Review Article

JOURNAL OF CLINICAL AND EXPERIMENTAL HEPATOLOGY

Emerging Pharmacotherapies in Alcohol-Associated Hepatitis

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The incidence of alcoholic-associated hepatitis (AH) is increasing. The treatment options for severe AH (sAH) are scarce and limited to corticosteroid therapy which showed limited mortality benefit in short-term use only. Therefore, there is a dire need for developing safe and effective therapies for patients with sAH and to improve their high mortality rates.

This review article focuses on the current novel therapeutics targeting various mechanisms in the pathogenesis of alcohol-related hepatitis. Anti-inflammatory agents such as IL-1 inhibitor, Pan-caspase inhibitor, Apoptosis signal-regulating kinase-1, and CCL2 inhibitors are under investigation. Other group of agents include gut-liver axis modulators, hepatic regeneration, antioxidants, and Epigenic modulators. We describe the ongoing clinical trials of some of the new agents for alcohol-related hepatitis. *Conclusion:* A combination of therapies was investigated, possibly providing a synergistic effect of drugs with different mechanisms. Multiple clinical trials of novel therapies in AH remain ongoing. Their result could potentially make a difference in the clinical course of the disease. DUR-928 and granulocyte colony-stimulating factor had promising results and further trials are ongoing to evaluate their efficacy in the large patient sample. (J Clin Exp Hepatol xxxx;xxx:xxx)

Alcohol-associated liver disease (ALD) encompasses a variable presentation, such as steatosis or fatty liver disease, alcohol-associated hepatitis (AH), alcohol-associated cirrhosis (ALC), and acute on chronic liver failure (ACLF).[1] These ALD spectrums can present in isolation or can overlap. Severe alcohol-associated hepatitis (sAH) is one of the most severe manifestations of ALD, with high mortality, morbidity, and a dismal short-term prognosis.[2–4] In recent years, AH-related hospitalizations have significantly increased, resulting in higher healthcare resource utilization and financial burden across the United States.[5] There has been a concurrent increase in the amount of alcohol consumption along with early-age access to alcohol use among teenagers.[6–8] Additionally, stressful times such as the SARS-CoV-2 pandemic led to an even higher alcohol consumption rate. It is noteworthy to mention that a recent national survey of 6000 individuals demonstrated a 41% increase in heavy alcohol consumption during the pandemic.[9] The diagnosis of AH is made based on multiple factors such as a history of significant alcohol consumption, clinical features of ALD, laboratory findings, and history whenever deemed necessary. Key histologic features to establish the diagnosis include macrovesicular steatosis, fatty metamorphosis of the hepatocytes, neutrophilic infiltration of the hepatic parenchyma, cholestasis, and Mallory-Denk bodies, and perivenular and pericellular fibrosis mimicking "chicken wire appearance". The clinical criteria for AH diagnosis proposed by the NIH–sponsored consensus meeting of the investigators[7] include chronic heavy alcohol consumption for >6 months, a serum bilirubin level >3 mg/dL, elevated aminotransferases with aspartate aminotransferase to alanine aminotransferase > 1.5:1 ratio, with both enzymes level not exceeding 500 IU/L. In patients meeting the clinical criteria, a diagnosis of probable AH can be established without the need for a histological confirmation through liver biopsy. When confounders are present, a liver biopsy is required to establish the AH diagnosis.[2,3] AH can be further classified as mild or severe based on well-validated scoring systems such as modified Maddrey's discriminant function (MDF) and model for end-stage disease (MELD) scores.[10,11] In mild AH cases, the prognosis is

Keywords: alcohol-associated hepatitis, anti-inflammatory, antioxidants, microbiome, liver-gut axis

Received: 14.4.2022; *Accepted:* 25.6.2022; *Available online:* xxx

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Abbreviations: AH: alcohol-Associated hepatitis; ALD: Alcohol-associated liver disease; ASK-1: Apoptosis signal-regulating kinase-1; AUD: alcohol use disorder; CCL2: C–C chemokine ligand type 2; CVC: Cenicriviroc; ELAD: Extracorporeal liver assist device; FMT: Fecal Microbiota Transplant; G-CSF: Granulocyte colony-stimulating factor; HA35: Hyaluronic Acid 35KD; IL-1: interleukin 1; IL-6: interleukin 6; LCFA: saturated long-chain fatty acids; LDL: low-density lipoprotein cholesterol; LPS: Lipopolysaccharides; MCP-1: monocyte chemoattractant protein −1; MDF: Maddrey's discriminant function; MELD: Model for end-stage disease; NAC: N-acetylcysteine; NLRs: nucleotide-binding oligomerization domain-like receptors; PAMPs: Pathogen-associated molecular patterns; RCT: Randomized controlled trial; sAH: severe alcohol-associated hepatitis; SAM: S-Adenosyl methionine; SCFA: short-chain fatty acids. 5; TLRs: Toll-like receptors; TNF: tumor necrotic factor

https://doi.org/10.1016/j.jceh.2022.06.012

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favorable with alcohol abstinence. However, severe AH (defined as MDF ≥32, or MELD score ≥20) is associated with high 30-day mortality.[1] The management of AH is focused on alcohol abstinence and nutritional support.[7] Therapeutic options for AH have been scarce for the past few decades and it is primarily limited to supportive care and corticosteroid therapy for a selected subset of patients.[12] In randomized controlled trials and meta-analysis, only a short-term mortality (28 days) benefit was demonstrated in the corticosteroid therapy receiving arm for patients diagnosed with sAH[13,14] A number of patients with sAH encounter contraindications to the administration of corticosteroid therapy such as gastrointestinal bleeding, acute pancreatitis, infections, and acute renal failure. Moreover, patients who are non-responders to corticosteroid therapy (defined as Lille score >0.45 at day 7) are currently offered supportive care. Early referral for liver transplantation for sAH showed significant survival benefits; [15–17] however, there is a universal donor organs shortage compared to demand and only a limited number of sAH patients qualify for liver transplantation.[17,18] As a result, identifying novel therapeutic targets for AH is critical.[19]

PATHOPHYSIOLOGY OF AH

The pathophysiology of ALD is complex and not well understood. Several factors and different pathways may play a pivotal role in the development of ALD and AH. Heavy alcohol consumption can result in hepatic steatosis by the upregulation of fatty acid synthesis and downregulation of fatty acid oxidation.[20] Alcohol and its toxic metabolites such as acetaldehyde can exert direct toxic effects on the hepatic parenchyma and subsequent oxidative stress.[21] Additionally, alcohol use can alter the integrity of the microbiome-gut axis leading to increased gut permeability which allows for bacterial lipopolysaccharide (LPS) translocation.[22,23] Toll-like 4 receptors (TL4R) on the hepatocytes can recognize LPS leading to the activation of an inflammatory cascade and recruitment of inflammatory cytokines resulting in apoptosis, necrosis, and hepatic stellate cell (HSC) activation.[24,25] The end results are steatosis, collagen production, fibrosis, and ultimately cirrhosis.

Therapies targeting those pathways can be classified into 5 main categories: (1) anti-inflammatory agents, (2) gut-liver axis modulators, (3) antioxidants, (4) anti-regenerative agents, and (5) epigenetic modulators (Figure 1). The current novel therapeutic agents are summarized in Table 1.

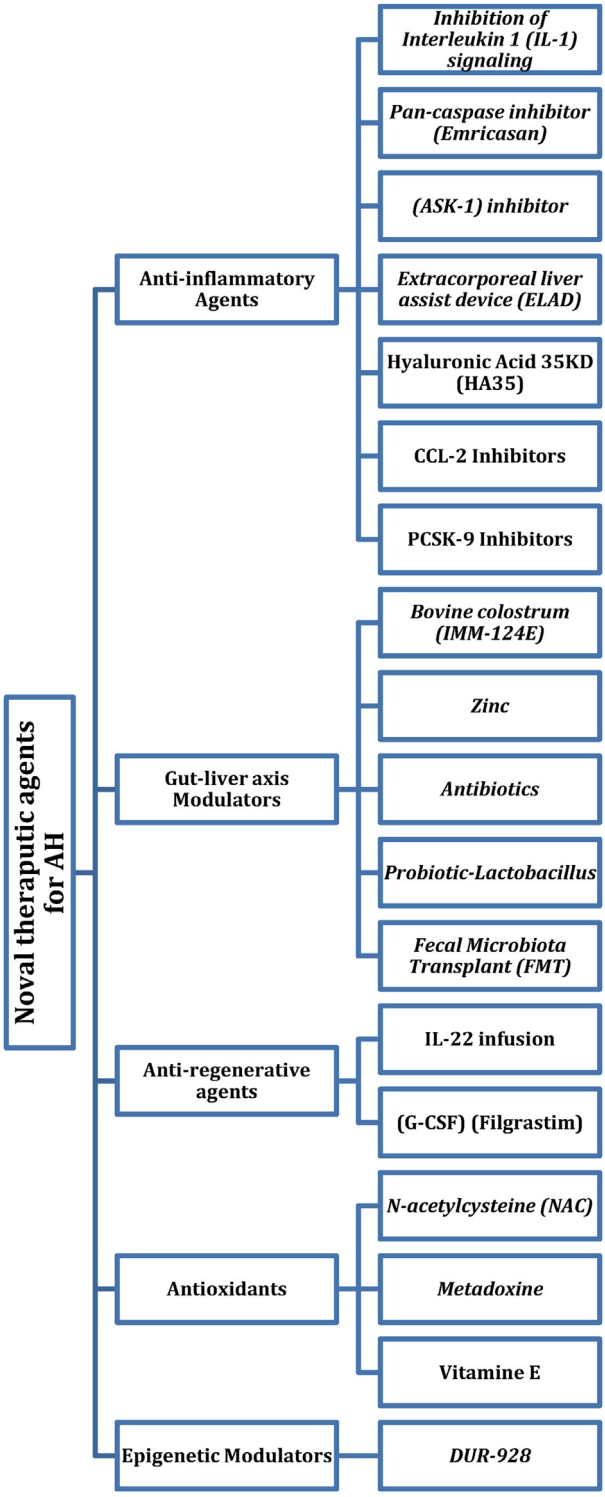

Figure 1 Categories of novel agents in therapeutics of alcohol-associated hepatitis.

Anti-Inflammatory Agents

Alcohol consumption induces inflammation in the hepatocytes through both innate and adaptive immune systems.[26,27] Increased gut permeability leads to a higher LPS concentration in the portal venous system which activates Kupffer cells via TLR-4 and nucleotide-like receptors signaling pathways, leading to the recruitment of pro-inflammatory cytokines such as interleukins 1 and 12 (IL-1 and IL-12) and tumor necrosis factor (TNF-a).[28,29] Additionally, Chemokines such as C-X-C Motif Chemokine

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Table 1 Summary of Trials Examining Novel Therapeutics in Alcohol-Associated Hepatitis.

Trial Identifier	Agent	Agent Pharmacology	Trial Design	1° Endpoint	Main Inclusion Criteria	Status
NCT01968382	Bovine colostrum (IMM-124E)	IgG against LPS	Placebo-controlled RCT	Reeducation endotoxin concertation	MELD range (20–28)	Phase 2, completed
NCT02473341	Bovine Colostrum	decrease the level of Endotoxemia and LPS	RCT, Bovine Colostrum Vs. Placebo	3 months survival benefits	MDF>32	Phase 3, recruiting
NCT02116556	Rifaximin	Antibiotic	Open-label	Rate of bacterial infection	MDF>32 or MELD>20	Phase 2, completed
NCT01922895	Lactobacillus	intestinal dysbiosis	Placebo-controlled RCT	Δ MELD at 30 days	MELD less than 21	Terminated (Lack of funding)
NCT04072822	Anakinra	IL-1 blockade	RCT Anakinra + Zinc vs corticosteroids	90 days survival	MELD range (20–35)	Phase 2
NCT01809132	Anakinra, Pentoxifylline, and Zinc	IL-1 and other cytokine blockade	RCT Anakinra, Pentoxifylline + Zinc vs corticosteroid	6-month mortality	MELD≥20	Phase 3, completed
NCT05285592	Fecal microbiota transplant	intestinal microbiota dysbiosis	RCT Fecal microbiota transplant vs SMT	3 months survival	MELD≥20	Not yet recruiting.
NCT03775109	Canakinumab	IL-1β monoclonal antibody	RCT	Histologic improvement of biopsy at 28 days	MDF≥32 MELD<27	Phase 2 Active, not recruiting
NCT01912404	Emricasan	Pan-caspase inhibitor	RCT	Survival at 28 days	MELD 21-34	Phase 2, terminated
NCT02854631	Selonsertib, GS-4997	ASK-1 inhibitor	RCT Selonsertib + Corticosteroid vs corticosteroids alone	Safety at 28 days	MDF>32	Phase 2, completed
NCT04563026	DUR-928	Sulfated oxysterol	Double-blind, RCT	90 days mortality	MELD 21-30	Phase 2, recruiting
NCT01471028	ELAD	Extracorporeal hepatic cell support	RCT	90 days survival	MDF≥32	Phase 3, terminated
NCT05018481	HA35	Normalized TLR-4 signaling	RCT HA35 vs Placebo	Change of skeletal muscle mass	MDF<21	Phase 1, not yet recruiting
NCT00863785	NAC	Antioxidant	RCT NAC plus corticosteroids vs corticosteroids alone	6-month survival	MDF≥32	Phase 3, completed
NCT02161653	Metadoxine	Antioxidant	RCT Metadoxine vs CS	3- and 6-month survival	MDF≥32	Phase 4, completed
NCT02655510	IL-22 infusion	Liver cell repair, anti-apoptotic, anti-inflammatory	Open-label	Serious adverse events at day 42	MELD 11-28	Phase 2, completed
NCT02442180	G-CSF	Hepatic progenitor	RCT G-CSF + steroids vs steroids vs G-CSF	2-month survival	MDF≥32	Phase 3, recruiting

RCT, randomized controlled trial; CS, corticosteroid; MDF, Maddrey's discriminant function; MELD, model for end-stage liver disease; SOFA, sequential organ failure assessment. SMT, Standard Medical Therapy; HA35, Hyaluronic acid 35; G-CSF, Granulocyte colony-stimulating factor; NAC, N-acetylcysteine; ASK-1, Apoptosis signal-regulating kinase; LPS, Lipopolysaccharides, TLR, Toll-like receptor; ELAD, Extracorporeal liver assist device; IgG, immunoglobulin G.

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Ligand 5 (CXCL5), C–C chemokine ligand type 2 (CCL2), interleukin- 8 (IL-8), and platelet factor 4 are also activated in AH and they play a pivotal role in leukocytes recruitment.[30,31] This inflammatory reaction exacerbates hepatic steatosis as demonstrated in multiple studies, showing LPS serum concentration was associated with a more severe ALD stage.[32,33] In addition, it has been published that CCL2 level correlates with AH severity, fibrosis, and portal hypertension.[34] Moreover, adaptive immunity plays a role in AH. The stimulation of natural killer T and T lymphocytes cells enhances the immunological response against hepatocytes with the activation of the TNF receptor 1 signaling pathway.[35,36] HSCs enhance fibroblast and extracellular matrix formation through the stimulation of cytokine release such as TNF-a, IL-1 IL-8, and CCL2.[36,37] The promotion of hepatic inflammation leads to apoptosis or hepatic necrosis and dysregulation of mitochondrial function.[38]

IL-1 Inhibitor Agents

IL-1 cytokine is involved in the activation of the inflammatory cascade as mentioned earlier. Antagonizing IL-1 receptor is a potential therapeutic target for sAH as shown in animal models with AH. The inhibition of IL-1 in mice improved hepatocyte inflammation resulting in hepatic regeneration.[39,40]

Anakinra is a recombinant IL-1 receptor antagonist, currently approved for administration in autoimmune conditions. In a multicenter, double-blinded randomized controlled trial (RCT), the combination of anakinra (100 mg daily subcutaneously for 14 days) with Pentoxifylline (400 mg orally three times per day for 28 days) plus zinc (220 mg orally daily for 180 days) in patients identified with sAH (defined as MELD >20 or MDF > 32) was compared to methylprednisolone (32 mg orally for 28 days). Patients with sepsis, gastrointestinal bleeding, acute renal injury (defined as creatinine >3.0 mg/dL), or recent immunosuppressive medication use were excluded. This study revealed a similar 30-day survival benefit of the treatment arm when compared to the corticosteroids arm. Despite the overall trend of higher survival benefit in the treatment arm (86.8% vs 82.0%, 69.8% vs 58.0%, 67.9% vs 56%) at 28 days, 90 days, and 180 days, respectively; there was no statistical significance (P = 0.30).[41] Currently, a multicenter RCT (NCT04072822) is recruiting subjects to evaluate the 90-days survival benefit in patients with sAH defined as a MELD score of 20–35, using a combination of Anakinra with Zinc compared to standard therapy with corticosteroid alone.

Canakinumab is a human monoclonal antibody that mitigates the activity of IL-1β by preventing its interaction with the IL-1 receptor and hence suppresses the inflammatory cascade.[42,43] In the United Kingdom, the recruitment process has been initiated in a randomized placebo-controlled trial to assess histologic improvement after 28 days of treatment with canakinumab in patients with sAH (MDF ≥ 32 and MELD < 27) (NCT03775109). However, safety concerns have been raised as the previous large CANTOS (Canakinumab Anti-Inflammatory Thrombosis Outcomes) study proved a higher infection rate in canakinumab-treated patients.[44]

Pan-Caspase Inhibitors

Caspases are a family of cysteine proteases that induces cell death, apoptosis, and hepatic inflammation with resulting fibrosis. Using caspase inhibitors in mice with NASH revealed promising effects on reducing hepatic fibrosis scoring and improvement in portal hypertension.[45,46] Emricasan is an oral caspase inhibitor that has previously demonstrated some improvement in aminotransferases in patients with NASH.[47] A RCT evaluated the use of Emricasan among patients with cirrhosis (MELD score of 11–18) showed improvement in Child-Pugh and MELD scores at 3 months among patients with MELD scores ≥15. However, the study included patients with cirrhosis secondary to another cause and not limited to ALC. In addition, more stable patients with lower MELD scores were recruited. There was a minimal improvement in the MELD score for patients with ALD in this study.[48] A randomized controlled placebo study (ENFORCE-PH trial (NCT029 60204) of Emricasan administered for 24 weeks failed to achieve the primary endpoint of the hepatic venous pressure gradient improvement when compared to placebo in NASH-related cirrhosis.[49]

Another randomized placebo-controlled phase 2 trial (NCT01912404) evaluated the use of Emricasan in patients with sAH (MELD 21–34); however, this study was terminated prematurely after the recruitment of only 5 subjects secondary to safety issues as elevated serum drug levels were found. A randomized placebo-controlled (ENCORE-NF) trial (NCT02686762) using Emricasan 50 mg, 5 mg, or placebo was given for 72 months and indicated no improvement in the histological fibrosis stage on liver biopsy. In fact, Emricasan may have worsened ballooning and fibrosis and the authors hypothesized that the use of Emricasan directed hepatocytes to an alternative mechanism for cell death.[50]

Apoptosis Signal-Regulating Kinase-1 Inhibitor

Apoptosis signal-regulating kinase-1 (ASK-1) is a ubiquitous kinase protein that is activated by pro-inflammatory LPS and cytokines in the hepatocytes.[51] When activated, ASK-1 activates mitogen-activated kinase (MAPK) and c-Jun N-terminal kinase, both of which lead to inflammation, apoptosis, and fibrosis.[52] Pre-clinical data indicated ASK-1 inhibition led to the improvement of inflammatory reactions, apoptosis, and steatohepatitis. Selonsertib, GS-4997 is an oral ASK-1 inhibitor that was evaluated in randomized clinical trials among 102 patients with AH (MDF ≥ 32) compared with prednisolone alone. Selon-

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sertib failed to demonstrate any survival benefit compared to prednisolone.[53]

Small Specific-Sized Hyaluronic Acid 35KD

Chronic alcohol consumption increases TLR-4 stimulation and subsequently sensitization of Kupffer cells. This process contributes to the continued state of chronic inflammation.[54] A recent animal study revealed that hyaluronic acid 35KD normalized the TLR-4-mediated signaling in rats after ethanol exposure.[55] An ongoing phase one, randomized, interventional clinical trial (NCT05018481) is assessing the effectiveness of hyaluronic acid 35KD taken once a day for 90 days in patients with AH and MELD <21.

CCL2 Inhibitor

ALD-induced inflammation is associated with an increase in the chemokines which serves to recruit peripheral T cell and macrophages. Cenicriviroc is a C–C chemokine receptor type 2 and 5 (CCR2 and CCR5) oral dual inhibitor and has been explored as a potential therapy for AH. When given to alcohol-fed mice, lower levels of macrophages, reduction in T cells and reduction in cell death, and steatosis were observed.[56] C–C chemokine ligand type 5 (CCL5) and type 2 (CCL2) have been extensively studied chemokines in liver injury and play a key role in monocyte, macrophage, and T cells recruitment via their receptor CCR2. Both chemokines are found to be unregulated in AH and they also play a role in hepatic steatosis.[57] Moreover, CCL2 deficient mice have been shown to downregulate cytokines and reduce oxygen-free radical formation with inhibition of oxidative stress.[37]

PCSK-9

Alirocumab is a monoclonal antibody that targets serine protease (PCSK-9) that usually plays an important role in low-density lipoprotein cholesterol metabolism in the liver is administered in a pre-clinical study.[58] Alirocumab is FDA approved for the treatment of familial hypercholesterolemia in selected patients. This medication was found to downregulate the mRNA expression that is responsible for pro-inflammatory cytokine production, thus reducing hepatocytes' inflammation and steatosis. It also alters fatty acid synthesis by changing the mRNA expression as it has been published in the rat model.[59]

CytoSorb®

CytoSorb® is a cytokine hemoperfusion adsorbent device authorized by the FDA for emergency treatment in SARS-CoV-2.[60] A new prospective, multicentric, propensity-matched, controlled case–control study will recruit subjects with ACLF grade ≥2 due to sAH to receive steroid plus CytoSorb® 300 mL device (NCT05131230).

Epigenetic Modulators

DUR-928 is an endogenous sulfated oxysterol molecule that modulates inflammatory signaling, hepatic regeneration, and cell survival. An open-label multicenter trial enrolled patients with AH who received an intravenous infusion of the compound on day 1 and day 4. DUR-928 was well tolerated by all study subjects; the results were promising as an overall 89% response rate (defined as Lille score <0.45) along with a reduction in serum bilirubin at day 28 were observed.[61] Currently, a phase 2b randomized, multicenter, placebo-controlled trial (NCT04563026) is recruiting subjects with AH. The primary outcome of the study is 90-day mortality, and the secondary outcome is 28-day mortality, with Lille score on day 7, and MELD scores on day 28.

Agents that Modulate the Gut-Liver Axis

The integrity of the gut mucosa is regulated by several components, namely: the apical protective layers, tight junctions in between epitheliums, and gut immune cells with abundant microbiome interactions.[62] Alcohol disrupts the gut permeability through direct acetaldehyde-induced toxic effects on the epithelium, reducing the expression of vital proteins involved in tight junction formation. Moreover, alcohol increases the expression of the circadian clock proteins (such as CLOCK and PER2) and reduces short-chain fatty acids resulting in intestinal hyperpermeability.[63,64] On the other hand, alcohol consumption induces gut dysbiosis with an imbalance between pro-inflammatory and anti-inflammatory flora organisms such as lactobacillus leading to bacterial translocation with the resulting PAMPs activation.[65,66] This process leads to the activation of cytokines and recruitment of inflammatory cells and activation of HSCs.[25] Thus, multiple clinical trials are ongoing to identify potential therapies targeting the gut microbiota.

Antibiotics

Chronic alcohol consumption induces alteration of the gut microbiome resulting in profound intestinal dysbiosis and increasing pro-inflammatory bacteria such as Actinobacteria.[68] In addition, the increase in gut permeability with bacterial translocation alters the immune reactions with subsequent hepatic injury.[67,68] Hence antibiotics are a therapeutic target of special interest since patients with AH not only are susceptible to infections owing to their immunocompromised state but also the use of corticosteroids in AH carries an independent infection risk.[69,70] Rifaximin, a derivative of Rifamycin has a wide coverage for intestinal bacteria. It has been published that an improvement in hepatic fibrosis, portal hypertension, and spontaneous bacterial peritonitis has been noted. Moreover, Rifaximin showed a survival benefit in patients with ALC.[71,72] A Danish study that compared Rifaximin with the standard of care revealed a trend toward a decrease in mortality rate in the Rifaximin group which was not statistically significant.[73] The current status of two Rifaximin trials contacted in South Korea and Spain is still pending

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(NCT02485106, NCT02116556). Augmentin (Amoxicillin-Clavulanic acid) has, also, been studied; a large multicenter double-blinded RCT is evaluating the survival benefits of combining Augmentin + prednisolone in patients with sAH (defined as MELD > 20) (NTC 02281929).

Probiotic-Lactobacillus

As previously discussed, alcohol consumption is well known to induce changes in gut microbiota including bacterial overgrowth and dysbiosis. This process, in addition to intestinal mucosa damage and increased permeability, leads to an increase of bacterial byproducts such as endotoxin (most importantly LPS) in the portal circulation.[21] Several animal studies have demonstrated the protective effects of probiotics after alcohol exposure acutely or chronically.[74] Stadlbauer *et al.* showed significantly lower IL-10 and TLR-4 expression in patients with ALC who received probiotics (*Lactobacillus* casei *Shirota*) vs the control group.[75] In a randomized clinical trial, Han *et al*. compared the efficacy of cultured *Lactobacillus/Streptococcus* with placebo in 117 patients with AH. The treatment arm displayed lower LPS serum level and restoration of bowel flora. The results of this study displayed an improvement in short-term outcomes (7 days) using probiotics, though it is imperative to mention that most patients enrolled were identified with mild AH.[76] The *Lactobacillus rhamnosus* GG trial was terminated in the United States due to a lack of funding (NTC01922895). There is an ongoing clinical trial in South Korea evaluating the efficacy of *Lactobacillus rhamnosus* on liver enzymes and cytotoxins levels in 140 subjects with AH (NCT02335632).

Bovine Colostrum (IMM-124E)

Bovine colostrum are molecules rich in immunoglobulin G (IgG) and additional proteins with anti-microbial properties that have been shown to bind LPS and decrease endotoxemia.[77] An open-label-controlled trial enrolled 25 patients with sAH (defined as MDF $\geq$ 54). An improvement in MDF score in the bovine + steroids combination group compared to the placebo group at 8 weeks with a survival rate approaching 90% at 1 month was found.[78] Further study with a phase 2 randomized trial of bovine colostrum IM124-E enrolled 57 subjects with sAH (MELD 20–28) and results are pending (NCT01968382). Finally, the (BASH) trial is a phase 3 RCT, currently recruiting patients with sAH (MDF > 32) to assess the survival rate at 3 months (NCT02473341).

Zinc

Zinc is a vital mineral that plays a role in gut mucosal integrity with tight junction regulation properties.[79] Alcohol-induced zinc deficiency leads to disruption of the gut permeability and activates inflammatory cascades, apoptosis, and oxidative stress.[80] Few studies evaluated the efficacy of zinc when used in combination with other agents. A multicenter RCT that enrolled 103 patients with sAH (MDF > 32) compared the use of a combination (zinc daily for 180 days, IL-1 receptor antagonist (Anakinra) for 14 days, and pentoxifylline for 28 days, to Methylprednisone given for 28 days. The study showed no significant difference between the two arms.[41] Another multicenter, randomized, placebo trial (NCT04072822) currently recruiting subjects are evaluating the 90-day mortality of AH (MELD 20–35) with the use of prednisone, Anakinra plus zinc vs prednisone alone.

Fecal Microbiota Transplant

In recent years, fecal microbiota transplant (FMT) administration has been studied in multiple disorders including *Clostridium difficile* colitis, hepatic encephalopathy, and metabolic-associated fatty liver disease. Repopulation of healthy intestinal microbiota by FMT might provide additional benefits in patients with AH.[81] The initial small pilot trial was conducted on 7 subjects deemed as steroid-ineligible. These patients received FMT for 7 days. The results of this study were promising with a decrease in mean bilirubin from 20.5 to 2.86 ($P < 0.001$), a decrease in the MELD score from 33.6 to 13.7 ($P < 0.001$), and an increase in the overall survival of 87% in the FMT group vs 33.3% in the control group ($P < 0.018$) were noted. Moreover, the level of Actinobacteria and Proteobacteria abundance was decreased after FMT.[82] In the study published by Phillips et all, 51 patients with sAH were enrolled of whom 16 patients received FMT, 8 patients were treated with corticosteroids, 17 with nutritional support, and 10 with pentoxifylline. The result demonstrated statistically significant lower mortality at 3 months (3-month survival was 75%, 38%, 29%, and 30%, respectively, $P = 0.036$).[83] Two trials in India are being conducted to evaluate survival and biochemical markers in FMT (NCT03091010, NCT03827772), while a third trial will also recruit patients who are steroid-ineligible (NCT05285592).

Antioxidants

In addition to inflammation, AH induces liver injury by oxidative stress with apoptosis and necrosis via mitochondrial dysfunction with the production of reactive oxygen species induced by cytokines such as TNF- α. Reactive oxygen species also depletes antioxidants such as glutathione rendering it more sensitive to TNF- α damage.[84] Silymarin was studied in ALC without any survival benefit or improvement of liver enzymes.[85] S-adenosyl methionine is the main methyl donor in methylation reactions. Therefore, it can up-regulate glutathione synthesis. A clinical trial of 37 patients with ALD who received SAM vs. placebo did not show a significant difference in outcomes of the groups.[86] A randomized clinical trial (NCT03938662) is comparing the effect of SAM and Choline combination vs placebo in patients with ALD. Moreover, a multicenter, randomized placebo-control clinical trial (NCT04250259) is actively

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recruiting patients with ALC (Child class A or B) to evaluate the effect of SAM on hepatic function.

N-Acetylcysteine

N-Acetylcysteine (NAC) is an antioxidant that replenishes glutathione-the hepatocytes antioxidant-since the thiol group in the NAC can reduce free radical formation. The hypothesis of the NAC mechanism behind mitigating infection is via the improvement of phagocyte oxidative burst.[87] The best evidence of NAC efficacy was demonstrated in a large RCT of 174 patients with sAH who received NAC for 5 days plus prednisolone for 4 weeks and compared it to the control group who received prednisolone alone. The study concluded a short-term 1-month mortality reduction in the combination group vs prednisolone alone group (8% vs 24%, $P < 0.005$). However, there was no difference between the two groups in mortality during 3-months survival analysis. Additionally, there was a lower incidence of hepatorenal syndrome in the combination group.[88] On the other hand, a different retrospective study demonstrated no survival benefits at 90 days when given NAC for 5 days, along with prednisone; the study included 68 patients with mortality being higher in patients with higher MDF score.[89] Moreover, a study of 57 patients with sAH failed to provide any additional survival benefit of NAC with granulocyte colony-stimulating factor (G-CSF) compared to G-CSF alone.[90] Currently, a randomized control trial is comparing the use of NAC plus prednisolone vs prednisone alone in patients with sAH (NCT05294744).

Metadoxine

Metadoxine is an antioxidant involved in mitochondrial glutathione synthesis. The addition of Metadoxine to glucocorticoids in patients with sAH was studied in a RCT done in Mexico. The study indicated a significant improvement in survival in the metadoxine + steroid group compared to steroids alone at 90 days (68% vs 20% $P < 0.05$)[91] Additional RCTs compared the use of Metadoxine in conjunction with prednisone or pentoxifylline in 135 patients with sAH. The Metadoxine group demonstrated improvement in 3 and 6 month survival rates compared to the prednisone or pentoxifylline alone group. Metadoxine has added benefits for alcohol abstinence maintenance effects.[92]

Vitamin E

Vitamin E is an antioxidant that was examined in AH. It was previously studied in the setting of fatty liver disease. A RCT compared vitamin E to placebo in patients with sAH demonstrated no survival benefits or effects on liver function values.[93] However, a more recent open-label randomized comparative study of vitamin E added to standard therapy revealed a reduction in Child-Pugh score in the treatment group. The study sample was small and included only 30 patients.[94] Trials using antioxidant cocktails with vitamin E and other antioxidants concluded a lack of significant difference in patients with sAH.[95]

Agents that Modulate Regenerative Pathway

The hepatocyte has an intense regenerative capacity through multiple progenitor cells. Inflammatory status such as the one seen in AH impairs growth factors and genetic singling which, in turn, affects hepatocyte maturity.[96] Repairs of the inflamed hepatocyte caused by AH are essential and there have been few regenerative targets for therapy that are studied.

IL-22 Infusion (F-652)

IL-22 is produced from the CD4+ T helper cells. It is one of the IL-10 derivate that functions to modulate tissue proliferation, remodeling, inflammation, and has the effects of antioxidant and anti-apoptosis. F-652 is a human IL-22 recombinant protein that resembles the effects of native IL-22 but with improved pharmacokinetics due to the addition of human immunoglobulins.[97–99] The TREAT 008 study (NCT02655510) was a dose-escalation study undertaken at Mayo clinic centers that included 18 subjects with sAH (MELD > 21) and used F-652 infusion at 10 μg/kg, 30 μg/kg, or 45 μg/kg on days 1 and 7. The study demonstrated that F-652 reduced the MELD score by 6 and 5 points on days 28 and 42 respectively. Additionally, on day 7 a Lille score of $\leq$0.45 was achieved in almost 83% of subjects. F-652 is a safe drug and was well tolerated by the study subjects.[100] These results are promising, and future RCTs is warranted to prove the efficacy of IL-22 infusion.

G-CSF (Filgrastim)

In animal models, the cytokine G-CSF was found to stimulate progenitor CD34+ stem cells to increase hepatocellular growth factors and subsequently lead to hepatocyte proliferation and maturation.[101,102] The safety and efficacy of G-CSF are being evaluated in previous and ongoing studies. Garg *et al.* randomly assigned 23 patients with ACLF (57% of which were AH) to subcutaneous 5 μg/kg G-CSF and compared them to 24 subjects who received a placebo. At 1-month follow-up, there was a survival benefit (69.6 vs 29% $P < 0.001$) with a significant reduction in MELD, Child-Pugh, and SOFA scores, in addition to improvement in the rate of encephalopathy and hepatorenal syndrome development in the treatment group.[103] Another study compared G-CSF (5 μg/kg for 5 days) to Pentoxifylline (1200 mg daily) and showed survival benefits with a reduction in MDF score at 3 months. The study did not use corticosteroids as standard therapy.[104] Another RCT enrolled 57 patients with sAH admitted to the ICU. Patients were randomized to three groups: (G-CSF + pentoxifylline) (G-CSF + pentoxifylline + NAC), and (pentoxifylline alone as control arm). The G-CSF group (either alone or in

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combination with NAC) had a 90-day survival benefit along with an improvement in MELD score at 3 months.[90] A randomized double-blind controlled trial examined the benefits of G-CSF in steroids non-responder sAH patients. When compared to the placebo, the G-CSF group displayed improvement in MELD, MDF score as well as 90-day mortality.[105] The above studies revealed excellent overall good safety and efficacy; however, it would be interesting to compare G-CSF with prednisolone standard therapy. Multiple RTCs are currently recruiting sAH patients to study the efficacy of G-CSF in adjunction with corticosteroid.

LIVER SUPPORT

Extracorporeal Liver-Assist Device

Extracorporeal liver assist device (ELAD) system is an extracorporeal hepatic cell treatment using cloned immortalized human hepatoblastoma cells (C3A). During ELAD treatment, the subject's blood is passed through a machine with ultrafiltration containing anti-inflammatory and antioxidant activity.[106] A Large phase 3 multicenter clinical trial enrolled 203 patients with sAH (defined as MDF $\geq$ 32) and compared subjects treated with ELAD vs standard therapy alone. There was a reduction in serum bilirubin and improvement in Lille score; however, the study failed to reach the primary endpoint as there was no difference in overall survival between the two groups after 90 days.[107] An additional RCT (NTC02621428) enrolled 151 patients with sAH. The study failed to meet the primary outcome of 3 months survival benefit; therefore, it was terminated early.

AH prevalence continues to rise, while the current therapeutic options are limited. The single available therapeutic agent currently administered for a limited number of patients is corticosteroid, which has not revealed mortality benefits beyond 28- days in patients with sAH. The need for novel therapies in AH is crucial. A combination of therapies has been investigated, providing additive through alternative pathways to target AH. Multiple clinical trials of novel therapies in AH remain ongoing. Their results could potentially make a difference in the clinical course of the disease.

CREDIT AUTHORSHIP CONTRIBUTION STATEMENT

Ali Wakil: Conceptualization, Methodology, Visualization, Writing - Original Draft, Project administration. **Mumtaz Niazi:** Writing - Original Draft, Reviewing and Editing **Mohamad Aghaie Meybodi:** Writing- Original draft preparation. **Nikolaos T. Pyrsopoulos:** Supervision, Writing- Reviewing and Editing.

CONFLICTS OF INTEREST

All authors have none to declare.

FUNDING

None.

REFERENCES

1. Singal AK, Kamath PS, Gores GJ, Shah VH. Alcoholic hepatitis: current challenges and future directions. *Clin Gastroenterol Hepatol*. 2014;12:555–564. quiz e531-552.
2. Barritt 4th AS, Jiang Y, Schmidt M, et al. Charges for alcoholic cirrhosis exceed all other etiologies of cirrhosis combined: a national and state inpatient survey analysis. *Dig Dis Sci*. 2019;64:1460–1469.
3. Singal AK, Bataller R, Ahn J, et al. ACG clinical guideline: alcoholic liver disease. *Am J Gastroenterol*. 2018;113:175–194.
4. Lucey MR, Mathurin P, Morgan TR. Alcoholic hepatitis. *N Engl J Med*. 2009;360:2758–2769.
5. Jinjuvadia R, Liangpunsakul S. Translational research and evolving alcoholic hepatitis treatment consortium. Trends in alcoholic hepatitis-related hospitalizations, financial burden, and mortality in the United States. *J Clin Gastroenterol*. 2015 Jul;49:506–511.
6. Singal AK, Kodali S, Vucovich LA, et al. Diagnosis and treatment of alcoholic hepatitis: a systematic review. *Alcohol Clin Exp Res*. 2016;40:1390–1402.
7. Crabb DW, Bataller R, Chalasani NP, et al. Standard definitions and common data elements for clinical trials in patients with alcoholic hepatitis: recommendation from the NIAAA alcoholic hepatitis consortia. *Gastroenterology*. 2016;150:785–790.
8. Singal AK, Shah VH. Alcoholic hepatitis: prognostic models and treatment. *Gastroenterol Clin N Am*. 2011;40:611–639.
9. Pollard MS, Tucker JS, Green HD. Changes in adult alcohol use and consequences during the COVID-19 pandemic in the US. *JAMA Netw Open*. 2020;3e2022942.
10. Dunn W, Jamil LH, Brown LS, et al. MELD accurately predicts mortality in patients with alcoholic hepatitis. *Hepatology*. 2005;41:353–358.
11. Louvet A, Naveau S, Abdelnour M, et al. The Lille model: a new tool for therapeutic strategy in patients with severe alcoholic hepatitis treated with steroids. *Hepatology*. 2007;45:1348–1354.
12. Maddrey WC, Boitnott JK, Bedine MS, et al. Corticosteroid therapy of alcoholic hepatitis. *Gastroenterology*. 1978;75:193–199.
13. Thursz MR, Richardson P, Allison M, et al. Prednisolone or pentoxifylline for alcoholic hepatitis. *N Engl J Med*. 2015;372:1619–1628.
14. Louvet A, Thursz MR, Kim DJ, et al. Corticosteroids reduce risk of death within 28 Days for patients with severe alcoholic hepatitis, compared with pentoxifylline or placebo-a meta-analysis of individual data from controlled trials. *Gastroenterology*. 2018;155:458–468 e458.
15. Mathurin P, Moreno C, Samuel D, et al. Early liver transplantation for severe alcoholic hepatitis. *N Engl J Med*. 2011;365:1790–1800.
16. Hasanin M, Dubay DA, McGuire BM, et al. Liver transplantation for alcoholic hepatitis: a survey of liver transplant centers. *Liver Transplant*. 2015;21:1449–1452.
17. Marot A, Dubois M, Trepo E, et al. Liver transplantation for alcoholic hepatitis: a systematic review with meta-analysis. *PLoS One*. 2018;13e0190823.
18. Singal AK, Bashar H, Anand BS, et al. Outcomes after liver transplantation for alcoholic hepatitis are similar to alcoholic cirrhosis: exploratory analysis from the UNOS database. *Hepatology*. 2012;55:1398–1405.
19. Singal AK, Shah VH. Current trials and novel therapeutic targets for alcoholic hepatitis. *J Hepatol*. 2019;70:305–313.
20. You M, Fischer M, Deeg MA, et al. Ethanol induces fatty acid synthesis pathways by activation of sterol regulatory element-binding protein (SREBP). *J Biol Chem*. 2002;277:29342–29347.

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21. Keshavarzian A, Farhadi A, Forsyth CB, et al. Evidence that chronic alcohol exposure promotes intestinal oxidative stress, intestinal hyperpermeability and endotoxemia prior to development of alcoholic steatohepatitis in rats. *J Hepatol*. 2009;50:538–547.
22. Szabo G. Gut-liver axis in alcoholic liver disease. *Gastroenterology*. 2015;148:30–36.
23. Wiest R, Lawson M, Geuking M. Pathological bacterial translocation in liver cirrhosis. *J Hepatol*. 2014;60:197–209.
24. Lowe PP, Gyongyosi B, Satishchandran A, et al. Alcohol-related changes in the intestinal microbiome influence neutrophil infiltration, inflammation and steatosis in early alcoholic hepatitis in mice. *PLoS One*. 2017;12e0174544.
25. Yiu JH, Dorweiler B, Woo CW. Interaction between gut microbiota and toll-like receptor: from immunity to metabolism. *J Mol Med (Berl)*. 2017;95:13–20.
26. Albano E. Role of adaptive immunity in alcoholic liver disease. *Int J Hepatol*. 2012;2012893026.
27. Szabo G, Petrasek J, Bala S. Innate immunity and alcoholic liver disease. *Dig Dis*. 2012;30(1):55–60.
28. Sandahl TD, Grùnbaek H, Mùller HJ, et al. Hepatic macrophage activation and the LPS pathway in patients with alcoholic hepatitis: a prospective cohort study. *Am J Gastroenterol*. 2014;109:1749–1756.
29. Afford SC, Fisher NC, Neil DA, et al. Distinct patterns of chemokine expression are associated with leukocyte recruitment in alcoholic hepatitis and alcoholic cirrhosis. *J Pathol*. 1998;186:82–89.
30. Taõeb J, Mathurin P, Elbim C, et al. Blood neutrophil functions and cytokine release in severe alcoholic hepatitis: effect of corticosteroids. *J Hepatol*. 2000;32:579–586.
31. Barnes MA, McMullen MR, Roychowdhury S, et al. Macrophage migration inhibitory factor contributes to ethanol-induced liver injury by mediating cell injury, steatohepatitis, and steatosis. *Hepatology*. 2013;57:1980–1991.
32. Mathurin P, Deng QG, Keshavarzian A, et al. Exacerbation of alcoholic liver injury by enteral endotoxin in rats. *Hepatology*. 2000 Nov;32:1008–1017.
33. Keshavarzian A, Choudhary S, Holmes EW, et al. Preventing gut leakiness by oats supplementation ameliorates alcohol-induced liver damage in rats. *J Pharmacol Exp Therapeut*. 2001;299:442–448.
34. Affò S, Morales-Ibanez O, Rodrigo-Torres D, et al. CCL20 mediates lipopolysaccharide induced liver injury and is a potential driver of inflammation and fibrosis in alcoholic hepatitis. *Gut*. 2014;63:1782–1792.
35. Minagawa M, Deng Q, Liu ZX, et al. Activated natural killer T cells induce liver injury by Fas and tumor necrosis factor-alpha during alcohol consumption. *Gastroenterology*. 2004;126:1387–1399.
36. Szabo G, Mandrekar P. A recent perspective on alcohol, immunity, and host defense. *Alcohol Clin Exp Res*. 2009;33:220–232.
37. Mandrekar P, Ambade A, Lim A, et al. An essential role for monocyte chemoattractant protein-1 in alcoholic liver injury: regulation of proinflammatory cytokines and hepatic steatosis in mice. *Hepatology*. 2011;54:2185–2197.
38. Louvet AMP. Alcoholic liver disease: mechanisms of injury and targeted treatment. *Nat Rev Gastroenterol Hepatol*. 2015;12:231–242.
39. Iracheta-Vellve A, Petrasek J, Gyogyosi B, et al. Interleukin-1 inhibition facilitates recovery from liver injury and promotes regeneration of hepatocytes in alcoholic hepatitis in mice. *Liver Int*. 2017;37:968–973.
40. Petrasek J, Bala S, Csak T, et al. IL-1 receptor antagonist ameliorates inflammasome-dependent alcoholic steatohepatitis in mice. *J Clin Invest*. 2012;122:3476–3489.
41. Szabo GMM, McClain C, et al. IL-1 receptor antagonist in combination with pentoxifylline and zinc for severe alcoholic hepatitis: a multicenter randomized double- bind placebo-controlled clinical trial. *Hepatology*. 2018;68:1444A.
42. Orrock JE, Ilowite NT. Canakinumab for the treatment of active systemic juvenile idiopathic arthritis. *Expet Rev Clin Pharmacol*. 2016;9:1015–1024.
43. Sfriso P, Bindoli S, Doria A, Feist E, Galozzi P. Canakinumab for the treatment of adult-onset Still's disease. *Expet Rev Clin Immunol*. 2020;16:129–138.
44. Ridker PM, Everett BM, Thuren T, et al. CANTOS trial group. Antiinflammatory therapy with canakinumab for atherosclerotic disease. *N Engl J Med*. 2017 Sep 21;377:1119–1131.
45. Witek RP, Stone WC, Gamze Karaca F, et al. Pan-caspase inhibitor VX-166 reduces fibrosis in an animal model of nonalcoholic steatohepatitis. *Hepatology*. 2009;50:1421–1430.
46. Gracia-Sancho J, Manicardi N, Ortega-Ribera M, et al. Emricasan ameliorates portal hypertension and liver fibrosis in cirrhotic rats through a hepatocyte-mediated paracrine mechanism. *Hepatol Commun*. 2019;3:987–1000.
47. Shiffman M, Freilich B, Vuppalanchi R, et al. Randomised clinical trial: emricasan versus placebo significantly decreases ALT and caspase 3/7 activation in subjects with non-alcoholic fatty liver disease. *Aliment Pharmacol Ther*. 2019;49:64–73.
48. Frenette CT, Morelli G, Shiffman ML, et al. Emricasan improves liver function in patients with cirrhosis and high model for end-stage liver disease scores compared with placebo. *Clin Gastroenterol Hepatol*. 2019;17:774–783 e774.
49. Garcia-Tsao G, Bosch J, Kayali Z, et al. Randomized placebo-controlled trial of emricasan for non-alcoholic steatohepatitis-related cirrhosis with severe portal hypertension. *J Hepatol*. 2020 May;72:885–895.
50. Harrison SA, Goodman Z, Jabbar A, et al. A randomized, placebo-controlled trial of emricasan in patients with NASH and F1-F3 fibrosis. *J Hepatol*. 2020 May;72:816–827.
51. Schuster-Gaul S, Geisler LJ, McGeough MD, et al. ASK1 inhibition reduces cell death and hepatic fibrosis in an Nlrp3 mutant liver injury model. *JCI Insight*. 2020;5.
52. Wada T, Penninger J. Mitogen-activated protein kinases in apoptosis regulation. *Oncogene*. 2004;23:2838–2849.
53. Mathurin PDJ, Bzowe NH, et al. Selonsertib in combination with prednisolone for the treatment of severe alcoholic hepatitis: a phase 2 randomized controlled trial. *Hepatology*. 2018;68:8A.
54. Nagy Laura E. The role of innate immunity in alcoholic liver disease. *Alcohol Res Curr Rev*. 2015;37:237.
55. Saikia Paramananda, et al. miR181b-3p and its target importin α5 regulate TLR4 signaling in Kupffer cells and liver injury in mice in response to ethanol. *Hepatology (Baltimore, MD*. 2017;66:602.
56. Ambade A, Lowe P, Kodys K, et al. Pharmacological inhibition of CCR2/5 signaling prevents and reverses alcohol-induced liver damage, steatosis, and inflammation in mice. *Hepatology*. 2019;69:1105–1121.
57. Marra F, Tacke F. Roles for chemokines in liver disease. *Gastroenterology*. 2014;147:577–594. e571.
58. Lambert G, Sjouke B, Choque B, Kastelein JJ, Hovingh GK. The PCSK9 decade. *J Lipid Res*. 2012;53:2515–2524.
59. Lee JS, Mukhopadhyay P, Matyas C, et al. PCSK9 inhibition as a novel therapeutic target for alcoholic liver disease. *Sci Rep*. 2019;917167.
60. Ruiz-Rodríguez Juan Carlos, et al. The use of CytoSorb therapy in critically ill COVID-19 patients: review of the rationale and current clinical experiences. *Crit Care Res Pract*. 17 Jul. 2021;2021:7769516. https://doi.org/10.1155/2021/7769516.

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61. Hassanein T, Stein LL, Flamm S, et al. Safety and efficacy of DUR-928: a potential new therapy for acute alcoholic hepatitis. *Hepatology*. 2019;70:1483A–1484A.
62. Schnabl B, Brenner DA. Interactions between the intestinal microbiome and liver diseases. *Gastroenterology*. 2014;146:1513–1524.
63. Summa KC, Voigt RM, Forsyth CB, et al. Disruption of the circadian clock in mice increases intestinal permeability and promotes alcohol-induced hepatic pathology and inflammation. *PLoS One*. 2013;8e67102.
64. Dunagan M, Chaudhry K, Samak G, Rao RK. Acetaldehyde disrupts tight junctions in Caco-2 cell monolayers by a protein phosphatase 2A-dependent mechanism. *Am J Physiol Gastrointest Liver Physiol*. 2012;303:G1356–G1364.
65. Konturek PC, Harsch IA, Konturek K, et al. Gut-liver axis: how do gut bacteria influence the liver? *Med Sci (Basel, Switzerland)*. 2018;6.
66. Cassard AM, Ciocan D. Microbiota, a key player in alcoholic liver disease. *Clin Mol Hepatol*. 2018;24:100–107.
67. Sarin SK, Pande A, Schnabl B. Microbiome as a therapeutic target in alcohol-related liver disease. *J Hepatol*. 2019;70:260–272.
68. Bull-Otterson L, Feng W, Kirpich I, et al. Metagenomic analyses of alcohol induced pathogenic alterations in the intestinal microbiome and the effect of Lactobacillus rhamnosus GG treatment. *PLoS One*. 2013;8e53028.
69. Vergis N, Atkinson SR, Knapp S, et al. In patients with severe alcoholic hepatitis, prednisolone increases susceptibility to infection and infection-related mortality, and is associated with high circulating levels of bacterial DNA. *Gastroenterology*. 2017;152:1068–1077. e1064.
70. Singal AK, Shah VH, Kamath PS. Infection in severe alcoholic hepatitis: yet another piece in the puzzle. *Gastroenterology*. 2017;152:938–940.
71. Vlachogiannakos J, Viazis N, Vasianopoulou P, Vafiadis I, Karamanolis DG, Ladas SD. Long-term administration of rifaximin improves the prognosis of patients with decompensated alcoholic cirrhosis. *J Gastroenterol Hepatol*. 2013;28:450–455.
72. Vlachogiannakos J, Saveriadis AS, Viazis N, et al. Intestinal decontamination improves liver haemodynamics in patients with alcohol-related decompensated cirrhosis. *Aliment Pharmacol Ther*. 2009;29:992–999.
73. Jimenez CVM, Sala M, et al. Use of rifaximin in alcoholic hepatitis: pilot study. *J Hepatol*. 2018;69:S816.
74. Li Fengyuan, et al. Probiotics and alcoholic liver disease: treatment and potential mechanisms. *Gastroenterol Res Pract*. 2016;20165491465.
75. Stadlbauer V, Mookerjee RP, Hodges S, Wright GA, Davies NA, Jalan R. Effect of probiotic treatment on deranged neutrophil function and cytokine responses in patients with compensated alcoholic cirrhosis. *J Hepatol*. 2008 Jun;48:945–951. https://doi.org/10.1016/j.jhep.2008.02.015. Epub 2008 Mar 25. PMID: 18433921.
76. Han SH, Suk KT, Kim DJ, et al. Effects of probiotics (cultured Lactobacillus subtilis/Streptococcus faecium) in the treatment of alcoholic hepatitis: randomized-controlled multicenter study. *Eur J Gastroenterol Hepatol*. 2015;27:1300–1306. https://doi.org/10.1097/MEG.0000000000000458.
77. Döhler JR, Nebermann L. Bovine colostrum in oral treatment of enterogenic endotoxaemia in rats. *Crit Care*. 2002;6:536–539. https://doi.org/10.1186/cc1819.
78. Sidhu SGO, Gupta A, et al. Corticosteroids and bovine colostrum in treatment of alcoholic hepatitis 'in extremis': a pilot study. *J Clin Exp Hepatol*. 2015;5:S19–S20.
79. Mohammad MK, Zhou Z, Cave M, Barve A, McClain CJ. Zinc and liver disease. *Nutr Clin Pract*. 2012;27:8–20.
80. Zhong W, Zhao Y, Sun X, Song Z, McClain CJ, Zhou Z. Dietary zinc deficiency exaggerates ethanol-induced liver injury in mice: involvement of intrahepatic and extrahepatic factors. *PLoS One*. 2013;8e76522.
81. Mullish BH, Quraishi MN, Segal JP, et al. The use of faecal microbiota transplant as treatment for recurrent or refractory Clostridium difficile infection and other potential indications: joint British Society of Gastroenterology (BSG) and Healthcare Infection Society (HIS) guidelines. *Gut*. 2018;67:1920–1941.
82. Philips CA, Pande A, Shasthry SM, et al. Healthy donor fecal microbiota transplantation in steroid-ineligible severe alcoholic hepatitis: a pilot study. *Clin Gastroenterol Hepatol*. 2017;15:600–602.
83. Philips CA, Phadke N, Ganesan K, Ranade S, Augustine P. Corticosteroids, nutrition, pentoxifylline, or fecal microbiota transplantation for severe alcoholic hepatitis. *Indian J Gastroenterol*. 2018;37:215–225.
84. Singal AKJS, Weinman SA. Antioxidants as therapeutic agents for liver disease. *Liver Int*. 2011;31:1432–1448.
85. Ferenci P, Dragosics B, Dittrich H, et al. Randomized controlled trial of silymarin treatment in patients with cirrhosis of the liver. *J Hepatol*. 1989 Jul;9:105–113. https://doi.org/10.1016/0168-8278(89)90083-4. PMID:2671116.
86. Mato Jose M, et al. S-adenosylmethionine in alcoholic liver cirrhosis: a randomized, placebo-controlled, double-blind, multicenter clinical trial. *J Hepatol*. 1999;30:1081–1089.
87. Benrahmoune M, Therond P, Abedinzadeh Z. The reaction of superoxide radical with N-acetylcysteine. *Free Radic Biol Med*. 2000;29:775–782.
88. Nguyen-Khac ETT, Piquet M, et al. Glucocorticoids plus N-acetylcysteine in severe alcoholic hepatitis. *N Engl J Med*. 2011;365:1781–1789.
89. Amjad W, Alukal J, Doycheva I, et al. A combination of N-acetylcysteine and prednisone has no benefit over prednisone alone in severe alcoholic hepatitis: a retrospective analysis. *Dig Dis Sci*. 2020 Dec;65:3726–3733.
90. Singh VKA, Bhalla A, et al. Efficacy of granulocyte colony-stimulating factor and N-acetylcysteine therapies in patients with severe alcoholic hepatitis. *Clin Gastroenterol Hepatol*. 2018;16:1650–1656.
91. Higuera-de la Tijera F, Servín-Caamaño AI, Cruz-Herrera J, et al. Treatment with Metadoxine and its impact on early mortality in patients with severe alcoholic hepatitis. *Ann Hepatol*. 2014;13:343–352.
92. Higuera-de la Tijera F, Servín-Caamaño AI, Serralde-Zúñiga AE, et al. Metadoxine improves the three- and six-month survival rates in patients with severe alcoholic hepatitis. *World J Gastroenterol*. 2015;21:4975–4985.
93. Mezey EPJP, Rennie-Tankersley L, et al. A randomized placebo controlled trial of vitamin E for alcoholic hepatitis. *J Hepatol*. 2004;40:40–46.
94. Kolasani BP, Sasidharan P, Kumar A. Efficacy of Vitamin E supplementation in patients with alcoholic liver disease: an open-label, prospective, randomized comparative study. *Int J Nutr Pharmacol Neurol Dis*. 2016;6:101–110.
95. Phillips M, Curtis H, Portmann B, et al. Antioxidants versus corticosteroids in the treatment of severe alcoholic hepatitis–a randomised clinical trial. *J Hepatol*. 2006;44:784–790.
96. Dippold RP, Vadigepalli R, Gonye GE, Patra B, Hoek JB. Chronic ethanol feeding alters miRNA expression dynamics during liver regeneration. *Alcohol Clin Exp Res*. 2013;37:E59–E69.
97. Kong X, Feng D, Mathews S, et al. Hepatoprotective and antifibrotic functions of interleukin-22: therapeutic potential for the treatment of alcoholic liver disease. *J Gastroenterol Hepatol*. 2013;28:56–60.

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98. Gao B, Xiang X. Interleukin-22 from bench to bedside: a promising drug for epithelial repair. *Cell Mol Immunol*. 2019;16:666–667.
99. Yang L, Zhang Y, Wang L, et al. Amelioration of high fat diet induced liver lipogenesis and hepatic steatosis by interleukin-22. *J Hepatol*. 2010;53:339–347.
100. Arab JP, Sehrawat TS, Simonetto DA, et al. An open-label, dose-escalation study to assess the safety and efficacy of IL-22 agonist F-652 in patients with alcohol-associated hepatitis. *Hepatology*. 2020;72:441–453.
101. Yannaki E, Athanasiou E, Xagorari A, et al. G-CSF-primed hematopoietic stem cells or G-CSF per se accelerate recovery and improve survival after liver injury, predominantly by promoting endogenous repair programs. *Exp Hematol*. 2005;33:108–119.
102. Theocharis SE, Papadimitriou LJ, Retsou ZP, Margeli AP, Ninos SS, Papadimitriou JD. Granulocyte-colony stimulating factor administration ameliorates liver regeneration in animal model of fulminant hepatic failure and encephalopathy. *Dig Dis Sci*. 2003;48:1797–1803.
103. Garg V, Garg H, Khan A, et al. Granulocyte colony-stimulating factor mobilizes CD34(+) cells and improves survival of patients with acute-on-chronic liver failure. *Gastroenterology*. 2012;142:505–512.e1.
104. Singh V, Sharma AK, Narasimhan RL, Bhalla A, Sharma N, Sharma R. Granulocyte colony-stimulating factor in severe alcoholic hepatitis: a randomized pilot study. *Am J Gastroenterol*. 2014;109:1417–1423.
105. Shasthry SM, Sharma MK, Shasthry V, Pande A, Sarin SK. Efficacy of granulocyte colony-stimulating factor in the management of steroid-nonresponsive severe alcoholic hepatitis: a double-blind randomized controlled trial. *Hepatology*. 2019;70:802–811.
106. Kumar A, Tripathi A, Jain S. Extracorporeal bioartificial liver for treating acute liver diseases. *J Extra Corpor Technol*. 2011;43:195–206.
107. Thompson J, Jones N, Al-Khafaji A, et al. Extracorporeal cellular therapy (ELAD) in severe alcoholic hepatitis: a multinational, prospective, controlled, randomized trial. *Liver Transplant*. 2018;24:380–393.

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