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Advances in the treatment of severe alcoholic hepatitis
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Abstract

Severe alcoholic hepatitis (SAH) is a costly and worldwide public health issue with high morbidity and mortality. Specific effective treatments for SAH have yet to be established. The aim of the present article is to review the current knowledge of the pathogenesis, assessment, and treatment options in patients with SAH. To date, alcohol abstinence and enteral nutrition are the recommended first-line treatments. Although corticosteroids remain the preferred therapy for certain patients with a modified Maddrey discriminant function level greater than 54, they only improve short-term survival rates. New research focuses on liver inflammation, liver regeneration, the gut-liver axis, human induced pluripotent stem cells, and extracorporeal albumin dialysis. Liver transplantation is considered the last medical option for patients with SAH who are nonresponsive to other medical treatments.

Keywords: severe alcoholic hepatitis, gut-liver axis, new therapy, interleukin-22
Introduction
Alcoholic liver disease (ALD) or alcohol-related liver disease is related to excessive alcohol consumption and includes a wide spectrum of injury, ranging from simple steatosis to alcoholic steatohepatitis, and to cirrhosis. The progression of liver fibrosis, in the initial stages, is usually asymptomatic, except in those patients with a heavy alcohol consumption (>100 g/day), that may result in an episode of acute alcoholic hepatitis (AH) [1]. Global Burden of Disease (GBD) studies concluded that alcohol consumption remains seventh-leading risk factor in 2016 in both the burden of disease and mortality in worldwide and ALD accounts for the majority of chronic liver diseases [2]. The threshold of excessive drinking is more than 14 drinks per week for men and seven drinks per week for women. As previously reported, up to 90% of cases of alcoholism will evolve into liver steatosis, 50% may develop into inflammation and fibrosis, and 25% will evolve into liver cirrhosis [3]. AH can present as either mild or severe alcoholic hepatitis (SAH). SAH is the most severe form of ALD and has a high incidence in young people. Its clinical manifestations include the rapid onset of jaundice and liver failure (whose clinical features include ascites, coagulopathy, and hepatic encephalopathy). The laboratory criteria for SAH are model for end-stage liver disease (MELD) levels greater than or equal to 21 or a modified Maddrey discriminant function (mDF) level of greater than or equal to 32, and/or hepatic encephalopathy. SAH generally has a one-month mortality rate of 30–40% and a three-month mortality rate of greater than or equal to 30–70% [4]. Patients with SAH require a combination of static and dynamic values to predict possible outcomes. SAH is better characterized by poor regeneration and systemic inflammation of the liver, instead of intrahepatic inflammation. The hallmark of SAH progression is an uncontrolled systemic inflammatory response, followed by a weak compensatory anti-inflammatory response that contributes to susceptibility to infection and multiple organ failure. Additionally, the extensive necrosis of hepatocytes limits their proliferative capacity. However, current treatment strategies of SAH are suboptimal. The standard of care involves combination therapy with pentoxifylline (PTX) and corticosteroids (CS).
Anti-inflammatory therapies are shifting to those involved in liver regeneration, such as liver dialysis plasmapheresis and faecal microbiota transplantation (FMT). Orthotopic liver transplantation (OLT) is typically reserved for patients with SAH who are nonresponsive to other medical treatments. This review will discuss various aspects of the pathogenesis, assessment, and treatment options in patients with SAH.

Pathogenesis of SAH
The major pathway of SAH pathogenesis involves hepatocyte damage by toxic effects of ethanol (EtOH) and its metabolites, oxidative stress and lipid peroxidation, immune system modifications and cytokines, the gut-liver axis, and apoptosis mediated by caspases. Multiple cellular and molecular targets within this pathway can be considered as therapeutic targets. There are two major enzyme systems that metabolize EtOH into acetaldehyde (AA) via oxidative degradation. Cytochrome P450 2E1 (CYP2E1) is upregulated by the excessive ingestion of alcohol (10- to 20-fold) and increases the production of reactive oxygen species (ROS). ROS cause lipid peroxidation, DNA adduct formation, and depletion of glutathione and S-adenosylmethionine, which change the fluidity and permeability of the membrane, produce new antigens to induce antibody formation, and make hepatocytes more susceptible to oxidative stress. When hepatocytes are damaged by proteins, DNA, and lipid adducts, endogenous damage associated molecular patterns are released to activate TLR4 molecules on Kupffer cells, leading to the
secretion of proinflammatory cytokines (TNF-α and IL-1β) and the activation of the inflammasome. LPS activation of Kupffer cells also causes the production of hepatoprotective cytokines (IL-6 and IL-10) that defend against ALD via the activation of signal transducer and activator of transcription 3 (STAT3).

Apoptosis is a common characteristic of the pathophysiology of SAH and is mediated by caspases, which are death-inducing molecules located downstream of TNF-α in the hepatocyte injury signalling cascade. Excessive hepatocyte apoptosis leads to inflammation and the production of ROS and proinflammatory cytokines by the innate immune system. Kupffer cells endocytose apoptotic bodies and stimulate the expression of death ligands, which then promote the apoptosis of hepatocytes. Chronic alcohol ingestion results in the overgrowth of intestinal bacteria and increased intestinal permeability. Acute alcohol binges cause increases in serum levels of bacterial products (including bacterial 16S rDNA and endotoxin), which interrupt the gut mucosal barrier and raise serum and hepatic pathogen associated molecular patterns (PAMPs), such as lipopolysaccharides (LPS), resulting in the increased translocation of bacterial LPS. After reaching Kupffer cells by the portal circulation, LPS binds to the endotoxin receptor (CD14) and activates the MyD88-independent signalling pathway through the TLR4 complex [3], resulting in the production of proinflammatory cytokines and contributing to liver injury [5]. Furthermore, the incidence and development of ALD are affected by many factors. The duration of alcohol intake and amount of ingested alcohol are the most important predictors [6]. Other factors, such as types of alcoholic beverage ingested, genetics, age and gender, obesity, Hepatitis B virus (HBV) or Hepatitis C virus (HCV) infection, coexistence of other liver diseases, metabolic syndrome, cumulative alcohol intake, and cigarette smoking, also contribute to the overall risk of developing ALD [7]. An exploratory genome-wide association study found that the patatin-like phospholipase domain-containing protein 3 (PNPLA3) single-nucleotide polymorphism rs738409 was associated with risk for AH [8].

Complications
Complications of SAH include liver failure, portal hypertension, encephalopathy, degraded synthetic liver function, and increased risk of infection, resulting in a poor short-term prognosis. Liver failure and severe portal hypertension cause increased susceptibility to renal failure and bacterial infection, resulting in a high mortality rate. Infections frequently occur in patients with SAH, especially those of bacterial origin, and commonly affect survival [9]. Combination therapies should be developed for those patients, such as immunosuppressive drugs plus anti-bacterial drugs and hepato- and renal-protective drugs [10]. Furthermore, HCV is frequently associated with alcohol abuse; many studies have reported that HCV-positive drinkers tend to have severe alcoholic cirrhosis and higher mortality rates [11].

Assessment of the severity and prognosis of alcoholic hepatitis
AH is a dynamic process with different developmental stages that affects its treatment and prognosis. Different scoring systems are recommended for the assessment of AH. Static scoring systems include the mDF score, MELD, MELD-Na, Glasgow AH score (GAHS), and the ABIC (age, bilirubin, INR, and creatinine) score. Dynamic scoring systems consist of Lille’s model and early changes in bilirubin levels. New scoring systems include an MDA assessment, transjugular liver biopsy, a MELD + Lille combination model, the alcoholic hepatitis histologic score (AHHS), and the gene signature MELD.
(gs-MELD) scoring system. GAHS and MELD are used to determine whether CS should be initiated, and the Lille score is used to evaluate whether patients would benefit from CS therapy.

Lille’s model is an internationally validated dynamic model, and a 25% decrease in bilirubin levels can predict responses to CS after seven days of treatment. Patients with a Lille score greater than or equal to 0.45 at one week have low survival rates at six months: CS therapy should be discontinued for these patients and alternative therapies initiated. Patients with a GAHS greater than or equal to 9 may benefit from treatment of AH. Patients with AH who have an mDF score greater than or equal to 32 may benefit from CS therapy. MELD and MELD-Na are both positive predictors of 180-day mortality. Furthermore, while hyponatremia may predict survival in patients with cirrhosis, MELD-Na may more accurately predict treatment outcomes in patients with AH. The AHHS, a semi-quantitative scoring system, uses four histological features (fibrosis, bilirubinostasis, neutrophil infiltration, and megamitochondria) and may serve as an independent tool for prognostic classification. This scoring system also reveals which histological features may impact patient outcomes [12]. AHHS stratified patients with low (0–3 points), moderate (4–5 points) and high (6–9 points) risk of death at 90-days (3%, 19%, and 51%, respectively; P < .0001) [12]. However, the use of the transjugular route is preferred to obtain a sample (instead of the more dangerous percutaneous liver biopsy) in SAH patients with abnormal coagulation and significant ascites. Recently, gs-MELD scoring system based on baseline liver gene expression pattern and MELD score can help to predict 90-day and 180-day mortality of patients with SAH. And it has a better prognostic association than MELD + Lille joint-effect model [13]. Calculating urinary albumin (u-Alb) levels can be an easy, reliable and non-invasive screening tool for early detection of steroid nonresponder and treatment outcomes in SAH patients [14]. U-Alb levels plus MELD score can improve the diagnosis accuracy of SAH patients who have poorer survival rate [14]. Apart from the above-mentioned single model scoring systems, joint-effect model systems, such as combination of the static scores with the dynamic scores or change in static scores, have been found to improve predictions of mortality and identify patients who could benefit from CS up to 90 days [15].

Treatment

**Abstinence from alcohol**

Abstinence from alcohol is the main way to reduce injury caused by alcohol-related liver disease. Treating alcohol use disorder (AUD) in patients with ALD is a major focus of clinical research. Currently, a combination of pharmacological therapy, psychosocial interventions, and medical management is considered to be the most effective strategy for such patients. Nonpharmacological methods include cognitive behavioural therapy, outpatient motivational interviews, and attendance at Alcoholics Anonymous meetings. According to patients with psychological problems who fail outpatient therapy and have an unstable home situation, in-patient therapy is recommended. Pharmaceutical approaches to treat AUD are also available. Acamprosate, disulfiram, naltrexone and nalmefene are the only approved drugs for treatment of “alcohol-specific” [16]. Acamprosate has a similar structure to the inhibitory neurotransmitter GABA and has been found to reduce withdrawal symptoms. With no hepatotoxicity, it is considered a potential useful drug in the treatment of AUD patients with liver disease. Disulfiram, one of the first agents to be used in these patients, inhibits aldehyde dehydrogenase and dopamine beta-hydroxylase, resulting in preventing the metabolism of AA and increase in dopamine brain concentrations. It can be used in AUD patients with inflammatory bowel disease, but it causes accumulation of acetaldehyde in the blood, which induces some side
Naltrexone blocks the μ and k-opioid receptor to exert its pharmacological effects; compared with placebo, it reduces alcohol consumption by modifying the hypothalamic-pituitary-adrenal axis. But it is forbidden in patients receiving long-term opioid therapy and may cause some gastrointestinal side effects [17]. Nalmefene is a μ and δ-opioid antagonist and k-opioid partial-agonist but its exact function and outcome in alcoholism is unclear controversial [18]. Besides, baclofen is a gamma-aminobutyric acid-β (GABA-β) receptor agonist, which act as an alcohol substitute in reducing alcohol reinforce and intake effectively and increasing cumulative abstinence duration[19]. Furthermore, baclofen has low side effects, a good tolerability and no risk of abuse[19]. However, in a multicentre, randomised, double-blind controlled trial (RCT), neither low nor high doses of baclofen had a positive effect on the treatment of alcohol dependence [20]. For now, it seems that prescribing baclofen widely should be reconsidered. Besides, baclofen is primarily excreted by the kidneys, so renal function should be considered in these patients. Topiramate, an antagonist at glutamate receptors, actions on GABA-ergic/glutamatergic pathways to reduce alcohol consumption effectively [18].

Nutritional support
Malnutrition is a clinical hallmark of prolonged excessive alcohol abuse [22]; while it is nearly always associated with poor outcomes, nutritional support has been found to reliably remedy such effects. Each patient should have a nutritional status assessment on hospital admission. Severe primary or secondary malnutrition often occurs in patients with ALD. The missing nutrients usually include thiamine, vitamin B6, vitamin B12, vitamin D, vitamin E, folate, and protein, which play important roles in glutathione formation and methionine metabolism. The absence of multiple trace elements, in addition to both water- and fat-soluble vitamins, can cause other clinical syndromes. Low dietary intake may be caused by an imbalanced diet composition, lack of appetite, malabsorption because of diarrhoea, or complications of liver disease. Hence, recent guidelines recommend adequate nutritional support. The European Society for Clinical Nutrition and Metabolism guidelines recommend an energy intake of 35–40 kcal/kg body weight (BW)/day (147–168 kJ/kg BW/day) and a protein intake of 1.2–1.5 g/kg BW/day [23].

Enteral nutrition (EN), which includes tube feeding and oral nutritional supplements, can help insure nutrient intake. Another advantage of EN is a reduction in the risk of complications, such as hepatic encephalopathy. However, an RCT [23] concluded that patients with SAH in whom intensive EN via a nasogastric (NG) tube was used with glucocorticoids did not have better survival compared with patients in whom glucocorticoids alone were administered, but tolerance of the feeding tube and a higher rate of NG tube complications were important considerations. In general, EN is preferable to parenteral nutritional support, because the delivery of nutrition to the gut strengthens gut mucosal immunity and subsequently decreases endotoxemia that may take effect during the pathogenesis of AH. A meta-analysis of seven studies found that additional nutritional supplementation for three to four weeks did not significantly reduce mortality. Furthermore, high calorie and high protein diets did not improve liver function parameters or ascites. However, encephalopathy was significantly ameliorated in such cases; thus, the use of nutritional supplements should be encouraged.

Treatment of liver inflammation
Corticosteroids (CS)
CS are the most widely studied interventions to treat liver inflammation. A meta-analysis [24]
showed that CS-treated patients with SAH have a higher 28-day survival compared to those treated with placebo (79.97 ± 2.8% vs. 65.7 ± 3.4%, \( P = 0.0005 \)), but these effects were not seen at 3 or 12 months. On the contrary, a systematic review of 15 clinical studies concluded that the use of glucocorticosteroids in patients with AH could not be supported and that more low-risk, placebo-controlled randomized trials were needed [25]. However, patients with SAH given prednisolone are at greater risk for developing serious infections, which may offset its therapeutic benefits [26]. To avoid these serious consequences and select therapies for patients with SAH, levels of circulating Bacterial DNA (bDNA) may help identify patients at high risk of infection prior to treatment [27]. Regarding the threshold values for the initiation of steroid therapy (MELD score > 21 or mDF score > 32), there is a ceiling beyond which the inflammatory cascade can be reduced without causing serious infections. Recent evidence suggests that in patients treated with CS, those with an mDF score greater than 54 may have a higher risk of mortality than those with foregoing treatment. Patients who are classified as responders by the Lille model are likely to have increased survival outcomes. Changes in the level of bilirubin can be assessed one week after treatment, and the Lille score can be used to quantify these levels. Patients who have a poor response to treatment are defined by a Lille score greater than or equal to 0.45 and may not benefit from continued CS. A study by Garcia-Saenz-de-Sicilia et al. [28] suggested that the day-4 Lille model plays an important role in accurately predicting the response to CS and mortality rates for patients with SAH. CS-treated patients have more frequent infections in contrast to patients with cirrhosis. Intensive care unit admission, CS treatment, and spontaneous infections of nosocomial origin are often regarded as characteristics of cirrhosis, often leading to respiratory infections. Glucocorticoid therapy is contraindicated in up to 25% of such patients because of coexisting renal failure, pancreatitis, gastrointestinal bleeding, or active infections (including hepatitis B, tuberculosis, and other serious bacterial infections). Additionally, the combination of CS and N-acetylcysteine (NAC) has a distinct advantage for reducing short-term mortality compared to the use of CS alone [29] and decreasing the incidence of non-lethal infections. Miyashima et al [30] concluded that Vitamin E in addition to CS improved leukophilia, liver enzymes and coagulopathy.

**Pentoxifylline (PTX)**
PTX has anti-inflammatory effects and can inhibit the production of TNF, which contributes to the initial inflammatory cascade in patients with AH. It also prevents the development of fatal hepatorenal syndrome (HRS). However, a 2 × 2 factorial RCT concluded that PTX had no effect on survival [31]. Furthermore, a recent systematic review failed to find significant differences in the serum levels of TNF-α between patients in PTX monotherapy and placebo groups, suggesting that there might be other mechanisms by which PTX reduces HRS or infection [32]. Therefore, PTX may serve as an alternative treatment for patients in early renal failure or with a contraindication for steroid administration, but not as a first-line drug. The use of PTX still requires validation from both clinical and pharmacoeconomic perspectives [33].

**Combination therapy (PTX in combination with CS)**
CS may reduce short-term mortality but increase infection rates, whereas PTX may not reduce short-term mortality but decreases HRS and acute kidney injury. There were no short-term survival benefits of dual therapy compared with either CS monotherapy or PTX monotherapy. Furthermore, a multicentre, randomized, double-blind clinical trial concluded that for patients with AH, those who
had a four-week dual therapy failed to show higher six-month survival than those treated with prednisolone alone; a day-7 Lille model failed to show a significant difference between the two groups [34]. However, the combination therapy reduced the incidence of HRS and infection compared with CS alone [32]. CS monotherapy and dual therapy are both regarded as bridges to liver transplantation [32].

**Sequential therapy**

Sequential therapy includes glucocorticoid infusions (1,000 mg per day for three or four days) followed by granulocyte-monocyte absorptive apheresis (GMA for three days). Except in patients with multiple organ failure and/or bacterial infections, this therapy is suggested to reduce liver injury in patients with SAH by relieving rebound inflammatory reactions, which are inevitable after the suspension of glucocorticoids. However, further examinations are needed, for example, the duration of the GMA procedures after discontinuation of glucocorticoid infusions [35].

**Anti-TNF**

TNF-α is an important contributor to the pathogenesis of AH, and the level of TNF-α is a major predictive indicator of long-term survival in patients with SAH. TNF-α stimulates genes involved in the production and regeneration of hepatocyte growth factor (HGF) and activates inflammatory pathways. TNF receptors are overexpressed in patients with AH; thus, TNF receptors may be potential targets for treatment. However, because of the remarkable increase in infections and lack of scientific validity, some agents, such as etanercept and infliximab, are not appropriate as anti-TNF treatments.

**Micro-RNA (miRNA)**

Noncoding RNAs participate in the regulation of various signalling pathways, which link the development of inflammation-related diseases and can serve as biomarkers of liver inflammation and hepatocyte damage due to their tremendous stability in extreme conditions [36]. A study found that miR-122 was a potential marker of liver injury and that miR-155 could be used as a marker of inflammation in various types of liver injury. An increase of serum/plasma miR-122 levels is related to different types of liver disease, but it cannot distinguish the aetiologies of hepatocyte damage [37]. A previous study showed that miR-155-deficient mice were protected from increased serum endotoxin levels, which were caused by chronic alcohol ingestion [38]. In addition, several miRNAs were found to control TNF-α production by increasing mRNA stability in macrophages [39]; in turn, TNF-α can modify the expression levels of several miRNAs [40]. MiR-155 levels were shown to increase only after chronic alcohol ingestion, with effects on the regulation of chronic inflammatory processes and innate immune responses [41] (e.g., MiR-155 modified the TLR/IL-1 pathway during dendritic cell maturation). At the same time, IL-1β and TNF-α can stimulate the induction of miR-146a and miR-155 in various cell types [40]. During the development of hepatic injury caused by APAP, alcohol, and TLR9 (CpG) + 4 (LPS) ligands, serum/plasma miR-122 causes an increase in the levels of alanine aminotransferase (ALT). Thus, administrating systemic miRNAs and introducing genes coding for miRNAs into liposomes or viral constructs may be a future targeted treatment in the future.

**IL-1 receptor antagonist (IL-1Ra): Anakinra**

In hepatic macrophages and Kupffer cells, the activation of TLR4 contributes to the stimulation of
cytokine signalling and inflammation. Inflammatory stimuli activate pattern recognition receptors (PRRs) in cytosolic CARD and PYHIN domains, which then recruit caspase-1 (Casp-1) and ASC to form the multiprotein complex called the inflammasome. After the activation of PRRs, pro-IL-1β is synthesized. Pro-Casp-1, which is activated by the inflammasome, cleaves pro-IL-1β into bioactive IL-1β. IL-1β then binds to the type I IL-1 receptor (IL-1R1) to function in an autocrine or paracrine manner. Furthermore, IL-1β recruits thymocyte 17 (Th17) cells, which activate hepatic stellate cells and neutrophils, causing necrosis of hepatocytes. IL-1 receptor antagonist (IL-1Ra) is a naturally occurring cytokine that can bind to the IL-1 receptor and prevent IL-1α or IL-1β from activating it [42]. IL-1 signalling can be blocked by recombinant IL-1Ra, which then markedly attenuates alcohol-induced liver inflammation and steatosis, and enhances the regeneration of hepatocytes [43].

Caspase inhibitors: Emricasan
Caspases are death-induction molecules that are located downstream of TNF-α in the hepatocellular injury signalling cascade. Casp-12 is an endoplasmic reticulum (ER)-specific caspase, which is specifically activated by disturbances in ER homeostasis and activates downstream molecules, resulting in apoptosis [44]. Ethanol metabolism, early apoptotic cell injury, and molecular machinery connected with the Casp-3 pathway all contribute to extracellular vesicle (EV) release and activation of macrophages via CD40L (TNFSF5), which is stored in EVs [45]. These molecules can be identified as potential therapeutic targets. Emricasan (IDN-6556), a pan-caspase inhibitor, inhibits IL-1β production and inflammasome activation of steatotic hepatocytes, and successfully improves hepatic fibrogenesis [46]. A phase 2 clinical trials evaluating Emricasan showed it attenuated apoptosis and inflammation and improved bilirubin, INR, MELD scores and Child-Pugh scores [47].

N-Acetylcysteine (NAC)
NAC, a potent antioxidant, can replenishes the hepatocytes glutathione stores, decreases levels of free radicals, and represses the expression of nuclear factor κB and TNF-α, so it is a possible adjunct therapy for SAH [48]. In a previous study, patients with SAH who were treated with NAC + CS had a higher one-month survival than those treated with CS alone (8% vs. 24%), but there were no beneficial effects observed on six-month survival or primary outcomes [48]. However, further studies are required to assess the safety and efficacy of the use of NAC in AH patients.

Metadoxine (MTD)
MTD, an antioxidant, controls the depuration and metabolism of AA and ethanol in the liver and plasma. MTD also restores the concentrations of glutathione, Nicotinamide adenine dinucleotide (NAD), and adenosine triphosphate in the liver and brain. MTD reduces triglyceride levels, inhibits the synthesis of fatty acids, and prevents damage associated with lipid peroxidation in the liver [49]. Further, according to patients with SAH, MTD helps maintain abstinence, improves three- and six-month survival rates and diminishes the development of HRS and encephalopathy [50].

S-adenosyl L-methionine (SAME)
SAME is not only a precursor of glutathione but the major methyl donor for methyltransferase reactions involved in the regulation of gene expression and processes that promote the generation of glutathione from homocysteine. SAME has other protective effects in patients with AH during the
course of alcoholic injury, including the downregulation of TNF-α and maintaining mitochondrial function. A recent study [51] showed that prednisolone plus SAMe induced a good therapeutic response in patients with liver disease and reduced HRS occurrence. SAMe (1,200 mg per day orally) was also shown to effectively reduce mortality in patients with alcoholic cirrhosis.

**Gut-liver axis**

**Zinc**

Alterations in zinc metabolism or zinc deficiency are commonly observed in patients with ALD [52]. Zinc supplementation can preserve intestinal integrity, reduce hepatocyte cell death by restraining the Fas/FasL-mediated pathway, and decrease oxidative stress, proinflammatory cytokine production, and endotoxemia, inhibiting experimental ALD [53]. In vitro studies, zinc deficiency caused by oxidative stress was shown to contribute to the disassembly of tight junction proteins and interfere with intestinal barrier function [54]. Although zinc supplementation can attenuate ethanol-stimulated CYP2E1 activity, it enhances the activity of glutathione reductase and alcohol dehydrogenase (ADH) in the liver and prevents alcohol-induced decreases in GSH levels and glutathione peroxidase activity, which may suppress alcohol-induced oxidative stress. As a treatment for liver disease, zinc is usually administered at a dose of 220 mg (50 mg elemental zinc sulphate) with a meal to reduce nausea, which is a potential side effect [53].

**Melatonin**

Oxidative stress mediated by CYP2E1 and decreases in melatonin levels may affect circadian gene expression/function, such as increasing the levels of PER2 and CLOCK, which increase intestinal hyperpermeability [55]. The onset of melatonin secretion can be determined using an overnight or 24-hour sample of blood or saliva; melatonin was found to attenuate oxidative stress and cholesterol homeostasis, alleviate bile acid levels by increasing miR-497 expression and reducing alcohol-stimulated bile acid synthetic gene expression in mice [56]. Melatonin may find utility as a treatment for AH.

**Bovine colostrum and hyperimmune bovine colostrum**

Bovine colostrum has few side effects and is rich in growth factors, antimicrobial compounds, immunoglobulins (IgG, IgM, and IgA), cytokines, immune-regulating factors, oligosaccharides, and nucleosides [57]. It can neutralize LPS, reduce the influx of LPS from the gut, and inhibit the development of enterogenic endotoxemia [58]. Hyperimmune bovine colostrum Imm 124-E is a type of hyperimmune bovine colostrum that is rich in anti-LPS IgG. Compared to steroids plus a placebo, steroids plus Imm 124-E more efficiently decreased mean circulating endotoxin levels [59].

**Farnesoid X receptor (FXR): WAY-362450 and obeticholic acid (OCA)**

FXR is a bile acid receptor that is expressed in tissues involved in bilirubin metabolism, such as the liver and small intestine. It can regulate the expression of the gene encoding cholesterol 7 alpha-hydroxylase (the rate-limiting enzyme in BA synthesis) and hepatic triglyceride levels, resulting in the inhibition of bile acid biosynthesis from cholesterol [60]. FXR activity was suppressed in a
murine model of ALD [61]. An FXR agonist—WAY-362450—was found to reduce ROS and suppress CYP2E1 in ethanol-fed mice, suggesting a possible therapeutic use [61]. Furthermore, toxic bile acids can stimulate liver proliferation after modest, short-term supplementation. OCA, a potent, first-in-class agonist of the FXR and a bile acid analogue, has been suggested to affect patients with moderate SAH by modifying FXR-mediated transcriptional mechanisms [62].

**Faecal microbiota transplantation (FMT)**
The absence (or defects) of the inner mucosal layer of the colon allows bacteria to reach intestinal crypts, triggering inflammation of the colon. FMT has been used for difficult-to-treat or recurrent (three or more episodes) *Clostridium difficile* infection [63]. FMT was shown to protect against the alcohol-induced depletion of *Bacteroides* and the disruption of gut homeostasis in alcohol-sensitive mice [64]. In a pilot study, one week of FMT treatment was found to safely and effectively reduce the severity of liver disease at one year and improve the survival of patients with SAH. New donor species of microorganisms can co-exist with and modify the bacterial communities of the recipients [65].

**Antibiotics and probiotics**
The gut microbiota, which encompasses 100 trillion bacteria of over 2,000 distinct species, can influence intestinal barrier integrity and intestinal epithelial cell function [66]. Gut-derived sepsis and bacteraemia are familiar conditions in alcoholic patients, particularly those with ALD, likely the result of the activation of the TLR/NLR by gut microbiota-produced compounds in the liver [66]. Some studies have concluded that the administration of probiotics could decrease systemic inflammation, portal pressure, and occurrence of minimal hepatic encephalopathy; stabilize physiological luminal permeability and lower ammonia adsorption; limit Gram-negative bacteria; prevent adherent pathogens; and induce anaerobic and Gram-positive bacterial growth [67]; thus, antibiotics and probiotics offer a safer and less expensive treatment for patients with SAH. Antibiotics are found to reduce the hepatic infiltration of neutrophils, gut bacterial load and circulating LPS [68]. However, prophylactic antibiotics failed to prevent subsequent infections or improve survival [69]. Administration of lactobacilli can reduce endotoxia and alcohol-induced liver injury, restoring a “leaky gut” state and serving as a potential therapy for ALD [66]. *Bifidobacterium* CECT 7765 can reduce liver steatosis and improve immunological alterations and metabolism by improving the function of macrophages and dendritic cells in relationship with CK production, phagocytosis, and induction of T-lymphocyte proliferation in high-fat diet-fed mice [70]. Probiotic *Escherichia coli* Nissle 1917 has been shown to inhibit a leaky gut and preserve intestinal barrier function against noxious or infectious agents by modulating tight junctional integrity [71]. However, a study showed that administration of probiotics (*Bifidobacterium lactis*, *Lactobacillus rhamnosus*, and *Lactobacillus acidophilus*) for four weeks alleviated small intestinal bacterial overgrowth but did not significantly improve intestinal permeability or liver function [67]. Apart from gut bacteria, fungal cell wall components, mainly β-glu, can induce hepatic inflammation and lead to steatosis and hepatocyte cell death, so antifungal agents can be used to ameliorate ethanol-induced liver disease and may be another effective strategy for patients with SAH [72].

**Orthotopic liver transplantation (OLT)**
For some steroid intolerant patients and those with end-stage liver disease, OLT remains the final
therapeutic option [73]. However, to avoid the unnecessary over-utilisation of resources, a psychosocial evaluation is recommended to identify nonresponders, as the anxiety and stress levels of liver transplant candidates are extremely high [74]. Equity in liver graft allocations is another problem for clinicians [75]. Before being considered for a liver transplant, a six-month period of abstinence from alcohol is required [65] for the following reasons: to allow the restoration of liver function, to judge whether OLT is necessary, and to decrease the risk of recidivism after transplant. Lee et al. [76] conducted a study of early transplantation in patients with SAH: Patients who received early transplantation had a high six-month survival rate. As described above, patients with a harmful pattern of drinking have lower survival rates than patients who only occasionally drink. Hence, it is important to investigate relapse/recidivism and use validated models to predict the chance of relapse [65]. A diagnosis of recidivism is made based on information obtained from the patient and/or family members/partners. Self-reported alcohol use after liver transplant may lead to the under-reporting of problems. However, one study showed that liver transplant recipients have a 2–3-fold increased risk of developing de novo malignancies, especially oropharyngeal malignancies [77]. The risk of malignancy was shown to increase in patients who continue to smoke after transplant. Thus, all patients with ALD, especially those with a history of smoking, require on-going monitoring and surveillance for malignancy (particularly oropharyngeal/laryngeal and lung) in post-transplant settings [78].

New therapies

Although conservative management can improve mild forms of AH, patients with SAH who have a Lille score of more than 0.45 after seven days of medical therapy and no response to glucocorticoids often have mortality rates greater than 70% at six months [79]. There are a number of patients with SAH who are steroid intolerant, with no specific treatment options available. However, some new options for the treatment of SAH are described below.

Liver regeneration treatment: Granulocyte-colony stimulating factor (G-CSF)

G-CSF is a glycoprotein that can stimulate the bone marrow to produce and release stem cells (CD34+) and neutrophils into the circulation. In patients with ALD, G-CSF can increase liver regeneration (by stimulating the engraftment of mobilized CD34+ stem cells, increasing HGF [80], and inducing the regeneration of hepatocytes and progenitors in the liver) and the phagocytic function of neutrophils to overcome immune paralysis [81]. Additionally, G-CSF decreases MELD, CTP, and SOFA scores significantly prevent the development of hepatic encephalopathy, sepsis, and HRS [82]. Visha et al. [80] administered 5 μg/kg G-CSF subcutaneously every 12 hours for five days to patients with SAH; they were able to induce a significant mobilization of CD34+ cells and achieve a significantly better 60-day survival. However, further studies are needed before G-CSF can serve as a treatment option, either in combination with prednisolone or alone, for patients with SAH.

IL-22/signal transducer and activator of transcription 3 (STAT3)

The cytokine interleukin-22 (IL-22), which is a member of the IL-10 superfamily and secreted by Th17 CD4+ cells, has proliferative, antiapoptotic, antioxidant, antimicrobial, and antisteatotic effects [83]. IL-22 treatment protects against liver injury, inhibits bacterial infection and promotes liver repair by activating STAT3 in hepatocytes and increasing the expression of two antioxidant genes (MT I/II) [84]. Furthermore, IL-22 downregulates several triglyceride synthesis- and lipogenesis-related genes,
leading to improvements in obesity-associated fatty liver [85]. IL-22 has a better therapeutic potential when used in combination therapy with CS or TNF-α inhibitors for treating AH than IL-6 because of its fewer side effects and the restricted expression of IL-22R on hepatocytes and epithelial cells. At the same time, the number of IL-22-producing Th17 cells was found to be increased in AH patients; IL-22 is also thought to function as a hepatocyte-preserving cytokine during the process of AH. (Table)

**Human induced pluripotent stem cells (iPSCs)**

The three primary functions of human iPSCs are as a source of cells for cell replacement therapy, drug screening, and disease modelling [86]. Human hepatocyte-derived iPSCs can differentiate directly into hepatic progenitors, endoderm, and mature hepatocytes [86]. A diagnostic liver biopsy or partial hepatectomy can be used to obtain liver tissue for the cultivation of liver disease-specific iPS cells; these cells can then be used to study liver disease pathogenesis, including cirrhosis, hepatocellular carcinoma, and inherited metabolic disorders [86]. The use of human iPS cell-derived hepatocytes can lead to efficacious drug development with fewer costs; these cells can also be used for drug metabolism analyses because of a lack of species differences [87]. However, there are several technical barriers that must be overcome, such as epigenetic memory, which is retained in iPSCs from adult somatic cells and may influence their differentiation potential for applications in disease modelling or treatment.

**Granulocytapheresis (GCAP)**

Granulocytapheresis (GCAP) has been found to reduce the levels of granulocyte expression of TNF-α receptors, activated neutrophils, and proinflammatory cytokines (e.g., TNF-α, IL-b, IL-6, IL-8, and IL-12) in the circulation [88, 89]. Additionally, GCAP increases HGF levels in neutrophils, contributing to liver regeneration [89]. GCAP alone or combined with CS has been considered a therapeutic option to control leucocytosis during the treatment of SAH and impacts patient prognosis significantly with no major adverse effects [88]. However, in a small study, GCAP failed to show any improvement in outcomes [89].

**Extracorporeal albumin dialysis**

Patients with acute-on-chronic liver failure, including those with AH, undergo extensive testing after extracorporeal albumin dialysis. This treatment has been found to increase platelet counts, decrease bilirubin, creatinine, prothrombin time, and portal pressure levels [90], improve haemodynamics, and reduce the incidence of hepatic encephalopathy [91]. However, extracorporeal albumin dialysis does not increase the probability of survival. As this treatment is safe and lacks major side effects, it can be a potential bridge to recovery or liver transplantation.

**Poly (ADP-ribose) polymerase1 (PARP-1) inhibitors**

Poly (ADP-ribose) polymerase1 (PARP-1) is overactivated in the sequel of alcoholic liver injury, inducing oxidative stress-induced cell death and pro-inflammatory mediator production [92]. In preclinical models of liver disease, PARP-1 inhibitors restore the hepatic NAD+ content, decrease NAD-dependent deacetylase sirtuin-1 (SIRT1) activation/expression, attenuate hepatic oxidative stress, mitochondrial dysfunction and LPS-induced Kupffer cell activation in vitro, contributing to attenuating alcohol induced hepatocellular injury, abnormal metabolic alteration, inflammation,
fibrosis and steatosis in mice exposed to EtOH feeding [92, 93]. PARP inhibitors may be of future potential clinical utility to treat SAH [93].

**Phytotherapy**

Besides all therapies above, phytotherapy has a long-standing and extraordinary role in ALD treatment, such as herbal medicines [Cnidium monnieri (L.) Cusson (Apiaceae), Curcuma longa L. (Zingiberaceae), Pueraria lobata (Willd.) Ohwi (Leguminosae)], some fruits (grapefruit, cranberries, and grapes), and plants (chamomile, silymarin, and spirulina), which can be the therapeutic options for the treatment of ALD [94, 95]. Silymarin, which was found in Silybum marianum (L.) Gaernt., has anti-oxidant, anti-inflammatory, anti-fibrosis effects by scavenging active oxygen, anti-lipid peroxidation, enhancing hepatic glutathione, protecting the stability of hepatic cell membrane, and increasing protein synthesis in hepatocytes[96]. However, it is of importance to obtain clinical data based on large populations of patients to evaluate its therapeutic efficacy.

**Conclusions**

The management of AH is still controversial. The combination of static (MELD score) and dynamic (Lille's score) approaches is the most accurate way to predict patient outcomes. Infection control is paramount and may be useful in predicting treatment responses. Abstinence from alcohol and provisions for EN are both essential for treatment success. When mDF scores are greater than 54, the combination therapy of PTX plus CS is the best option. When patients with SAH are not responsive to glucocorticoids, liver transplantation is a sound option with low relapse rates. Apart from this approach, new therapies, including G-CSF, liver dialysis/plasmapheresis, FMT, IL-22, and CS plus IV NAC for 2–4 weeks, may be effective choices. Liver transplantation should be offered to select patients with SAH who are nonresponsive to conventional medical treatments.

**Future perspectives on the management of SAH**

Many questions must still be addressed with regard to the treatment of patients with SAH. Therapies promoting liver regeneration may replace anti-inflammatory therapies. Promoting abstinence from alcohol, suppression of hepatic inflammation, and decreasing susceptibility to infection may be key points for future research [31]. Because of the nexus of genetic traits, learned behaviours, and environmental risks, patients with AH may return to drinking after nearly dying. Considering that some patients conceal a history of secret drinking, we suggest the use of a lexicon to capture variations in drinking patterns, biomarkers of alcohol use that monitor clandestine drinking, and a mechanism that protects patient privacy regarding drinking [97]. Furthermore, changing attitudes about alcohol in patients with AUD affects the treatment of AH, so seeking the views of more groups, including addiction specialists, patients with AUD, psychiatrists, and social psychologists, may lead to the development of innovative treatments [97]. Finally, the addition of HCV into model scoring systems may further improve their accuracy [11]. For HCV-positive patients with SAH, antiviral therapy is a promising area for future research.
References

13. Trepo E, Goossens N, Fujiwara N, et al. Combination of Gene Expression Signature and Model


76. Lee BP, Chen PH, Haugen C, et al. Three-year Results of a Pilot Program in Early Liver


### Table. Therapeutic perspectives in severe alcoholic hepatitis

<table>
<thead>
<tr>
<th>Targets</th>
<th>Drug Name</th>
<th>Dose</th>
<th>Mechanisms of action</th>
<th>Beneficial effects</th>
<th>Deficits</th>
<th>Stage of development and clinical trial number</th>
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<tbody>
<tr>
<td>Abstinence from alcohol</td>
<td><strong>Acamprosate</strong></td>
<td>666 mg tablets, three times a day, for people over 60 kg</td>
<td>similar structure to GABA</td>
<td>reduces hyperglutamnergic activity and glutamate levels</td>
<td>increases risk of diarrhea and vomiting</td>
<td><strong>1.</strong> approval in U.S. and Europe [13]</td>
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<td></td>
<td><strong>Disulfiram</strong></td>
<td>250 mg/day orally [14]</td>
<td>inhibits aldehyde dehydrogenase (ALDH) and dopamine beta-hydroxylase</td>
<td>prevents the metabolism of acetaldehyde</td>
<td>accumulation of acetaldehyde in the blood and hepatotoxicity</td>
<td><strong>2.</strong> disulfiram-alcohol reaction (DAR) [14]</td>
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<td></td>
<td><strong>Naltrexone</strong></td>
<td>50 mg/day orally or intramuscular injection of 380 mg. for 4 weeks</td>
<td>blocks the μ and κ-opioid receptor</td>
<td>reduces alcohol consumption by modifying the hypothalamic-pituitary-adrenal axis</td>
<td>not be used in patients receiving long-term opioid therapy</td>
<td><strong>2.</strong> gastrointestinal</td>
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<tr>
<td>Drug</td>
<td>Dosage and Route</td>
<td>Effects and Side Effects</td>
<td>Study References</td>
<td></td>
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<tr>
<td>Nalmefene</td>
<td>18 mg/day orally [14]</td>
<td>μ and δ-opioid antagonist and k-opioid partial-agonist</td>
<td>unclear and controversial</td>
<td></td>
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<tr>
<td>Baclofen</td>
<td>5–10 mg, 3 times/day orally</td>
<td>GABA-β receptor antagonist</td>
<td>1. enhances the rate and duration of abstinence and 2. no gastrointestinal side effects</td>
<td>temporary recommendation for use in France [13]</td>
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<tr>
<td>Topiramate</td>
<td>200 mg/day</td>
<td>Antagonist at glutamate receptors</td>
<td>1. affects cognitive function and 2. drowsiness, dizziness, hyperammonaemia, loss of appetite/weight loss, nausea and taste changes.</td>
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<tr>
<td>Corticosteroids (CS)</td>
<td>40mg/day prednisolone orally or 32mg/day methylprednisolone</td>
<td>Decrease transcription factor levels and proinflammatory</td>
<td>reduces short-term mortality and infection as a first-line drug</td>
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<tr>
<td>Drug</td>
<td>Dose/Route</td>
<td>Effects</td>
<td>Trial ID</td>
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<tr>
<td>Pentoxifylline (PTX)</td>
<td>400 mg, 3 times/day for 28 days</td>
<td>Has anti-inflammatory effects and inhibits the production of TNF</td>
<td>Human clinical trial NCT02 796469</td>
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<tr>
<td>Combination therapy</td>
<td>PTX + CS</td>
<td>Decreases HRS and infections</td>
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<tr>
<td>Anakinra</td>
<td>100 mg or 0.67 mL/day subcutaneous injection</td>
<td>Anti-inflammatory, reduces steatosis, and enhances the regeneration of hepatocytes</td>
<td>Human clinical trial NCT01 809132</td>
<td></td>
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<tr>
<td>Emricasan</td>
<td>25 mg, twice/day orally</td>
<td>Inhibits IL-1β production and inflammasome activation of steatotic hepatocytes and improves hepatic fibrogenesis</td>
<td>Human clinical trial NCT01 912404</td>
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<tr>
<td>N-Acetylcysteine (NAC)</td>
<td>NAC + CS</td>
<td>Replenishes the hepatocytes glutathione stores, no beneficial effects observed on</td>
<td>Human clinical trial</td>
<td></td>
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<tr>
<td>Metadoxine (MTD)</td>
<td>1500 mg/day in divided doses [44]</td>
<td>antioxidant</td>
<td>decreases levels of free radicals, and represses the expression of nuclear factor κB and TNF-α six-month survival or primary outcomes</td>
<td>approved in several European countries, India, the Russian Federation and Brazil for treating acute alcohol intoxication [44] NCT02 161653 NCT01 504295 NCT02 019056</td>
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<tr>
<td>S-adenosyl L-methionine (SAMe)</td>
<td>1.200 mg/day orally</td>
<td>precursors of glutathione and the major methyl donor for methyltransferase reactions</td>
<td>downregulates of TNF-α and maintain mitochondrial function</td>
<td>Human clinical trial [45] NCT00 573313 NCT00 851981</td>
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<tr>
<td>Gut-liver axis</td>
<td>Substance</td>
<td>Dosage/Composition</td>
<td>Format/Mode</td>
<td>Action/Effect</td>
<td>Clinical Trials</td>
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<td></td>
<td>Zinc</td>
<td>220 mg (50 mg elemental zinc sulphate) with a meal</td>
<td>trace element</td>
<td>preserves intestinal integrity, reduce hepatocyte cell death</td>
<td>Human clinical trial NCT01 809132 NCT01 899521</td>
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<td></td>
<td>Melatonin</td>
<td>—</td>
<td>—</td>
<td>increasing miR-497 expression and reducing alcohol-stimulated bile acid synthetic gene expression</td>
<td>Preclinical</td>
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<td></td>
<td>Bovine colostrum</td>
<td>200 ml (20 g), 3 times/day orally</td>
<td>neutralizes LPS</td>
<td>attenuates oxidative stress and cholesterol homeostasis, alleviated bile acid levels</td>
<td>—</td>
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<tr>
<td></td>
<td>Hyperimmune bovine colostrum</td>
<td>2400 mg or 4800 mg/day orally</td>
<td>neutralizes LPS</td>
<td>decreases mean circulating LPS levels</td>
<td>Human clinical trial NCT01 968382</td>
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<td></td>
<td>WAY-362450</td>
<td>—</td>
<td>agonist of the Farnesoid X receptor (FXR)</td>
<td>attenuates hepatic liver injury, steatosis and cholestasis [55]</td>
<td>Preclinical</td>
<td></td>
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<tr>
<td>New therapeutics</td>
<td>obeticholic acid (OCA)</td>
<td>10 mg/day orally</td>
<td>agonist of the FXR and a bile acid analogu e</td>
<td>modifies FXR-mediated transcriptional mechanisms</td>
<td>Human clinical trial NCT02 039219</td>
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<tr>
<td>Antibiotics</td>
<td>Ampicillin, Neomycin, Metronidazole and Vancomycin [62]</td>
<td>—</td>
<td>reduce the hepatic infiltration of neutrophils, gut bacterial load and circulating LPS</td>
<td>prophylactic antibiotics failed to prevent subsequent infection or improve survival</td>
<td>Preclinical trial</td>
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<tr>
<td>probiotics</td>
<td><em>Bifidobacterium lactis</em>, <em>Lactobacillus rhamnosus</em>, and <em>Lactobacillus acidophilus</em></td>
<td>—</td>
<td>alleviate small intestinal bacterial overgrowth</td>
<td>—</td>
<td>Human clinical trial NCT01 501162 NCT01 922895</td>
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<tr>
<td>Granulocyte-colony stimulating factor (G-CSF)</td>
<td>5 μg/kg subcutaneously every 12 hours for 5 days</td>
<td>stimulate the bone marrow to produce and release stem cells (CD34+) and neutroph</td>
<td>1. increases liver regeneration 2. prevents the development of hepatic encephalopathy, sepsis, and HRS</td>
<td>—</td>
<td>Human clinical trial NCT02 442180 , NCT02 451033 , NCT01 820208 NCT02 971306</td>
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</tbody>
</table>
| Interleukin-22 (IL-22) | Th17 cell hepatoprotective cytokine | ils | 1. activates STAT3 in hepatocytes  
2. increases the expression of two antioxidant genes (MT I/II)  
3. downregulates several triglyceride synthesis- and lipogenesis-related genes | Human clinical trial NCT02655510 |
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<tr>
<td>5-aminoisoquinoline hydrochloride (AIQ), N-(5,6-Dihydro-6-oxo-2-phenanthridinyl)-2-(dimethylamino)acetamide hydrochloride (PJ34) or Olaparib</td>
<td>Poly(ADP-ribose) polymerase 1 (PARP-1) inhibitors</td>
<td>—</td>
<td>restores the hepatic NAD+ content, decreases NAD+-dependent deacetylase sirtuin-1 (SIRT1) activation/expression, attenuates hepatic oxidative stress, mitochondrial dysfunction and LPS-induced Kupffer cell activation</td>
<td>Preclinical</td>
</tr>
</tbody>
</table>