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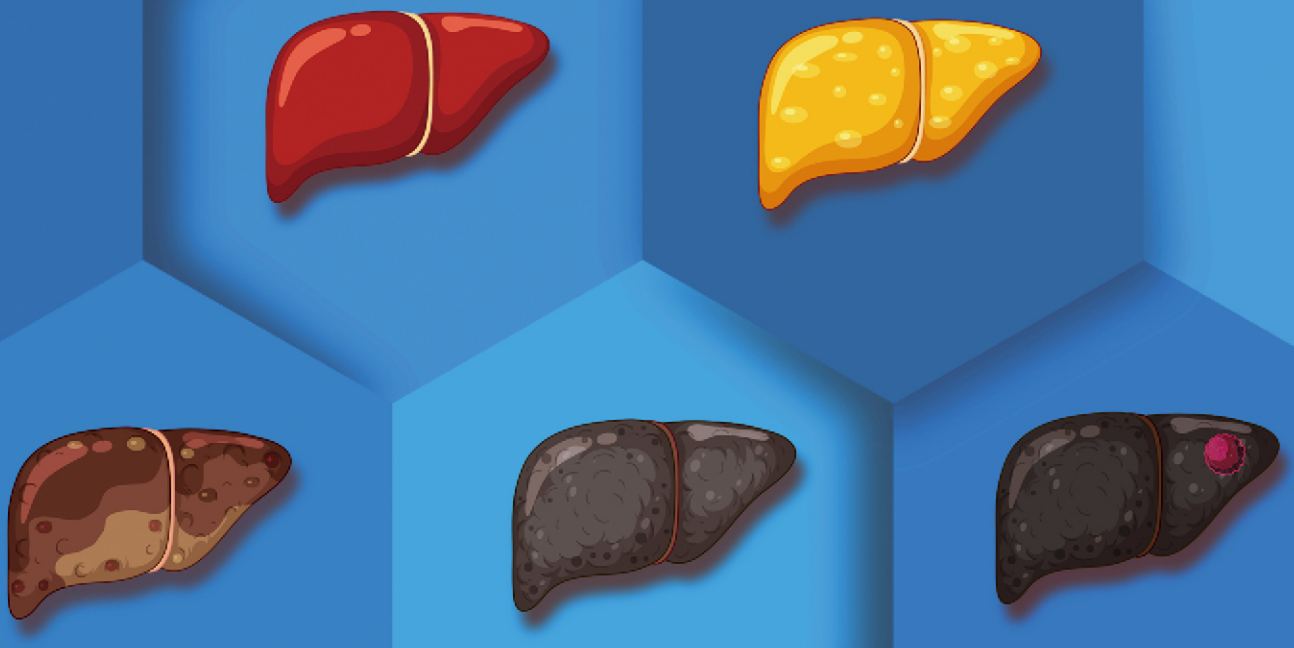

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Review

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Alcohol-associated liver disease: Natural history, management and novel targeted therapies

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Alcohol consumption is a leading cause of preventable morbidity and mortality worldwide and the primary cause of advanced liver disease. Alcohol use disorder is a chronic, frequently relapsing condition characterized by persistent alcohol consumption despite its negative consequences. Alcohol-associated liver disease (ALD) encompasses a series of stages, from fatty liver (steatosis) to inflammation (steatohepatitis), fibrosis, and, ultimately, liver cirrhosis and its complications. The development of ALD is complex, involving both genetic and environmental factors, yet the exact mechanisms at play remain unclear. Alcohol-associated hepatitis (AH), a severe form of ALD, presents with sudden jaundice and liver failure. Currently, there are no approved targeted therapies able to interfere in the pathogenesis of ALD to stop the progression of the disease, making alcohol abstinence the most effective way to improve prognosis across all stages of ALD. For patients with advanced ALD who do not respond to medical therapy, liver transplantation is the only option that can improve prognosis. Recently, AH has become an early indication for liver transplantation in non-responders to medical treatment, showing promising results in carefully selected patients. This review provides an update on the epidemiology, natural history, pathogenesis, and current treatments for ALD. A deeper insight into novel targeted therapies investigated for AH focusing on new pathophysiologically-based agents is also discussed, including anti-inflammatory and antioxidative stress drugs, gut-liver axis modulators, and hepatocyte regenerative molecules. **(Clin Mol Hepatol 2025;31(Suppl):S112-S133)**

Keywords: Alcohol-associated hepatitis; Alcohol use disorder; Corticoids

INTRODUCTION

Alcohol consumption is one of the leading causes of preventable death and disability worldwide.[1,2] Gastrointestinal diseases and alcohol-associated liver disease (ALD) are important health issues contributing to the overall alcohol-associated burden.[1] The prevalence of advanced ALD is increasing worldwide, especially in young women.[3] Despite the importance of ALD at a global level, research attention and financial support have been scarce for this condition.[4] However, the new consensus definition of steatotic liver disease (SLD),[5] including patients with metabolic

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dysfunction-associated steatotic liver disease (MASLD), ALD, and a new concept named metabolic and alcohol-associated liver disease (MetALD), has increased awareness within the liver community. A very recent study showed that low-to-moderate alcohol consumption is prevalent among patients with MASLD, and alcohol consumption increases the risk of significant fibrosis in a dose-dependent super-additive interaction with cardio-metabolic risk factors.[6-8] Recent translational studies have uncovered the key mechanisms leading to ALD, including the gut-liver axis, immune dysfunction, and poor hepatocyte regeneration.[9] Novel targeted therapies for advanced forms of ALD are currently being developed.

EPIDEMIOLOGY AND NATURAL HISTORY OF ALD

Epidemiology

Chronic liver diseases are a prominent cause of mortality at the global level, accounting for 4% of all deaths worldwide.[10] ALD is one of the most prevalent causes of liver disease. It is the leading cause of cirrhosis, accounting for almost 60% of cirrhosis diagnoses in Europe, North America, and Asia.[11,12] Moreover, ALD is the second-leading cause of liver-related deaths worldwide and by far the leading cause in Europe.[13] The Asia-Pacific region is home to more than half of the world's population and is reported to account for 62.6% of global deaths from liver disease.[14] Previous studies analyzing the burden of liver disease in Asian populations have either focused on individual countries or regions, individual years, or a subset of the most common etiologies, such as hepatitis B or C virus (HBV or HCV, respectively). However, due to the hepatitis B vaccine and the effective application of antiviral therapy, the status of HBV as a major cause of chronic liver disease is gradually declining, while alcohol has gained increasing attention. According to the World Health Organization (WHO) 2018, the Western Pacific region has had the second-highest increase in alcohol consumption. The disease burden of ALD in Asia is likely to have increased in a similar way over the last 21 years and is expected to emerge as a leading cause of chronic liver disease.[14,15] ALD-related mortality has been increasing since the start of the COVID-19 pandemic in 2020,[16,17] possibly owing to a shift in drinking patterns and decreased accessibility to health care.

Stages of ALD

The term ALD encompasses several clinical phenotypes and different degrees of anatomopathological liver injury, ranging from asymptomatic disease in patients with steatosis to life-threatening complications in patients with advanced fibrosis and steatohepatitis. The pathogenesis of ALD begins with the deposit of fatty droplets in the cytoplasm of the hepatocytes as a result of alcohol metabolization; this phenomenon, called steatosis, occurs in most patients with a pattern of prolonged heavy alcohol use[18] (Fig. 1). In approximately one out of four patients, intrahepatic fat deposition generates a local inflammatory response, leading to the development of steatohepatitis. Sustained inflammation in the liver is known to be the main trigger of liver fibrosis, which consists of progressive collagen deposition and extracellular matrix remodeling. Liver fibrosis is the main driver of ALD progression.[19] In the advanced stages, collagen bridges develop between portal tracts and central veins and ultimately form nodules within the liver. Cirrhosis occurs in 8–20% of patients with fibrosis throughout the natural history of the disease,[20-22] with an increase in intrahepatic vascular resistance and a subsequent onset of portal hypertension.[23] A cross-sectional analysis of patients with liver disease worldwide found that patients with ALD are characterized by a more advanced-stage disease than patients with HCV-associated liver disease.[24]

Abbreviations:

ACLF, acute-on-chronic liver failure; AH, alcohol-associated hepatitis; ALD, alcohol-associated liver disease; AUD, alcohol use disorder; ASH, alcohol-associated steatohepatitis; DAMPs, danger-associated molecular patterns; EMA, European Medicines Agency; FDA, Food and Drug Administration; GGT, gamma-glutamyl transpeptidase; FMT, fecal microbiota transplantation; HSC, hepatic stellate cell; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; iNOS, inducible nitric oxide synthase; LT, liver transplantation; LPS, lipopolysaccharide; MAFLD, metabolic associated fatty liver disease; MELD, Model for End-Stage Liver Disease; MetALD, metabolic and alcohol associated liver disease; MAMPS, microbe-associated molecular patterns; PAMPs, pathogen-associated molecular patterns; SLD, steatotic liver disease; TNF-α, tumour necrosis factor alpha; WHO, World Health Organization

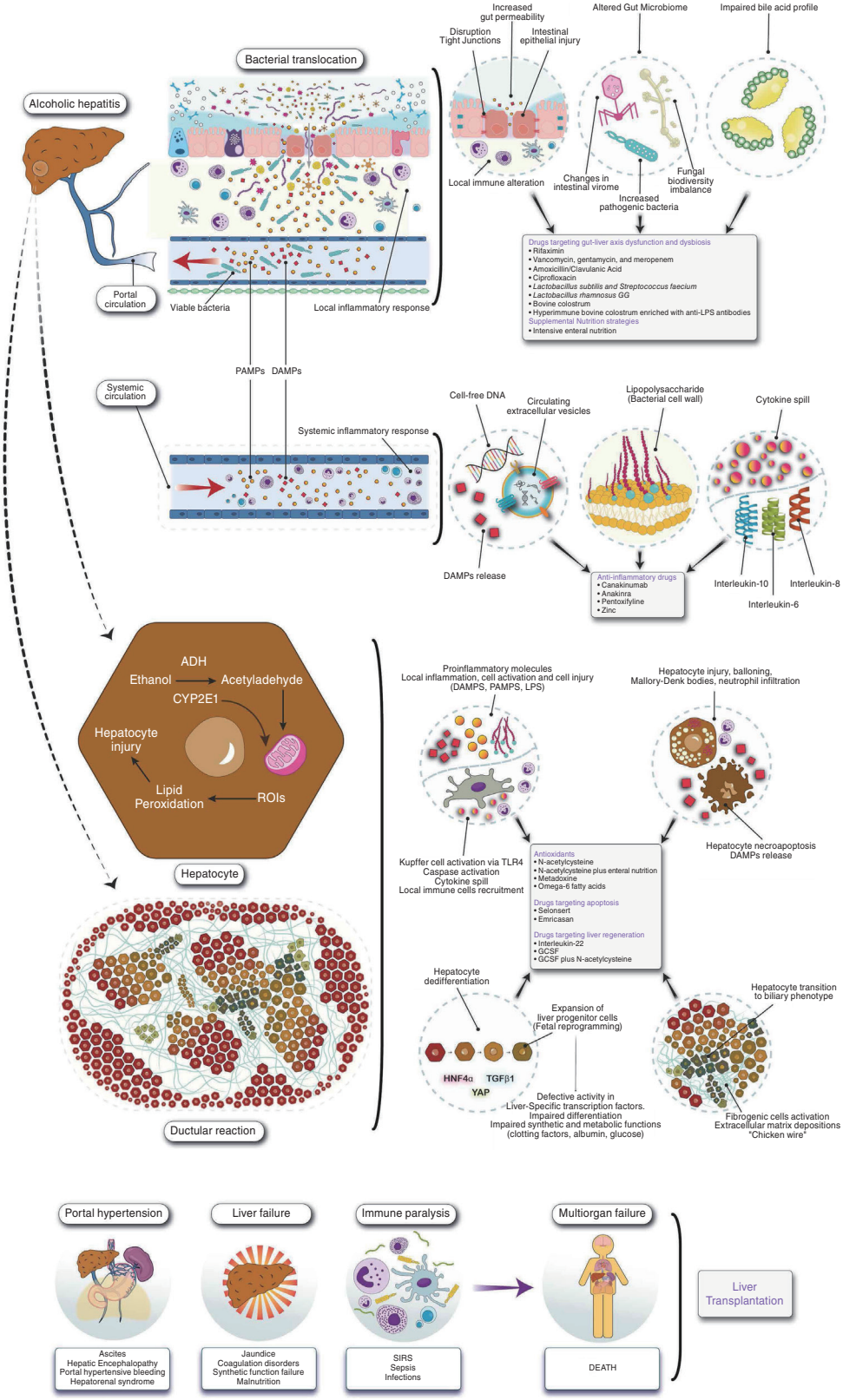

Figure 1. Pathogenesis of alcohol-associated hepatitis. ADH, alcohol dehydrogenase; DAMPs, danger-associated molecular patterns; GCSF, granulocyte-colony stimulating factor; LPS, lipopolysaccharide; PAMPs, pathogen-associated molecular patterns; ROIs, reactive oxygen intermediates; SIRS, systemic inflammatory response syndrome.

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Regarding the clinical presentation of ALD, two different stages can be distinguished: the first stage of asymptomatic or scarcely symptomatic disease, in which patients may not have any clinical manifestation of liver disease, and the clinical stage of the disease, characterized by the development of liver cirrhosis and portal hypertension complications such as ascites, hepatic encephalopathy, variceal bleeding, acute kidney injury (AKI), and infections. The symptomatic stage of the disease, termed decompensated cirrhosis, arises in 20–40% of patients with cirrhosis.[25] Moreover, liver cirrhosis significantly increases the probability of developing hepatocellular carcinoma, which occurs in 3–10% of patients.[25]

Alcohol-associated hepatitis (AH) is the most severe manifestation of ALD and is characterized by steatosis, bilirrubinostasis, massive pericellular fibrosis, neutrophil infiltration, and profound metaplasia of hepatocytes.[26,27] AH can occur at any stage of liver disease, yet most patients have advanced fibrosis/cirrhosis,[28,29] which greatly impacts the prognosis of patients with ALD. In severe cases, bacterial infections and/or a systemic inflammatory response trigger acute-on-chronic liver failure (ACLF), a syndrome characterized by multiorgan failure and associated with very high short-term mortality.[30,31]

Determinants of disease progression

The development and progression of ALD are dependent on several factors, including a) the amount of alcohol intake,[32,33] b) the pattern of alcohol consumption, such as binge drinking (drinking 4–5 alcoholic beverages in a short period), is a pattern of alcohol consumption associated with changes in multiple inflammation-related markers, all of them implicated in alcohol metabolism and hepatocellular damage,[34] c) the type of alcohol, which could impact the degree of liver injury (e.g., wine drinkers, but not exclusive beer drinkers, are less likely to have advanced liver fibrosis).[35]

Over the last few years, there has been significant progress in our understanding of the pathogenesis and natural history of ALD. Genome-wide association studies have revealed some of the genetic risk factors of ALD, such as variations in the genes encoding patatin-like phospholipase domain-containing protein 3,[36] transmembrane six superfamily two and membrane-bound O-acyltransferase domain containing 7.[37] Furthermore, population-based studies have identified specific characteristics, such as alcohol consumption,[38] female sex,[39] previous bariatric surgery,[40,41] and metabolic risk factors as important accelerators of disease progression.[31-34,42] Metabolic risk factors have come under intense scrutiny in recent years; several studies, some of which derive from large databases like the Genomic Alcohol Cohort Consortium or the United Kingdom Biobank, have found body mass index, diabetes, and metabolic syndrome to be associated with the development of advanced liver disease in both ALD patients[28] and the general population.[42-47] Moreover, the presence of metabolic risk factors has also been linked to increased overall and liver-related mortality in patients with ALD.[43,44] The high prevalence of coexisting alcohol and metabolic risk factors for liver disease has led to the proposal of the new nomenclature of MetALD, which refers to patients with both etiological factors.[5]

Other known risk factors for ALD progression are Hispanic ethnicity,[48] tobacco smoking,[49] and other underlying liver diseases.[50] Several protective factors for ALD have also been proposed, mainly genetic variants in hydroxysteroid 17-beta dehydrogenase 13 and mitochondrial amidoxime-reducing component 1 gene[51,52] and coffee consumption.[53,54] Many determinants of disease progression are associated with specific genetic alterations or with comorbid conditions.

Therefore, targeted treatment for ALD in the future might include other strategies, such as gene therapy or medications for metabolic syndrome in selected patients.

ALCOHOL USE DISORDER

Alcohol use disorder (AUD) is a chronic, frequently relapsing condition characterized by persistent alcohol consumption despite its negative consequences.[55] The prevalence of AUD is approximately 5% globally.[1] Importantly, alcohol contributes to almost 50% of cases of liver-related mortality.[1] In this sense, the two main therapeutic goals are the prevention and treatment of alcohol withdrawal syndrome in the short term[56] and the induction and maintenance of alcohol abstinence in the long term.

An optimal treatment for AUD in patients with ALD should have complete alcohol abstinence as its main objective.[57]

Harm-reduction strategies that are effective in the general population[58] might also be effective in ALD; unfortunately, evidence regarding this issue is scarce.

Psychosocial interventions

The cornerstones of AUD management are psychosocial interventions, which focus on promoting the motivation to stop drinking. Among the strategies available are brief interventions and counseling, psychotherapy (motivational enhancement therapy and cognitive behavioral therapy), peer-support groups, and contingency management. These strategies have proven to be very effective in reducing harmful drinking in primary health care[59] and have even been shown to reduce the risk of developing ALD.[60] Nevertheless, information on their effectiveness in key groups, such as comorbid drinkers, is limited. Several studies have investigated the use of psychosocial interventions in patients with liver diseases. Most of these studies included patients with AUD and viral hepatitis infection with or without advanced fibrosis.[61-64] In this setting, psychotherapy alone, with either motivational enhancement or cognitive behavioral therapy, is effective in the induction but not in the maintenance of alcohol abstinence.[65] These strategies might be less effective in patients with ALD, who, by definition, have a more severe AUD. In a classical clinical trial including hospitalized patients with alcohol-related digestive conditions (most with cirrhosis), a 2-hour in-hospital motivational intervention did not improve alcohol abstinence at three months compared to medical care alone.[66] In contrast, in another trial in liver transplant candidates, the authors reported a reduction in drinks per drinking day in patients receiving motivational enhancement therapy.[67]

Pharmacological interventions

Several anti-craving medications for AUD have proven to be effective, either alone or in combination with psychosocial interventions. Medications approved by the Food and Drug Administration (FDA) and the European Medicines Agency (EMA) for the treatment of AUD are disulfiram, naltrexone, and acamprosate (Table 1).[68,69] The EMA also approves Nalmefene. Additionally, sodium oxybate is approved for AUD only in Italy and Austria and baclofen only in France.[70] Disulfiram was the first treatment to be approved for AUD and is still widely used by addiction specialists. It is an inhibitor of acetaldehyde dehydrogenase and thus causes distressing symptoms when consumed together with alcohol, acting as a dissuasive medication. Disulfiram should be avoided in patients with ALD, especially those with advanced fibrosis, as it can cause acute liver failure and death.[71,72] Naltrexone is an opioid receptor antagonist that acts by reducing dopamine release and decreasing the sensation of reward. Despite a warning being issued by the FDA regarding its potential to induce hepatocellular injury, two recent observational studies have suggested it is safe and effective in patients with ALD.[73,74] Nalmefene is another opioid receptor antagonist that has been shown to reduce heavy drinking; therefore, it is also indicated for harm-reduction strategies,[75] but its use in patients with ALD is lacking. Acamprosate is an N-methyl-D-aspartate glutamate receptor antagonist that reduces withdrawal-induced hyper-glutamatergic states, which are thought to trigger relapse. Data on its efficacy and safety in patients with ALD is limited to retrospective cohorts.[76] Sodium oxybate is a gamma-aminobutyric acid agonist that reduces craving in patients with AUD.[77] However, there are some concerns regarding the potential abuse of the drug, especially in patients with a psychiatric comorbidity.[78] Its efficacy and safety in patients with ALD are unknown. Finally, baclofen is a selective gamma-aminobutyric acid B receptor agonist approved for spasticity conditions. It has an inhibitory effect on the dopamine network, reducing alcohol-reinforced behaviors. Several cohort studies and randomized clinical trials support its efficacy and safety in patients with alcohol-associated cirrhosis.[79,80] Other medications have shown beneficial effects in ALD, such as topiramate,[81] ondansetron, and gabapentin.[82] Lastly, fecal microbiota transplantation (FMT) has shown promising preliminary results for the treatment of AUD in both animal models and humans.[83,84]

Despite the absence of high-quality evidence, particularly clinical trials, regarding the effects of anti-craving medications for AUD on patients with ALD, recent cohort studies have found an association between anti-craving medications for AUD and long-term survival in patients with cirrhosis.[85-87] Moreover, the use of these drugs in patients with compensated alcohol-associated cirrhosis provides cost-savings, meaning that they provide more benefits than no intervention, with lower costs.[88] Consequently, their use

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Table 1. Pharmacological interventions in alcohol use disorder management

Drug***	Doses	Main contraindications	Liver safety	Mechanism of action	EMA approval	NNT	Gender
Disulfiram	250–500 mg once per day	Seizures Acute heart disease Uncontrolled Diabetes mellitus Liver disease	Avoid in advance liver disease Caution in early liver disease	Inhibits aldehyde dehydrogenase (ALDH1A1)	Yes	N/A	Higher efficacy in men
Naltrexone	50 mg once per day (long-acting 190–380 mg every 4 wk*)	Active use of opioids	Warning, but cohorts' studies showed safety	Antagonist opioid system	Yes	7–20	Higher efficacy in men, higher incidence of side effects and lower efficacy in women
Acamprosate	666 mg three times per day	Avoid in severe kidney failure (50% dose in moderate-mild)	Safe	Antagonist glutamatergic and agonist gabaergic system	Yes	8–12	Higher incidence of side effects in women
Nalmefene	18 mg once per day	Active use of opioids	Probably safe	Antagonist and partial agonist opioid system	Yes	6–10	No differences
Topiramate	50–150 mg twice per day	Cognition problems Low weight	Probably safe	Agonist gabaergic system	No	5	Higher efficacy in men
Gabapentine	300–600 mg three times per day	Risk of abuse	Probably safe (50% dose in sever kidney failure)	Agonist gabaergic system	No	5–8	No data
Sodium oxybate	3.3–3.9 g/day (split three times per day)	Risk of abuse	Probably safe. Not enough data available.	Agonist gabaergic system	No	N/A	No data
Baclofen	10–25 mg three times per day†	Suicidal behavior (caution in patients with affective disorders) Sleep apnea or severe respiratory failure Severe cardiovascular disease Urinary incontinency	Probably safe	Agonist gabaergic system	No	13	Higher efficacy in women with low dose, but higher in men with high dose

EMA, European Medicines Agency; NNT, number needed to treat.
*Not available in Europe. †Some clinical trials with higher doses (150 mg/day) and case report/case series at 300 mg per day. ***No safety data against its use on pregnancy/breastfeeding for any of these drugs.

should be key in inducing and maintaining alcohol abstinence in patients with ALD, in whom psychosocial interventions alone are not effective and are hindered by treatment adherence.

Other interventions

Several interventional studies have demonstrated that screening for liver disease with transient elastography associated with a brief counseling session increases alcohol abstinence rates.[89,90] However, we need studies to assess the impact of follow-up with transient elastography on AUD.

Advances in technology in recent years have also provided physicians with interesting tools to improve AUD management. A recent study including patients with ALD and AUD suggested that monitoring the signs associated with alcohol craving using a smartphone application was feasible,[91] which is a step forward in the prediction of alcohol relapses. Concerning novel treatment approaches, a recently published trial showed that proactive therapy for AUD by videoconference increased treatment initiation and compliance rates and reduced alcohol consumption compared to standard of care with on-site visits.[92]

Integrated care

An important hurdle for effective treatment is adherence, which is highly variable and influenced by poor physical condition,[93] a common feature in patients with ALD. Consequently, integrating psychosocial interventions into the routine medical care of these patients in the same clinic is feasible and increases treatment adherence.[94] Multidisciplinary-based models aimed at providing integrated psychosocial and pharmacological interventions for patients with ALD and AUD have been associated with increased abstinence[78,79] and even higher survival rates in some settings.[80]

PATHOGENESIS OF ALCOHOL-ASSOCIATED LIVER DISEASE

Pathogenesis of alcohol-associated liver disease and AH

Our understanding of the cellular and molecular mechanisms underlying ALD remains incomplete. ALD encompasses a wide range of liver conditions, from an initial stage of alcoholic fatty liver/steatosis to more severe liver injury, such as steatohepatitis, fibrosis/cirrhosis, and hepatocellular carcinoma. Most research employs animal models, primarily exhibiting signs of moderate ALD, such as steatosis and mild inflammation.[89] However, there is a lack of models encompassing advanced fibrosis and cholestasis, two key histological features in the evolution from early to advanced ALD.

The pathogenesis of ALD varies according to the disease stage. Initially, *steatosis* emerges as the liver's primary response to alcohol abuse but is clinically asymptomatic, characterized by fat deposition in the hepatocytes.[95,96] Additionally, alcohol intake increases fatty acid and triglyceride synthesis and enhances the influx of free fatty acids from adipose tissue, chylomicrons from the intestinal mucosa, and hepatic lipogenesis while reducing lipolysis.[97] Moreover, alcohol damages the mitochondria and microtubules, accumulating very low-density lipoprotein.[96] In addition, alcohol leads to reduced fatty acid synthesis and increased fatty acid oxidation, promoting steatosis[92,93] and inducible nitric oxide synthase, which contributes to steatosis development[95,98,99] and hepatocellular lipid accumulation.

In individuals with prolonged alcohol abuse, simple steatosis is followed by hepatocellular injury and inflammatory changes, alcohol-associated steatohepatitis (ASH). Patients with ASH are usually asymptomatic and associated with liver biochemistry abnormalities. In the liver, alcohol is primarily metabolized into acetaldehyde by alcohol dehydrogenases and the cytochrome P450 2E1 enzyme. This oxidate metabolism induces glutathione depletion, mitochondrial damage and endoplasmic reticulum stress, reactive oxygen species, altered autophagy, lipid peroxidation, and finally, a significant hepatocyte injury.[100,101] Damaged hepatocytes release danger-associated molecular patterns (DAMPs), such as mitochondrial DNA and high mobility group box protein 1[102]; chemokines (e.g., CXC chemokine-ligand-1/5, monocyte chemoattractant protein-1, macrophage migration inhibitor factor), and inflammatory cytokines (e.g., tumor necrosis factor-alpha [TNF-α], interleukins [IL]-1/8/13). This increase in the release of DAMPs drives the activation of the inflammasome caspase-1 complex,[96] as well as inflammatory cytokines, pro-

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moting an inflammatory infiltrate consisting mainly of neutrophils and CD4+ T cells, which ultimately results in sterile hepatic inflammation,[103] which plays a crucial role in the pathogenesis of AH[104-106] (Fig. 1).

Chronic alcohol intake leads to an intestinal endotoxin build-up and increased intestinal wall permeability, intestinal dysbiosis, with a significant increase in pathogenic bacteria[107] (e.g., *Enterococcus faecalis*), and is characterized by fungal (mycobiome) alterations and an abundance of immunogenic fungi (e.g., *Candida*).[108-110] All these alterations facilitate lipopolysaccharide (LPS) and fungal (exotoxins) translocation from the gut to the portal and systemic circulation.[111] The translocation of bacterial and gut-derived microbial products to the liver (PAMPs, pathogen-associated molecular patterns) and microbe-associated molecular patterns (MAMPS) increases inflammation and induces hepatocyte death and fibrotic response. LPS recognition is mediated by the receptor (TLR4) on the macrophage resident in the liver - Kupffer cells - in the hepatic stellate cells (HSCs) and sinusoidal endothelial cells. This interaction triggers the release of cytokines and inflammatory substances, the promotion of fibrogenesis, and the regulation of angiogenesis.[112,113] Recent studies have shown that miRNAs and extracellular vesicles play a critical role in controlling liver inflammation in ALD[103] (Fig. 1).

All these inflammatory processes culminate in hepatocyte ballooning, the development of hepatic inclusions that aggregate cytokeratin, which is known as the Mallory–Denk body, accompanied by a superimposed inflammatory infiltrate.[100,101] The final step is the activation and proliferation of HSC, enhancing transforming growth factor-β (TGF-β) secretion, collagen synthesis, and accumulation of extracellular matrix around hepatocytes and sinusoidal cells, generating a “chicken wire” pattern and favoring the development of portal hypertension.[114,115] Some studies have indicated that bilirubinostasis and severe fibrosis are major histological components of AH and are associated with a poor prognosis.[116,117] Interestingly, the presence of neutrophils is associated with a better prognosis, probably reflecting the fact that livers with active wound healing are more prone to regenerating upon cessation of alcoholic intake.[104] However, as well as inducing liver injury, inflammation can also play a key role in promoting liver repair and anti-bacterial immunity in ALD (Fig. 1).

Several mechanisms have been associated with cell death pathways, such as apoptosis, necroptosis-pyroptosis, and ferroptosis (related to AH endotoxemia).[103] Some studies of liver explants from patients with AH showed an accumulation of hepatic progenitor cells, which differentiated mainly into biliary cells, considering that impaired regeneration is a hallmark finding in patients with severe AH.[118] It has been suggested that the action of upstream regulators such as TGF-β1 leads to the impairment of hepatocyte regeneration and dedifferentiation. These effects are mediated by an inefficient activation of hepatocyte nuclear factor 4 α and a defective Hippo-yes-associated pathway in the hepatocytes.[112,119] This failure in differentiation results in a ductular reaction, which does not yield mature hepatocytes and is related to a worse prognosis.[9,118,120] Intriguingly, in patients with AH, the ductular reaction is associated with hepatocyte dedifferentiation into a cholangiocyte-like phenotype,[118,120] hampering hepatocyte turnover, which is crucial for adequate liver function and regeneration. Interventions aimed at reducing the futile ductular reaction and promoting hepatocyte differentiation appear to be promising approaches as AH therapies (Fig. 1).

CURRENT TREATMENT OPTIONS AND THERAPEUTIC TARGETS OF ALD

General management

The cornerstone of the management of patients with ALD and AH is prolonged alcohol abstinence. This essential intervention improves long-term prognosis but requires a multidisciplinary approach by liver disease specialists, together with psychiatrists and addiction units.[121] Several anti-craving medications for AUD in ALD[122] (see pharmacological and other interventions) are effective either alone or in combination with psychosocial interventions in the management of these populations.

The second strategy in the management of ALD-AH patients is the evaluation of malnutrition and micronutrient deficiencies; malnutrition is directly associated with liver disease severity and survival impairment.[123-125] For enteral nutrition, an intake of 35 to 40 kilocalories per kilogram of body weight daily, along with 1.5 grams of protein per kilogram per day,[126,127] is the recommended goal. The benefits of micronutrients (e.g., Zinc) with corticoids or Anakinra

were limited in clinical trials.[128]

The specific treatment approaches in the setting of acute episodes of AH (Fig. 2) glucocorticoids have demonstrated a short-term impact on patients with AH since 1971.[129] A randomized control trial (RCT) demonstrated a tendency towards enhanced 28-day survival, with an elevated risk of infections.[130] A meta-analysis from 2018 showcased improved 30-day survival rates, though there was no impact on 60- or 90-day mortality.[131] Two large, real-world studies have identified a Model for End-Stage Liver Disease (MELD) 21–39 as the optimal therapeutic window for the use of corticosteroids.[132,133] Similarly, people with AH and a rapid decline in total bilirubin (rapid fallers) do not benefit from corticosteroids. Current evidence underscores the ineffectiveness of pentoxifylline.[130] There have been promising findings regarding the addition of N-acetylcysteine (NAC), a potent antioxidant, to prednisolone therapy. This combination notably improved 1-month survival rates and reduced infection occurrences.[134] However, when survival was assessed at six months, no discernible differences were observed between applying combination therapy and prednisolone alone. In addition, when combined with granulocyte-colony stimulating factor (G-CSF), NAC failed to demonstrate a mortality benefit.[135] Response to steroid treatment should be assessed by the Lille score (dynamic score) on the fourth and seventh days. A Lille score of

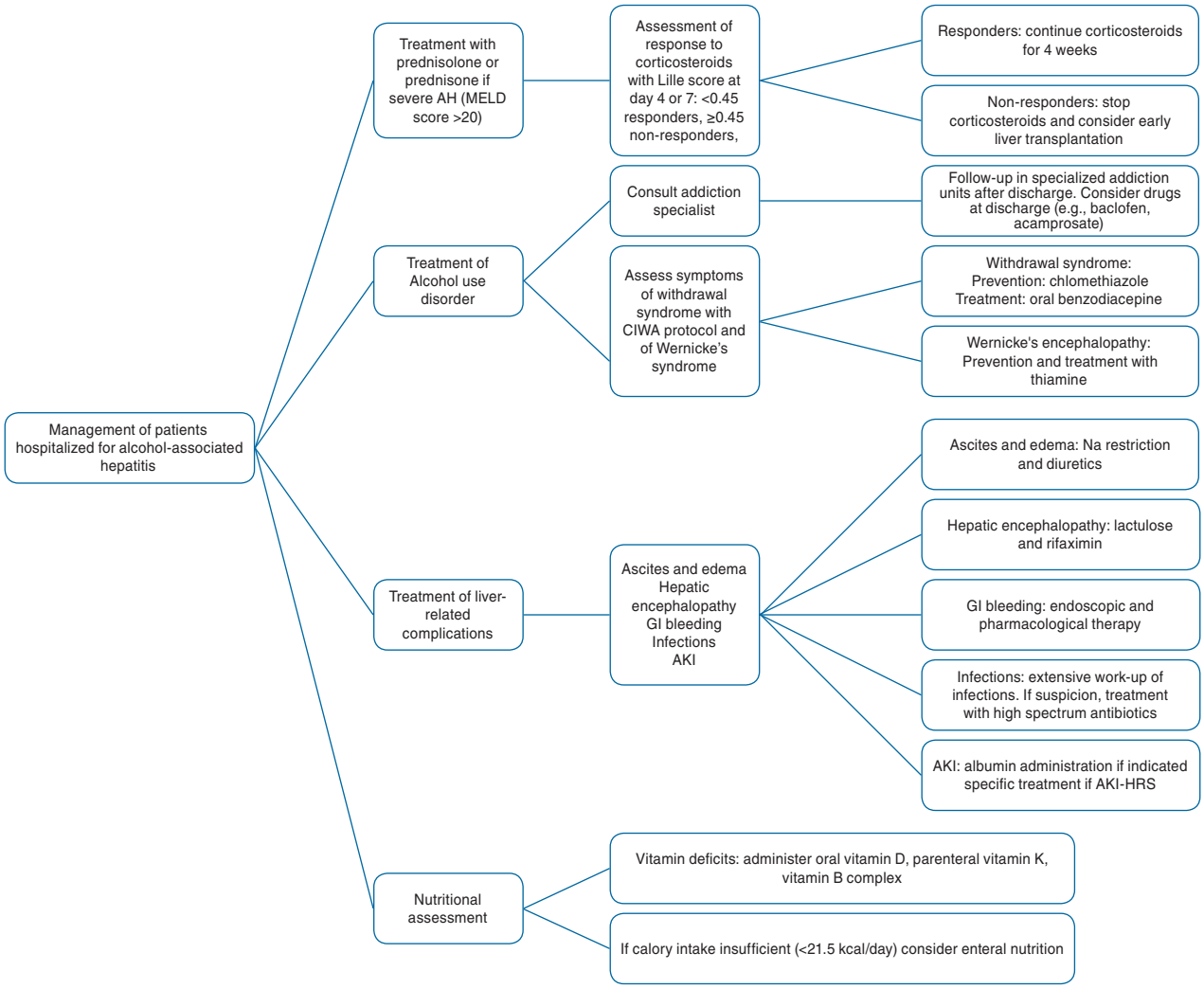

Figure 2. Algorithm for the management of patients hospitalized for alcohol-associated hepatitis. AH, alcohol-associated hepatitis; MELD, Model for End-Stage Liver Disease; CIWA, Clinical Institute Withdrawal Assessment for Alcohol; GI, gastrointestinal; AKI, acute kidney injury; AKI-HRS, acute kidney injury due to hepatorenal syndrome.

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>0.45 indicates no response, and corticosteroids must be discontinued. A Lille score of <0.45 identifies corticosteroid responders, and treatment should be maintained for 28 days.[136,137]

In the last 13 years, early liver transplantation has been explored as a therapeutic option for patients who do not respond to corticoids. A pioneering European study demonstrated that a small cohort (26 patients with severe AH) who had failed to respond to glucocorticoids underwent early liver transplantation and had a significantly higher cumulative 6-month survival rate than in a historical series of patients with similarly severe disease.[138] Follow-up studies, including the American Consortium of Early Liver Transplantation for Alcoholic Hepatitis (ACCELERATE-AH) trial, have confirmed the benefits of early liver transplantation in selected patients with AH.[139-142] Furthermore, in 2022, a follow-up study from the European group showed that 2-year survival was similar in the early and standard transplantation groups.[143] One of the main problems with this therapeutic approach is the high incidence of alcohol relapse; the international cohorts have shown a higher incidence of relapse than other transplant recipients with advanced ALD (20% to 35% in the early transplant groups compared with 10% to 25% in the standard transplant groups). Nevertheless, there is a high degree of heterogeneity in how alcohol relapses are detected in the different studies and the biomarkers or strategies used to assess alcohol use after liver transplantation.[144] In future studies, it will be necessary to identify risk factors for worse outcomes after liver transplantation to make a better selection of patients.

Regarding the clinical limitations of corticoid treatment, it is essential to perform an early screening of infections (bacterial or fungal) and appropriate treatment.[145-147] Moreover, AKI can occur frequently, affecting up to a third of patients with AH and escalating the 90-day mortality risk.[148,149] Alcohol-withdrawal syndrome (AWS) and Wernicke's encephalopathy are two conditions that should be prevented. A recent study showed that AWS commonly occurs in patients hospitalized with AH and complicates the course of hospitalization.[56] Routine prophylaxis is associated with a lower prevalence of AWS. Severe AWS (CIWA-R >21 points) requires intravenous benzodiazepine administration, which is usually contraindicated in these patients because it may precipitate an episode of hepatic encephalopathy.

Emerging targeted therapies for AH

From a pharmacological point of view, several biological molecules have been tested to identify new therapeutic strategies for AH, focusing on three main mechanisms: (1) anti-inflammatory and antioxidative stress agents, (2) gut-liver axis modulators, (3) hepatocyte regenerative agents, 4) other emerging therapies (Table 2).

Anti-inflammatory and antioxidative stress agents

Due to the extensive role of inflammation in liver injury associated with harmful alcohol consumption, a multitude of anti-inflammatory agents have been studied as possible AH therapies. Among them, TNF-α inhibitors such as etanercept and infliximab are not useful in treating AH and result in a worse prognosis with higher rates of infectious complications.[150,151] Obeticholic acid and Emricasan (caspase inhibitor) failed to show efficacy, and two phase 2 RCTs were stopped due to hepatotoxicity. The IL-1 antagonist has been studied in animal models with promising results. A study of IL-1 inhibition by anakinra, pentoxifylline, and zinc showed an increase in short-term mortality in treated patients, largely due to the development of AKI.[128] A promising anti-IL-1 beta, canakinumab, is also being studied against placebo in a British multicentre clinical trial. Larsucosterol (DUR-928) has shown a safe profile at 28 days and reduced the bilirubin and MELD score (at days seven and 28) in a phase 2a trial. The two doses (30–90–150 mg) were well tolerated in a phase 2b trial, and there are now two trials in the recruitment phase.

Some clinical trials have been initiated recently to investigate other anti-inflammatory agents, such as hyaluronic acid fragment HA35. This molecule preserved the intestinal barrier and decreased hepatocyte apoptosis in a mouse model of alcohol-induced liver injury.[152] HA35 has also been shown to have a modulating effect on Kupffer cell overactivation in murine models of ethanol-liver injury.[153] TAK-242, a suppressor of the TLR signaling pathway, has shown efficacy in suppressing inflammation in AH.[154] Digoxin has also been shown to be effective in modulating inflammation in alcohol and non-AH in murine models via downregulation of the hypoxia-inducible factor family of proteins.[155] The antagonist of C-C chemokine receptors 1 and 5, cenicriviroc, recently studied for NASH, might also be a therapeutic option for AH in the future.[156-158] The ago-

Table 2. Emerging treatment options

Drug class	Drug	Target mechanism	Comments
Anti-inflammatory and antioxidative stress agents	Canakinumab	Inhibition of IL-1, ↓inflammation and liver injury	Beneficial effects on liver inflammation, steatosis and cell injury. Phase 2 UK multicenter clinical trial study (recruiting, NCT03775109)
	Anakinra	Inhibition of IL-1, ↓inflammation and liver injury	No benefits in 90-day mortality in completed phase 2 study (Anakinra+Zinc vs. Prednisolona). The main side effect was acute kidney injury (completed, NCT 04072822)
	DUR-928 (Larsucosterol, endogenous sulphated oxysterol)	Modulation of inflammatory response (anti-inflammatory, anti-apoptotic). Reduction in lipotoxicity. Improvement in liver tissue regeneration and cell survival	Safety profile, and reduced serum bilirubin levels at day 7 and day 28; and MELD score at day 28 (completed, NCT03432260). Phase 2b clinical trial, Larsucosterol was well tolerated at all 3 doses (30–90–150 mg) in AH without safety concerns (recruiting, NCT03917407, NCT04563026)
	TAK-242	Inhibition of Toll-like receptor 4 (TLR4)	Preclinical studies demonstrated reduction in liver inflammation. Phase 2a RCT (unknown status, NCT04620148)
	Digoxin	Reduction of oxidative stress. Improvement in intracellular redox status	Preclinical studies showed a reduction of liver inflammation and macrophage activation. Phase 2 USA RCT (recruiting, NCT05014087)
	N-Acetylcysteine (NAC)	Antioxidant. Reduces susceptibility to infection through improvement of phagocyte oxidative burst (neutrophils and macrophages)	NAC combined with prednisolone showed a moderate reduction in short-term mortality. Phase 3 UK RCT (recruiting, NCT03069300). Phase 3 Spain RCT (corticoids vs. corticoids) (unknown status, NCT05294744)
	Pentoxifylline	↓TNF-α inflammation	Failed to show efficacy
	Infliximab	↓TNF-α inflammation	Failed to show efficacy
	Etanercept	↓TNF-α inflammation	Failed to show efficacy and increased mortality
	Metadoxine	Antioxidant and antifibrotic. Inhibition of hepatic lipid accumulation	Improvement in 90-day and 6-mo survival, increase in the rates of sustained abstinence from alcohol at 6 mo, although an RCT has not yet been performed
	INT-787 (farnesoid X receptor (FRX) agonist)	Anti-inflammatory and anti-fibrotic effects through the modulation of bile acid signaling	Phase 2a USA RCT (recruiting, NCT05639543)
	Obeticholic acid	Anti-inflammatory and anti-oxidant effect by regulating lipid and bile acid metabolism	Phase 2 USA RCT, failed to show efficacy (stopped due to hepatotoxicity, NCT 02039219)
	Small-sized hyaluronic acid fragments (H35, sodium hyaluronate)	Preclinical model (mouse), decreased liver inflammation and hepatocyte apoptosis. Modulated Kupffer cell overactivation	Phase 1 USA RCT in moderate alcohol-associated hepatitis (recruiting, NCT05018481)
	Dual CCR2/5 blockers (Cenicriviroc)	↓CCL2-CCR2/5 signaling and macrophage recruitment	Promising results in mouse ALD model
	Emricasan (IDN-6556)	Inhibition of apoptosis by caspase inhibition	High toxicity in phase 2 study (NCT 01912404)

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Table 2. Continued

Drug class	Drug	Target mechanism	Comments
Modulators of gut-liver axis	Healthy donor FMT	Improvement in microbial diversity	FMT from healthy donors was effective, safe and significantly improved 1-yr survival. Long-term outcomes: 3-yr survival, lower rates of decompensations and lower rates of alcohol relapse in ALD. Phase 2 RCT (recruiting, NCT04758806); (unknown, NCT05285592)
	Anti-LPS (Bovine colostrum)	↓ LPS, intestinal permeability and portal endotoxemia	Phase 2a USA RCT, awaiting results (closed, NCT01968382). Phase 3 RCT India (recruiting, NCT02473341)
	Bacteriophages	Viruses that infect bacteria as host cells, thereby mediating the destruction of pathogenic bacteria. They induce a strong immune reaction	Preclinical data shown to be effective in the phage-mediated reduction of cytolytic *Enterococcus faecalis*. Denmark observational study (recruiting, NCT 024773341)
	Probiotics (*Lactobacillus subtilis*/*Stretococcus faecium*, *Lactobacillus rhamnosus*)	Impact of intestinal dysbiosis	Reduce circulation and hepatic LPS. Improved liver function test (closed, NCT01922895)
	Antibiotic prophylaxis: Amoxicilin/clavulanic	Reduction of infections during prednisolone therapy	Reduction in infectious complications, no improvement in 2-mo survival (completed, NCT02281929)
	Antibiotic treatments: vancomicine, gentamicin, meropenem. Rifaximin+Corticoids	Impact on intestinal dysbiosis through the elimination of pathogenic bacteria	Heterogeneous results. The combination of vancomycin+gentamycin+meropenem failed to improve bacterial translocation, inflammation, or survival. Rifaximin reduced the number of infection-associated ACLFs
Hepatocyte regeneration	G-CSF pegfilgastrim	Proliferation of progenitor, parenchymal cells, and immunomodulatory properties	Heterogeneous results. In India, a reduction in 3-mo mortality and MELD was observed; in USA no reduction in 3-mo mortality with pegfilgastrim. Phase 3 RCT in null or partial response to corticoids (completed, NCT0242180)
	ASK-1 inhibitor (selonsertib GS-4997)	↓Apoptosis, and stellate cell activation	No benefits from a phase 2a RCT (completed, NCT02854631)
	F-652 (recombinant IL-22 agonist)	Anti-bacterial, anti-apoptotic, anti-oxidative, anti-inflammatory, ↑hepatocyte regeneration	Phase 2b study, F-652 was safe, reduced inflammatory markers, and increased liver regeneration. Ongoing phase 2b trial on ACLF (NCT20212657)

ACLF, acute-on-chronic liver failure; AH, alcohol-associated hepatitis; ALD, alcohol-associated liver disease; ASK-1, apoptosis signal-regulating kinase 1; FMT, fecal microbiota transplantation; G-CSF, granulocyte-colony stimulating factor; IL-1, interleukin 1; IL-22, interleukin 22; LPS, lipopolysaccharide; MELD, Model for End-Stage Liver Disease; RCT, randomized control trial; TNF-α, tumour necrosis factor alpha.

nist of the farsenoid X receptor (INT-787), through its anti-inflammatory and anti-fibrotic effects, could be a therapeutic strategy via the modulation of bile acid metabolism and is currently the focus of a phase 2a trial RCT in the recruitment stage.

Metadoxine is an antioxidant drug studied over recent years, involved in the restoration of intrahepatic glutathione and the inhibition of hepatic lipid accumulation. In patients with AH, metadoxine induced a significant improvement in 3 and 6-month survival rates and increased rates of sustained abstinence from alcohol at six months (74.5% vs. 59.4%, *P*=0.02) when combined with prednisolone or pentoxifylline.[159,160]

Finally, recently, there have been promising advances in using mesenchymal stem cells (MSCs) and microRNAs for treating AH. MSCs have shown their potential for reducing liver damage and oxidative damage due to their immunomodulatory and anti-inflammatory properties. Preclinical models suggest that MSCs can significantly reduce oxidative stress, inflammation, and lipid dysregulation in the liver .[161-163] In addition, specific microRNAs, such as miR-21 and miR-34a, are dysregulated in ALD. For instance, miR-21 has been found to contribute to liver inflammation and fibrosis by modulating the TGF-β signaling pathway, and its inhibition in preclinical models has shown potential in attenuating liver injury and inflammation, making it a potential therapeutic target for AH treatment. Furthermore, miR-34a has been associated with oxidative stress and mitochondrial dysfunction in ALD, targeting miR-34a or related miRNAs involved in regulating liver inflammation and fibrosis may offer new avenues in the treatment of AH.[164,165] While clinical applications are still in the developmental stages, the modulation of these miRNAs or the use of MSCs could be promising strategies in the reduction of inflammation and fibrosis in AH, potentially leading to more effective treatment options in the future.

Gut-liver axis modulators

The gut-liver axis has become an important area of research, including the use of probiotics, bacteriophages, non-absorbable or absorbable antibiotics, and FMT.

Regarding the management of intestinal dysbiosis, the use of probiotics containing *Lactobacillus rhamnosus Gorbach-Goldin* in AH[166,167] and *Lactobacillus subtilis and Streptococcus faecium* showed a reduction in the levels of TNF and LPS in AH.[168] In 2019, a pre-clinical study in a humanized mouse model of ALD[111] demonstrated the successful use of bacteriophage therapy to selectively target cytolytic *E. faecalis*, with a reduction of cytolysin levels in the liver and the abrogation of ethanol-induced liver injury. These findings provide a novel approach to the precise editing of altered intestinal microbiota in AH, though further studies are needed. The oral administration of hyperimmune bovine colostrum enriched with anti-LPS IgG antibodies to reduce endotoxemia and endotoxin-mediated inflammatory liver cell injury has also been tested (Table 2).

Several studies have investigated the elimination of potential disease-mediating microbes through the use of antibiotics, with heterogeneous results. The effects of a combination of three absorbable antibiotics (vancomycin, gentamycin, and meropenem) administered once daily for seven days failed to show any effect on the markers of bacterial translocation, systemic inflammation, or 90-day mortality.[169] In line with this, a recent RCT evaluated the prophylactic use of amoxicillin-clavulanate in patients with biopsy-proven severe AH combined with prednisolone. The group treated with amoxicillin-clavulanate three times daily for 30 days showed a decreased rate of all types of infections, although the combination therapy failed to show a reduction in 2-month mortality and had no effect on the therapeutic response to prednisolone, liver function, or the incidence of hepatorenal syndrome.[170] Likewise, the addition of non-absorbable antibiotic rifaximin to corticosteroids demonstrated a significant reduction in the number of infections and the incidence of infection-associated ACLF in patients treated with rifaximin.[171]

Additionally, a recent study suggested that FMT from healthy donors to patients with severe AH was safe and significantly reduced ALD severity and one-year survival.[172] The beneficial effects of FMT have been confirmed in other studies, showing a sustained favorable long-term outcome at three years, lower rates of liver-related complications, and lower rates of alcohol relapse in ALD.[173-175]

Hepatocyte regenerative agents

In the pathogenesis of AH, an inadequate regenerative capacity is correlated with worse outcomes. Among the therapeutic agents with pro-regenerative hepato-protective properties that have been studied, selonsertib (ASK-1 inhibitor) provided no benefits in a phase 2 RCT, but G-CSF

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and IL-22 agonists were observed to be more likely therapeutic options. The two studies regarding the use of G-CSF in AH showed heterogeneous results,[176,177] and a recent meta-analysis[178] confirmed these conflicting results. Consequently, further studies are needed.

The IL-22 antagonist exhibits anti-apoptotic, anti-oxidative, anti-steatotic, and anti-inflammatory properties and also improves hepatocyte regeneration. A phase 2 study evaluated the administration of IL-22 agonist (F-652), showing a significant reduction in inflammatory markers, MELD score, and transaminases at days 28 and 42, together with increased liver regeneration markers.[179] These promising findings support the performance of further RCTs.

CONCLUSION

ALD is the main cause of advanced liver disease globally, and its prevalence is increasing in young women. The most effective therapeutic strategy seems to be sustaining long-term alcohol abstinence and attenuating the local and systemic inflammatory response. In patients with AH, attenuating the futile ductular reaction and promoting hepatocyte epithelial differentiation are promising approaches to restoring liver function and regeneration. Several clinical trials have evaluated promising drugs, including modulators of the gut-liver axis, molecules that promote hepatocyte regeneration, and anti-inflammatory agents. The development of safe and effective drugs in the coming decade is anticipated.

Authors' contributions

All authors contributed to writing original draft, as well as manuscript review and editing.

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Conflicts of Interest

The authors declare no conflicts of interest.

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