have been considered the leading cause of acute death from alcohol-attributable injuries. While the incidence and prevalence of NAFLD is on the rise with each passing decade. Presently, 25%-35% and 5%-15% of the general population of Western and Asian countries, respectively, are affected by this disease^[2]. This proportion is even higher in people with type 2 diabetes (60%-70%), and in those who are obese or morbidly obese (75%-92%) compared to the general population^[3-5]. The prevalence of obesity in the United States has increased from 10% to 60% of the total population in the last three decades and is considered to be one of the main factors for the increasing prevalence of NAFLD^[6].

The risk factors for both these diseases are well known. Patients with ALD consume an excessive amount of alcohol while NAFLD patients are usually obese; have insulin resistance and/or metabolic syndrome. Available data from various studies show that NAFLD may be the hepatic manifestation of metabolic syndrome^[7]. The spectrum of both diseases ranges from benign steatosis to hepatitis to cirrhosis and hepatocellular carcinoma. Most patients with NAFLD or ALD have hepatic steatosis which is usually asymptomatic; only 20%-35% of these

patients' progress to steatohepatitis or cirrhosis^[8]. The role of genetic polymorphism, mainly the patatin-like phospholipase domain containing 3 (*PNPLA3*) gene (rs738409 variant), has also recently been shown to be a risk factor for progression to advanced liver disease in both NAFLD and ALD that could explain why only a subset of patients who are chronic alcohol abusers or have high caloric intake present with progressive liver injury. Evidence from recent studies has shown this variability may be related to *PNPLA3* variant (rs738409). The single nucleotide polymorphism rs738409 variant within the *PNPLA3* causes a substitution of methionine for isoleucine at position 148. The GG phenotype of this *PNPLA3* variant, rs738409, predicts a greater risk of progression to cirrhosis and HCC than the GC and CC phenotype which have shown to have a smaller risk for progression^[9-12]. Despite an increased understanding of the pathophysiology and risk factors for ALD and NAFLD, we still do not have an appropriate therapeutic regimen for either disease.

The treatment options of ALD have not changed in the last four decades, and abstinence is still the cornerstone of treatment. This is supported by nutrition therapy and steroids^[13,14]. Unfortunately, alcoholic hepatitis, which is the most serious manifestation of ALD, has a short term mortality of up to 50% in patients who are unresponsive to corticosteroid treatment^[15]. Furthermore, limited treatment options are available for patients who are steroid non-responders or have contraindications to steroid usage (upper gastrointestinal bleed, impaired renal functions and sepsis). While the treatment for NAFLD is mainly directed toward attenuating the risk factor such as gradual weight loss by lifestyle modification with a focus on nutrition and exercise^[16,17], other therapies utilizing insulin sensitizers (thiazolidinediones) and antioxidants (vitamin E) also have been found to be useful. However, their long-term safety and adverse effects have not been rigorously evaluated.

Thus, effective and safe therapeutic regimens are needed for these liver diseases. In this review, we present the current therapies as well as upcoming potential new approaches and treatment strategies for both diseases.

ALD TREATMENT

General management

For the last 50 years, abstinence has remained the primary therapy for ALD treatment. However, serious symptoms develop with the abrupt cessation of alcohol. Treating the alcohol withdrawal syndrome is thus extremely important and requires administration of fluid, calories, vitamins and minerals. Unstable patients need to be admitted to a critical care unit and airway protection is often required in patients with hepatic encephalopathy. Table 1 summarizes the treatment options and potential new options for ALD

Table 1 Treatment options for alcoholic liver disease and alcoholic steatohepatitis

General management
Abstinence
Nutritional support
Glucocorticosteroids
Pentoxifylline
Anti-TNF therapy
Antioxidants
Liver transplantation
Potential new therapies
Probiotics and antibiotics
S-adenosylmethionine
Betaine
Targeting various chemokines and interleukins
Endocannabinoids antagonists
Osteopontin inhibition
Stem cell therapy

and ASH (alcoholic steatohepatitis).

Alcohol withdrawal syndrome: This syndrome is characterized by symptoms that occur 6-24 h after abrupt cessation of alcohol in patients who drink consistently and excessively. Long acting benzodiazepines like chlordiazepoxide or diazepam are administered for prevention of seizures while intermediate acting benzodiazepines like lorazepam are recommended in withdrawal patients who are elderly or have had recent head trauma or liver or respiratory failure^[18]. Antiepileptic like carbamazepine can also be used as a benzodiazepine substitute for preventing seizures. Antipsychotics like haloperidol can be used if patients have excess agitation or psychotic symptoms^[18]. Alcoholics are usually malnourished and deficient in vitamins, especially vitamin B1 (thiamine), thus putting them at risk of developing Wernicke encephalopathy, so all such patients should be given thiamine^[19]. Parenteral thiamine is preferred over oral thiamine because in addition to impaired gastrointestinal absorption in alcoholics, oral thiamine has poor bioavailability that does not allow for attaining a sufficient concentration in cerebrospinal fluid. However, parenteral thiamine has a short half-life, thus multiple high-dosing is required to achieve sufficient concentration for active and passive diffusion through the blood brain barrier^[20-22]. An IV dose of 500 mg (three times daily for two consecutive days) is recommended, followed by 500 mg of IV or IM thiamine for five more days if a response to the therapy is seen^[23-25]. Another dosing regimen is 500 mg of IV thiamine (three times daily for 2-3 d), followed by 250 mg of IV thiamine for the next 2-3 d. The intravenous regimen is then followed by oral thiamine treatment indefinitely^[26,27]. Thiamine should be given before fluids containing glucose to prevent neurological damage.

Abstinence: The first step towards treatment requires the patient to accept the fact that they are

dependent and addicted to alcohol. Abstinence can resolve alcoholic fatty liver disease and can improve the survival rate of cirrhotic or decompensated liver failure patients. Thus, motivating the patients to abstain from alcohol and follow the proper treatment regime are major steps. However, preventing relapse in such patients has always been a big challenge. Patients can participate in Alcoholics Anonymous group meetings for self-control and motivation. Psychological support by an addiction specialist can also help in maintaining sobriety. Recognizing and treating any associated psychiatric conditions can be helpful in such patients^[28]. Pharmacotherapy also helps in maintaining sobriety; drugs like naltrexone and acamprosate assist in reducing alcohol intake in heavy drinkers^[29,30]. Topiramate has found to be effective in decreasing craving and withdrawal symptoms in alcoholics^[31]. Disulfiram, an acetaldehyde dehydrogenase inhibitor, is also being used. It causes accumulation of serum acetaldehyde, which produces unpleasant sensations of nausea, vomiting, abdominal pain and dizziness. Such sensations deter patients from consuming alcohol^[32]. Baclofen, a γ -amino butyric acid agonist, has also been found effective in promoting abstinence^[33]. Most of these drugs (disulfiram, acamprosate, naltrexone, topiramate and baclofen), are used only for treatment of alcohol dependence^[34] but are not FDA approved for ALD treatment. Of these, only baclofen has been studied for its safety and efficacy in clinical trials that compared placebo and baclofen treatment for ALD patients. In this trial, baclofen (10 mg or 20 mg twice daily) was more effective than placebo in maintaining abstinence. A 53% reduction in the number of drinks per day in the 10 mg baclofen group ($P < 0.0001$) and a 68% reduction in the number of drinks per day in the 20 mg baclofen group was reported, thus demonstrating a dose response effect of baclofen^[35]. Naltrexone and disulfiram should be avoided in patients with liver problems because of hepatotoxicity^[36]. Moreover, naltrexone should also be avoided in patients with renal failure due to its active tubular secretion^[37]. Acamprosate, topiramate and baclofen were found to be safe in such patients^[33,38,39]. Another drug which can help to maintain abstinence and reduce craving is metadoxine (MTD). Although not available in the United States, MTD is approved for use in several European countries. Apart from sustaining abstinence, oral MTB is also useful in acute ethanol intoxication since it is rapidly absorbed and augments alcohol metabolism by enhancing acetaldehyde dehydrogenase activity^[39]. In a clinical trial with ASH patients, MTX improved liver function tests in 1 mo compared to the placebo^[40]. In another trial, improved 3-6 mo survival of severely ill ASH patients who received the combination therapy with MTX compared to those that received monotherapy with either steroids or pentoxifylline (PTX) was observed. The survival rate was higher of the MTD-treated groups at

3 mo (PTX + MTD 59.4% vs PTX 33.3%, $P = 0.04$; steroids + MTD 68.6% vs steroids 20%, $P = 0.0001$) and at 6 mo (PTX + MTD 50% vs PTX 18.2%, $P = 0.01$; steroids + MTD 48.6% vs steroids 20%, $P = 0.003$) than in the non-MTD treated groups. Furthermore, the patients receiving MTD maintained greater abstinence than those not on MTD (74.5% vs 59.4%, $P = 0.02$)^[41]. Smoking and obesity are independent risk factor for the progression of ALD^[42,43]. Hence, lifestyle modifications like weight loss and smoking cessation are also helpful. Hepatitis C virus (HCV) is another independent risk factor for ALD progression due to synergistic deleterious effects of both agents in promoting liver injury and HCC development^[44,45]. The main mechanisms of this effect are that both alcohol and HCV alter cellular immunity, increase free radical oxidative damage, and in the case of alcohol exposure, promote replication of HCV. Thus, the combination often result in the presence of advanced liver disease with severe histological features at a much younger age and a decreased survival^[46,47]. It has been reported that alcoholic patients with HCV infection have a 30 fold increased risk of getting cirrhosis^[48] and two to eight fold increased risk of all-cause mortality compared with those without the HCV infection^[49,50]. Thus, all ALD patients should be screened for HCV before starting treatment and all HCV patients should be advised to stop or reduce alcohol consumption^[51].

Nutritional support: Most patients with ALD are malnourished, and disease severity often correlates with the degree of malnutrition^[52]. Most of the complications of ALD are strongly associated with protein calorie malnutrition^[53]. Thus, nutrition support is one of the important steps in ALD treatment. Vitamins (like folate, vitamin B6, vitamin B12^[54,55], vitamin A and thiamine^[56] and minerals (like selenium, zinc, copper, and magnesium) are often found to be altered in ALD and some believe that these alterations play a role in initiation and progression of liver injury^[57]. Especially, zinc levels are decreased in ALD patients and in animal models, and its supplementation has been shown to improve ALD^[58]. A major study has also shown that enteral nutrition reduces infectious complications and improves 1-year mortality in such patients^[59,60].

The American College of Gastroenterology and the American Association for the Study of Liver Diseases guidelines recommend 1.2 to 1.5 g/kg per d of protein intake and 35 to 40 kcal/kg per d of body weight for energy intake in patients with ALD^[61]. This type of malnourished patient is often predisposed to infections so empiric antibiotic treatment is also advised.

Glucocorticosteroids: There have been various clinical trials on the use of corticosteroids for treating ALD patients^[62-64]. Despite mixed outcomes, corticosteroids are overall beneficial for survival of these patients. Unfortunately, 40% of patients are unresponsive to corticosteroid with virtually no other treatment options.

Hence, new target oriented therapies are critically required for the management of such patients^[15].

A meta-analysis which pooled data from 3 randomized control trials, found that patients with modified DF ≥ 32 or MELD score ≥ 21 treated with prednisolone at 40 mg/d for 28 d and then a tapered dose over 2-4 wk (Class I, level A), conferred a 28-d survival benefit of glucocorticoids (85%) vs placebo (65%), with mortality decreasing from 35% in controls to 15% in patients on steroids^[64]. Early changes in bilirubin levels (at day 7 of treatment) and the Lille score were used to predict the prognosis following steroid administration^[65]. A Lille's score greater than 0.45 on the 7th d after initiation of the treatment indicated that the patient was unresponsive to steroid therapy and predicted a lower survival rate of 25% at 6 mo. Recently this score has been re-classified as complete responders (score ≤ 0.16), partial responders (score 0.16-0.56), and null responders (score ≥ 0.56), and is associated with the 28-d survival rate of 91%, 79% and 53%, respectively, with $P < 0.0001$ ^[13]. Steroids have been found to have a significant beneficial effect in complete and partial responders but not in null responders, hence discontinuation of steroid therapy is recommended for non-responders^[66]. In addition to non-responders, steroids are generally avoided in patients with active infection, gastrointestinal bleeding, chronic hepatitis B virus infection or hepatorenal syndrome (HRS) because of adverse effects in these patient populations^[67]. Steroids are relatively contraindicated in severe AH patients with coexistent sepsis. Thus, such patients may be treated with second line drug PTX^[68]. Patients should also be screened for any infection before starting steroids and for infective complications while on steroids. Occurrence of sepsis and infective complications while the patient is on steroids is a poor prognostic sign^[69]. It has been reported that patients infected after initiation of steroids had a significant lower 2-mo survival than patients with no infection (46.4% \pm 6.9% vs 77.5% \pm 3.2%, $P < 0.00001$). Thus, it is very important to differentiate infection at admission from that which occurs after starting the steroid treatment, as survival rates differ significantly. Overall, infection was more common in steroid null responders than responders^[70].

PTX: Steroids are generally used as the first line of treatment in severe alcoholic hepatitis patients with DF ≥ 32 , except in those with renal failure or HRS or contraindication to steroids^[71]. PTX (400 mg 3 times per day for 28 d) is a substitute in such cases (Class I, level B). PTX decreases pro-inflammatory cytokines like TNF- α , has anti-fibrotic properties^[72] and confers a mortality benefit by reducing the incidence of HRS^[73]. A pilot study in ASH patients using PTX demonstrated reduced mortality and HRS incidence when compared to patients given a placebo^[74]. These findings were later confirmed in a double-blind placebo controlled trial, where PTX decreased the 28-d mortality compared to

placebo (24.5% vs 46%). Also, 50% of those who died in the PTX group developed HRS, while 91.7% who died in the placebo group developed HRS, confirming that PTX reduces the incidence of HRS in such patients^[75]. A study in ASH patients comparing PTX and prednisolone have shown a better survival rate of 35.29% in the PTX group vs 14.71% on steroids. This reduced mortality was presumably because of a decrease in incidence of HRS and gastrointestinal bleeding in the PTX group. However, this study was underpowered^[76]. To date, no other study has shown any additional survival benefit of the combined PTX and corticosteroid treatment^[77,78]. A recently conducted randomized, multicenter, double-blind trial (STOPAH) across 65 hospitals in the United Kingdom that recruited more than a thousand patients revealed no impact of PTX on survival or disease progression in severe non-alcoholic steatohepatitis (NASH) patients in comparison to placebo^[79,80]. However, because of a lack of other treatment options, PTX is being used in some centers.

Anti-TNF therapy: Intestinal gut permeability is increased in chronic alcoholics that promotes the translocation of gut luminal antigens especially endotoxin to reach the liver and enhance TNF- α production^[81]. TNF- α has been found to correlate with disease severity in severe alcoholic hepatitis patients^[82], and also play a vital role in alcohol induced liver injury in various animal models of alcoholic liver injury^[83]. Further, mice deficient in TNF receptor 1 do not develop liver injury when administered alcohol^[83]. Based on these considerations, various human studies were undertaken using anti-TNF therapy. While initial studies were found to be promising, the results could not be duplicated in larger clinical trials. A large randomized controlled trial comparing prednisolone alone with a combination of prednisolone and infliximab had to be stopped before completion because of an increase in infection rate in the prednisolone and infliximab combination group^[84]. Further, patients had to be screened for tuberculosis and nocardia infection prior to participation in the study, thus limiting its clinical utility^[85].

Antioxidants: Alcohol causes oxidative stress by increasing reactive oxygen species (ROS), and decreasing endogenous antioxidant levels^[86]. But to date, all trials examining antioxidants (such as lecithin, β -carotene, vitamin C, vitamin E, allopurinol, desferrioxamine, and N-acetylcysteine) either alone or in combination with steroids have been disappointing^[87,88].

Liver transplantation: Liver transplantation remains the definitive therapy for end stage decompensated cirrhosis due to ALD. Severe alcoholic hepatitis patients nonresponsive to steroids have a 3 mo mortality rate of 70% and with HRS the mortality rate is $\geq 90\%$ unless the patients get liver transplantation^[89,90]. At

present, there are very few options for treating severe alcoholic hepatitis patients who are non-responsive to steroids and have a Lille score > 0.56 . Thus, liver transplantation remains the only hope for such patients, but the issue of transplantation in alcoholics has always remained controversial. Concerns include the risk of recidivism, poor compliance with postoperative care, and ALD being a self-inflicted disease^[91]. Recidivism following transplantation is a major challenge, which occurs at a rate of 10%-50%^[92,93]. A meta-analysis reviewing factors responsible for recidivism found 3 major variables: a poor social support system, a family history of alcohol abuse/dependence and pre-transplant abstinence of 6 mo or less^[94]. Thus, we need a multidisciplinary approach including the presence of an Alcohol Addiction Unit which can significantly contribute in reducing alcohol relapse after transplantation. Also, there should be psychological evaluation for any mental illness to determine patient suitability for transplantation.

Most transplant programs require the patients to undergo a 6-mo period of abstinence prior to transplantation^[95]. Studies over the years have provided data both for and against the 6-mo abstinence rule. One report suggested that the 6-mo period of abstinence would allow the liver to recover with medical treatment and possibly there would be no need for transplantation^[96]. Another study revealed that some recovery in liver function can take place within 3 mo of abstinence while many patients may die during the 6 mo of waiting period. This led to the suggestion of possibly reducing the period of abstinence to 3 mo^[97]. Yet another study has also challenged the 6-mo abstinence rule by showing beneficial effects of early liver transplantation in steroid non-responding severe alcoholic hepatitis patients. In this study patients (with Lille score of 0.88) after 13 d of being unresponsive to steroids were put on the transplant list and it was found that the 6-mo survival rate was higher in patients who received early transplantation than those who did not (77% vs 23%, $P < 0.001$)^[98].

However, patients who have received liver transplantation show a high incidence of de novo cancer^[99,100], lymphoproliferative disorder and skin cancer. In some cases, squamous cell carcinoma of the oropharynx or esophagus has also been detected, likely due to the cumulative effects of smoking and post-transplant immunosuppressive drugs. Also, liver transplantation due to ALD is associated with a high rate of cardiovascular complications^[101].

Potential new therapeutic options in ALD

Advances in basic science have helped to gain better insights into the pathophysiology of ALD that have provided new treatment options as discussed below.

Role of probiotics and antibiotics: Healthy intestinal flora is critically important for our well-being.

An alcohol-induced change in the gut microflora plays a major role in the pathogenesis of alcoholic hepatitis. Equally important in liver disease progression is the alcohol-induced increased intestinal permeability that allows for the gut luminal antigens, including endotoxin/LPS (component of the cell wall of gram negative bacteria), to reach the liver and promote the synthesis and secretion of several inflammatory cytokines^[102]. Various studies have proposed the use of probiotics in restoring the normal bowel flora in patients with ALD^[103]. In a study performed on patients with ALD it was shown that using probiotics (*Bifidobacterium* or *Lactobacillus*) for 4 wk enhances and normalizes neutrophil phagocytic capacity and helps in reducing endotoxin-driven elevation in cytokine levels^[104]. A similar study revealed significant improvement in AST, ALT and γ -glutamyl transferase levels in ALD patients administered probiotics (*Bifidobacterium* or *Lactobacillus*) for 5 d^[105]. Rifaximin, a biochemical derivative of Rifamycin, the drug for hepatic encephalopathy, given for 28 d in a clinical trial decreased systemic endotoxin levels^[106]. Indeed, blood LPS levels help in predicting response to steroids and mortality of alcoholic hepatitis patients^[107]. Thus, modifying the gut microbe flora by probiotics and antibiotics could be a potential therapeutic approach for treating ALD which is being actively pursued.

Role of S-adenosylmethionine and betaine:

S-adenosylmethionine (SAM) is a key methyl donor that is involved in many methylation reactions critical for normal liver function. SAM also acts as an antioxidant by activating the pathway for GSH synthesis. Decreased SAM levels have been reported in ALD patients; thus, elevating SAM levels could be a potential therapy. Various animal studies have shown liver injury can be reversed by preventing a decrease in SAM levels^[108]. Also, SAM administration decreases oxidative stress and hepatic stellate cell activation^[109]. A randomized controlled trial using SAM or placebo for 2 years in alcohol cirrhotic patients found that the mortality and liver transplantation rates were higher in the placebo group than in the SAM group (29% vs 12%)^[110]. Thus, there is need for long-term, high quality trials in the future to establish its effectiveness. Along the same line as SAM, betaine treatment has been very effective in improving liver injury in various animal models^[111,112]. By remethylation homocysteine to generate methionine, betaine not only removes the toxic metabolites homocysteine and S-adenosylhomocysteine, but also generates SAM and normalizes the methylation potential^[113]. Betaine is hepato-protective and prevents alcohol-induced steatosis, oxidative stress, apoptosis and abnormal protein accumulation^[111,112], and breakdown of sulphur containing amino acid^[114]. Clinical trials using betaine should be conducted.

Role of targeting various chemokines and

interleukins: Chemokines play a pivotal role in the pathogenesis of alcoholic hepatitis. Studies have shown that various chemokines and their subfamily members, including CXCL5, CXCL6, CXCL10 and CCL20, are notably high in ASH livers compared to normal control livers and higher levels correlate with worse prognosis and outcomes^[115,116]. Of these, CCL20 is the most elevated chemokine in ASH livers that attracts lymphocytes, monocytes, Th17 (Helper T17) cells, and dendritic cells. The consequent production of more chemokines and inflammatory mediators ultimately causes heavy neutrophilic infiltration and liver damage^[117,118]. Additional studies in the future are required to determine if targeting CCL20 and other chemokines can be an effective and safe therapeutic approach for ALD patients.

IL-8 is one of the most important chemoattractant of neutrophils, which further causes hepatic infiltration as well as increased portal pressure^[115]. A higher level of IL-8 in alcoholic hepatitis patients is associated with worse prognosis^[115]. A therapeutic approach towards counteracting IL-8 levels should be considered as it will decrease neutrophil infiltration of the liver and prevent progressive liver damage.

IL-22 plays a critical role in bacterial infections and tissue repair. It is a part of the IL-10 family which decreases the production of various pro-inflammatory cytokines^[119]. IL-22 has been found to have anti-apoptotic, antimicrobial, antioxidant and anti-steatotic effects, thus it can be used as a therapeutic option in ALD patients. It has been found that levels of T helper cells producing IL-22 correlate with improvement in alcoholic hepatitis patients^[120]. Recombinant IL-22 administration showed improvement of liver injury in ethanol-fed mice^[121] and in an animal model of acute hepatitis while blocking the IL-22 receptor led to worsening of the disease^[122]. Thus, up regulating IL-22 levels can be a potential therapy for ALD.

IL-17 increases chemotaxis of neutrophils and various other chemokines and its levels are found to be increased in alcoholic hepatitis^[123]. Secukinumab, an anti-IL-17 monoclonal antibody has shown favorable results in clinical trials of rheumatoid arthritis, psoriasis and uveitis^[124]. Up until now, no study has been done in patients with liver disease using this monoclonal antibody, which can be a potential therapy.

Role of endocannabinoids: Endocannabinoids signalling through cannabinoid receptors, CB-1 and CB-2, has been implicated in the pathogenesis of ALD^[125]. Studies using animal models of alcoholic liver injury revealed that CB1-deficient mice are resistant, whereas CB2-deficient mice are more susceptible to fatty liver damage^[126,127]. These findings suggested that therapy targeting CB1 and CB2 receptors should be utilized as an alternative for the management of ALD.

Role of osteopontin: There is substantial evidence

Table 2 Treatment options for non-alcoholic fatty liver disease and non-alcoholic steatohepatitis

Lifestyle changes	Weight loss
	Dietary changes
	Exercise
Insulin sensitizers	Thiazolidinedione's
	Metformin
Lipid lowering agents	Statins
	Ezetimibe
Hepatoprotective agents	UDCA
Antioxidants	Vitamin E
Incretin analogues	GLP-1 agonists
	DPP-IV inhibitors
Anti-inflammatory agents	PTX
Others	Probiotics
	Angiotensin receptor blockers
	Endocannabinoid antagonists
	Bariatric surgery
	Liver transplantation
Potential new therapeutic options	Caspases inhibitors
	ASK1 inhibitors
	p38 MAPK inhibitors
	PPAR- alpha and delta agonists
	FXR agonists
	NOX-1/4 inhibitors
	Galectin-3 antagonists
	Acetyl CoA carboxylase inhibitors
	FGF-21 and FGF-19 analogues
	CCR2 and CCR5 inhibitors
	SCD-1 inhibitors
	Lysyl oxidase-like 2 inhibitors
	Sirtuins

GLP-1: Glucagon-like peptide 1; DPP-IV: Dipeptidyl-peptidase IV; PTX: Pentoxifylline; PPAR: Peroxisome proliferator activated receptor; NOX: NADPH oxidase; FGF-21: Fibroblast growth factor 21; SCD1: Stearoyl coenzyme A desaturase 1.

suggesting that osteopontin (OPN) plays a notable role in wound healing in response to injury in many organs^[128]. It is an extracellular matrix protein with pro-fibrogenic properties, and is found to be highly expressed in alcoholic hepatitis patients^[129]. One study demonstrated attenuation of alcohol mediated liver disease in mice lacking OPN^[130]. More studies should be conducted to assess OPN as a potential therapeutic target.

Stem cell therapy: Hematopoietic stem cell transplantation is an evolving field. Though limited research has been performed in this area, it could be a promising therapeutic approach in the future. Recent studies have suggested that stem cell transplantation may reduce liver inflammation and improve fibrosis in patients with liver cirrhosis^[131]. Mesenchymal stem cells (MSC) directly inhibit the activation of hepatic stellate cells and may also induce apoptosis of hepatic stellate cells^[132]. They have also been reported to stimulate proliferation of endogenous hepatocytes^[133,134]. A pilot study performed on 12 patients with ALD to assess the regenerative capacity of the liver after infusion of bone marrow derived-MSC through the hepatic artery showed improvement in the histological grading with

an overall decrease in TGF- β , type 1 collagen and smooth muscle actin^[135]. A significant improvement in the Child-Pugh score and albumin levels was noted in another similar study on 9 cirrhotic patients given bone marrow derived stem cells *via* the portal vein^[136]. Liver function was also reported to be better after stem cell therapy in cirrhotic patients^[137]. Results of these studies are encouraging and stem cell therapy could serve as a potential breakthrough treatment for ALD. However, the benefits and safety of stem cells should be examined in a large sized RCT.

NAFLD TREATMENT

Like ALD there is no effective treatment to date for NAFLD. In the absence of a proven effective therapy, we must follow a multi-disciplinary approach in NAFLD treatment, where a combination of drugs and factors are taken into consideration to counter multiple pathological risk factors involved in NAFLD. These are summarized in Table 2 and are further discussed below.

Weight loss, dietary modification and changes in lifestyle

Treatment is mainly directed towards weight loss and risk factor reduction, as most patients are obese or have metabolic syndrome^[138]. A weight loss of 3%-5% reduces steatosis while a $\geq 5\%$ -7% drop in weight has been shown to resolve NASH. Greater reductions in weight (*i.e.*, $\geq 10\%$) may also improve hepatic fibrosis. Weight loss is mainly due to diet modification and exercise. However, the shortcoming of this approach is the lack of adherence and non-compliance with time^[139]. Various studies have shown the benefit of weight loss in NAFLD^[140]. Dietary modification also plays a key role since a carbohydrate-rich diet, especially with high fructose, is the major cause of obesity, insulin resistance and NAFLD development^[141]. Thus, sugar consumption should be kept below 10% of total caloric intake in a day and a fructose-rich diet should be avoided in such patients. Food rich in omega-3 fatty acid should be included and those rich in saturated fat and omega-6 fatty acid should be excluded from the diet^[142]. An omega-3 fatty acid rich diet promotes fatty acid oxidation and decreases fatty acid synthesis, thus improving the lipid profile. Fish and fish oil consumption should be promoted as they are rich in omega-3 fatty acid^[143]. Thus, diet and moderate exercise are preferred methods of natural weight loss. A study also revealed that a combination of diet changes and exercise lowered ALT levels better in NAFLD patients than insulin sensitizers or other hypoglycaemic drugs^[144]. Weight loss is also beneficial as it improves the cardiovascular risk profile^[145]. Nevertheless, it should be noted that weight loss should be gradual, as very rapid weight loss has been associated with a worsening of steatohepatitis and an increased risk for liver failure^[146] and gallstones^[147].

Apart from natural weight loss, drugs like Orlistat and Sibutramine are also being used for controlling weight. Orlistat is a lipase inhibitor, that prevents fat absorption in the liver and intestine, thus causing weight loss. Sibutramine on the other hand is a serotonin reuptake antagonist which suppresses appetite. Both agents have shown to reduce serum transaminase levels and hepatic steatosis^[148,149].

Insulin sensitizers

Since NAFLD is closely associated with obesity and metabolic syndrome, and both conditions cause insulin resistance, treatment strategies invariably include agents which enhance insulin sensitivity.

Thiazolidinedione: Thiazolidinediones (TZDs) are peroxisome proliferator activated receptor (PPAR)- γ agonists, which improve hepatic and peripheral insulin sensitivity^[150] via increasing plasma adiponectin levels^[151]. In addition, adiponectin is also shown to have anti-fibrotic and anti-inflammatory properties. Thus, multiple factors involved in pathogenesis of NAFLD such as high insulin resistance, low adiponectin levels and high pro-inflammatory cytokines are all targeted by these drugs. First generation TZDs (troglitazone) have shown improvement in steatohepatitis but had to be stopped due to hepatotoxicity^[152]. However, it paved the way for second generation TZDs (rosiglitazone and pioglitazone) which are not hepatotoxic and showed improvement in insulin resistance, hepatic steatosis and aminotransferases levels^[153,154]. A long-term therapy with second generation TZDs may be required as their benefits tend to reverse on discontinuation; however long term therapy is associated with various adverse effects like congestive heart failure, weight gain, peripheral oedema, anaemia and osteoporosis^[155,156]. Also, it has been found that TZD therapy alone without nutrition and lifestyle changes is often not effective^[154]. Thus, we need additional studies on a larger population with a combination of other drugs to find safe and efficacious treatment options.

Metformin: Metformin, a hypoglycaemic drug, is used for treatment of type 2 diabetes mellitus. Metformin improves hepatic and peripheral insulin resistance by decreasing hepatic gluconeogenesis, lipogenesis and glucose reabsorption from the gut and increasing fatty acid oxidation^[157]. While metformin does not cause weight gain as TZDs, it can cause some minor gastrointestinal adverse effects and sometimes lactic acidosis is seen in patients with renal impairment. Various studies have documented an improved insulin sensitivity, cholesterol and aminotransferase levels in NASH patients on metformin but the results are mixed when assessing biopsy-guided improvement in steatosis and NASH activity score (NAS)^[158]. Thus, while its effectiveness as a monotherapy is debatable,

metformin could be a part of a multi-therapeutic regimen for the management of NAFLD patients.

Lipid lowering agents

NAFLD is often associated with obesity and metabolic syndrome which is characterized by hypercholesterolemia and hypertriglyceridemia. Therefore, the use of lipid lowering agents could be beneficial. While, clofibrate did not show any beneficial effect on the liver tests or the histological scores^[159], gemfibrozil showed improvement in ALT levels in NAFLD patients compared to the placebo^[160]. Statins have also been tried but have shown variable effects. Nevertheless, lipid-lowering agents should be given as most NAFLD patients are hyperlipidemic and thus have a high risk of developing cardiovascular issues.

Ezetimibe, a drug that inhibits the reabsorption of lipids from the intestine, reduces serum TNF- α levels^[161], hepatic lipid content and ALT levels in a mouse model of NAFLD^[162]. Human studies for this drug are awaited.

UDCA

This drug has hepatoprotective properties and has been studied in various clinical trials for NAFLD treatment. Initial small studies revealed an improvement in liver enzyme levels and hepatic steatosis^[159], but a subsequent RCT showed no improvement in liver histology or aminotransferases^[163]. Thus, UDCA is not approved as a monotherapy but is part of a drug combination regime in various trials on NAFLD in progress.

Vitamin E

ROS generation plays an important part in the progression of NASH^[164]. Vitamin E and C decrease oxidative stress and thus have been evaluated in patients with NASH. Various clinical trials with vitamin E have revealed an improvement in liver test functions and reduction in oxidative stress markers but significantly less improvement in the histological grading of the disease has been noted^[165,166]. A recent trial using a combination of vitamins E and C for 6 mo showed that these were no better than placebo for treating patients with NASH^[167]. One study with a three arm trial involving placebo, UDCA and Vitamin E/UDCA combination showed improvement in histology only in the Vitamin E/UDCA combination arm^[168]. Another trial comparing a combination of pioglitazone and vitamin E with vitamin E alone over a period of 6 mo showed a decrease in serum ALT in both groups, but a significant histological improvement was only seen in the combination group^[169]. A meta-analysis involving high-dose vitamin E supplementation has shown an increase in all-cause mortality and cardiovascular deaths, thus decreasing the enthusiasm for vitamin E therapy^[170].

Incretin analogues

Glucagon-like peptide 1 agonists: Glucagon-like peptide 1 (GLP-1) is an incretin hormone that is

produced by intestinal mucosa L cells. GLP-1 has a short half-life, as it is rapidly degraded by dipeptidyl-peptidase IV (DPP-IV). GLP-1 agonists are resistant to DPP-IV and are useful since they lower blood glucose levels by decreasing glucagon secretion, delay gastric emptying and stimulate pancreatic β cells to increase insulin secretion. Furthermore, these agonists have a central appetite suppressive effect and promote weight loss which are favorable outcomes for obese NAFLD/NASH patients^[171]. In an obese mouse model, it has shown to improve insulin sensitivity and reduce hepatic steatosis^[172].

In various clinical trials, liraglutide has proven to be an effective therapeutic drug for type 2 diabetics producing a good glycemic control and significant weight loss in such patients. Since diabetes is an important component of metabolic syndrome and associated NAFLD development, the effective glycemic control and weight loss makes liraglutide a suitable therapeutic option for NAFLD^[173]. In a phase 2 clinical trial study (LEAN study) with 52 NASH subjects using liraglutide compared to placebo, 39% of patients using liraglutide vs 9% using placebo attained the primary endpoint (histological resolution of NASH without worsening of fibrosis). Two (9%) of 23 patients in the liraglutide group vs eight (36%) of 22 patients in the placebo group had progression of fibrosis. The trial was designed using A'Hern's single-group method, which required eight (38%) of 21 successes in the liraglutide group for the effect of liraglutide to be considered clinically significant. The liraglutide treatment group has also shown improved insulin sensitivity, reduced hepatic glucose production and lipogenesis (ClinicalTrials.gov-NCT01237119). Thus, liraglutide was safe, well-tolerated, and led to histological resolution of NASH, warranting longer term studies in such patients^[174,175].

DPP-IV inhibitor: DPP-IV inactivates both incretin hormones (GIP, GLP-1), therefore DPP-IV inhibitors are used in the treatment of type 2 diabetes^[176]. NASH patients exhibit higher DPP-IV expression^[177]. A cross sectional study on type 2 diabetics without any evident liver disease and NAFLD patients revealed a strong positive correlation of serum DPP-IV activity and insulin resistance with liver enzymes only in NAFLD patients^[178]. Serum DPP-IV activity was not increased in the type 2 diabetics with no evidence of liver disease. This led the authors to postulate that the increased serum DPP-IV reported in earlier studies in type 2 diabetics may have been due to some un-diagnosed liver disease and that the excess DPP-IV found in the serum of NAFLD patients is of hepatic origin. They further suggested that serum DPP-IV should be considered as a potential liver disease biomarker^[178]. This supposition was also corroborated by another study which analyzed human liver biopsy specimens and showed a strong correlation of DPP-IV expression with stages of

fatty liver and NASH^[179].

Furthermore, a DPP-IV inhibitor like sitagliptin, decreases hepatic steatosis and serum transaminases levels when given to diabetic NAFLD patients^[180,181]. In a recent randomized, double-blind, placebo controlled study, sitagliptin was shown to be safe but no more effective than placebo in improving hepatic steatosis and fibrosis in NAFLD patients. However, in comparison to sitagliptin, an increase in hyaluronic acid levels and increase in FIBROSpect II index (measure of liver fibrosis) was reported in the placebo arm^[182]. Another RCT comparing sitagliptin to placebo also revealed no improvement in fibrosis score or NAS after 24 wk of therapy, but reported that sitagliptin increased adiponectin and decreased γ -glutamyl transferase levels^[183]. There have been only a few clinical trials with sitagliptin till date. However, despite the lack of convincing evidence, the efficacy of sitagliptin in improving liver fibrosis in NAFLD cannot be ruled out. This is because not only were the trials underpowered but were possibly not long enough to evaluate its effectiveness. Hence, sitagliptin effect should be assessed in clinical trials of longer duration with larger number of enrolled patients with NAFLD/NASH.

PTX

PTX can be of potential benefit in NAFLD due to its effects on reducing free radical oxidative stress, TNF- α levels, and potential anti-fibrotic properties^[184]. In some trials, PTX has shown improvement in steatosis, lobular inflammation and ballooning degeneration in comparison to baseline, but improvement was not clinically significant when compared to placebo^[185]. In a small RCT on NASH patients, 400 mg PTX given three times per day for a period of 1 year decreased hepatic steatosis, inflammation and NAS by ≥ 2 points and modestly reduced fibrosis^[186]. This favorable response was due to a reduction in free-radical-mediated lipid peroxidation^[187]. In two recent small RCT evaluating the role of PTX has also shown beneficial effect by improving liver enzymes and histology in NAFLD patients^[188,189]. In a recent meta-analysis it was found that only PTX and OCA improve fibrosis in NASH patients^[190]. Therefore, further studies are warranted to determine its role in NAFLD/NASH treatment.

Others

Probiotics: Like alcoholic patients, NAFLD patients also exhibit gut bacterial overgrowth, enhanced gut permeability and increased paracellular leakage of gut luminal antigens, factors that promote NASH development. Thus, probiotics can be a therapeutic option for NASH patients^[191,192]. In a RCT, improvement in liver enzymes was noted in NAFLD patients on *Lactobacillus bulgaricus* and *Streptococcus thermophilus* treatment compared to placebo^[193]. In another study, patients randomized to a combination of *Bifidobacterium longum* with fructo-oligosaccharides plus lifestyle

modification (diet and exercise) or lifestyle modification alone for 24 wk^[194], showed a significant decrease in steatosis, TNF- α , AST and NAS in the combination treatment group. Thus, probiotics could also be a part of a combination therapy for NAFLD patients.

Angiotensin receptor blockers: NAFLD is often associated with metabolic syndrome and hypertension is an important component of metabolic syndrome. Thus, angiotensin receptor blockers can be a part of combination therapy regimen of NAFLD. A small pilot study of patients with NASH showed improvements in necro-inflammation and fibrosis with losartan (an angiotensin II receptor antagonist) treatment^[195]. Larger studies are required to explore their potential in the management of NAFLD.

Endocannabinoid antagonists: CB1 and CB2 are two receptors which mediate endocannabinoid (EC) activity. The CB1 receptor is mainly expressed in the brain and liver, while CB2 is mainly expressed in the immune cells. These receptors are found to be upregulated in various liver diseases^[196]. Anandamide, a highly potent endogenous agonist, has been shown to promote diet-induced obesity and hepatic steatosis in mice *via* acting on the CB-1 receptors^[197]. Conversely, CB-1 knockout or rimonabant (CB-1 receptor antagonist)-treated high-fat diet fed mice have less steatosis and weight gain than controls^[198]. However, while rimonabant was effective in promoting weight loss of obese patients in many clinical trials, it also caused intolerable adverse effects like depression, anxiety and increased suicidal tendencies that has led to its discontinuation for routine use. Thus, novel cannabinoid type 1 receptor blockers with selectivity for peripheral receptors are required which can have favorable metabolic benefits but decreased psychiatric adverse effects^[199,200].

Bariatric surgery: Steady weight loss with exercise and lifestyle modification has been found to increase insulin sensitivity and improve liver histology of NAFLD patients. But the rapid weight loss induced by bariatric surgery increases the risk of developing hepatic failure especially in the cirrhotic patients^[201,202]. Bariatric surgery is mostly done in non-cirrhotic NAFLD patients who are morbidly obese. It is, however, not recommended as a primary mode of treatment in such patients as there is still a risk of developing liver failure postoperatively.

Liver transplantation: NAFLD patients with end-stage decompensated liver disease should be considered for liver transplantation. But this is not a permanent cure as NAFLD has been shown to recur in post-transplant liver^[203]. This is because transplantation does not correct the multifactorial pathway alteration(s) responsible for NAFLD/NASH development. Therefore, the goals of therapy before and after transplant should be always

towards weight management, proper diet consumption and adequate control of glucose and lipids.

Potential new therapeutic options in NAFLD

With advancement in the field of technology, especially bioinformatics and biogenetics, new therapies are currently being tried for managing NASH, some of which are reviewed below.

Caspase inhibition/emricasan: Caspases are enzymes which are required for completion of various apoptotic pathways and for stimulation of various cytokines and therefore, can be a potential therapeutic target. Various animal studies in the past have supported this approach^[204,205]. Emricasan, a pan-caspase protease inhibitor, has been shown to inhibit apoptosis, inflammation and fibrosis in a preclinical model of NASH. A preliminary report of a phase II clinical trial showed significantly decreased serum ALT and cCK18 levels in NAFLD patients^[206]. The therapeutic effects of this drug have also been examined in various other fibrotic liver diseases where it has been shown to reduce hepatic venous pressure gradient (HVPG). A phase II trial on NASH patients with fibrosis (ClinicalTrials.gov Identifier: NCT02686762) is ongoing to evaluate the efficacy of emricasan (10 mg and 100 mg/d for 72 wk) to improve fibrosis without worsening of NASH (primary endpoint) and to assess histological improvement or resolution of NASH (secondary endpoint).

ASK1 inhibitors/ASK1-I: Apoptosis signal regulating kinase 1/ASK1 is a MAP3 kinase (mitogen activated protein 3 kinase) which induces apoptosis and fibrosis when activated by stimuli like hyperglycaemia, TGF- β and ROS. This enzyme has been shown to be activated in patients with NASH. GS 4997, a first-in-class, oral small molecule ASK1 inhibitor, given to animals with established NASH showed a significant reduction in hepatic steatosis, fibrosis, body weight, fasting blood glucose, insulin resistance, lipogenesis, cholesterol biosynthesis, plasma AST/ALT levels, and soluble/insoluble collagen and many metabolic parameters of NASH^[207-209]. GS-4997 is currently being investigated in a phase II clinical trial of patients with NASH (ClinicalTrials.gov Identifier: NCT02466516).

p38 MAPK inhibitors: Chronic inflammation is one risk factor that contributes to progression of NAFLD. p38 mitogen activated kinases (p38 MAPK) is a stress kinase whose activation has been shown to promote inflammation^[210-212]. In mammals, four p38 MAPK isoforms have been identified: p38a, b, c and d. p38 MAPK isoforms -c and -d have recently been shown to contribute to the development of steatosis and NASH in various models of NAFLD by regulating T-cell activation, neutrophil recruitment and macrophage production of TNF- α ^[213,214]. Studies have shown higher liver expression of p38 protein in obese individuals

with steatosis. Thus, deletion of p38 α and δ in the myeloid cells prevents neutrophil migration to the liver, protecting these animals against diet induced steatosis and inflammation^[215]. Therefore, p38 MAPK can be an effective potential target for NAFLD therapy.

PPAR- α and δ agonists (Elafibranor): PPAR- α is mainly expressed in liver and is principally involved in lipid metabolism, while PPAR- δ is found in various tissues of the body and is involved in fatty acid oxidation and insulin sensitivity. In various animal models, PPAR has been shown to be hepato-protective *via* its effect on decreasing lipid accumulation, inflammation and fibrosis^[216-218]. In a RCT (clinicaltrials.gov NCT01694849), a daily dose of 80 or 120 mg Elafibranor or placebo was given to non-cirrhotic NASH patients for 52 wk^[219]. The primary endpoint of this study (i.e. resolution of NASH without worsening of fibrosis), was not met. However, it was found that patients with an initial NAS of ≥ 4 on 120 mg/d of drug showed significant improvement in hepatic inflammation. Nevertheless, Elafibranor efficacy was described as sub-optimal. Another study is in phase 3 clinical trial to clarify Elafibranor's (GFT505) effectiveness (ClinicalTrials.gov: NCT02704403) to improve the histological grade and reduce all-cause mortality and liver-related outcomes in patients with NASH and fibrosis.

Farnesoid X receptor/FXR agonists (Obeticholic acid): Obeticholic acid (OCA) is a Farnesoid X receptor agonist. It is a synthetic derivative of natural bile acid chenodeoxycholic acid (CDCA), with potency 100 times more than CDCA. Farnesoid X receptor is a nuclear hormone receptor which regulates bile, cholesterol, glucose and lipid metabolism^[220,221]. These receptors act *via* multiple pathways; they inhibit hepatic lipogenesis, gluconeogenesis, glycogenolysis and maintain cholesterol balance and improve insulin sensitivity^[222,223]. In various animal models, OCA has shown anti-inflammatory and anti-fibrotic properties and also improves insulin resistance and hepatic steatosis^[224]. In an animal model, OCA was shown to reduce hepatic inflammation and fibrosis and also decreased intrahepatic vascular resistance and improved portal hypertension^[225]. Also in an animal model with advanced cirrhosis, treatment with OCA was shown to reduce gut bacterial translocation from 78.3% to 33.3% ($P < 0.01$) indicating its effect in maintaining intestinal barrier integrity. Thus, it can be used as an option to prevent bacterial infection in such patients^[226]. In a small pilot trial of diabetic patients with NAFLD, it was shown to decrease weight and serum γ -glutamyl transferase levels as well as an improvement in liver fibrosis^[227]. The multicenter trial (FLINT trial: NCT01265498) showed a decrease in NAS, an improvement in hepatic steatosis, and a small decrease in liver fibrosis in non-cirrhotic NAFLD patients on a daily dose of 25 mg OCA compared to

placebo^[228]. A phase 3, double blind RCT multicenter study is ongoing to evaluate the safety and efficacy of OCA in NASH patients (ClinicalTrials.gov Identifier: NCT02548351). The effect of OCA on liver histology in non-cirrhotic NASH patients with stage 2 or 3 fibrosis will be compared to placebo. 2065 patients are randomized in 1:1:1 to receive 10 mg OCA, 25 mg OCA or placebo. An interim analysis is to be done at 18 mo and the study is expected to end in 6 years. However, an increase in total cholesterol and triglycerides with a decrease in high density lipoprotein was also seen in the OCA group when compared to placebo^[228]. Two phase I studies conducted in healthy individuals given OCA for 14-20 d also reported decreased HDL and increased LDL cholesterol, regardless of the dose of OCA (5, 10 or 25 mg daily)^[229,230]. These pro-atherogenic effects can be a concern for NAFLD patients that already have a high risk for cardiovascular adverse events because of dyslipidemia. Therefore, combination therapies with FXR agonist and agents that prevent atherosclerosis are warranted. Apart from OCA, various other FXR agonists such as GW4064, PX20606, GS-9674 and INT-767 are being tested. GW4064, PX20606 and GS-9674 are synthetic non-steroidal FXR agonists. INT-767 is a dual agonist for FXR and TGR5 (the transmembrane G-protein bile acid receptor) while BAR502 is a dual agonist for FXR and GPBAR1 receptors. In various animal models, these agonists have been shown to improve NASH histological features, steatosis and fibrosis^[231-234]. Thus, clinical trials are anticipated for these agents as well.

NOX-1/4 inhibitors: NADPH oxidase (NOX), is an enzyme which catalyzes the production of ROS^[235]. In various animal models these enzymes are expressed on hepatic stellate cells and promote liver fibrosis and inflammation^[236]. In a murine model, NOX 1/4 inhibitor (GKT137831) has been found to decrease ROS production and fibrotic gene expression, thus decreasing liver inflammation and fibrosis^[235]. Therefore, these agents can have a beneficial effect in decreasing liver fibrosis in NASH patients but require further studies.

Galectin-3 antagonists: Galectins are proteins that bind to terminal galactose residues on glycoproteins^[237]. They are usually expressed in immune cells and are at very low levels in the body but their levels are increased during inflammation and fibrosis^[238,239]. Galectin-3 knockout mice show reduced hepatic fibrosis after liver injury. GR-MD-02, a galectin-3 inhibitor, has shown a decrease fibrosis, hepatic steatosis and collagen deposition in various animal models with NASH^[240]. A Phase II clinical trial for evaluation of the safety and efficacy of GR-MD-02 for the treatment of liver fibrosis and associated portal hypertension in patients with NASH cirrhosis is currently underway (ClinicalTrials.gov Identifier: NCT02462967). This study has enrolled

subjects with portal hypertension and biopsy proven NASH cirrhosis (excluding subjects with medium and large varices and those with decompensated cirrhosis). The expected primary completion date is October 2017 while the study is expected to complete in February 2018.

Acetyl CoA carboxylase inhibitor: Malonyl coenzyme A plays a key role in fatty acid metabolism that maintains a balance between lipogenesis and lipid oxidation^[241]. It promotes fatty acid synthesis, and inhibits β -oxidation of lipids. Malonyl CoA is generated from acetyl CoA and the key enzyme regulating this process is acetyl CoA carboxylase (ACC). Therefore, inhibiting ACC prevents fatty acid synthesis and promotes its oxidation. In a murine model of NAFLD, inhibition of ACC has been shown to decrease hepatic steatosis, lipogenesis and increase insulin sensitivity and fatty acid oxidation^[241]. Chronic administration of ND-630 (ACC isozyme 1 and 2 inhibitor) to diet-induced obese rats and Zucker diabetic fatty rats caused a reduction in hepatic steatosis, lowered haemoglobin A1C (0.9% reduction) and improved insulin sensitivity^[242]. Also in a crossover, randomized, double-blind trial, administration of a single dose of NDI-010976 (a highly potent and selective inhibitor of both ACC1 and ACC2) to overweight/obese subjects inhibited *de novo* lipogenesis in a dose dependent manner^[243]. Together, all these results suggest its usefulness in treating metabolic syndrome, type 2 diabetes mellitus, and fatty liver disease. Thus, large long term clinical trials in humans are needed.

FGF-21 and FGF-19 analogues: FGF-21 (fibroblast growth factor 21) is a hormone which is secreted mainly from the liver. It is a starvation-induced peptide hormone with pleiotropic effects whose levels are mainly increased during fasting^[244,245]. While FGF-21 concentrations are elevated in human subjects with NAFLD, a lack of FGF-21 worsened the metabolic disorders in an animal model of NASH^[246]. Conversely, treatment with FGF-21 analogue (BMS-986036) was found to improve insulin sensitivity, hepatic steatosis and decrease lipogenesis^[247]. In another animal model of NASH, LY240531 (a FGF-21 variant) was shown to increase fatty acid oxidation by enhancing hepatic mitochondrial oxygen consumption. Also, various inflammatory markers and AST and ALT levels were reduced, suggesting an attenuation of liver injury^[248]. BMS-986036 is currently being evaluated in a phase II trial of NASH patients (ClinicalTrials.gov Identifier: NCT02413372).

FXR activation in terminal ileum by bile acid promotes FGF-19 secretion which, in turn, decreases bile acid synthesis and gluconeogenesis^[245]. It also results in the activation of the FGFR4 receptor which has a proliferative impact on hepatocytes, thus raising the potential for tumorigenesis^[249]. NGM-282, a variant of FGF-19 has been shown to decrease bile acid synthesis

and gluconeogenesis without having a tumorigenic effect^[245]. In a preliminary pre-clinical study, NGM-282 was shown to improve hepatic steatosis and histological features of NASH in an animal model^[250].

CCR2 and CCR5 inhibitor (cenicriviroc): CCR2 and CCR5 are chemokine receptors which are mainly expressed in various immune cells like monocytes, macrophages, Kupffer cells, natural killer cells, T cells and stimulate hepatic stellate cells thus promoting fibrosis. These receptors can be inhibited by cenicriviroc (CVC) which is an inhibitor of the CCR2 and CCR5 receptors. CVC has been shown to decrease fibrosis and inflammation in various animal models of diet-induced NASH or substance-induced NASH^[251-254]. There is an ongoing trial (ClinicalTrials.gov Identifier: NCT02217475) with CVC to examine its efficacy in NASH patients with fibrosis. It will compare shorter vs longer CVC treatment and assess correlations between decreased inflammation and fibrosis^[255].

SCD-1 inhibitors (aramchol): Aramchol is a synthetic lipid molecule which decreases hepatic fat accumulation by decreasing lipogenesis and increasing fatty acid oxidation by inhibiting stearoyl coenzyme A desaturase 1 (SCD1) enzyme^[256]. This drug was found to decrease liver fat content significantly in 60 NAFLD patients who were given 100 or 300 mg of this drug daily for 3 mo; the effect of the drug on fibrosis was not determined^[256]. A phase II clinical trial of this drug is ongoing on NASH patients with fibrosis (ClinicalTrials.gov Identifier: NCT02279524).

Lysyl oxidase-like 2 inhibitor (sintuzumab): Lysyl oxidase-like 2 inhibitor is an enzyme which causes cross linkage of collagen, thus preventing its degradation^[257]. This enzyme has been found to promote fibrosis in liver diseases of various etiologies. A monoclonal antibody (sintuzumab) to this enzyme has been studied in various animal models and has shown to decrease fibrosis^[258]. Two big trials are ongoing to examine the efficacy of this drug in decreasing fibrosis and preventing progression to cirrhosis in such patients (ClinicalTrials.gov Identifier: NCT01672866 and NCT01672879).

Sirtuins: Sirtuins (SIRT) are information regulator proteins. There are various types of SIRT found in mammals. SIRT-1, a member of this family of proteins, has anti-inflammatory effects and increases insulin secretion and sensitivity^[259]. A decreased liver expression of SIRT-1 was observed in an animal model of NAFLD^[260]. Since SIRT-1 activator (resveratrol) was shown to improve hepatic steatosis and insulin sensitivity^[261], SIRT-1 could be a potential target for treatment of NAFLD patients' in future clinical studies.

Betaine: A phase II clinical trial of betaine in patients with a clinical diagnosis of NAFLD is close to completion.

This trial (ClinicalTrials.gov Identifier: NCT03073343) will evaluate the effect of two doses of oral betaine in reducing ALT levels in NAFLD patients with and without diabetes.

CONCLUSION

Both ALD and NAFLD are chronic liver diseases with similar spectrums from simple steatosis to cirrhosis with basic differences only in their etiology. Despite understanding much of the pathophysiology of both diseases, there is still no effective treatment for either disease. The treatment for ALD basically relies on alcohol abstinence, nutritional support, lifestyle modifications, steroids and symptomatic treatment of complications of cirrhosis while for NAFLD, the focus of treatment is on weight loss, exercise and the use of insulin sensitizers. Removal of the cause would be the most efficient way of treating both diseases. However, the involvement of several inter-related pathways in the pathogenesis of these diseases indicates that a single therapeutic agent is unlikely to be an effective treatment strategy. Hence, a combination therapy towards multiple targets would eventually be required. Future areas of research also include the safety, efficacy, and ethical considerations of liver transplant in severe ASH for patients who are not responding to medical therapy. Various new target-oriented therapies are under investigation for both diseases and hopefully soon we will be having an effective multi-therapeutic regimen for each disease.

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