Review

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Current trials and novel therapeutic targets for alcoholic hepatitis

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Summary

Alcoholic hepatitis is a clinical syndrome in which patients present with acute-on-chronic liver failure and a high risk of short-term mortality. The current treatment of alcoholic hepatitis is suboptimal. Results recently published from the STOPAH study have improved our understanding of how best to design clinical trials for this condition. Although emerging data on liver transplantation for patients with alcoholic hepatitis are encouraging, less than 2% of these patients qualify. Clearly, there is an unmet need for novel treatments to improve the survival of these patients. Changes in the gut microbiota, inflammatory and cytokine signalling, oxidative stress and mitochondrial dysfunction, and abnormalities in the hepatic regenerative capacity alone or in combination contribute to the pathology of alcoholic hepatitis. In this chapter, we will describe the novel therapeutic agents targeting various pathways in the pathophysiology of alcoholic hepatitis. Specifically, we will describe the ongoing clinical trials in which some of these agents are being studied.

Keywords: Corticosteroids; STOPAH, Therapeutic; ALD.

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Introduction

Alcoholic hepatitis (AH) is a unique syndrome, which presents with features of acute and chronic liver failure and with a high short-term mortality rate approaching up to 40% within a month of clinical presentation.[1–3] In this chapter we will discuss novel pharmacological targets for AH and clinical trials in which the efficacy and safety of these targets and agents are currently being investigated. Before we delve into novel therapeutic targets, we will discuss the current management and therapeutic options for AH, while briefly reviewing the pathophysiology of AH.

It is critical to make a diagnosis of AH among patients with decompensated alcohol-related cirrhosis. A recent consensus document provides guidance on how liver biopsy should be used in this regard.[4] Liver biopsy in combination with the appropriate clinical profile confirms a "definite" diagnosis of AH.[4] However, as these patients are sick with coagulopathy and ascites, liver biopsy is logistically difficult and is often not acceptable for patients or physicians.[5] Therefore, in the majority of the patients, the diagnosis of AH has to be made on clinical grounds. Clinical criteria for the diagnosis of AH include recent onset or worsening of jaundice in a patient with chronic heavy alcohol use until at least 6 weeks prior to presentation, elevated liver enzymes with an aspartate aminotransferase to alanine aminotransferase ratio of >1.5:1, with absolute values of these enzymes not exceeding 500 IU/L, and exclusion of other liver diseases. Patients meeting all these criteria in the absence of a liver biopsy qualify for the diagnosis of "probable" AH and can be initiated on specific treatment and included in clinical trials.[4] However, whenever the clinical diagnosis is uncertain, diagnosis of AH may be classified only as "possible" and liver biopsy may be needed to confirm the diagnosis of AH.[4] Findings that confirm the diagnosis of AH on liver biopsy include hepatocyte ballooning, neutrophil infiltrate and Mallory-Denk bodies, on a background of variable degrees of steatosis and fibrosis.[2,6–8] When a biopsy is needed, the transjugular approach is preferred because of the concomitant presence of tense ascites and severe coagulopathy. However, transjugular liver biopsy is not available in all centres and is expensive in some countries,[9] which makes some clinicians reluctant to recommend it. In this regard, emerging data on noninvasive biomarkers for the diagnosis of AH among patients with decompensated alcoholic cirrhosis are encouraging.[10,11]

It is important to stratify the severity of an episode of AH, as a severe episode can be treated specifically with pharmacological agents that improve survival. Of the various scoring systems available,[12] model for end-stage disease (MELD) and modified discriminant function (mDF) or Maddrey's scores are commonly used in technical practice to stratify disease severity and estimate prognosis.[13,14] MELD scores of >20 or mDF scores of >32 or the presence of hepatic encephalopathy signify a severe episode of AH.[13,14] Liver biopsy also helps with determining and estimating the prognosis of an AH episode. Using the findings of megamitochondria on electron microscopic examination and of neutrophil infiltrate, cirrhosis, and bilirubin stasis on haematoxylin and eosin stains, a histologic score can stratify patients with similar disease and estimate short-term survival.[15]

Once the diagnosis of AH is made, apart from treatment of liver disease and its complications, it is important to address alcoholism, alcohol withdrawal, and specific pharmacological options for AH, while providing nutritional support and interventions.[3,16,17] Corticosteroids, the current first-line treatment for severe AH have remained

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Key points

Alcoholic hepatitis is a unique syndrome associated with high short-term mortality and a dearth of effective treatment options.

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controversial ever since their first use in 1971.[18] Although, meta-analyses have shown the efficacy of steroids in improving short-term survival,[19] the recently published results of the STOPAH study have further complicated the controversy surrounding their benefits in the treatment of AH. The results of the study demonstrated only a marginal short-term survival benefit of corticosteroid therapy in the treatment of severe AH. The study also showed no clear benefit of pentoxifylline, an alternative therapy in the treatment of severe AH.[20] Recent meta-analyses including the STOPAH study have confirmed short-term survival benefit from corticosteroids among patients with severe AH.[21,22] Based on these data, corticosteroids are currently recommended for severe AH if there are no contraindications for their use.[17,23] Further, there are issues surrounding the use of corticosteroids, such as the unpredictable response (only about 50% of patients respond[24]) and the risk of complications including bacterial and fungal infections. Hence, these drugs are used by only 25 to 40% of treating physicians among patients with a severe episode of AH.[25,26] Other pharmacological therapies including anti-tumor necrosis factor (TNF) agents, growth factors, and antioxidants have been shown to be ineffective for treating severe AH.[1,3] In this regard, emerging data on the benefit of salvage liver transplantation for patients with severe AH who remain non-responders to steroid therapy are encouraging.[27–29] However, these results are from rigorously selected patient cohorts, only including patients with excellent psychosocial support, experiencing their first decompensation of alcohol-related liver disease, and who are non-responders to steroids. Based on these criteria, only about 1 to 2% of patients with severe AH qualify for liver transplantation.[27,30] Clearly, there is an urgent unmet need for new therapies to salvage the remaining patients with severe AH.

Pathophysiology of AH

Alcohol has been recognised as a direct hepatotoxin for over 5 decades now. Once consumed, alcohol is metabolised to acetaldehyde by alcohol dehydrogenase in the liver and in the intestines. Alcohol-related liver injury results from both the direct effects of alcohol on the liver as well as the indirect effects of acetaldehyde-mediated damage on the gastrointestinal mucosa. Over the last 3 decades, the importance of the "gut-liver axis" in alcohol-induced liver damage has been recognised.[31] There are over 100 trillion bacteria living within our gastrointestinal lumen and its mucosa, where they perform the important functions of maintaining gut integrity and innate immunity.[32] There is evidence that alcohol consumption changes the gut flora, reducing the levels of beneficial microorganisms and increasing the levels of harmful bacteria in the intestines.[33] Further, patients susceptible to alcohol-induced liver disease develop increased permeability of the gastrointestinal mucosa. This increased permeability allows translocation of bacterial lipopolysaccharide (LPS) through the portal circulation into the liver. The toll like-4 receptors (TLR-4) on hepatic macrophages recognise the modular patterns on these pathogens leading to activation of inflammatory pathways in the macrophages. It has been shown that this inflammatory upregulation in the macrophages and other liver cell subtypes is mediated through inflammasome activation, which in turn leads to sterile necrosis and or apoptosis, recruitment of neutrophils from the peripheral circulation into the liver, and crosstalk between hepatocytes and hepatic stellate cells (Fig. 1). This cycle is perpetuated by the activation of TLR4 receptors which also recognise the damage-associated molecular patterns released after cellular damage. In the last few years, emerging evidence has come to light on the role of extracellular vesicles, which are released in the circulation during intercellular crosstalk between different liver cell types[8,34]. These extracellular vesicles not only perpetuate the pathophysiology of AH, but are also measurable in the plasma, and are emerging as important biomarkers in the management of alcohol-associated liver disease. Upregulation of inflammation, direct damage to the intestinal mucosa, and necro-apoptosis of hepatocytes and macrophages result in mitochondrial dysfunction and oxidative stress, which are classical features of the pathophysiology of alcohol-associated liver diseases, including AH. The activation of stellate cells and the changes in nitric oxide in the hepatic microcirculation that result from inflammatory signalling lead to collagen production, liver fibrosis, and portal hypertension.

Key point

Several new treatment options are being trialled for alcoholic hepatitis, including those that target the gut-liver axis, anti-inflammatory drugs, antioxidants, and drugs with regenerative potential.

Novel agents in the management of severe alcoholic hepatitis

As mentioned earlier, the STOPAH study taught us a very important lesson, that we need to take a fresh look at how we address and manage our patients with severe AH.[20] Over the last few years the National Institute on Alcohol Abuse and Alcoholism (NIAAA) have encouraged and supported many consortia in the US to conduct clinical trials to examine novel targets and to develop viable treatments options for the management of severe AH.[1] Based on their mechanism of action, these drugs can be classified into 4 different sections, namely: a) drugs acting on the gut-liver axis, b) anti-inflammatory agents, c) antioxidants, and d) drugs with regenerative benefits (Table 1).[1,2,12]

Drugs acting on the gut-liver axis

The increase in intestinal permeability in patients with alcohol-associated liver disease and AH has been shown to occur before the onset of bacterial translocation, suggesting this to be a cause and not

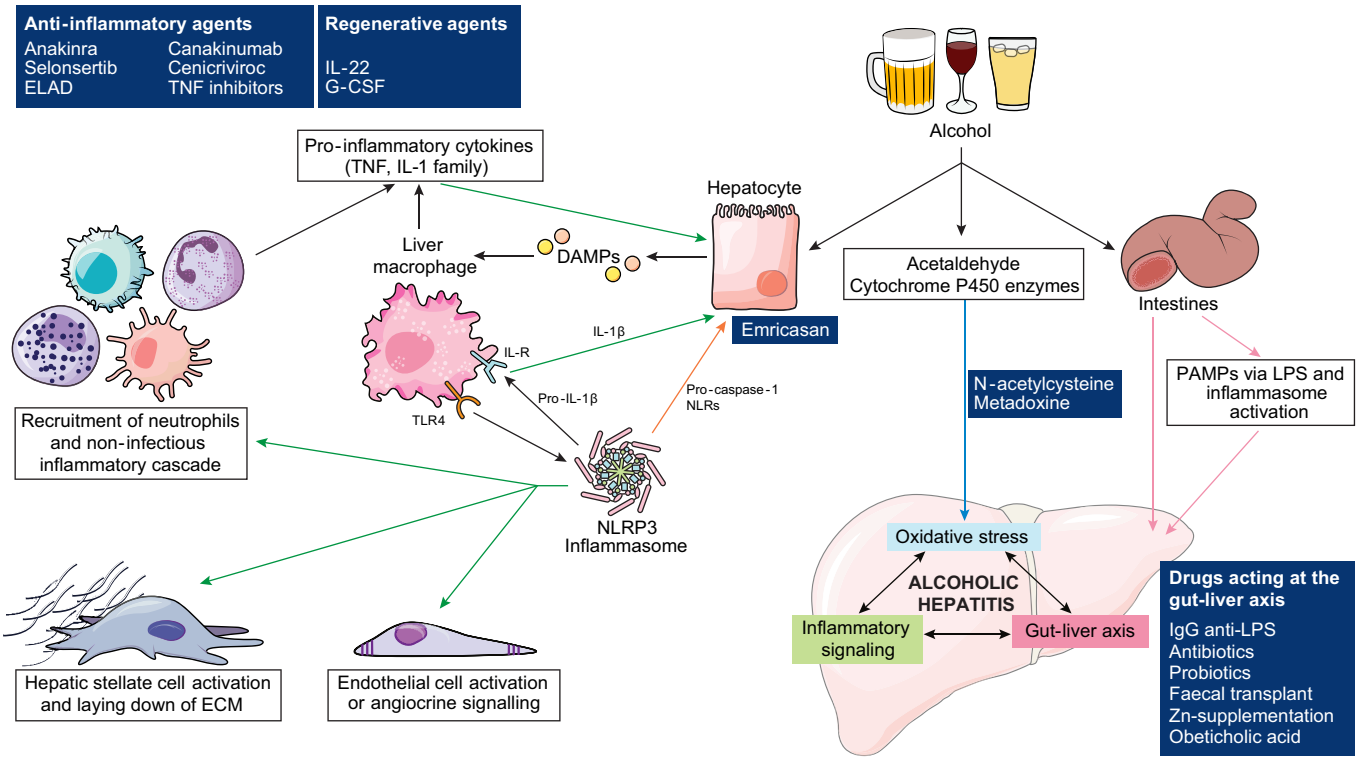

Fig. 1. Pathophysiology of alcoholic hepatitis and novel therapeutic targets in current clinical trials. Alcohol ingestion results in liver injury through multiple effects and pathways including a) its toxic effect on the gut with increase in permeability resulting in translocation of bacterial LPS that leads to IL-1 beta production from hepatic macrophages and b) direct toxic effects of alcohol on hepatocytes producing acetaldehyde with consequent oxidative stress and apoptosis of apoptosis. Inflammation perpetuates through cytokines with other liver cells such as recruited PMN, HSCs, and endothelial cells with development of portal hypertension and fibrosis. The novel agents in currently ongoing clinical trials target a) the gut-liver axis (IgG-LPS, antibiotics, probiotics such as *Lactobacillus*, and faecal transplantation or FMT); b) inflammatory signalling (IL-1 receptor antagonist anakinra, or ASK-1 inhibitor selonsertib, and IL-22); and c) apoptosis, oxidative stress, and hepatic regeneration (IL-22, OCA, metadoxine, selonsertib, pan caspase inhibitor emricasan, and G-CSF). *Slide courtesy Dr. Tejasav Sehrawat.* FMT, faecal microbiota transplantation; G-CSF, granulocyte colony stimulating factor; HSC, hepatic stellate cell; IL, interleukin; LPS, lipopolysaccharide; OCA, obeticholic acid; PMN, polymorphonuclear.

an effect of the disease process.[35] As described earlier, bacterial LPS plays an important role in initiating disease pathophysiology. Thus, strategies antagonising this effect should be effective in disease management. This can be achieved naturally with the use of purified hyper immune bovine colostrum (IMM-124E), which contains IgG antibodies against LPS (Fig. 1). A randomised clinical trial (NCT01968382) was recently completed by the NIAAA consortium on 56 participants with severe AH (MELD score 20–28), to examine the benefit of IMM 124-E as an adjuvant therapy to corticosteroids. The primary endpoint of this phase II study was a reduction in plasma endotoxin (LPS) after 7 months, with the aim of providing proof of concept for the use of IMM 124-E as an adjuvant to corticosteroids. As LPS activates the TLR4 receptors to initiate inflammatory signalling, TLR4 antagonists are another potential therapeutic target in the management of this disease.

Malnutrition and zinc deficiency occur in all liver diseases including AH.[36] Zinc deficiency potentiates increased gut permeability, promotes the effect of caspase-3 in mediating apoptosis, and is also involved in endoplasmic reticulum stress (Fig. 1).[37,38] A randomised clinical trial (NCT01809132) was recently completed, comparing zinc sulfate 220 mg daily as an adjuvant therapy to pentoxifylline and an IL-1 receptor antagonist (anakinra) against standard therapy with corticosteroids in patients with severe AH. The primary endpoint of the study was mortality at 6 months from presentation (Table 1).

As mentioned, alcohol-associated liver disease and AH are associated with bacterial overgrowth in the gut, as well as changes in the composition of the gut microflora, leading to a predominance of harmful bacteria, such as Actinobacteria and Firmicutes, and a reduction in useful bacteria, such as Bacteroides.[39] These pathological changes lay the foundation for probiotics and antibiotics as potential therapeutic agents in the management of severe AH (Fig. 1). Currently, a randomised clinical trial is ongoing, within the NIAAA consortium, to examine the efficacy and safety of *Lactobacillus rhamnosus* GG for patients with AH and MELD scores of 11–20. The primary endpoint of this phase II study is a change in the MELD score. *Post hoc* results from the STOPAH study have shown that in patients with high bacterial DNA levels, treatment with corticosteroids increases the risk of acquiring infections and of adverse outcomes.[40,41] Another large French trial (NCT02281929) is currently ongoing to examine

Table 1. Current clinical trials with novel therapeutic agents for treatment of alcoholic hepatitis.

Pharmaceutical agent	Mechanism of action	Study design [N]	Main inclusion	Primary endpoint	Status
Bovine colostrum (IMM-124E)	IgG to LPS and reduces bacterial translocation	Placebo controlled RCT	MELD score ≥20 but ≤28	Decrease in serum endotoxin levels at 7 months	Phase II, active, not recruiting
Lactobacillus rhamnosus GG	Change in gut microbiome	Placebo controlled RCT	MELD score <21	Change in MELD score at 30 days	Phase II, active and recruiting
Augmentin	Antibiotic amoxicillin plus clavulanic acid	Placebo controlled RCT with CS	MELD score ≥21	Survival at 2 months	Phase III, active and recruiting
Faecal transplant	Change in gut microbiome	RCT FMT *vs.* CS[42]	Eligible for CS treatment	Survival at 3 months	Active and recruiting
Anakinra	Antagonist to IL-1 receptor	RCT Anakinra + Zn + PTX *vs.* CS[42]	MELD score ≥20 and Madre DF ≥32	Survival at 6 months	Phase II, active and recruiting
Obeticholic acid [INT-747]	FXR activation, bile acid agonist, and anti-inflammatory	Placebo controlled RCT	MELD score >11 and <20	Change in MELD score at 6 weeks	Phase II, completed
Selonsertib [GS-4997]	ASK-1 antagonist to inhibit MAPK, JNK, p38	Placebo controlled RCT with CS	Maddrey DF score ≥32	Safety and SAE at 28 days plus 30 days	Phase II, completed
Emricasan [IDN-6556]	Pan caspase inhibitor	Placebo controlled RCT[42]	MELD score >20 but <35 or 35–40 if SOFA score <10	Survival at 28 days	Phase II, terminated after 5 patients
Metadoxine	Antioxidant and promotes abstinence	Placebo controlled RCT with CS[42]	Severe alcoholic hepatitis	Survival at 30 days	Phase IV, completed
IL-22 [F-652]	Anti-inflammatory and hepatic regeneration	Open label	MELD score 11–28	Safety and SAE at 42 days	Phase I completed Phase II planned
G-CSF [Filgrastim]	Increase neutrophils, hepatic regeneration	Placebo controlled RCT with CS in partial responder and without CS in null responder	Maddrey DF score ≥32	Survival at 2 months in null responder to CS and at 6 months in partial responder	Phase IV, active and recruiting

CS, corticosteroid; MELD, model for end-stage liver disease; PTX, pentoxifylline; RCT, randomised controlled trial; SAE, serious adverse event; SOFA, sequential organ failure assessment.

the benefit of an antibiotic, augmentin (amoxicillin plus clavulanic acid) as an adjuvant to corticosteroids in patients with severe AH (Fig. 1). In this randomised clinical trial, of the proposed 280 patients, 200 patients had been recruited at the time of the last update. The primary endpoint of this study is mortality up to 2 months from presentation. We eagerly await results confirming the proposed benefit of prophylactic antibiotics in the management of severe AH.

Another potential therapeutic option at the level of gut bacteria is faecal microbiota transplantation. In an open label study, 8 male patients with severe AH who were ineligible to receive corticosteroids received faecal microbiota transplants from healthy relatives. Outcomes were compared between these 8 patients and 18 matched patients with severe AH receiving standard of care. The results showed that faecal microbiota transplantation reduced disease severity, reduced or resolved liver disease complications such as ascites or hepatic encephalopathy, and improved 1-year survival compared to standard of care (88% *vs.* 33%, $p = 0.018$).[42] Larger studies are needed before recommending this as an option in routine clinical practice.

Drugs acting as anti-inflammatory agents

TLR4 receptors on the hepatic Kupffer cells mediate cytokine signalling and inflammation via the inflammasome pathway, a complex consisting of pro-interleukin-1 and pro-caspase-1.[43,44] The inflammatory signalling is mediated by IL-1.[43] Taken together, there is a rationale for IL-1 receptor antagonism in the management of AH (Fig. 1). A commercially available IL-1 receptor antagonist (anakinra) has been successfully used in clinical trials in patients with inflammatory diseases such as rheumatoid arthritis and sepsis.[45,46] Based on its clinical efficacy in an animal model of AH,[44] a phase II randomised clinical trial has been initiated within the NIAAA consortium.

Farnesoid X receptor (FXR) is expressed in the liver and small intestine, and its agonists provide hepatoprotective effects by controlling lipid and bile acid metabolism,[47] anti-inflammatory and antioxidant effects, and improving portal hypertension via the haemodynamic effects on the liver vasculature, with decreased nitric oxide (Fig. 1).[48,49] Recently, a phase II placebo-controlled randomised clinical trial using 10 mg of obeticholic acid daily for 6 weeks in patients with moderate to severe AH (MELD 12–19) was

completed. The primary endpoint of the study was a decrease in MELD score and serious adverse events with intervention. The results of this study are not yet published and are awaited.

Caspases not only mediate inflammation via caspase-1, as described, but also mediate apoptosis and necrosis.[50] Specifically, apoptosis is mediated by the caspase group of enzymes, particularly caspase-8 (Fig. 1). Emricasan, a pan caspase inhibitor has been shown to be effective in inflammatory conditions, especially sepsis. Encouraged by these results, a clinical trial was initiated by the NIAAA consortium. However, the study was unable to identify a safe dosing regimen in these sick patients with AH, mainly because of poor pharmacokinetic data and excessively high blood levels of the caspase inhibitory compound. Hence, the study was discontinued after recruiting 5 patients with severe AH. Additional dose ranging studies are needed before testing this agent again in the treatment of AH. In another study on 86 patients with cirrhosis (38% due to alcohol), use of emricasan for 3 months improved patient survival compared to placebo. However, it must be noted that patients included in the study were Child-Pugh stage A or B with MELD score 11–18, suggesting less severe dysfunction compared to patients with severe AH.[51] It remains to be seen whether emricasan will be useful in patients with moderately severe AH, or whether similar problems of pharmacodynamics and drug availability will be encountered as in patients with severe AH.[51]

Apoptosis signal regulating kinase-1 (ASK-1) enzyme is activated in AH pathology, and mediates multiple effects including apoptosis, cytokine signalling, and stellate cell activation.[52] Selonsertib (GS-4997), an oral inhibitor of ASK-1 has been used in a phase II clinical trial in patients with severe AH. The results of the study will decide whether the drug has potential to be tested in a phase III clinical trial. Other potential therapeutic options for downregulating inflammation with potential clinical benefit in patients with AH include: a monoclonal antibody targeting IL-1β (canakinumab), an antagonist to chemokines CCR2/5 (cenicriviroc), inhibition of monocyte chemoattractant protein-1 (MCP-1) which contributes to recruitment of macrophages in the liver,[53] inflammasome inhibition by decreasing uric acid levels (allopurinol and probenecid),[54,55] and micro-RNA (miRNAs) or their inhibition.[56] Indeed, in miR-155 knockout mice, levels of endotoxin and cytokines were lower, with higher levels of miR-122, and miR-34.[57]

Extracorporeal liver assist device (ELAD) provides cellular therapy using hepatoblastoma C3A cell products, which have numerous proteins with anti-inflammatory properties, especially increasing the expression of IL-1 receptor antagonist activity. In a recently published study, ELAD was examined in a randomised placebo-controlled trial in 203 patients (107 receiving standard of care and 96 receiving ELAD). Although the results of the study did not show any survival benefit, the *post hoc* analysis and regression analysis showed that elevated international normalized ratio and creatinine are predictors of a negative response with this treatment. Based on this data, another randomised controlled trial has been initiated in younger patients with reasonable renal function and less severe coagulopathy.[58]

Drugs acting on the regenerative pathway

It has long been known that the liver has a remarkable regenerative capacity. More recently, seminal randomised controlled trials using drugs that neutralise TNF, such as infliximab and etanercept, have revealed the importance of TNF in driving this regeneration.[59,60] These clinical trials showed no clinical efficacy and instead the treatments were associated with higher mortality and more side effects, especially infections, than in the treatment arm.[59,60] It turns out that the TNF antagonists not only downregulate inflammation but also antagonise the important function of TNF in hepatic regeneration.[61] These novel findings laid the foundation to examine hepatic regeneration as a therapeutic target in the treatment of severe AH. For the last few years, many prospective studies have shown regeneration as an important predictor and biomarker for disease severity, response to corticosteroids, and patient survival in those with severe AH.[62]

The cytokine load mediated by inflammatory signalling in AH consists of pro-inflammatory cytokines (IL-1 family) which drive the systemic inflammatory response as well as anti-inflammatory cytokines (IL-10 family) which drive the compensatory anti-inflammatory response (Fig. 1).[63–65] One of the major cytokines of the anti-inflammatory family is IL-22 which provides liver protection and promotes regeneration.[66] The major functions of this cytokine, which is released from peripheral blood immune cells, are antioxidant and antimicrobial effects, prevention of fibrosis, and promotion of apoptosis and liver repair.[63] In one prospective clinical study, the density of IL-22 producing immune cells in patients with AH correlated with survival. These strong data make IL-22 an attractive target for the treatment of AH. Recently a phase II open label clinical trial using recombinant fusion protein IL-22 (F652) was completed in 24 patients with AH and MELD scores of 11–28. The primary aim of this study was to assess the safety of this product and assess its clinical efficacy. Three doses were examined in this dose-escalation study, namely 10, 30, and 45 μg. Encouraged by the excellent safety profile of this drug in this study, a randomised placebo-controlled study of IL-22 infusion was proposed. The primary aim of this study is to examine the efficacy of F652 in improving 90-day survival in patients with AH and MELD

scores of 11–20. The other aim of the study is to confirm the efficacy and primarily assess the safety of F652 in patients with AH and MELD scores of 21–28. We await the final analysis and publication of the results of this small pilot study. Meanwhile, a larger study is being planned based on the encouraging signals from this pilot.

Inflammatory signalling is the hallmark of AH pathology, leading to recruitment of inflammatory cells and neutrophils to the liver.[64,67] The density of neutrophils in the peripheral blood and especially in the liver parenchyma on biopsy is a favourable sign, predicting response to treatment with corticosteroids and improved outcome in patients with AH.[15,68] In another study liver progenitor cells and bone marrow derived stem cells including neutrophils have been shown to promote liver regeneration.[69] Based on these data, growth factors such as granulocyte colony stimulating factor (G-CSF) appear an attractive agent for treatment of severe AH (Fig. 1). For example in a few randomised controlled clinical trials in patients with liver failure including patients with AH, the use of G-CSF has been shown to stimulate CD34 positive haematopoietic stem cells, increase the density of these cells on the liver tissue, increase the neutrophil blood count, improve liver disease and decrease MELD score, decrease infections and sepsis rate, and improve overall survival.[70–72] More prospective randomised controlled trials are needed from the Western hemisphere before recommending the use of G-CSF in routine clinical practice for the management of patients with severe AH.

Key point

The results of the STOPAH study have led to changes in the way clinical trials for alcoholic hepatitis are being designed.

Drugs acting as antioxidants

Multiple pathways in the pathology of AH contribute to generation of reactive oxygen species and development of oxidative stress. These pathways include metabolism of alcohol, apoptosis and necrosis of cells, inflammatory signalling and recruitment of inflammatory cells, and mitochondrial dysfunction.[6] In general, antioxidants have not shown any major benefit in the treatment of AH. Many antioxidants like vitamin E, silymarin, and antioxidant cocktails have been tested without any clinical benefit.[73] The only antioxidant which has shown some clinical efficacy is N-acetylcysteine (NAC). In a double-blind randomised controlled clinical trial in patients with severe AH, NAC infusion as an adjuvant therapy to corticosteroids improved short-term mortality at 1 month, however no long-term benefit was observed. This benefit was mainly due to decreases in infection rates and the development of hepatorenal syndrome.[74] Similar data on the benefit of NAC have not been reported by other clinical trials.[75,76] In another study NAC used as an adjuvant therapy to G-CSF failed to provide additional benefit compared to G-CSF alone.[77] Another antioxidant, metadoxine as an adjuvant therapy to steroids or pentoxifylline provided a survival benefit at 3 and 6 months.[78] Larger multicentric randomised studies are needed before recommending the routine use of NAC or metadoxine in the treatment of severe AH. One of the reasons for failure of antioxidants in the treatment of liver diseases and especially AH may be the lack of a specific mitochondrial antioxidant effect of these drugs. In this regard, antioxidants with specific mitochondrial localisation and effect, such as mitoquinone, may have better efficacy than other non-specific antioxidants.

Lessons learnt from the STOPAH study: Current clinical trial design

The results of the STOPAH study have taught us the very important lesson that the current treatment of AH is suboptimal. Hence, current clinical trials are being designed differently to the traditional trial design of the past. Some of these changes in the ongoing clinical trials are highlighted below:

Corticosteroids or placebo in the control arm

Corticosteroids although a suboptimal treatment for AH,[79] are recommended first-line treatment for severe AH in the absence of other safer and more effective therapies.[17,23] Hence, it is relevant to think about whether the control arm should include standard of care with corticosteroids or placebo. If the study design justifies the rationale and is approved by the IRB, both study designs are reasonable and are currently being used in clinical trials (Table 1).

General treatment and candidacy for liver transplantation in the two arms

It is also important to homogenise the study arms regarding general aspects of AH treatment including treatment of liver disease complications, nutritional support, antibiotics, vasoconstrictors for hepatorenal syndrome, and treatment of alcohol use disorder.[16] Further, the emerging data on clear survival benefit of liver transplantation among select patients with severe AH may introduce heterogeneity across study arms.[28] As long as the criteria for these interventions is established in the protocol and followed through the study, a randomised double-blind clinical trial will hopefully take care and match these various characteristics across the study arms.

Disease severity for patient recruitment

Patients with moderately severe AH (MELD 11–20) may progress to severe disease with short-term mortality in about 10%.[12] Similarly, patients with very severe disease (MELD score >35 and Maddrey score >90) have a high risk of multiorgan failure and are therefore excluded. Hence, most trials currently recruit patients with MELD scores between 11 and 35 (Table 1).

Combining pharmacological therapies

As the pathophysiology of AH involves multiple pathways, combination therapies using agents active against different pathways may provide synergistic action.[80] An example would be the ongoing clinical trial of an anti-inflammatory agent anakinra (IL-1 receptor antagonist), and anti-TNF drug pentoxifylline, along with zinc, which is believed to reverse the increased intestinal permeability (Table 1).

Timing of endpoint on patient survival

The marginal survival benefit of corticosteroids is limited to 1 month only.[79] Prospective studies have shown that the outcome of patients with AH is determined by progressive liver inflammation and failure in the first month, liver disease complications at up to 3 months, and by patient behaviour and alcohol abstinence after 3 months [81] Hence, the current clinical trials are focusing on examining primary outcome at 2–3 months from presentation (Table 1).

Pharmacokinetics and safety data with phase I trials

Any new drug being investigated in a clinical trial traditionally undergoes phase I safety assessment prior to phase II efficacy studies. This is especially important in a disease such as AH with the potential for changes in drug pharmacodynamics and pharmacokinetics, which potentially impact on drug bioavailability, safety, and drug-drug interactions. For example, the study involving the pan caspase inhibitor emricasan, was terminated early due to poor bioavailability of the drug and concerns relating to serious adverse events (Table 1).

Liver biopsy for patient recruitment

Liver biopsy is a definitive way of diagnosing AH.[4] Recognising liver biopsy's invasive nature, the risk of complications and its poor acceptance by physicians and patients,[5,25] clinical criteria for probable diagnosis of AH have been defined.[4] These criteria are acceptable for recruitment of patients into clinical trials, with liver biopsy only needed if the clinical diagnosis is uncertain.[4]

Conclusion

In summary, the treatment for AH currently remains suboptimal, with corticosteroids the only available pharmacological treatment option with a marginal short-term survival benefit. Clearly, there remains an unmet need for the development of newer safer and more effective therapeutic drugs and the identification of new therapeutic targets for this potentially lethal condition. The enthusiasm of investigators, changes in study designs of ongoing clinical trials, and interest of the NIAAA in sponsoring multiple consortia in the US are encouraging and provide a ray of hope in the development of newer pharmacological therapies for patients with severe AH.

Conflict of interest

The authors declare no conflict of interest relating to this manuscript. Please refer to the accompanying ICMJE disclosure forms for further details.

Authors' contributions

Both the authors wrote the first draft and then reviewed to approve the final draft.

Supplementary data

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