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Review

Therapeutic targets in alcohol-associated liver disease: progress and challenges

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***Abstract*:** Alcohol-associated liver disease (ALD) is a complex disease with rapidly increasing prevalence. Although there are promising therapeutic targets on the horizon, none of the newer targets is currently close to an Food and Drug Administration approval. Strategies are needed to overcome challenges in study designs and conducting clinical trials and provide impetus to the field of drug development in the landscape of ALD and alcoholic hepatitis. Management of ALD is complex and should include therapies to achieve and maintain alcohol abstinence, preferably delivered by a multidisciplinary team. Although associated with clear mortality benefit in select patients, the use of early liver transplantation still requires refinement to create uniformity in selection protocols across transplant centers. There is also a need for reliable noninvasive biomarkers for prognostication. Last but not the least, strategies are urgently needed to implement integrated multidisciplinary care models for treating the dual pathology of alcohol use disorder and of liver disease for improving the long-term outcomes of patients with ALD.

Keywords: AH, ALD, cirrhosis, transplantation

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The burden of alcohol-related liver disease (ALD) has been increasing in recent years.[1–5] The coronavirus pandemic has further exacerbated the problem by creating an upsurge in excessive alcohol consumption and consequently, morbidity and mortality attributable to ALD.[6] For example, during the pandemic, there was over twofold increase in ALD-related hospitalizations and alcoholic hepatitis (AH)-related liver transplant (LT) waitlist additions.[1,2] At present, ALD is the most common indication for LT in the United States.[2,5]

The current management strategies include treatment of alcohol use disorder (AUD), the use of corticosteroids for severe AH, management of cirrhosis and its complications, and LT in severe ALD.[7,8] Corticosteroid, currently the only and a first-line pharmacological therapy for severe AH remains a suboptimal treatment. Response rates as determined by a Day 7-Lille score of $\leqslant$0.45 (Figure 1) are 50–60%. In non-responders, early LT (eLT) is a viable alternative. However, it can be applied in only about 3–4% of all the severe AH patients.[8]

Despite the proven benefit of treatment of AUD in ALD patients, it is rarely used in clinical practice.[9,10] Multidisciplinary integrated care models have been shown to be effective; yet, implementation in clinical practice remains challenging.[10–12] Furthermore, ineligibility for corticosteroids in 40–50% of severe AH patients, response rate of 50–60% among those who are eligible, and survival benefit lasting only for a short-term period of 1 month limit their widespread and homogeneous use.[13–22] Moreover, LT although beneficial in ALD can only be applied to 3–4% of highly select severe AH patients with an excellent psychosocial support.[23,24] As criteria for patient selection for LT in AH remain subjective, there remains significant heterogeneity in the use of this modality of treatment across providers and centers.[25] In the light of these limitations, the quest for novel,

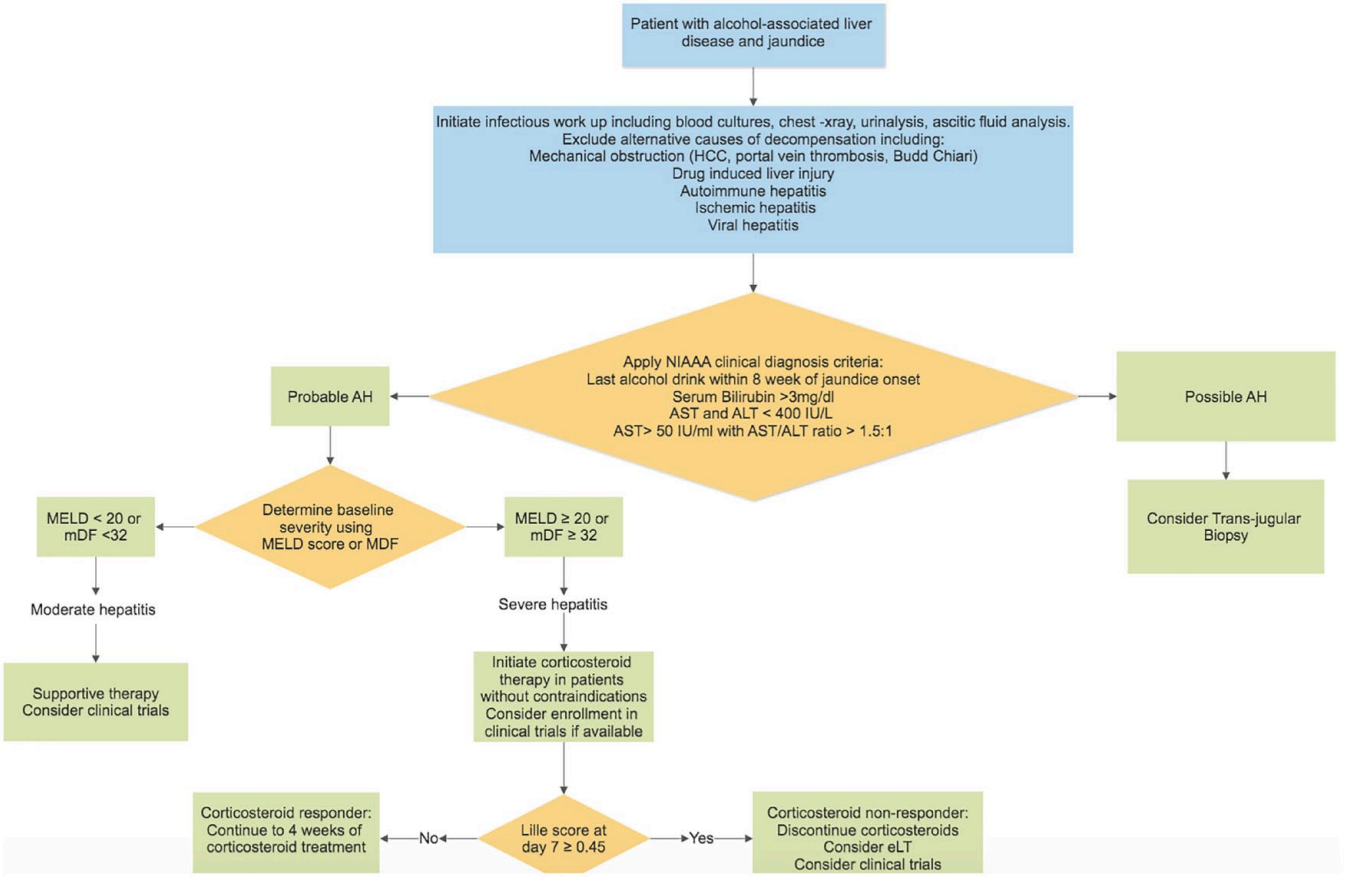

Figure 1. Algorithm in the management of AH.
AH, alcoholic hepatitis; mDF, modified discriminant function; MELD, model for end-stage liver disease.

diverse therapeutic agents remain a worthy and much needed endeavor. In this review, we will discuss the emerging therapeutic targets in ALD, current challenges, and future directions. Since experimental targets are guided by current understanding of pathophysiologic mechanisms, we will begin with a review of pertinent pathophysiology to create a framework for understanding the therapeutic targets.

Pathophysiology of ALD

The spectrum of liver injury in ALD from ranges from steatosis, steatohepatitis (inflammation and hepatocyte death), fibrosis, and ultimately cirrhosis and its complications.[26–28] The pathogenesis includes direct ethanol induced liver injury *via* its metabolism, and indirect injury *via* changes in gut permeability leading to endotoxemia, immune-mediated inflammation, and impaired liver regeneration.[27,29,30] Ethanol is metabolized by alcohol dehydrogenase into acetaldehyde, which is further metabolized by acetaldehyde dehydrogenase into acetate. Once acetaldehyde dehydrogenase is saturated, ethanol is channeled to other metabolic pathways including the cytochrome P450 2E1 (CYP 2E1) system.[31] The metabolism of ethanol via this system results in production of reactive oxygen species with many downstream effects such as activation of lipid peroxidase reactions, inhibition of membrane antioxidant enzyme activity, biomembrane dysfunction, mitochondrial damage, and cell death.[27,32] The ensuing inflammation and cell damage causes release of damage-associated molecular patterns that attract inflammatory cells and induce sterile inflammation.[27] The process involves the formation of inflammasomes and the release of proinflammatory cytokines including tumor necrosis factor alpha (TNFα), interleukin 1 (IL1).[33,34]

Alcohol also exerts a direct effect on the gastrointestinal tract. It disrupts the tight junctions of the intestinal epithelial barrier, inducing an increase in gut permeability.[35,36] This increased permeability increases bacterial translocation and delivery of pathogen-associated molecular patterns including endotoxin into the portal circulation.[30,35,37] These gut-derived endotoxins act through toll-like receptor 4 (TLR-4) to activate innate immune cells, release chemokines and cytokines such as IL-1, IL-6, and monocyte chemoattractant protein MCP1, and upregulate proinflammatory and profibrotic pathways.[33,34,36,38]

Alcohol also induces changes in the gut microbial flora in both small and large intestines.[39,40] One study found reduced numbers of *bifidobacteria, lactobacillus*, and *enterococcus* species in the stool cultures of individuals who habitually consumed alcohol.[39] In addition, jejunal aspirates of individuals who consume alcohol excessively have been shown to have more abundant coliforms compared to controls.[40] Reduced fungal biodiversity has also been described in severe AH.[41]

Alcohol induces metabolic and cellular changes which contribute to liver inflammation.[42,43] It upregulates several proteins including carbohydrate-responsive element binding protein, steroid response binding protein-1c, and glucose-responsive transcription factor, that mediate hepatic steatosis.[44–47] It is also thought to induce insulin resistance in adipose tissues, resulting in an increase in circulating non-esterified fatty acids.[48,49] Alcohol also affects other regulators of steatosis including the liver X receptor (LXR), farnesoid X receptor (FXR) and peroxisome proliferator-activated receptor (PPAR) α.[49] The resultant accumulation of free fatty acids in the liver induces hepatic inflammation by activating TLR-4-mediated inflammatory pathways, activating inflammasome and stimulating chemokine production.[43,50–52]

Alcohol-induced changes in iron metabolism have also been implicated in ALD. Alcohol is believed to upregulate iron absorption by downregulating expression of hepcidin[53,54] The resultant iron overload contributes to ethanol induced oxidative stress by activating Kupffer and hepatic stellate cells, and triggering ferroptosis, a programmed iron-dependent cell death.[53]

AH is characterized by hepatocyte injury, inflammation, ballooning degeneration, disruption of the cytoskeleton, and formation of Mallory–Denk bodies.[55] In addition to hepatocyte damage, there is direct impairment of liver regeneration, especially in patients with severe refractory AH. A study of explanted livers from patients undergoing salvage transplants for AH revealed a lack of proliferative hepatocytes and a diminished expression of cytokines involved in liver regeneration.[29] The same study also demonstrated an accumulation in the livers of affected patients, of a substantial amount of hepatic progenitor cells which are inefficient at yielding mature hepatocytes.[29]

Emerging therapeutic targets

The above pathophysiologic mechanisms have been the targets of investigational therapies for the treatment of ALD in recent years. While some have yielded no benefit, others have shown varying degrees of promise and are currently the subject of further investigation.[56] Experimental agents have aimed at inhibiting inflammatory pathways including blockade of gut liver axis activation, reducing oxidative stress, inhibiting apoptosis, and promoting liver regeneration. More recently, interest has arisen in targeting metabolic pathways with the aim of inhibiting steatosis – an important shared underlying mechanism of injury in alcohol and non-alcohol-mediated liver disease. Published clinical trials of agents targeting the aforementioned pathophysiologic mechanisms and ongoing clinical trials for ALD treatment are summarized in Table 1.

Inhibition of inflammatory pathways

IL1 inhibition

Canakinumab. Canakinumab is a fully human monoclonal antibody which blocks inflammation by targeting IL-1β and subsequently, the IL-6 signaling pathway.[57,58] The anti-inflammatory effect of canakinumab has been employed in the treatment of rheumatologic conditions.[58] It has also been explored in diabetes and atherosclerotic cardiovascular disease[57,59] The IL-1 signal inhibition in alcoholic hepatitis trial, a multicenter randomized controlled trial (RCT) investigated the effect of canakinumab in 48 patients with biopsy confirmed AH who had discriminant function $\geqslant 32$ and model for end-stage liver disease

Table 1. Currently ongoing clinical trials in ALD.

Trial title (brief)	Trial design	Intervention	Study population	Primary outcome (s) of interest	Target pathway	NCT number
Phase 1						
Safety evaluation of FMT in severe AH	Double-blinded randomized placebo-controlled trial	FMT	Patients with SAH MELD score > 15 and/or MDF ⩾ 32	-Survival in treatment group -Change in gut microbiome population associated with severe AH patients at 4, 6, 9, and 12 weeks	Gut–liver axis modification	NCT05006430
Safety and efficacy of IMM 124-E for patients with severe AH	Multicenter randomized placebo-controlled	IMM 124-E (Hyperimmune Bovine Colostrum)	MELD ⩾ 20 but ⩽ 28 with < 7 days of steroid treatment, or treatment naive	Safety	Gut–liver axis modification	NCT01968382
Phase 2						
DUR-928 in patients with AH	Open-label dose-escalation trial	DUR-298	Part A: patients with MELD 11–20 Part B: patients with a MELD score of 21–30	-Safety and tolerability -Pharmacodynamic of DUR-298: liver biochemistry Quality of life Biomarkers of inflammation (IL-6, IL-8 and CRP) Biomarkers of liver cell death (cytokeratin 18), measured at baseline, Day 7, and Day 28	Liver regeneration boosting	NCT03917407
A phase IIb study in subjects with AH to evaluate safety and efficacy of DUR-928 treatment	Randomized, double-blind, placebo-controlled	DUR-298	Patients with MELD 21–30 and MDF ⩾ 32	90-day mortality or LT comparing 30 mg or 90 mg of DUR-928, and placebo	L\Boosting liver regeneration	NCT03917407
TAK-242 in patients with acute AH	Randomized, double-blind, placebo-controlled, multicenter	TAK-242	Acute decompensating event with a clinical and/or liver biopsy diagnosis of AH	Change in CLIF-C ACLF score (chronic liver failure consortium organ failure acute on chronic liver failure score) from baseline to Day 8	Inflammatory pathway inhibition (TLR 4 signaling inhibitor)	NCT04620148
Phase III						
Fecal microbial transplantation in severe AH	Open-label, single-arm trial	FMT	Severe AH	Mortality at 28 days, 90 days, and 1 year	Gut–liver axis modification	NCT04758806
Comparison of bovine colostrum *versus* placebo in treatment of severe AH: A randomized double-blind controlled trial	Randomized controlled, parallel, double-blind trial	Bovine colostrum	Severe AH MDF > 32 MELD ⩾ 21	Survival at 3 months	Gut–liver axis modification	NCT02473341
NAC to reduce infection and mortality for AH	Randomized controlled, open-label trial	NAC	Severe AH MDF > 32	Improvement in monocyte oxidative burst at 24 h and at 5 days	Oxidative stress inhibition	NCT03069300
Phase IV						
Efficacy and safety of S-adenosyl-l-methionine in treatment of AH with cholestasis	Randomized, parallel, open-label trial	Ademethionine	AH Serum total bilirubin from 2 to 10× ULN ALP > 1.5× ULN or GGT > 3× ULN	Response rate of serum total bilirubin at 6 weeks	Oxidative stress inhibition	NCT02024295

(Continued)

Table 1. (Continued)

Trial title (brief)	Trial design	Intervention	Study population	Primary outcome (s) of interest	Target pathway	NCT number
G-CSF in AH	Randomized control parallel, open-label trial	G-CSF	Severe AH DF of ⩾32	Survival at 3 months	Boosting liver regeneration	NCT03703674
Unspecified phase						
Utility of the use of NAC associated with conventional treatment in patients with severe AH (Maddrey > 32)	Randomized controlled, multicenter parallel and open trial	NAC	Severe AH	All-cause mortality at 6 months	Oxidative stress inhibition	NCT05294744
Efficacy of monotherapy *versus* combination therapy of corticosteroids with G-CSF in severe AH patients	Randomized controlled open-label trial	G-CSF	Severe AH, DF of ⩾32	Improvement in CTP (Child-Pugh Score) and MELD in at 28 days and 180 days	Boosting liver regeneration	NCT04066179
Fecal microbiota therapy in steroid ineligible AH	Randomized controlled, parallel open-label trial	Fecal microbiota therapy	Steroid ineligible severe AH (MELD) ⩾ 20 and MDF ⩾ 32)	Mortality at 3 months LT-free survival	Gut–liver axis modification	NCT05285592
Integrating care for patients with alcohol liver disease and AUDs	Single-arm, open-label trial	ICP	Patients with clinical or biopsy-proven alcohol-associated cirrhosis or acute AH	Acceptability of and retention to the ICP	Integrated AUD treatment	NCT05375682
Alcohol treatment outcomes following early *versus* standard LT for SAH	Randomized controlled single-blinded trial	Integrated AUD treatment	Patients who have undergone LT for AH	Treatment engagement Alcohol relapse Post-LT survival	Integrated AUD treatment	NCT03845205
Corticosteroids in AH	Randomized controlled double-blinded trial	Corticosteroids	Biopsy proven Severe AH (MDF ⩾ 32) with spontaneous liver function improvement within day admission and days 5–10 of admission	Mortality at 90 days	Inflammatory pathway inhibition	NCT03160651
ALD and gut microbiome	Randomized controlled double-blinded trial	VSL #3 112.5 Capsule (probiotic)	Adults with diagnosis of AUD and ALD	Sex differences within ALD (from baseline to 6 months) Sex differences in the rate abstinence and the proportion of resolution of ALD as measured by the MDF, MELD-Na score, GAHS, and transaminases	Gut–liver axis modification	NCT05007470
CytoSorb® in patients with acute on chronic liver failure	Prospective case–control	Device: CytoSorb® treatment	Patients with ACLF due to severe AH in combination with systemic inflammation and ACLF grade ⩾2	-Safety and tolerability -Effectiveness by comparing the proportion of patients in each group with ACLF grade < 2 at the end of Day 7	Inflammatory pathway inhibition	NCT05131230
Effect of omega 5 fatty acid as an adjuvant treatment to prednisone in patients with severe AH	Randomized controlled double blinded trial	Dietary supplement: omega 5 fatty acid supplement	Patients with severe AH treated with prednisone	30-day survival	Influencing metabolic pathways – PPAR γ agonist	NCT03732586

ACLF, acute on chronic liver failure; AH, alcoholic hepatitis; ALD, alcohol-associated liver disease; ALP, alkaline phosphatase; AUD, alcohol use disorder; G-CSF, granulocyte colony-stimulating factor; GGT, gamma-glutamyl transferase; FMT, fecal microbiota transplant; ICP, Integrated care program; LT, liver transplant; MDF, Maddrey discriminant function; MELD, model for end-stage liver disease; NAC, N-acetylcysteine; PPAR, peroxisome proliferator-activated receptor; SAH, severe acute alcoholic hepatitis; ULN, upper limit of normal.

(MELD) ⩽ 27 at baseline visit (Table 1).[60] Compared to the placebo group, the canakinumab-treated group demonstrated a higher rate of histological improvement (58.3 *versus* 41.7%). In an adjusted exploratory analysis, the canakinumab-treated group demonstrated improvement in alanine aminotransferase ($p = 0.02$), mononuclear cell infiltration ($p = 0.06$), and histology ($p = 0.04$). However, there was no significant improvement noted in MELD and Lille scores.[61]

Anakinra. Anakinra, an IL-1 receptor antagonist blocks IL-1α and IL-1β biologic activity. Findings from a multicenter trial, defeat alcoholic steatohepatitis trial comparing the efficacy of Anakinra in combination with zinc and pentoxifylline to that of prednisolone in the treatment of severe AH, suggested lower mortality at 180 days.[62] Results are awaited from a recently completed multicenter, randomized, double-blinded, placebo-controlled trial investigated the effect of Anakinra combined with zinc *versus* prednisone in patients with severe AH (MELD 20–35).[63]

Initial studies suggested that pentoxifylline might be beneficial in reducing acute kidney injury and hepatorenal syndrome (HRS) in severe AH.[64] A subsequent network meta-analyses of 22 RCTs concluded that pentoxifylline has no benefit in severe AH patients.[64] Although anti-TNFα agents (infliximab and etanercept) initially showed promise in smaller studies, successive studies revealed unacceptable infection and mortality rates.[65–68] Caspase inhibitors, selonsertib and emricasan, have also not shown any survival benefit. The study investigating emricasan in patients with severe AH and contraindications to steroid therapy was terminated due to concerns about toxicity and bioavailability of the drug.[69,70]

Modulating gut–liver axis and inflammation

Fecal microbiota transplant

Fecal microbiota transplant (FMT) has been explored as a potential way to ameliorate gut dysbiosis in AH.[71] FMT has previously been tremendously successful in the treatment of recurrent *Clostridioides difficile* infection but is now being explored in other gastrointestinal diseases.[72,73] An open-label trial comparing 90-day survival in corticosteroids, pentoxifylline, nutritional therapy, or FMT in male patients with AH revealed an improved mortality at 1 month and 3 months in the group treated with FMT compared to all the other groups. Improvement in infections, inflammation, and oxidative stress were also noted.[74] More recently, in a retrospective study comparing FMT to standard of care among patients with AH, the incidence of ascites, hepatic encephalopathy, critical infection, and need for hospitalization were found to be lower in the FMT group compared to the SOC group. There was also a trend toward improvement in mortality at 3 years.[75] Findings from further ongoing trials investigating this are awaited (Table 1). FMT can also be a double-edged sword, with its additional benefit on reducing alcohol use relapse. In a pilot randomized trial on 20 patients with alcohol-associated cirrhosis, FMT-treated patients compared to those receiving placebo showed a significant reduction in craving (90 *versus* 30%), lower urinary ethylglucoronide levels, ($p = 0.03$), and an improvement in psychosocial quality of life and cognition.[76]

Probiotics

Studies exploring the role of various combinations of probiotics including *Bacillus subtilis* and *Enterococcus faecium*, *Lactobacillus casei* as well as *Bifidobacterium* and *Lactobacillus* have shown varying degrees of benefit. The areas of improvement have included reduction in endotoxemia, improvement in liver function,[77] improvement in neutrophilic phagocytic function, and a decrease in TLR expression.[39,78] One US-based trial that had been investigating the safety and efficacy of *Lactobacillus rhamnosus* GG compared to placebo on MELD score after 30 days was terminated due to lack of funding.[79] Another trial investigating the therapeutic effect of *Lactobacillus rhamnosus* R0011/*acidophilus R0052* on primary outcome of liver enzymes at 7 days has been completed but results are yet to be published.[80]

Bovine colostrum

Bovine colostrum, the first milk produced from cows after parturition is immunoglobulin rich and has been shown to decrease bacterial translocation and endotoxemia in rats.[81,82] The rationale for its use is that IgG and lactoferrin, both present in bovine colostrum can neutralize endotoxemia within the lumen and portal system. The IgG can also bind to the lymphoid tissue of leaky gut and reduce permeability.[83,84] A randomized double-blinded placebo-controlled trial aiming to

compare bovine colostrum *versus* placebo in treatment of severe AH (BASH) is currently recruiting participants in India (Table 1). A second trial investigating the safety and efficacy of hyperimmune bovine colostrum enriched with IgG anti-LPS, IMM I24-E in patients with severe AH (MELD 20–28) on steroids is ongoing (Table 1).

Antimicrobial agents

Rifaximin, a minimally absorbed broad spectrum antibiotic agent, has been shown to decrease endotoxemia.[85] However, clinical trials with this agent did not yield any significant benefit in patients with AH.[86,87] Other microbial agents including amoxicillin plus clavulanic acid as well as a combination of meropenem, vancomycin, and gentamycin also failed to demonstrate any survival benefit in severe AH patients.[88,89]

Phage therapy

Patients with AH have been shown to have higher fecal counts of cytolysin producing *E. faecalis* species, which have been correlated with increased severity and mortality in AH. In a recent study, targeting this cytolysin using a bacteriophage abolished ethanol-induced liver disease in humanized mice. These interesting findings are yet to be translated in humans.[90,91]

Inhibition of oxidative stress

Antioxidants

N-acetylcysteine. N-acetylcysteine (NAC), an antioxidant, has shown some benefit in AH in combination with corticosteroids.[92] An RCT involving 174 participants randomized to NAC plus prednisolone *versus* prednisolone alone showed improved mortality at 1 month with decreased rates on infection and HRS. However, there was no survival benefit at 3 months or 6 months.[92] A subsequent systematic review and network meta-analysis of 22 RCTS found an improvement in survival with NAC combined with corticosteroids.[64] An RCT investigating the impact of prednisolone plus NAC *versus* prednisolone alone on several AH outcomes is currently recruiting participants (Table 1).

S-adenosyl methionine. S-adenosyl methionine (SAMe), a methyl donor, facilitates generation of glutathione from homocysteine. Abnormal methionine metabolism has been implicated in the pathophysiology of liver disease.[93,94] Findings on the benefit of SAMe in alcohol-associated cirrhosis have been conflicting.[95,96] Other RCTs are currently ongoing to investigate the role of SAMe in ALD patients (Table 1).

Metadoxine. Metadoxine, a combination of pyridoxine and pyrrolidone carboxylate, has been shown to protect against ethanol-induced glutathione depletion in animal models.[97] An open-label RCT including 70 patients randomized to treatment with metadoxine plus glucocorticoids *versus* glucocorticoids alone showed an improvement in mortality at 30 and 90 days, and a reduction in encephalopathy in the metadoxine-treated group compared with the glucocorticoid only group.[98] Another open-label RCT of 135 patients showed improved survival at 3 months and 6 months in patients treated with metadoxine plus prednisone compared with those treated with prednisone alone as well as among those treated with metadoxine plus pentoxifylline compared to pentoxifylline alone.[99] While these studies suggest a potential role for metadoxine in treatment of AH, double-blinded placebo-controlled trials are needed.

A placebo-controlled RCT testing the efficacy of Vitamin E in mild to moderate AH did not find any benefit on liver function.[100] Similarly, studies of antioxidant cocktails including various combinations of β-Carotene, Vitamin C (ascorbic acid), desferrioxamine, selenium, zinc, manganese, copper, magnesium, folic acid, and Coenzyme Q did not prove beneficial.[101–103]

Boosting liver regeneration

Hepatic regenerating agents

Granulocyte colony stimulating factor. Granulocyte colony stimulating factor (G-CSF), a glycoprotein, that has shown effectiveness in mobilizing bone marrow stem cells and neutrophils with hepatoprotective effects of regeneration and repair has been associated with accelerated recovery and improved survival after liver injury.[104,105] Consequently, it has been tested as a potential treatment agent for AH based on its potential to stimulate liver regeneration.[106] An earlier pilot RCT evaluating the efficacy of G-CSF plus standard of care compared to standard of care alone found an improvement

in survival with G-CSF at 3 months.[107] Subsequent studies have also demonstrated benefit, including among steroid non-responsive patients.[108,109] A meta-analysis of 7 RCTs including 336 patients with AH evaluating the effect of GCSF on risk of infection and risk of death after 90 days found a reduced risk of death in the Asian studies mainly due to reduced risk of infection, but not in two studies reported from Europe.[110] Clearly, larger studies are needed in the West to substantiate the status of G-CSF in the management algorithm of AH patients.

Interleukin-22. IL-22 is a member of the IL-10 family that has pro-proliferative, antioxidant, antisteatotic, and antimicrobial properties.[111–113] Treatment with IL-22 has previously been shown in murine models to ameliorate alcohol-induced liver injury.[114] An open-label phase II dose-escalating trial of F652, a recombinant fusion protein consisting of human IL-22 and human IgG2 fragment crystallizable with similar mechanism of action to native IL-22 found significant improvements in MELD score and serum aminotransferases at Days 28 and 42 from baseline. The drug was also associated with a decrease in levels of cytokines and extracellular vesicles.[115] Findings from another study which sought to further shed light on the role of IL-22 using hepatic biopsies from patients with AH are yet to be published.[116,117]

Sulfated oxysterol. Sulfated oxysterol (DUR-298) is an endogenous regulatory molecule that has been shown in murine models to exhibit anti-inflammatory and antifibrotic effects.[118] Findings from a phase II open-label, dose-escalation study were promising. There were significant improvements in bilirubin, MELD, and Lille scores.[119] Another open-label, dose-escalation study to assess the safety and pharmacodynamics signals of DUR-928 in patients with AH is currently recruiting participants (Table 1). Results will shed light on potential benefit or lack thereof of DUR-298 in treatment of AH.

Several other agents including insulin and glucagon, propylthiouracil, and anabolic steroids have shown no benefit while others are promising.[120–122]

Potential future targets

Metabolic-associated fatty liver disease (MAFLD) and ALD, although distinct entities, share certain underlying mechanisms of hepatic steatosis and resultant hepatic injury.[123] As described in the pathophysiology section, alcohol induces metabolic and cellular changes. It upregulates proteins that mediate hepatic steatosis, increase de novo lipogenesis, and induces insulin resistance in adipose tissue.[48,49] Regulators of de novo lipogenesis including LXR, FXR, and PPAR have been considered potentially viable targets in the treatment of MAFLD and could prove to be beneficial targets in ALD as well.[124]

FXR receptor agonists

FXR activation has beneficial effects in decreasing de novo lipogenesis. Obeticholic acid, a semisynthetic FXR agonist, regulates homeostasis and reduces accumulation of toxic bile acids and has shown promise in the treatment of MAFLD.[125,126] However, a phase II RCT evaluating its role in ALD was terminated due to hepatotoxicity concerns. Several other FXR ligands are in multiple stages of development and may prove beneficial but this remains to be seen.[126–129]

LXR inverse agonists

LXR promotes hepatic steatosis by increasing de novo lipid synthesis, hepatic fatty acid uptake, and impairing lipid droplet triglyceride hydrolysis.[130–132] LXR inverse agonists may be useful in inhibiting alcohol-associated steatosis and are currently under investigation as potential targets in MAFLD.[133] It is yet unclear, if this agent will prove useful in managing ALD.

PPAR agonists

PPARs-α, -δ, and -γ play major roles in the liver, muscle, and adipose tissues, respectively. Targeting these receptors results in oxidative fatty acid metabolism and energy disposal.[134,135] PPAR-α and PPAR-δ agonists including bezafibrate and pioglitazone have shown varying degrees of promise in MAFLD trials.[136–138] More recently, Lanofibranor, a pan-PPAR receptor agonist, showed benefit in producing resolution of non-alcoholic steatohepatitis in a recently published phase IIb trial.[139] Although the benefit or lack thereof of these agents in ALD is yet to be demonstrated, the findings from MAFLD trials are promising.

Non-pharmacological treatment modalities

Nutritional support

Malnutrition is a common among patients with ALD, particularly those with acute severe AH, and has been associated with worse outcomes.[140] Although intensive enteral nutrition has no proven survival benefit, inadequate calorific intake <21.5 kcal/kg per day has been associated with a higher frequency of complications including infections.[141] Therefore, adequate nutrition that includes adequate protein intake and correction of specific nutrient deficits should be provided.[142]

Treatment of AUD

Current AH treatment targets, although useful in the short term, do not provide any long-term mortality benefit. Continued alcohol consumption remains a major determinant of long-term prognosis.[143,144] In one French multicenter study, severe relapse occurred in 20% of post-LT patients and of these, 35% developed recurrent alcohol-related cirrhosis.[145] Accordingly, patients with ALD should undergo screening for possible AUD using tools such as the AUDIT questionnaire.[146] Those with comorbid AUD should receive appropriate treatment with the goal of achieving long-term abstinence and preventing relapse.[8] Both psychosocial and pharmacological interventions are beneficial.[21] In a recently published retrospective cohort of 9635 patients with AUD who were followed for a mean period of 9.2 years, patients who received medical therapy for AUD were found to have 63% lower odds of being diagnosed with ALD and those with preexisting comorbid ALD were found to have a 65% lower odds of developing hepatic decompensation.[147]

Pharmacological agents approved by the Food and Drug Administration (FDA) in the United States include acamprosate, disulfiram, and naltrexone. Non-FDA-approved agents including baclofen, gabapentin, topiramate, and varenicline have shown varying degrees of benefit (Table 2).[148–152] Newer targets are also being explored. A recently published double-blinded RCT including 93 patients evaluated the effectiveness of psilocybin-assisted psychotherapy *versus* psychotherapy with placebo (diphenhydramine) in the treatment of AUD. The authors found a 13.9% reduced heavy drinking days in the psilocybin-treated group. No serious adverse events were reported.[153]

Table 2. Pharmacotherapies for management of AUD.

Medication	Mechanism of action/efficacy	Dose	Contraindications
Naltrexone[151,154,155]	Mu-opioid receptor antagonist which has shown benefit in reducing alcohol consumption and risk of relapse to heavy drinking	Initial: 25–50 mg daily orally Maintenance: titrate to 50–100 mg daily IM: 380 mg monthly	Avoid in patients on opioids for pain management And in patients with acute hepatitis, hepatic failure or Child-Pugh class C
Acamprosate[151,156,157]	Glutamate neurotransmission modulator which has shown efficacy in reducing risk of any drinking and maintaining abstinence from alcohol	666 mg three times daily orally Dose adjustment required in patients with CrCl of 30–50 ml/min	Avoid in patients with CrCL ⩽30 ml/min
Disulfiram[155,158,159]	Aldehyde dehydrogenase inhibitor which has shown efficacy in maintaining abstinence from alcohol when taken under supervised conditions	Loading dose: 250–500 mg/day orally Maintenance dose: 250 mg daily (range: 125–500 mg/day) orally	Avoid use within 12 h of alcohol consumption. Not recommended for the purpose of reducing drinking
Nalmefene[155,160,161]	Mu and deLTa opioid receptor antagonist and partial kappa opioid receptor agonist which has shown benefit in reducing total alcohol consumption in patients with AUD	18 mg orally daily as needed	Hypersensitivity to nalmefene or any of its components

(Continued)

Table 2. (Continued)

Medication	Mechanism of action/efficacy	Dose	Contraindications
Topiramate[162–164]	Inhibitor of mesocorticolimbic dopamine release that has shown benefit in reducing cravings and alcohol drinking, increasing duration of abstinence and decreasing heavy drinking days	Loading dose: 25 mg once daily orally Maintenance: titrate dose by 25 mg per week for 4 weeks then by 50 mg per week to maximum of 300 mg per day in divided doses	Serious hypersensitivity to topiramate or any of its components
Baclofen[162,165,166]	γ-amino butyric acid $GABA_B$ agonist that has shown benefit in increasing length of time to relapse and achieving higher abstinence rates than placebo	Initial dose: 5 mg three times daily Maintenance dose: up-titrate dose every 3–5 days to a maximum of 15 mg three times daily	Serious hypersensitivity to Baclofen or any of its components
Gabapentin[162,167,168]	GABA receptor modulator that has been shown benefit in increasing abstinent days and prolonging time to return to heavy drinking	Initial dose: 300 mg daily Maintenance dose: up-titrate by 300 mg every 2 days to a maximum dose of 600 g three times daily	Serious hypersensitivity to gabapentin or any of its components
Varenicline[162,169,170]	Partial α4β2 nicotinic acetylcholine agonist which has shown limited benefit in AUD patients, particularly those who smoke	Initial: 0.5 mg once daily orally Maintenance: titrate by 0.5 mg every four days to a maintenance dose of 1 mg twice daily Dose adjustment required in severe renal disease	Serious hypersensitivity to varenicline or any of its components

AUD, alcohol use disorder.

Psychosocial interventions are also beneficial in the treatment of AUD. A meta-analysis of 13 studies comprising 1945 patients with chronic liver disease revealed significantly lower rates of abstinence and relapse among patients who received an integrated therapy that combined cognitive behavioral therapy and motivational enhancement therapy with comprehensive medical care.[171] An integrated multidisciplinary care approach which involves collaboration between a variety of clinicians including hepatologists, addiction specialists, psychiatrist, psychologists, nurses, and social workers is optimal and should be the aim when feasible.[10,172] In a recent study of 89 patients with ALD who were not in the transplant evaluation process, had had less than 6 months of sobriety and who were willing to engage in AUD treatment, a multidisciplinary ALD clinic was found to be attainable. In addition, among the 38 patients followed through the study period, the intervention was associated with decreases in average MELD scores and hospital utilization.[173] While findings from this study suggest feasibility, more work is needed to evaluate barriers, feasibility, and implementation models in diverse practice settings.

Liver transplantation

LT is beneficial in the treatment of severe liver disease from various etiologies including alcohol. Traditionally, many centers maintained 6-month abstinence requirements in attempts to select patients with low risk of relapse.[174,175] Evidence supporting this duration of abstinence is however conflicting.[176–178] Several studies have shown excellent outcomes among select patients receiving eLT with abstinence duration of <6 months, with relapse of alcohol use similar to those receiving traditional LT after minimum 6 months of abstinence.[179–182] However, a recent prospective RCT comparing early with traditional LT failed to demonstrate non-inferior alcohol relapse rates among recipients of eLT.[183]

Among patients with severe AH, the short-term mortality risk is such that they may not survive long enough to qualify for LT using prolonged abstinence requirements.[24] eLT might represent the only option for meaningful survival, especially among subsets who do not respond to medical therapy.[8,25,184] A fast-growing body of evidence supports the use of eLT among eligible patients.[24,180] Professional societies recommend eLT in carefully selected patients who are experiencing their first episode of severe AH, have good social support, and who have minimal psychiatric comorbidities.[21,185] Lack of social support, comorbid psychiatric conditions, polysubstance use, and a history of non-compliance with medical treatment have been associated with increased risk of relapse.[186] However, it should be acknowledged that significant barriers exist to eLT including insurance approval, sociocultural issues, organ shortage as well as concerns about lack of insight and an inability to maintain a therapeutic relationship on the patients' part.[187,188] In addition, concerns have also been raised about disparities in organ distribution with studies showing a disproportionate representation of white, privately insured males among transplant recipients.[180,189]

Challenges and future directions

Despite the progress in the understanding the pathophysiology and potential therapeutic targets in recent years, little progress has been made in the realm of pharmacologic management. There have been several challenges in the drug development for ALD and AH since the funding of four consortia by the National Institute on Alcohol Abuse and Alcoholism over a decade ago.

Liver disease-related challenges

Lack of universally effective treatments. Presently, corticosteroids remain the only treatment with a robust supporting body of evidence. Their benefit is however observed in only about 60% of patients with severe AH and their use is not recommended patients with moderate AH.[14,21] The population with moderate AH, although considered to have a more favorable prognosis, still experience significant mortality rates of as high as 10% in the short-term period.[190] Nonetheless, there are currently no specific treatments other than nutrition and hydration support for them.[21] Effort is needed to address this gap and develop safer and effective therapies for this population.

Lack of predictive biomarkers for treatment response. In patients with severe AH, there is a need for predictive biomarkers to optimize and personalize corticosteroid use to likely responders. The neutrophil to lymphocyte ratio (NLR) has recently shown promise in this regard. A retrospective analysis of 789 patients from the Steroids or Pentoxifylline for Alcoholic Hepatitis trial revealed that among the 393 patients who received steroids, NLR was useful in predicting corticosteroid-related mortality benefit. In addition, they found that substituting NLR for white cell count in the Glasgow Alcoholic Hepatitis Score was a strong predictor of 28 and 90-day survival.[191] A recent retrospective multicenter study identified a therapeutic window with MELD score of 25–39, with best possible response to corticosteroids.[192] Although Keratin 18 (K18) has been shown to be associated with severity and with corticosteroid response in severe AH, most non-invasive biomarkers including K-18 are not yet available for routine use in clinical practice.[193,194] Other biomarkers that have been studied for predicting mortality include procalcitonin, SIRs, and neutrophils and have shown varying degrees of utility.[195,196] Further research into potential biomarkers for diagnosis and risk stratification of ALD are needed.

Heterogeneity of ALD. ALD is a complex heterogenous disease with multiple pathways in its pathophysiology. Furthermore, none of the animal models so far can mimic the human phenotype of AH with organ failure and potential for high short-term mortality. For instance, while neutrophilic infiltration has been shown to be prominent in human phenotypes of alcohol-associated steatohepatitis, animal models demonstrate little to no neutrophilic infiltration

LT-related challenges

Heterogeneity of the selection process. Among ALD patients who qualify for LT, significant barriers exist to access. In addition, there is significant heterogeneity in the selection process. A study of LT centers in the United States found that about half of centers were not adhering to criteria used in the seminal Franco-Belgian study.[187] In addition, a recently published study of LT protocols in 100 LT centers revealed that 70% reported no minimum sobriety requirements, while 21% centers still require minimum 6 months of sobriety. Other themes in many

transplant protocols include insight into AUD, social support, and ability to maintain a therapeutic relationship with the transplant team.

In addition, there were significant differences in practices surrounding pre- and post-transplant monitoring of alcohol use.[197]

Lack of accurate predictors of relapse. Most LT programs seek to allocate organs to patients with minimal risk of relapse. However, there is currently no recognized consensus definition of relapse.[162] As harmful alcohol use after LT impacts long-term survival, the clear definition of clinically relevant relapse to alcohol use needs to be homogenized.[162,144] Furthermore, there is a need for more accurate tools and models to predict clinically relevant alcohol relapse after LT.[198,199] Given lack of resources currently, there is a need for dedicated efforts to support patients in the post-transplant setting and reduce risk of relapse to harmful alcohol use.

Ethical challenges in LT. The allocation of organs from a scarce deceased donor pool to patients with ALD who are still drinking raises questions about fairness and equity of organ allocation. Given the perpetual gap between demand and supply, the allocation of organs to patients with ALD could potentially mean the withholding of those organs from patients with liver disease due to causes other than alcohol. As a growing number of organs are being allocated to patients with ALD, effort must be made to ensure that organ distribution is equitable.[200]

AUD-related challenges

Despite benefits of treating AUD, it continues to be undertreated in patients with ALD with high rates of relapse to alcohol use.[148,198] For example, in a retrospective study of 35,682 veterans with cirrhosis and AUD, only 14% received AUD treatment including 12% who received behavioral therapy alone and 1% who received both behavioral and pharmacotherapy.[9]

Patient-level challenges. At the patient level, denial of extent of alcohol use could prevent adequate assessment of AUD severity. Furthermore, psychological barriers such as the perception of stigma, feelings of guilt, and shame may impede treatment uptake.[201] Patients may also have competing demands on their time that preclude meaningful participation in treatment programs.[202,203] In addition, in severely ill patients, the extent of debilitation may be such that patients feel too sick to focus on seeking treatment for their AUD. Emphasis should be placed on destigmatizing AUD treatment and creating less cumbersome treatment processes.

Systemic- and provider-level challenges. Systemic barriers to AUD treatment include insurance coverage levels, limited resources, and lack of integrated multidisciplinary structures.[10] Provider-level barriers include knowledge constraints and low comfort level due to lack of adequate training to address AUD in ALD patients.[204] An approach integrating pharmacological and behavioral therapy is optimal, but not consistently utilized.[21] In the light of the recent proliferation of telehealth usage during the COVID pandemic, studies investigating the role of telemedicine in promoting multidisciplinary care are needed.[205]

Clinical trial-related challenges

Challenges with study design. There is a paucity of studies that incorporate standard of care, that is, corticosteroids, management of organ failures, AUD treatment, and LT. Stratified randomization allows the grouping of trial participants into strata first based on factors that could affect prognosis and then randomizing within those strata. This kind of design could help improve the power and reduce the chances of a type 1 error in small AH trials that incorporate standard of care.[206] Adaptive trial designs which utilize accumulating data to decide how to modify aspects of an ongoing study, without undermining the validity and integrity of the trial can also be used. They are of advantage because they are flexible, can allow for smaller trial size, and increase the chances of success.[207] The use of these designs in AH trials can allow for early termination of trials with no benefit and facilitate the finding of significant effects when they do exist.[207]

Challenges with recruitment and retention. Another issue with AH trials is suboptimal recruitment and retention.[208] There are several reasons for this including but not limited to lack of interest in research, desire to concentrate on abstinence, lack of transportation for follow-up visits, and feeling too sick to participate. Structural, system-level

barriers especially coordinator time in prescreening and recruitment of patients are important limiting adequate number of participants.[209] Study design to ease the burden on participants as well as research personnel, establishment of protocols for real-time tracking of and response to lack of follow-up; provision of adequate educational materials and improved communication between study teams and potential participants, and financial support for participation in trials.[209]

Conclusion

In conclusion, ALD is a complex disease with rapidly increasing prevalence. Although there are promising therapeutic targets on the horizon, currently none of the newer targets is close to an FDA approval. Strategies are needed to overcome challenges in study designs and conducting clinical trials and provide impetus to the field of drug development in the landscape of ALD and AH. Management of ALD is complex and should include therapies to achieve and maintain alcohol abstinence, preferably delivered by a multidisciplinary team. Although associated with clear mortality benefit in select patients, the use of eLT still requires refinement to create uniformity in selection protocols across transplant centers. There is also a need for reliable noninvasive biomarkers for prognostication. Last but not the least, strategies are urgently needed to implement integrated multidisciplinary care models for treating the dual pathology of AUD and of liver disease for improving the long-term outcomes of patients with ALD.

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Not applicable.

Author contribution(s)

Ayooluwatomiwa Deborah Adekunle: Writing – original draft.

Adeyinka Adejumo: Methodology; Visualization.

Ashwani K. Singal: Conceptualization; Methodology; Resources; Supervision; Writing – review & editing.

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