

Therapeutic Pipeline in Alcohol-Associated Liver Disease

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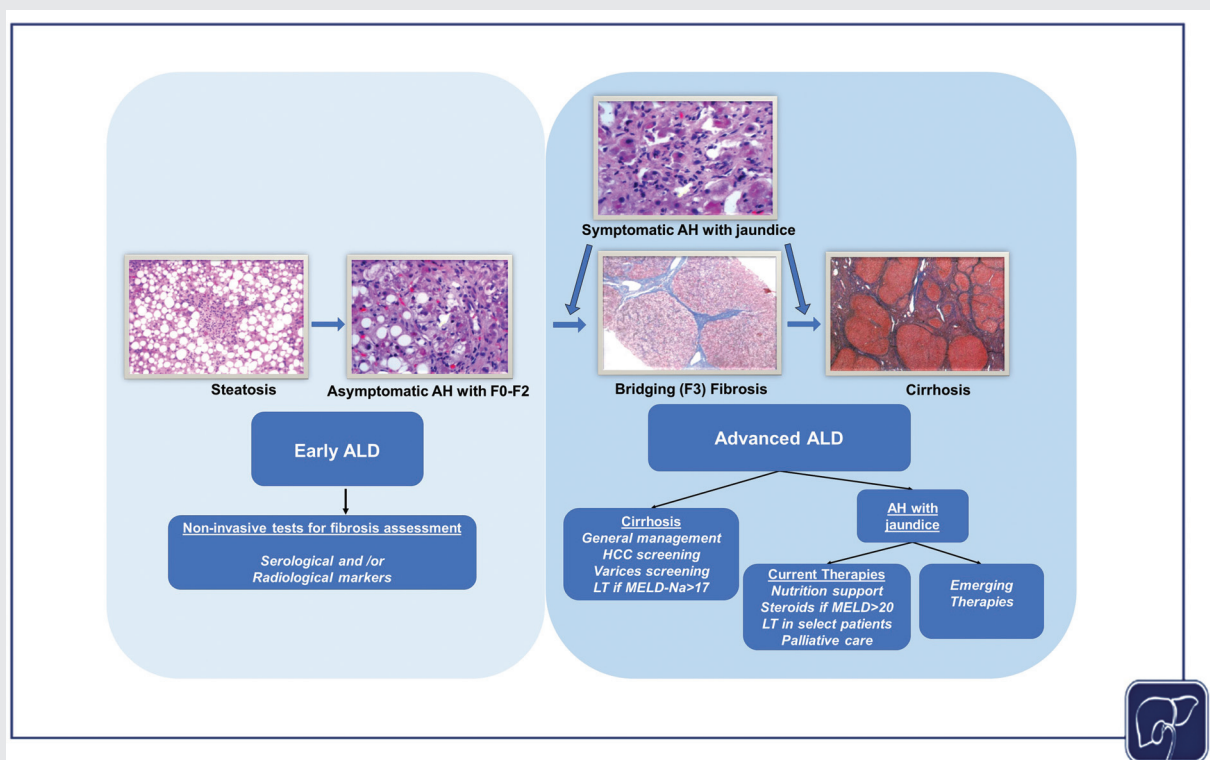
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Semin Liver Dis 2023;43:60–76.

Graphical Abstract



Abstract

Alcohol-associated liver disease is a leading cause of mortality and morbidity worldwide. Patients with alcohol-associated liver disease are often diagnosed at advanced stage and disease spectrum including alcoholic hepatitis, a severe manifestation with a high short-term mortality. Corticosteroid, recommended first-line treatment for patients with alcoholic hepatitis, is a very suboptimal treatment. Although the use of early liver transplantation has increased with consistent benefit in select patients with alcoholic hepatitis, its use remains heterogeneous worldwide due to lack of uniform selection criteria. Over the last decade, several therapeutic targets have evolved of promise with ongoing clinical trials in patients with cirrhosis and alcoholic hepatitis. Even with availability of effective medical therapies for alcohol-associated liver disease, long-term outcome depends on abstinence from alcohol use in any spectrum of alcohol-associated liver disease. However, alcohol use disorder treatment remains underutilized due to several barriers even in patients with advanced disease. There is an urgent unmet need to implement and promote integrated multidisciplinary care model with hepatologists and addiction experts to provide comprehensive management for these patients. In this review, we will discuss newer therapies targeting liver disease and therapies targeting alcohol use disorder in patients with alcohol-associated liver disease.

Keywords

- alcohol-associated liver disease
- alcoholic hepatitis
- alcohol-use disorder
- therapeutic
- emerging therapies

Worldwide, approximately 1 million deaths occur due to cirrhosis.¹ Alcohol-associated liver disease (ALD) contributes to over 2 million cases of cirrhosis and 25% of deaths due to cirrhosis.² ALD burden parallels alcohol use patterns, with the highest burden in Europe and the lowest in Africa.³ Approximately 66.3% of the adult population in the United States consume alcohol and 5.1% report harmful alcohol use (> 3 drinks on any day or > 7 per week for women and > 4 drinks on any day or > 14 per week for men), which is higher than the global average of 43% of the adult population.^{4,5} During the COVID-19 pandemic, psychological stress from multiple factors has led to further increase in alcohol consumption. This combined with diversion of resources for taking care of COVID-19 pandemic leads to delayed care of cirrhosis patients, resulting in accelerated increase in ALD-related hospital admissions with severe forms of the disease, and subsequent increase and liver transplant activity.^{6–8} As we recover from the pandemic, we will continue to expect an increase in the healthcare burden of ALD in the upcoming years.⁹

Individuals with harmful alcohol use are at risk for the development of ALD.¹⁰ Almost all patients with ALD have a history of alcohol use disorder (AUD), a chronic medical condition characterized by a pattern of alcohol use which is diagnosed within the previous 12 months of 2 or more of 11 criteria as defined by 5th edition of Diagnostic and Statistical Manual of Mental Disorders, with the severity of AUD increasing with the number of criteria present in that respective individual (► **Table 1**).^{11,12} Shorter version of Alcohol Use Disorders Identification Test (AUDIT-C) is another accurate tool for use in routine clinical practice to identify AUD, with a score 4 or more in men and 3 or more in women diagnostic of AUD^{13–15} (► **Table 2**). The histological spectrum of ALD (► **Fig. 1**) can be an early disease with asymptomatic alcohol-associated fatty liver (AFL) and/or

asymptomatic AH with fibrosis up to stage 2 (F0–F2), and advanced disease with advanced fibrosis (F3), cirrhosis (F4), or symptomatic AH. Patients with ALD are often diagnosed at an advanced stage and progress faster to complications as compared with other liver diseases.^{16,17} Hence, it is crucial to diagnose the disease in an early stage, as it can help ensure timely intervention for control of risk factor of alcohol use, and prevent long-term outcomes and development of advanced forms of ALD.¹⁶ Patients with asymptomatic disease presenting with incidental detection of elevated liver enzymes and/or steatosis on liver imaging should be assessed using noninvasive serum tests and radiological biomarkers (fibroscan or MR elastography) for risk of fibrosis (► **Fig. 1**). As detailed discussion on noninvasive tests for fibrosis risk assessment is beyond the scope of this review, which is focused on the current and emerging therapies of ALD targeting AUD and those targeting liver disease.

Treatment of Alcohol Use Disorder

Despite the increasing global prevalence of AUD and its emergence as a major public health issue, it remains under-treated. Epidemiological data for the year 2020 revealed that out of 17.7 million adults who were reported to have harmful alcohol use, only 4% received treatment for AUD.¹⁸ Specific to ALD patients, a recent retrospective cohort on Veterans with a diagnosis of cirrhosis and AUD showed that specific AUD treatment was used in only 14% patients, with only 1.4% treated with pharmacological therapies.¹⁹

Complete cessation of alcohol is the cornerstone of treatment for any spectrum of ALD. Abstinence can reverse the progression of early ALD to more advanced disease.^{20–23} Among those with advanced disease, AUD treatment reduces liver disease severity, decompensation, readmission to the hospital, and consequently improve patient survival. For

Table 1 Diagnostic and statistical manual vs. diagnostic criteria for alcohol use disorder (AUD)

1. Alcohol is often taken in larger amounts over a longer period than was intended
2. There is a persistent desire or unsuccessful efforts to cut down or control alcohol use
3. A great deal of time is spent in activities necessary to obtain alcohol, use alcohol, or recover from its effects
4. Craving, or a strong desire or urge to use alcohol
5. Recurrent alcohol use resulting in a failure at work, school, or home
6. Continued alcohol use despite having persistent or recurrent social or interpersonal problems caused or exacerbated by the effects of alcohol
7. Important social, occupational, or recreational activities are given up or reduced because of alcohol use
8. Recurrent alcohol use in situation in which it is physically hazardous
9. Alcohol use is continued despite knowledge of having a persistent or recurrent physical or psychological problem that is likely to have been caused or exacerbated by alcohol
10. Tolerance, as defined by either of the following: (A) a need for markedly increased amounts of alcohol to achieve intoxication; (B) a diminished effect with continued use
11. Withdrawal symptoms may include headaches, nausea, tremors, anxiety, hallucinations, or seizures

Note: Greater than 1 positive criterion is needed for diagnosis of AUD (moderate with > 3 criteria and severe with > 5 criteria).

Table 2 Alcohol use disorders identification test—consumption (AUDIT-C) screening tool for alcohol use disorder

1. How often did you have a drink containing alcohol in the past year?					Score
Never (0)	Monthly or less (1)	Two or four times a month (2)	Two to three times per week (3)	Four or more times a week (4)	
2. How many drinks containing alcohol do you have in a typical day when you are drinking?					
1 or 2 (0)	3 or 4 (1)	5 or 6 (2)	7 to 9 (3)	10 or more (4)	
3. How often do you have six or more drinks on one occasion?					
Never (0)	Less than monthly (1)	Monthly (2)	Two or three times per week (3)	Four or more times per week (4)	

Note: With a maximum total score of 12, score > 3 in men and above 2 in women is considered positive for harmful alcohol use.

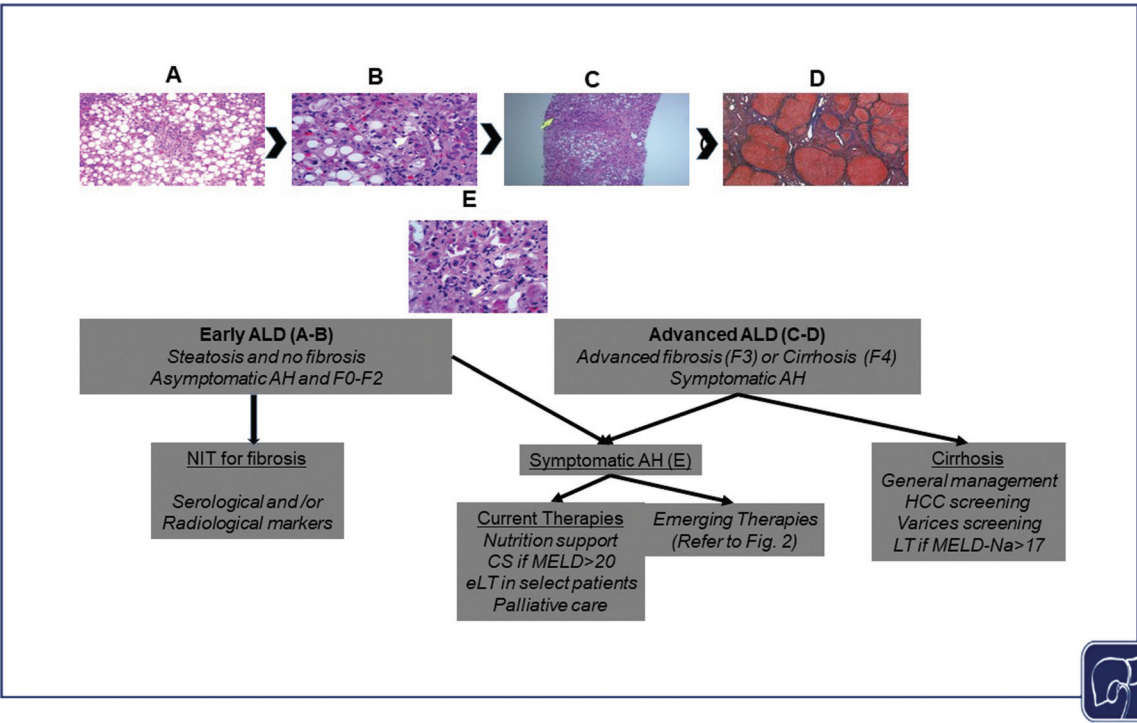


Fig. 1 Spectrum of alcohol-associated liver disease. A (steatosis), B (steatohepatitis), C (F3 fibrosis), D (cirrhosis), E (alcoholic hepatitis). ALD, alcohol-associated liver disease; AH, alcoholic hepatitis; HCC, hepatocellular carcinoma; CS, corticosteroids; LT, liver transplant.

example, in a study on Veterans with AC, AUD treatment was associated with reduction in decompensation and mortality at 6 months from index diagnosis compared with those who did not receive AUD treatment.²⁴ Similar findings were reported in another retrospective study on 388 ALD patients from Brazil.²⁵ In yet another study on hospitalized patients with AC in the United States, just addressing the problem of AUD at the time of discharge was associated with reduced 30-day readmission to the hospital.²² In a prospective study on hospitalized patients with severe AH, an addiction medicine consult during the index admission reduced 30-day readmission rate and recurrence of AH.²⁶ In a longer follow-up of patients who survived the initial episode of AH, long-term outcomes at 5 years improved with complete abstinence to alcohol. Although those who reduced their alcohol use below harmful limits had better outcomes compared with those with harmful alcohol use, these patients still had an elevated risk of dying over a long-term period.²⁰ Although abstinence is the ideal goal, a lower safe threshold of alcohol use after surviving an acute decompensation of ALD remains to be defined.²⁷

Pharmacotherapies for Treatment of Alcohol Use Disorder

None of the Food and Drug Administration (FDA)-approved medications for AUD (naltrexone, acamprosate, disulfiram) have been evaluated in ALD patients in a randomized controlled trial (► **Table 3** and ► **Fig. 2**). In a small retrospective cohort study of 92 patients with alcohol-associated cirrhosis,²⁸ acamprosate compared with baclofen was associated with similar AUD outcomes, and lower rates of hospital admissions. Adverse effects were similar across groups. In another retrospective cohort study, AUD treatment with several relapse-prevention medications was associated with lower likelihood of hepatic decompensation.²⁹ However, this study did not include a comparator arm, which is recommended for pharmaco-epidemiologic studies to minimize study bias.³⁰ Disulfiram is not recommended in patients with preexisting liver disease, as it undergoes hepatic metabolism and is associated with a risk of potentially fatal drug-induced hepatitis in these patients.^{11,31} In another retrospective cohort study, naltrexone use in ALD patients including those with cirrhosis was associated with reduced complications and hospitalizations, and there were no naltrexone-related hepatic adverse effects.³²

Of the non-FDA-approved medications, baclofen has been studied the most in ALD. The first published RCT on 84 patients reported a twofold increase in cumulative abstinence duration and overall abstinence in patients treated with baclofen.³³ In another placebo-controlled randomized trial in patients with AUD, 12 weeks of baclofen use did not improve in abstinence or reduction in heavy drinking days.³⁴ A recent RCT examined 104 patients with ALD randomized to baclofen 30 mg/day, 75 mg/day, or placebo.³⁵ Patients randomized to baclofen experienced significant benefit on time to relapse and percentage of days abstinent; no differences between the two doses were observed. Although other non-FDA-approved medications have not been studied in ALD,¹¹

gabapentin has demonstrated benefit in reducing heavy drinking days in a non-ALD population,³⁶ and is generally considered to be safe in chronic liver disease. Other potential safe medications are topiramate and varenicline with documented hepatic safety.^{37,38} Varenicline may be particularly useful in patients with cooccurring tobacco use.³⁹

Acamprosate is considered first-line in ALD patients, because it has the strongest data in RCTs in the non-ALD population.⁴⁰ The mechanism of action for acamprosate is not fully defined, but is thought to modulate GABA and glutamate activity in the brain, which is disrupted in AUD. It is dosed at 666 mg three times a day (TID), which can be challenging in those who struggle with adherence. In patients with renal disease, if the glomerular filtration rate (GFR) is 30 to 50, it is dosed at 333 mg TID, and if the GFR is less than 30, it is contraindicated. The main side effects reported are diarrhea and mood symptoms. Due to its primarily renal clearance, it is thought to be safe in decompensated cirrhosis with stable renal function. Naltrexone, an opioid-receptor antagonist, can also be used (if not otherwise contraindicated). It blocks the endogenous opioid system, which is thought to mediate some of the rewarding effects of alcohol. It is dosed at 50 mg daily, though some providers may start at a lower dose in patients with cirrhosis due to hepatic metabolism and higher levels of circulating serum naltrexone.⁴¹ It has, actually, been studied in the short term in very small studies examining cholestatic pruritus in patients with compensated and decompensated cirrhosis, without evidence of hepatotoxicity; however, its safety is not fully proven in this population.⁴² Common side effects include diarrhea, nausea, and changes in mood, and it is absolutely contraindicated in patients on chronic opioids.

The non-FDA-approved medications for AUD can also be considered in ALD.¹¹ Baclofen is a GABA_B receptor agonist and is dosed at 10 mg TID. Although higher doses are sometimes used, it is unclear if there is any benefit to dose escalation. It is well studied in ALD and can be used in both compensated and decompensated cirrhosis. Common side effects include fatigue, sedation, and dry mouth. Gabapentin is dosed at 300 to 600 mg TID and should be dosed reduced if the GFR is less than 60. It can be used to augment other anti-craving medications when there is partial response and is generally considered safe in compensated and decompensated cirrhosis. Common side effects include headache and fatigue. Topiramate, like acamprosate, modulates GABA and glutamate activity in the brain. It is initially dosed at 25 mg daily and slowly up-titrated as needed/tolerated to 150 mg BID. Hepatotoxicity is very rare with topiramate, and, when reported, has usually been in the setting of coadministration of valproic acid.⁴³ Common side effects include decreased appetite, weight loss, mental fog, and paresthesias. Finally, varenicline, a partial agonist at the nicotinic receptor, can be considered in patients with AUD, and particularly in those with cooccurring tobacco use. It is dosed at 0.5 mg daily for 3 days, 0.5 mg twice daily (BID) for 3 days, and then 1 mg BID going forward. It should be dose-reduced if the GFR is less than 30, and hepatotoxicity is rare. Fatigue and nausea are the main side effects reported.

Table 3 Emerging pharmacotherapies for treatment of alcohol use disorder

Pharmaceutical agent	Mechanism of action	Clinical trial number	Study design	Inclusion criterion	Primary endpoint	Proposed sample size
Baclofen	GABA _B receptor agonist	NCT01711125	Placebo controlled RCT: baclofen 30 mg vs. baclofen 75 mg vs. placebo	Alcohol dependence, resolution of alcohol withdrawal	Alcohol consumption at 12 wk	104
Metadoxine	Increases the level of GABA and acetylcholine in the frontoparietal cortex	NCT01504295	Placebo controlled RCT	DSM-IV diagnosis of AUD in patients with ALD	Percent days abstinent at 12 wk	38
Cannabidiol (CBD)	Modulation of neuronal immune response through cerebral adenosine regulation	NCT05159830	Placebo controlled RCT	DSM-V criteria for AUD, average alcohol use: 12 drinks/day	Total alcohol consumption from week 8 to week 12 of the study	76
Michigan Alcohol Improvement Network-Alcohol Reduction and Treatment tool (MAIN-ART)	Online web application	NCT04473482	Single group assignment	1. Diagnosis of AUD with AH or ALD 2. Enrolled in University of Michigan Healthcare System 3. Compatible smartphone	1. Feasibility of MAIN-ART as measured by recruitment and retention rates up to 6 mo 2. Acceptability of MAIN-ART tool by post-intervention surveys	60
Alco-Change	Breath analyzer with smartphone application	NCT03474328	Single group assignment	Clinical diagnosis of ALD, compatible smartphone	Self-reported alcohol consumption (average/week)	60
A-CHESS	Smartphone application	NCT03388320	Single group assignment	1. ALD 2. Enrolled in New York Presbyterian Hospital/Weill Cornell Medical Center 3. Compatible smartphone	Rates of return to alcohol use at 6 mo	30
Integrated addiction team in posttransplant patients	System-based intervention	NCT04964687	Retrospective cohort	1. Patients transplanted for ALD from January 2000 to December 2015 2. Patients who survived > 6 mo posttransplant	Overall survival of patients transplanted for ALD at 5 y	616

Abbreviations: AH, alcoholic hepatitis; ALD, alcohol-associated liver disease; AUD, alcohol use disorder; DSM, Diagnostic and Statistical Manual of Mental Disorders; GABA, gamma amino butyric acid.

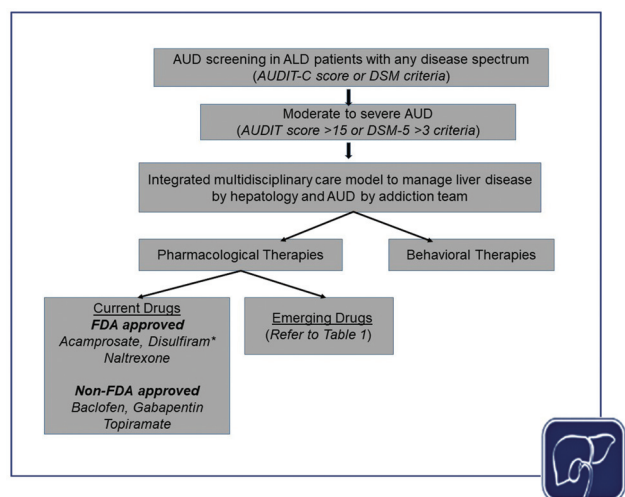


Fig. 2 Treatment of alcohol use disorder (AUD).

In light of sparse data for FDA-approved medications in ALD, society guidelines do not unilaterally recommend their use in patients with AUD and ALD. The American Association for the Study of Liver Disease (AASLD) guidelines, for instance, state, “Based on limited data, the use of acamprosate or baclofen can be considered for the treatment of AUD in patients with ALD.”⁴⁴ The American College of Gastroenterology (ACG) guidelines also recommend baclofen in the treatment of AUD in ALD, but do not recommend other agents due to lack of evidence.⁴⁵ The American Psychiatric Association guidelines recommend against naltrexone in patients with “acute hepatitis or hepatic failure” and do not make any specific recommendations as to what medications can or should be used in patients with ALD.⁴⁶

In spite of strong observational data on the benefit of treating AUD in improvement of liver-related outcomes, treatment of AUD in clinical practice is limited by several barriers at multiple levels. For example, patients with ALD often are unaware of the threshold amount of alcohol which can cause liver disease.^{47–49} The perceived shame and societal stigmatization plays a key role in patients delaying or not seeking care for AUD.⁵⁰ Systemic barriers include absence of adequate insurance coverage, lack of access to mental health resources, geographic limitations, a national shortage of addiction providers, logistical difficulties owing to geographical separation of hepatology and addiction medicine practices, and absence of specific protocols for AUD monitoring and care.⁵¹ Finally, many providers, including hepatologists, do not feel comfortable prescribing medications for AUD due to lack of specific addiction medicine training.⁵² Strategies to overcome these barriers include integrated multidisciplinary care models with hepatology and addiction medicine experts that address dual pathology of liver disease and of AUD during the same clinic encounter. In a recently reported pilot program, an integrated care model among candidates receiving early LT for ALD tended to reduce recurrence of alcohol use compared with usual care and follow-up of these patients (6.8 vs. 16.2%, $p=0.21$).⁵³ Similar results have been reported from Italy, in which a

multidisciplinary team composed of a clinical toxicologist, hepatologist, psychiatrist, and a surgeon demonstrated lower mortality among patients treated by the multidisciplinary team ($p=0.02$); however, there was no statistically significant difference in the rates of relapse among the two arms ($p=0.06$).⁵⁴

Management of Liver Disease

Alcohol-Associated Cirrhosis

Once patients develop cirrhosis, their management largely revolves around preventing and treating secondary complications of cirrhosis including signs of portal hypertension (ascites, variceal bleeding, and hepatic encephalopathy), bacterial/fungal infections, hepatocellular carcinoma, and sarcopenia. Patients with ALD are at particular risk of malnutrition, which can exacerbate cirrhosis-related sarcopenia. The role of nutritional deficiencies in the progression of liver disease is unknown; however, published literature recommends a daily caloric intake of 2,000 kcal with approximately 1.2 to 1.5 g/kg/day protein distributed between small meals throughout the day, with short intervals between meals to reduce post-absorptive catabolism.⁵⁵ Liver transplantation (LT) is an approved therapeutic modality for worsening liver disease as defined by a model for end-stage liver disease (MELD) score of 15 or more or complicated by hepatocellular carcinoma.⁵⁶

Alcoholic Hepatitis

Symptomatic alcoholic hepatitis (AH) is a distinct clinical entity often characterized by rapid onset of jaundice, leukocytosis, portal hypertension, and ascites in the context of either ongoing or recent cessation of long-term harmful alcohol use.^{10,57} The National Institute on Alcohol Abuse and Alcoholism (NIAAA) clinically defines AH with the following criteria: onset of jaundice within the past 8 weeks, ongoing alcohol consumption of over 40 g (female) and over 60 g (male) for 6 months or more, less than 60 days of abstinence before the onset of jaundice, AST more than 50 with AST:ALT more than 1.5 (both values less than 400 IU/L), and serum total bilirubin more than 3.0 mg/dL.⁵⁸

Current Medical Therapies

Of the pharmacological therapies, corticosteroid (prednisolone 40 mg/d or methylprednisolone 32 mg/d) is the only available and recommended first-line treatment for patients with severe AH (modified discriminant function index or mDF more than 32 or MELD score of over 20).^{59–61} Since first published study in 1971, the results have remained controversial.⁶² The largest randomized controlled clinical trial, the STOPAH (Steroids or Pentoxifylline for Alcoholic Hepatitis) study on 1,103 patients with severe AH, demonstrated only a modest short-term mortality benefit of prednisolone in severe AH at 28 days in comparison to placebo (13.8 vs. 18%, $p=0.056$). In a multivariate regression model after controlling for other baseline variables, prednisolone use was associated with survival benefit at 28 days. Since then, two meta-analyses including the STOPAH study showed

short-term survival benefit of prednisolone at 28 days of 46 and 36%, respectively.^{63,64} There was no benefit at 3 or 6 months which is mainly determined by alcohol use and abstinence.^{63,64}

There are several limitations for use of corticosteroids in clinical practice. First, as of today there are no specific pharmacological treatments for patients with moderate AH (MELD score 11–20), a disease with potential of up to 10% mortality within 3 months from presentation.⁶⁵ Even among severe AH patients, other than survival benefit for a short period of 28 days, there are several other limitations of corticosteroids in the treatment of severe AH. These include ineligibility for corticosteroids at admission in 30 to 40% of patients due to relative contraindications (active bacterial infection, gastrointestinal bleeding, acute kidney injury–hepatorenal syndrome, and poorly controlled diabetes mellitus); unpredictable response to treatment in 50 to 60% patients; and risk of bacterial/fungal infections, especially among nonresponders to treatment.⁶⁶ Furthermore, the response to corticosteroids can be evaluated only after 4 to 7 days of treatment.⁶⁷

Clearly, there remains an unmet need of accurate biomarkers which can predict steroid response at baseline, so that treatment can be personalized to those who are likely to respond. In a translational study on post hoc analysis of participants enrolled in the STOPAH study, serum levels of bacterial DNA at baseline correlated with risk of infections after exposure to corticosteroids.^{68,69} There have been several other attempts like monocyte oxidative stress with bioenergetics and gene expression studies of genes mediating inflammation and regeneration, which have shown encouraging data.^{70–72} Although emerging literature is encouraging, their translation to clinical practice is limited by lack of validation, cost, and complexity in measurement. In this regard, a recent multicenter international study on 3,380 patients with severe AH showed interesting findings. The study showed that corticosteroids benefit patients with MELD over 20 as reported earlier, and this benefit is not seen after MELD score of 51. Furthermore, the benefit is maximum in patients with MELD score between 21 and 39 (HR: 0.61; 95% CI: 0.39–0.95; $p=0.027$). Corticosteroids are currently recommended for patients with severe AH by the ACG, European Association for the Study of Liver, and the AASLD.^{59–61} Based on these data, corticosteroids can be personalized in eligible patients with MELD score between 25 and 39 for the maximum survival benefit.

Emerging Therapeutic Targets

Aligned with the pathophysiology of AH, emerging therapies are reviewed targeting (1) gut–liver axis, (2) hepatic inflammation and fibrosis, (3) hepatic regeneration, and (4) oxidative stress (–Fig. 3).

Drugs Acting on Gut–Liver Axis

Purified hyperimmune bovine colostrum (IMM-124E): Alcohol consumption can alter gut flora by reducing the levels of beneficial microbiota and increasing the level of harmful microbiota (dysbiosis). Alcohol also increases gut permeabil-

ity in ALD patients, which can induce translocation of pathogen-associated molecular patterns (PAMPs) through portal circulation into the liver, especially bacterial lipopolysaccharide (LPS). These PAMPs are recognized by the toll-like receptor-4 on hepatic cells leading to downstream inflammatory signaling pathways.⁷³ IMM-124E is an immunoglobulin G against bacterial LPS and is obtained in purified form from bovine colostrum. A pilot open-label study on 10 patients with severe AH (mean mDF: 78.1) showed improvement in mDF at 8 weeks, with a mean reduction of 37.7 from baseline, $p=0.001$. The survival was 90 and 70% at 1 and 3 months, respectively.⁷⁴ The NIAAA consortium recently completed a placebo-controlled randomized clinical trial (NCT01968382), in which 56 participants with severe AH (defined by a MELD score 20–28) were randomized in a 1:1:1 to receive IMM 124-E 2,400 mg/day, IMM 124-E 4,800 mg/day, or placebo (in addition to prednisolone 40 mg/day for 28 days). The primary outcome of the study was reduction in circulating endotoxin level.

Zinc: Malnutrition and zinc deficiency is observed frequently in ALD patients, which can increase gastrointestinal permeability as zinc regulates interepithelial tight junctions.^{75,76} Zinc deficiency in the hepatic endoplasmic reticulum and mitochondria induces caspase-3 and hepatocyte apoptosis.^{77,78} In a recently completed NIAAA-sponsored study in severe AH patients, zinc sulfate 220 mg BID as an adjuvant to IL-1 receptor antagonist (anakinra) and pentoxifylline tended to improve 6-month patient survival compared with patients treated with corticosteroids.⁷⁹

Fecal microbiota transplant (FMT): As mentioned previously, heavy alcohol consumption in ALD can lead to dysbiosis, with reduced *Bacteroides* and *Firmicutes* species, and increase in *Actinobacteria* species, *Corynebacterium*, *Proteobacteria*, and *Alcaligenes*.⁸⁰ In a French study, intestinal microbiome (IM) from patients with severe AH when given to mice induced susceptibility to ALD. Interestingly, a subsequent inoculation of microbiome from a healthy donor improved ALD changes.⁸¹

In an open-label clinical trial of 8 patients with steroid-refractory AH (mean MELD: 31 and Child–Turcotte–Pugh [CTP] score: 14), FMT from a healthy blood relative as compared with matched historical cohort of 18 patients with severe AH (mean MELD: 27.5 and CTP: 11.7) receiving standard of care resolved dysbiosis and α -diversity at 1 year, which translated into improved liver disease severity and patient survival (87.5 vs. 33.3%, $p=0.018$).⁸² In another randomized open label trial in 51 patients with severe AH, 16 received FMT and remaining patients received pentoxifylline ($n=10$), corticosteroids ($n=8$), or nutritional supplementation ($n=17$). Patient survival at 90 days in the FMT group was 75%, significantly higher than the other arms. Patients in the FMT arm also had lower risk of hepatic encephalopathy and of acute kidney injury at 30 days.⁸³ In a longer-term follow-up study on 61 patients with severe AH, 35 receiving FMT versus 26 treated with standard of care had fewer episodes of HE, infections, hospitalizations, and alcohol recurrence at 3 years of follow-up (28.6 vs. 53.8%, $p=0.04$), with a trend for improved patient survival (65.7

vs. 38.5%, $p = 0.052$).⁸⁴ Interestingly, 81% of deaths in control group were due to sepsis. A recently completed Phase I placebo controlled randomized trial evaluated 6-month safety data in patients with alcohol-associated cirrhosis and harmful drinking (AUDIT 10 score >8). The study showed reduction in serum IL-6 ($p = 0.02$), LPS-binding protein ($p = 0.04$) with increased in butyrate in the FMT arm compared with the placebo group ($p = 0.05$). Additionally, the FMT arm demonstrated significant reduction in alcohol craving at day 15 (90 vs. 30%, $p = 0.02$).⁸⁵ Another study from India evaluated the clinical outcomes in 61 patients with severe AH (35 FMT vs. 26 standard of care—corticosteroids). The FMT arm had higher hyperbilirubinemia, MELD score, and ACLF (acute on chronic liver failure) grade. Interestingly, the 3-year follow-up results showed significant reduction in the incidence of ascites, HE, infections, and major hospitalization in the FMT arm ($p < 0.05$). Additionally, the alcohol relapse rate was lower (28.6 vs. 53.8%) and the time to relapse was higher (413.5 vs. 224.7 days, $p = 0.04$) in the FMT arm.⁸⁶ There are several other ongoing studies examining FMT in AH (►Table 4).

Antibiotics and probiotics: A large Phase III randomized controlled trial evaluated the efficacy of amoxicillin and clavulanic acid as an adjunct to corticosteroids in patients with severe AH on 284 patients (142 received prednisolone plus antibiotics). Although infection at 2 months was lower in the antibiotic group (29.7 vs. 41.5% $p = 0.015$), adjuvant antibiotic treatment failed to improve Lille score on day 7 (0.37 vs. 0.39, $p = 0.8$) or 60-day survival (82.7 vs. 78.1%, $p = 0.3$).⁸⁷ No safety concerns were noted.

Drugs Targeting Hepatic Inflammation

TLR-4 receptor activation initiates inflammation involving inflammasome pathway consisting of pro-interleukin-1 (IL-1) and pro-caspase-1.⁸⁸ Subsequent inflammatory signaling is mediated through secretion of cytokines like IL-1, IL-6, tumor necrosis factor (TNF), etc.⁸⁹ During this cascade, chemokines, such as chemokine ligand type 2 (CCL2) and IL-8, result in hepatic leukocyte recruitment which results in the amplification of the inflammatory response.^{90,91} Cellular products released from cell death or damage-associated molecular patterns in addition to already activated PAMP stimulate hepatocytes and stellate cells propagating inflammation and hepatic fibrosis.^{92,93} The end result is mitochondrial dysfunction and oxidative stress, which is a critical component in the pathogenesis of AH.⁹⁴

Anakinra (IL-1 receptor inhibitor): IL-1 receptor antagonist, anakinra, has been successfully used in systemic inflammatory conditions such as rheumatoid arthritis, familial Mediterranean fever, Stills disease, and sepsis.⁹⁵ A phase 3, double-blind, randomized trial led by the NIAAA consortium evaluated the efficacy of anakinra in combination with pentoxifylline and zinc in severe AH patients, and compared with the control arm of corticosteroid-treated patients. A total of 103 patients were evaluated (53 Anakinra, Zn, and Pentoxifylline vs. 50 corticosteroids). The study failed to show improvement in the 30-day and 90-day survival. However, the 180-day survival in patients with initial MELD scores of 20 to 25 was significantly higher than ones with initial MELD scores of 26 to 31 (HR: 2.9, $p = 0.003$). Both MELD strata showed nonsignificant treatment effects in

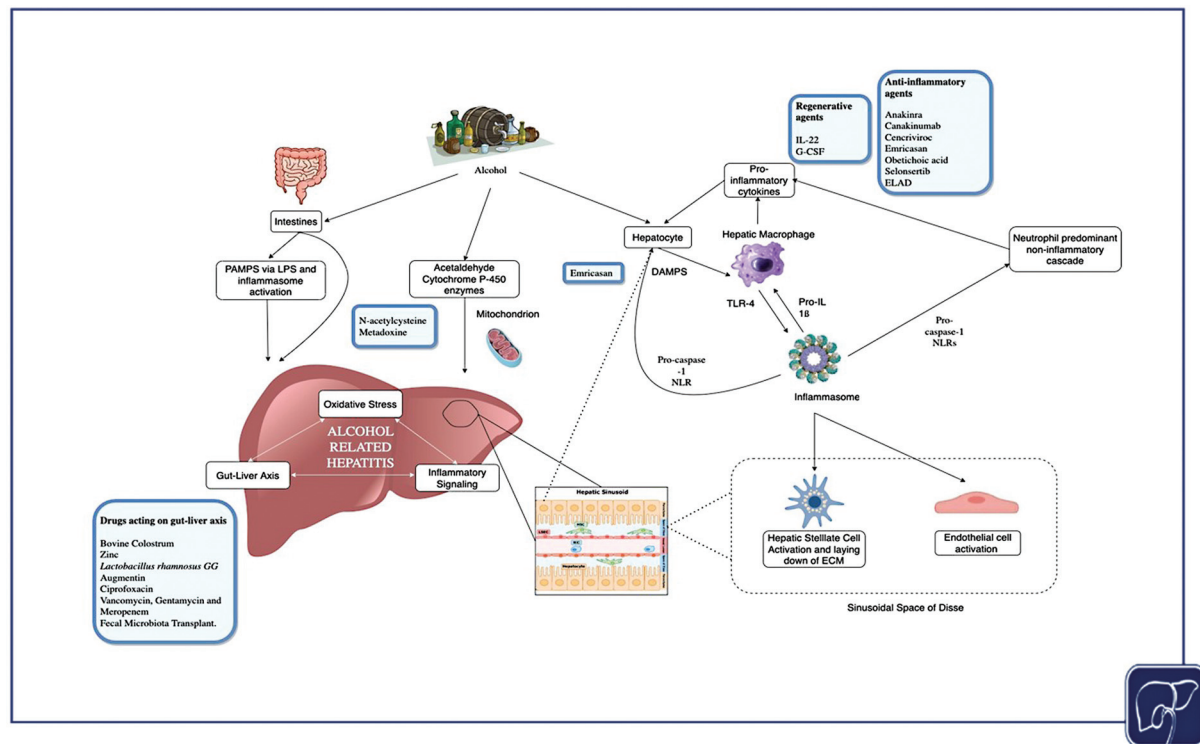


Fig. 3 Pathogenesis of alcohol-associated liver disease and emerging therapies targeting various pathogenesis pathways. PAMPS, pathogen-associated molecular patterns; DAMPS, damage-associated molecular patterns; NLR, nod-like receptor; TLR-4, toll-like receptor 4; pro-IL-1 β , pro-interleukin 1 β .

favor of the IL-1 receptor inhibitor arm.⁷⁹ There is another ongoing trial of anakinra in combination with zinc in patients with severe AH (►Table 5).

Canakinumab (IL-1β inhibitor): Damage-associated molecular patterns (DAMPs) from the injured hepatocytes activate serine pro-tease caspase-1 (CASP-1), resulting in release of cytokines such as IL-1β and IL-18.⁸⁹ Canakinumab, a recombinant monoclonal antibody, inhibits IL-1β, reduced cardiovascular events over a median follow-up period of 3.7 years in a study on 10,061 patients with a history of myocardial infarction. However, it was associated with a safety concern of fatal infections.⁹⁶ In a recent multicenter placebo controlled clinical trial on 57 patients with biopsy proven AH (mDF ≥ 32 and MELD ≤ 27), canakinumab (N = 28) improved liver histology (58.3 vs. 41.7%, *p* = 0.025), but failed to improve 28-day patient survival (93% in each group).⁹⁷ There were no drug-related safety concerns in this study.

Selonsertib: The apoptosis signal regulating kinase-1 (ASK-1) enzyme mediates multiple steps in the pathology of AH including hepatocyte apoptosis, cytokine signaling, and stellate cell activation. A phase 2, double-blind, randomized study evaluated the safety of the oral inhibitor of this enzyme, selonsertib (GS-4997), as adjunct to prednisolone in 99 patients (51 received selonsertib) with severe AH (median mDF: 38 and MELD: 22). Comparing intervention versus prednisolone alone, there was no difference in treatment response on day 7 (77.1 vs. 86.3% with Lille score < 0.45, *p* = 0.30) or on 28-day survival (95.7 vs. 96%, *p* = 1.00).⁹⁸

Emricasan: While inflammation is mediated and initiated via caspase-1, apoptosis and necrosis are regulated by caspase-8. A pan-caspase inhibitor, emricasan has shown efficacy in inflammatory conditions, primarily sepsis. An NIAAA consortium-led study exploring the efficacy of emricasan in severe AH was discontinued after recruiting only five patients, as a safe dosing regimen could not be reached due to poor bioavailability of the drug. Additional studies are needed to determine dose safety prior to evaluating its use in the treatment of AH. In a study of 86 patients with Child–Pugh class A or B cirrhosis (38% alcohol associated) and MELD score 11 to 18, emricasan significantly reduced the mean MELD (*p* = 0.03) and Child–Pugh scores (*p* = 0.003) in individuals with MELD score of 15 or higher.⁹⁹

Obeticholic acid: Bile acids are physiologic ligands of farnesoid X receptor (FXR), a nuclear hormone receptor present in the liver and small intestine. Activation of this ligand receptor complex results in hepatoprotective effects by regulating the lipid and bile acid metabolism, hepatic inflammation, and nitric oxide expression in the hepatoportal vasculature.¹⁰⁰ A double-blind, placebo-controlled trial by the NIAAA consortium (NCT02039219) has completed recruitment in patients with moderate AH (MELD 11–20) and is currently in Phase II (►Table 5). The primary outcome measures of this study are median MELD score, incidence of serious adverse events, and change in MELD score from baseline at 6 weeks.

Extracorporeal liver assist device (ELAD): ELAD is a form of cellular therapy utilizing hepatoblastoma-derived HepG2/C3A cells that express numerous anti-inflammatory

Table 4 Emerging pharmacotherapies for the treatment of alcoholic hepatitis (drugs targeting gut–liver axis)

Pharmaceutical agent	Mechanism of action	Clinical trial number	Study design	Inclusion criterion	Primary endpoint	Proposed sample size
Ciprofloxacin	Change in gut microbiome	NCT02326103	Placebo controlled RCT	DF > 32	Patient survival at 1, 3, and 6 mo	22
Fecal microbiota transplant	Change in gut microbiome	NCT05285592	RCT FMT vs. CS	MELD ≥ 20, DF ≥ 32, steroid ineligible AH	LT-free patient survival at 3 mo	84
Fecal microbiota transplant	Change in gut microbiome	NCT05006430	Placebo controlled RCT, FMT vs. CS + placebo	MELD > 15, DF ≥ 32	1. 12-mo patient survival 2. Change in gut microbiome at 4 wk, 6 mo, 9 mo, and 12 mo	25
Fecal microbiota transplant	Change in gut microbiome	NCT04758806	Prospective open label	MELD ≥ 20, DF ≥ 32, steroid nonresponsive AH	Overall mortality at 28 d, 90 d, and 1 y	50
Rifaximin	Change in gut microbiome	NCT02116556	Nonrandomized, placebo-controlled trial	DF ≥ 32, steroid nonresponse	Mortality at 28 d, 90 d, and 1 y	29
Probiotics	Restoration of gut microbiome	NCT01501162	Placebo controlled RCT	DF < 32, AST: ALT > 1	Change in liver enzymes at day 7	130

Abbreviations: AH, alcoholic hepatitis; Alk Phos, alkaline phosphatase; ALT, alanine transaminase; AST, aspartate transaminase; CS, corticosteroids; DF, Maddery's discriminant factor; FMT, fecal microbiota transplant; GGT, gamma glutamyl transpeptidase; LT, liver transplant; MELD, model of end-stage liver disease; RCT, randomized controlled trial; SIRS, systemic inflammatory response syndrome.

Table 5 Emerging pharmacotherapies for the treatment of alcoholic hepatitis (drugs targeting hepatic inflammation)

Pharmaceutical agent	Mechanism of action	Clinical trial number	Study design	Inclusion criterion	Primary endpoint	Proposed sample size
Hyaluronic acid 35	Modulation of TLR-4 signaling through downregulation of microRNA-219b	NCT05018481	Placebo controlled RCT	MELD < 21, histological or clinical diagnosis of AH	Percent change of skeletal muscle mass at 90 d	54
TAK-242	Inhibition of TLR-4 signaling	NCT04620148	Placebo controlled RCT with CS in everyone	Clinical or histologic diagnosis of AH and CLIF-C ACLF score 36–63	Change in CLIF-C ACLF score from baseline to day 8	100
Pentoxifylline	Modulation of cytokine response by increasing intracellular cAMP and cGMP	NCT02458079	RCT: PTX vs. FMT	DF ≥ 32, steroid nonresponse	Patient survival at 3 mo	32
Pentoxifylline	Modulation of cytokine response by increasing intracellular cAMP and cGMP	NCT01214226	Placebo controlled RCT—PTX + CS vs. placebo + CS	DF ≥ 32, onset of jaundice within the last 3 mo, biopsy-proven AH	Overall survival at 6 mo	278
Pentoxifylline	Modulation of cytokine response by increasing intracellular cAMP and cGMP	NCT01455337	RCT—prednisolone vs. PTX	DF ≥ 32	Patient survival at 1 mo	126
Digoxin	Downregulation of H1F-α, inhibition of PKM-2-dependent genes	NCT05014087	Prospective open label	DF 32–60, MELD 20–30, everyone on CS therapy	Ability to recruit 4 patients a month (primary recruitment feasibility objective)	60
DS-102	Anti-inflammatory and antifibrotic lipid	NCT03452540	Placebo controlled RCT	Clinical or histological AH, Total bilirubin ≥ 5 mg/dL	Percent change in MELD at 28 d	120
IDN-6556 (Emricasan)	Pan-caspase inhibitor	NCT01912404	Placebo controlled RCT	MELD 21–34 or 35–40 if SOFA score < 10, corticosteroid ineligible	Patient survival at 28 d	5
CytoSorb hemoadsorption column	Removal and regulation of proinflammatory cytokines, free hemoglobin and bilirubin	NCT05131230	Prospective case-controlled CytoSorb + CS	DF ≥ 32, ACLF grade 2–3, bilirubin ≥ 8 mg/dL, creatinine ≥ 2 mg/dL	ACLF < 2 at 7 d	30
Candesartan	Decrease in stellate cell stimulation through blocking angiotensin II	NCT00990639	RCT with ursodeoxycholic acid in everyone	1. Clinical diagnosis of ALD 2. METAVIR fibrosis score ≥ 2 3. Alcohol intake stopped during last 6 mo	Histological improvement in hepatic fibrosis at 6 mo	85

Abbreviations: ACLF, acute on chronic liver failure; AH, alcoholic hepatitis; Alk Phos, alkaline phosphatase; ALT, alanine transaminase; AST, aspartate transaminase; cAMP, cyclic adenosine monophosphate; cGMP, cyclic guanosine monophosphate; CS, corticosteroids; DF, Maddrey's discriminant factor; GGT, gamma glutamyl transpeptidase; H1F-α, hypoxia inducible factor 1α; MELD, model of end-stage liver disease; PKM-2, pyruvate kinase isoenzyme-2; PTX, pentoxifylline; RCT, randomized controlled trial; SIRS, systemic inflammatory response syndrome; TLR-4, toll-like receptor 4.

proteins and growth factors, specially increased expression of IL-1 inhibitor. In an open-label, multicenter, randomized, placebo-controlled trial in 203 (96 randomized to ELAD) severe AH patients, ELAD failed to improve patient survival at 90 days.¹⁰¹ All follow-up studies were subsequently terminated.

Drugs Targeting Hepatic Regeneration

IL-22: While the proinflammatory subset of cytokines (IL-1) drive the systemic inflammatory response, the anti-inflammatory response is governed by the IL-10 group.⁸⁹ IL-22, a pluripotent cytokine within the IL-10 family, exerts hepatoprotective effects through its antiapoptotic, antioxidative, anti-lipogenic, and proliferative effects on hepatocytes. It also promotes production of antimicrobial proteins. A small phase 2 dose-escalating study recruited 18 patients with MELD scores 11 to 28 to examine the safety and efficacy of F-652, a recombinant fusion protein of human IL-22. After examining the three doses (10, 30, and 45 µg), a dose of 45 µg/kg was found to be safe.¹⁰²

Granulocyte colony-stimulating factor (G-CSF): Density of neutrophils in the peripheral blood and in the liver parenchyma on biopsy predicts the response to corticosteroids and is associated with improved outcomes in AH.¹⁰³ Hepatic progenitor cells and bone marrow-derived stem cells (including neutrophils) also promote hepatic regeneration.^{91,104} Data on the use of G-CSF have shown mixed results with conflicting results. In a pilot clinical trial in severe AH patients, G-CSF use was associated with reduction in CTP, MELD, and DF scores at 1 and 3 months.¹⁰⁵ In a meta-analysis of 7 studies on 396 patients (197 received G-CSF) including 336 with AH, heterogeneous pooled data showed a 72% 90-day survival benefit (0.28 [0.09–0.88], *p* = 0.03). Benefit was from five Asian studies with a 85% improved survival (0.85 [0.08–0.25], *p* < 0.001), but no benefit in two studies from Europe (1.89 [0.90–3.98], *p* = 0.09).¹⁰⁶ In a recently published “GRAFT” randomized trial on 176 patients with ACLF (52% ALD), G-CSF 5 µg/kg for 5 days in 88 patients failed to improve liver disease and achieve primary endpoint of 90-day transplant-free survival (34.1 vs. 37.5%, *p* = 0.80).¹⁰⁷ Clearly, more data are needed on the role of G-CSF in the management of AH before recommending its routine use in clinical practice (► **Table 6**).

Sulfated oxysterol (DUR-928): DUR-928 (larsucosterol), a sulfated oxysterol is an epigenetic regulator which down-regulates inflammation and enhances regeneration, leading to beneficial effects on lipid homeostasis, inflammation, cell survival, and tissue regeneration.¹⁰⁸ In a murine model, DUR-928 decreased TNF-α and monocyte chemoattractant protein-1, with reduction in hepatic inflammation and fibrosis.¹⁰⁸ In a phase II-a, open-label, dose-escalation study, DUR-928 infusions on days 1 and 4 in 18 patients with AH (MELD: 11–30) were better compared with a historic control patients treated with corticosteroids, median (95% CI) Lille score of 0.10 (0.08–0.28) versus 0.5 (0.2–0.86), *p*-value less than 0.05.¹⁰⁹ Similar results were shown in another study on seven patients with AH (MELD: 21–30) receiving DUR-928 compared with 13 patients receiving standard of care.¹¹⁰

Table 6 Emerging pharmacotherapies for the treatment of alcoholic hepatitis (drugs enhancing hepatic regeneration)

Pharmaceutical agent	Mechanism of action	Clinical trial number	Study design	Inclusion criterion	Primary endpoint	Proposed sample size
G-CSF	Recruitment of CD34+ cells from bone marrow, hepatic regeneration	NCT02442180	Placebo controlled RCT with CS in partial responder and without CS in null responder	DF ≥ 32, histological or clinical diagnosis of AH, Lille score > 0.16 on day 7 of treatment	Patient survival at 2 mo in null responder and at 6 mo in partial responder	268
G-CSF	Recruitment of CD34+ cells from bone marrow, hepatic regeneration	NCT04066179	RCT: G-CSF + CS vs. G-CSF	DF ≥ 32	Survival at 90 d	126
DUR 928	Decreased hepatic TNF-α and monocyte chemoattractant protein 1 causing decreased inflammation and fibrosis	NCT03917407	Placebo controlled RCT with CS	MELD 11–30	Safety and tolerability of DUR-928	36
DUR 928	Decreased hepatic TNF-α and monocyte chemoattractant protein 1 causing decreased inflammation and fibrosis	NCT04563026	Placebo controlled RCT with CS	MELD 11–30	90-d mortality	300
Mycophenolate mofetil	Decrease T cell and B cell proliferation through inhibition of purine synthesis	NCT01903798	RCT: CS + MMF vs. CS + rilonacept vs. CS alone	DF ≥ 32, biopsy-proven AH	Patient survival at day 29	4

Abbreviations: AH, alcoholic hepatitis; Alk Phos, alkaline phosphatase; ALT, alanine transaminase; AST, aspartate transaminase; CS, corticosteroids; DF, Maddery’s discriminant factor; G-CSF, granulocyte colony-stimulating factor; GGT, gamma glutamyl transpeptidase; MELD, model of end-stage liver disease; MMF, mycophenolate mofetil; RCT, randomized controlled trial; TNF-α, tumor necrosis factor-α.

Drugs Targeting Oxidative Stress

N-acetylcysteine: Oxidative stress with generation of reactive oxygen species is multifactorial in ALD and AH including metabolism of alcohol within hepatocytes, cellular apoptosis and necrosis, hepatic inflammation, and mitochondrial dysfunction.¹¹¹ In a double-blind randomized controlled trial in patients with severe AH, use of antioxidant N-acetylcysteine (NAC) as an adjunct to corticosteroids as compared with steroids alone improved short-term patient survival at 1 month (92 vs. 76%, $p=0.006$), but the drug failed to meet the primary end-point of improvement in 6-month survival. There was lower risk of infection and of hepatorenal syndrome with the use of NAC.²² Similar data have been reported by other clinical trials.^{42,112,113}

Metadoxine: Metadoxine is an ionized salt composed of pyrrolidone carboxylate and pyridoxine. Pyrrolidone carboxylate facilitates ATP synthesis by stimulating the “de novo” synthesis of the purine nucleotide.¹¹⁴ In addition, pyridoxine is a precursor of various coenzymes including pyridoxal 5'-phosphate, which enhances the metabolic breakdown of ethanol and prevents ATP inactivation by acetaldehyde. Two Mexico-based randomized placebo-controlled trials evaluated metadoxine as adjunct to corticosteroids in AH patients. Metadoxine as compared with placebo significantly improved patient survival at 30 and 90 days, with a decrease in the incidence of encephalopathy and hepatorenal syndrome. However, both studies were limited with a small sample size of less than 50 each. Data from ongoing studies are awaited to validate these findings before recommending its use in AH patients (→ **Table 7**).

Metabolic Targets

Alcohol induces hepatic steatosis through multiple mechanisms including augmenting lipolysis of adipose tissues.^{115,116} Accumulation of complex lipids such as ceramides and alcohol-mediated adipose tissue inflammation induces impaired glucose metabolism and insulin resistance. Learning from the NASH therapeutics landscape, several therapies targeting lipid and glucose metabolism have application in ALD.¹¹⁷ For example, de novo lipogenesis can be targeted including inhibition of rate-limiting enzyme acetyl-coenzyme A, fatty acid synthase, stearoyl-coenzyme A desaturase-1, and diacylglycerol acyltransferase. Agonists of nuclear receptors peroxisome proliferator-activated receptors such as elafibranor and saroglitazar and those of fibroblastic growth factors such as pegbelfermin can reduce lipogenesis by augmentation of β oxidation of fatty acids. Inhibition of ceramide synthesis, GLP-1, and GIP improves insulin resistance and targeting hepatocyte nuclear factor- α improves glucose uptake by the hepatocytes in patients with severe AH.¹¹⁸

Liver Transplant in Severe Alcoholic hepatitis

ALD is an acceptable indication for LT with excellent long-term posttransplant graft and patient survival.^{56,119} A period of 6 months of abstinence was recommended to

allow for recovery of liver function from the acute effects of alcohol intake. However, this has been since used as a criterion before considering an ALD patient for LT. Because of very high short-term mortality in most severe forms of AH, this 6-month abstinence rule cannot be applied to these patients. Several studies have shown that “6-month rule” is not a strong predictor of recurrence of alcohol use after LT. In a systematic review, more important predictors were social support, psychiatric comorbidities, previous failed rehabilitation attempt, and younger age.⁵³ Based on these data, the 6-month rule was challenged in a Franco-Belgian study in which an early liver transplant (eLT) improved 6-month survival in 26 select severe AH patients compared with 26 who were not selected for eLT (77 vs. 23%, $p < 0.001$).⁶⁵ Since then, several retrospective and prospective studies have confirmed this benefit of eLT in ALD patients with less than 6 months of abstinence.^{120–122} In the seminal Franco-Belgian study, recurrent alcohol use occurred in 3 of 26 patients at 2 years of follow-up, with only one patient reporting harmful alcohol use.⁶⁵ In a meta-analysis of eight studies, recurrent alcohol use was 14% at 2 years of follow-up after eLT, with no difference comparing eLT in ALD versus traditional LT after a minimum of 6 months of abstinence.¹⁰⁶

Despite promising results and increasing awareness and enthusiasm for eLT in ALD patients, its use remains heterogeneous across centers and providers. One of the main reasons is lack of uniform protocol and selection criteria for this therapy.¹²³ A recent survey showed that of 3,290 LTs performed from 2015 to 2020 at 11 major transplant centers, 45 (1.4%) were performed for severe AH.¹²⁴ Although this impacts very little on the donor pool with approximately 138 LT performed for AH in 2019 in the United States,¹²³ it potentially can negatively impact organ donation as public surveys have shown reluctance to allocate a deceased donor from public pool to an ALD patient who is actively consuming alcohol.^{125–128} A recent prospective nonrandomized non-inferiority controlled study recruited patients (68 severe AH receiving eLT, 47 severe AH not selected for eLT, and 93 receiving LT for ALD cirrhosis with ≥ 6 months of abstinence) from 19 centers in France and Belgium. The selection process used an objective point scoring system based on medical and addiction criteria, with patient selection at ≥ 220 of maximum 250 points. After 2 years, patient survival was 73% better with eLT versus no LT in severe AH, 0.27 (0.16–0.47), and similar to traditional LT, 0.87 (0.33–2.26). However, noninferiority on recurrence of alcohol use could not be documented (34 vs. 25%), and harmful alcohol use was higher with eLT group (22 vs. 5%) with over fourfold relative risk, 4.10 (1.56–10.75).¹²⁹ Clearly, multicenter prospective consortia and studies are needed as a basis for developing uniform protocol and criteria for patient selection for eLT in patients with ALD.

Summary and Conclusion

ALD remains one of the leading causes of liver disease worldwide, and the disease burden is increasing

Table 7 Emerging pharmacotherapies for the treatment of alcoholic hepatitis (drugs targeting oxidative stress)

Pharmaceutical agent	Mechanism of action	Clinical trial number	Study design	Inclusion criterion	Primary endpoint	Proposed sample size
N-acetyl cysteine	Replenish hepatic glutathione reserve and reduction of free radicals	NCT05294744	RCT: NAC + CS vs. CS	DF ≥ 32 , histological or clinical diagnosis of AH	All-cause mortality at 6 mo	390
N-acetyl cysteine	Replenish hepatic glutathione reserve and reduction of free radicals	NCT03069300	RCT: NAC + CS vs. CS	DF ≥ 32 , serum bilirubin > 4.6 mg/dL	1. Improvement in monocyte oxidative burst at 24 h 2. Improvement in ex vivo monocyte burst at 5 d	42
S-adenosyl methionine	Replenish hepatic glutathione reserve	NCT02024295	RCT: SAME vs. polyene phosphatidylcholine	Total bilirubin 2–10 mg/dL, Alk Phos $> 1.5 \times$ ULN or GGT $> 3 \times$ ULN	Decline in serum bilirubin by 30% at 6 wk	118
MG (Metadoxine + Garlic Oil)	Prevention of ATP inactivation by acetaldehyde	NCT02019056	Placebo controlled RCT	Current alcohol use > 60 g/d in males and > 40 g/d in females	Change in AST, ALT, and total bilirubin at 14 wk	90
Omega 5 fatty acid	PPAR γ agonist	NCT03732586	Placebo controlled RCT with CS in everyone	DF > 32 , serum bilirubin > 5 mg/dL	Patient survival at 30 d	40
Vitamin C	Reduction in secondary hepatic iron overload through modulation of hepcidin and tfr1	NCT03829683	Placebo controlled RCT	Histological or clinical diagnosis of AH, suspected or proven infection, presence of SIRS, and organ failure	Change in MELD score at 96 h	20

Abbreviations: AH, alcoholic hepatitis; Alk Phos, alkaline phosphatase; ALT, alanine transaminase; AST, aspartate transaminase; ATP, adenosine triphosphate; CS, corticosteroids; DF, Maddery's discriminant factor; GGT, gamma glutamyl transpeptidase; MELD, model of end-stage liver disease; NAC, N-acetyl cysteine; RCT, randomized controlled trial; SAME, S-adenosyl methionine; SIRS, systemic inflammatory response syndrome; tfr1, transferrin receptor 1.

particularly since the COVID-19 pandemic. Screening for alcohol use should be performed at every medical encounter and those at high risk should be screened for ALD, to implement measures to control the risk factor and prevent development of advanced forms of cirrhosis and AH. Current pharmacological treatment with corticosteroids for severe AH is a very suboptimal treatment. eLT among individuals with severe forms of ALD and AH who have not yet attained 6 months of abstinence is a salvage option in highly select patients. Over the last decade, several novel targets have been identified, with completed or ongoing clinical trials in ALD patients. Even with availability of effective medical therapies for ALD, long-term outcome depends on abstinence from alcohol use in any spectrum of ALD. However, AUD treatment remains underutilized due to several barriers even in patients with advanced disease. It is time that physicians recognize dual pathology in ALD patients of liver disease and of AUD, with a need for an integrated multidisciplinary care model with hepatologists and addiction experts to provide comprehensive management for these patients.

Lay Summary

ALD is a leading cause of end-stage liver disease worldwide. It represents the sequelae of alcohol use in the liver, and represents a spectrum that ranges from fatty liver to progressive forms of AH, cirrhosis, and its complications. Alcoholic hepatitis is characterized by rapidly progressive jaundice in the context of recent alcohol use and carries a high short-term mortality. Currently, corticosteroid is the mainstay for treatment of this condition, with LT available to a select few patients. Here we comprehensively review various therapies in the pipeline targeting liver disease and those targeting treatment of AUD.

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