HHS Public Access

Author manuscript

Hepatol Int. Author manuscript; available in PMC 2017 May 31.

Published in final edited form as:

Hepatol Int. 2014 September ; 8(Suppl 2): 475–480. doi:10.1007/s12072-014-9516-x.

New drug targets for alcoholic liver disease

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Abstract

Alcoholic liver disease (ALD) represents a spectrum of disorders, ranging from simple steatosis to severe alcoholic hepatitis and cirrhosis. The severe form of ALD comprises multiple problems in the liver, including inflammation, hepatocellular damage, fibrosis, and impaired liver regeneration, and likely requires combinational therapies. In this review, we discuss recently identified therapeutic targets that inhibit inflammation, ameliorate hepatocyte death, and promote liver repair in ALD, with a focus on our recent studies on the immunosuppressive drug prednisolone and the hepatoprotective cytokine interleukin-22. Clinical trials examining prednisolone plus interleukin-22 therapy for severe alcoholic hepatitis are currently under consideration.

Keywords

Prednisolone; Interleukin-22; Inflammation; Liver; Ethanol

Chronic alcohol consumption is a leading cause of chronic liver disease worldwide and causes a broad spectrum of disorders, ranging from simple steatosis to severe forms of steatohepatitis, fibrosis, and cirrhosis. Although more than 95 % of heavy drinkers develop fatty liver, only 20–40 % of them may progress to steatohepatitis and cirrhosis. Despite extensive research for more than 5 decades, the cellular and molecular mechanisms underlying the progression of alcoholic liver disease (ALD) are not fully understood, and there are no FDA-approved therapies for the treatment of ALD [1]. In this review, we briefly discuss several therapeutic targets for ALD that were recently identified from studies of human ALD samples and animal models, with a focus on our recent studies on the immunosuppressive drug prednisolone and the hepatoprotective cytokine interleukin-22 in animal models.

Inflammatory targets in ALD

Alcohol is a hepatotoxin that is primarily metabolized by hepatocytes, followed by generation of oxidative stress, which leads to hepatocellular damage and inflammation (e.g., neutrophil infiltration) [1, 2]; therefore, inflammation is likely not the primary source of

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Compliance with ethical requirements and Conflict of interest Mingjiang Xu, Binxia Chang, Stephanie Mathews, and Bin Gao have nothing to disclose. This article does not contain any studies with human or animal subjects.

hepatocellular damage in alcoholic hepatitis (AH). Inflammation may occur as a result of hepatocyte necrosis, which may not only further exacerbate liver damage but also play an important role in promoting tissue repair and the healing process [1, 2]. Despite its obscure roles in the pathogenesis of ALD, inflammation has been actively investigated as a therapeutic target for the treatment of AH [2]. For example, the immunosuppressive drug prednisolone has been used for the treatment of AH for more than 5 decades, but the results have been mixed. In addition, several novel therapeutic targets, which may play important roles in controlling liver inflammation, have been recently identified from the analyses of human AH liver tissues and animal models of alcoholic liver injury, and they are briefly discussed in this article. Many of these targets are currently listed in the clinical trials registered at ClinicalTrials.gov and summarized in Table 1.

Steroids

Because of their broad anti-inflammatory effects, synthetic glucocorticoids such as prednisolone have been used for the treatment of AH for many years, but the results have been controversial [3–7]. In addition, steroid treatment for a variety of neutrophil-mediated disorders (e.g., asthma, septic shock) has been disappointing and even detrimental, which is, at least in part, mediated by promoting neutrophil survival [8–10]. This may also contribute to the ineffectiveness of steroid therapy in AH, a disease characterized by hepatocyte necrosis and infiltration of neutrophils [3]. However, steroid therapy may preserve some beneficial effects in tempering the systemic inflammatory responses and improving short-term survival in patients with severe AH. Interestingly, autoimmune responses have been observed in some patients with AH [11]. If these responses are the primary source of liver injury in AH, steroid therapy may be effective. There is an urgent need to identify the main mechanisms that contribute to hepatocellular damage in AH, which may help us to generate a more effective strategy for using steroids to treat these patients.

Despite the controversial reports, it is now generally accepted that prednisolone treatment reduces short-term mortality in patients with severe AH, but has no beneficial effects on long-term survival rates [3–7]. Prednisolone therapy is recommended for the treatment of severe AH by the AASLD and EASL guidelines for ALD. Surprisingly, although steroids have been used to treat inflammatory liver diseases for more than 5 decades [12], how prednisolone affects liver disease pathogenesis and progression has not been explored. Recently, we have demonstrated that prednisolone treatment effectively prevents T/NKT cell-mediated hepatitis induced by injection of Concanavalin A or α-galactosylceramide, but exacerbates liver injury induced by chronic-binge ethanol feeding, injection of hepatotoxin carbon tetrachloride, or by ethanol plus carbon tetrachloride [13]. The beneficial effect of prednisolone on T/NKT cell-mediated hepatitis is mediated by attenuating the production of proinflammatory cytokines [13]. Although it also inhibits proinflammatory responses in ethanol- or hepatotoxin-induced liver injury in mice, prednisolone administration markedly reduces neutrophil/macrophage-mediated phagocytosis (e.g., removal of dead hepatocytes) and inhibits liver regeneration, which likely contribute to the detrimental effects of prednisolone in these animal models, and likely also contribute to the ineffectiveness of prednisolone therapy in many AH patients [13].

Chemokines, chemokine receptors, and adhesion molecules

By using microarray analyses of human AH liver tissue samples, Dr. Bataller's group has identified a variety of chemokines, chemokine receptors, and adhesion molecules that are upregulated in livers from patients with AH [14, 15]. For example, hepatic expression of the CXC family of chemokines, including IL-8 and Gro-α, is elevated and correlates with mortality, neutrophil infiltration, and the degree of portal hypertension in patients with AH [14, 15]. These CXC chemokines may play an important role in promoting neutrophil infiltration in AH. Thus, reagents that target CXC chemokines and reduce neutrophil infiltration might be used as therapeutics for AH.

Our recent studies from a mouse model of chronic plus binge ethanol demonstrated that hepatic E-selectin expression was upregulated ten-fold, whereas expression of other neutrophil infiltration-related adhesion molecules (e.g., P-selectin, ICAM-1, VCAM-1) was slightly up- or downregulated [16]. Genetic ablation of E-selectin ameliorated chronic-binge ethanol-induced hepatic neutrophil infiltration and liver injury (elevation of transaminases) but did not affect steatosis [16]. Although our findings suggest an important role of E-selectin in neutrophil infiltration and liver injury in the chronic-binge feeding model, the roles of E-selectin in human ALD remain obscure. By using real-time PCR analyses, we found that hepatic expression of E-selectin was significantly upregulated in human alcoholic fatty livers, but not in alcoholic cirrhotic livers, compared to normal livers [16]. This is consistent with previous findings that hepatic E-selectin immunostaining was generally weak in ALD patients with severe AH or cirrhosis [17]. Collectively, E-selectin may play a role in promoting neutrophil infiltration and liver injury in the early stages of ALD but not in the severe form of ALD.

Genetic ablation of monocyte chemoattractant protein-1 (MCP-1) inhibits expression of proinflammatory cytokines and the genes related to fatty acid oxidation in a mouse model of alcoholic liver injury [18], suggesting that MCP-1 antagonist might be developed for the treatment of AH.

Osteopontin

Osteopontin is an extracellular matrix protein that has been implicated in the pathogenesis of liver injury, inflammation, and fibrogenesis [19, 20]. Hepatic expression of osteopontin is markedly elevated and correlates with neutrophil infiltration and severity of diseases in AH patients [21]. Disruption of the osteopontin gene reduced liver injury and inflammation in a mouse model of chronic plus binge ethanol feeding [21]; however, a recent study revealed that osteopontin knockout mice had comparable or slightly enhanced liver injury after chronic ethanol feeding or chronic plus binge ethanol feeding [22]. Additionally, genetic ablation of the osteopontin gene did not affect liver injury in a severe form of alcoholic liver injury induced by intragastric ethanol feeding plus multiple binges [23]. This suggests that osteopontin many play a role in the pathogenesis of ALD in the early stages, but not in severe form of ALD and that blockade of osteopontin might not be effective for the treatment of severe ALD.

Gut microbiota, LPS, and TNF pathways

Studies from animal models suggest that the gut microbiota, LPS, and TNF pathways contribute to the inflammation and pathogenesis in the early stages of chronic ALD in mice [24–26]. Therefore, probiotics and antagonists for LPS and TNF pathways have been proposed as therapeutic agents for the treatment of chronic ALD [24–26]; however, the roles of gut microbiota, LPS, and TNF in the pathogenesis of acute AH have not been identified. Despite their obscure roles, several drugs that target gut microbiota, LPS, and TNF are listed in current and upcoming clinical trials for the treatment of acute AH (Table 1).

Complement

Emerging evidence suggests that activation of complement plays an important role in initiating early ALD in mice [27]. Blockage of complement activation may be beneficial for patients with ALD.

Interleukin-1 inhibitors

A recent study revealed an important role for IL-1 signaling in ethanol-induced liver injury in mice, suggesting the therapeutic potential of IL-1 inhibitors for the treatment of ALD [28, 29]. Several IL-1 inhibitors have been approved for the treatment of several types of inflammatory disease because of their good safety profiles and low tendency to adverse side effects, and some of them are also listed in current and upcoming clinical trials for the treatment of AH (Table 1).

Hepatoprotective targets in AH

ALD is often associated not only with hepatocellular damage but also with impairment of liver regeneration, as evidenced by accumulation of liver progenitor cells [30, 31]. Thus, it may be important to include hepatoprotective agents for ALD therapy to protect against hepatocellular damage and promote liver regeneration. We have previously demonstrated that IL-6 treatment ameliorates alcoholic fatty liver and injury via the activation of hepatic STAT3 [32]. However, the therapeutic application of IL-6 for ALD is limited by the many potential side effects of IL-6, which result from the ubiquitous expression of the IL-6 receptor. Our recent studies demonstrated that IL-22, which induces STAT3 activation in hepatocytes similar to IL-6, has many beneficial effects in the liver but may have minimal side effects because of the restricted expression of IL-22 receptor, suggesting that IL-22 may have therapeutic potential for the treatment of ALD. In addition, cell death inhibitors could be developed as hepatoprotective drugs for ALD therapy.

IL-22

IL-22 is mainly produced by activated Th17, γδT cells, and Th22 cells. IL-22 receptor is restricted to epithelial cells and is not expressed by immune cells; therefore, IL-22 does not directly affect immune cells; instead, it targets epithelial cells including hepatocytes in the liver, playing an important role in protecting against epithelial cell damage and promoting epithelial cell repair. We and others have previously demonstrated that IL-22 treatment may have many beneficial effects in the liver, such as ameliorating hepatocellular damage, promoting liver regeneration, and alleviating liver fibrosis (Fig. 1) [33–36]. In addition,

IL-22 treatment may effectively inhibit bacterial infection [37] and ameliorate kidney injury [38], two deleterious conditions that are often associated with severe AH and contribute to the death of patients. More importantly, IL-22 therapy may have minimal side effects because of the restricted expression of IL-22 receptor on epithelial cells (e.g., hepatocytes and liver progenitor cells) and hepatic stellate cells (HSC). Although IL-22 has been shown to promote liver cancer cell proliferation and survival [35, 39], the fact that IL-22 transgenic mice with high levels of IL-22 did not spontaneously develop liver cancer suggests that IL-22 itself does not initiate liver cancer development [39]. Thus, IL-22 therapy should be safe for AH patients without liver cancer, used with caution in those with liver cirrhosis, and should not be used for those with liver cancer. A phase I clinical trial examining IL-22 treatment in healthy volunteers was completed by Generon (Shanghai) Corp., Ltd; phase Ib clinical trials examining IL-22 therapy for the treatment of patients with severe AH and acute liver failure caused by other insults are currently under consideration.

Necroptosis inhibitors

Apoptosis has been implicated in the pathogenesis of chronic ALD [40], and caspase inhibitors are listed in current and upcoming clinical trials for the treatment of AH (Table 1). However, a recent study reported that CYP2E1-dependent RIP3 expression plays an important role in inducing hepatocyte necroptosis during ethanol feeding in mice [41]. This suggests that intervention of the necroptotic pathways may be more effective than inhibition of apoptosis for the treatment of ALD.

In summary

During the last 10 years, many inflammatory mediators have been shown to play important roles in inducing liver injury and inflammation in rodent models with mild alcoholic liver injury and to correlate with mortality and prognosis in patients with severe AH [2]. These mediators probably synergistically or additively promote liver inflammation in ALD. Clinical trials are needed to identify the inflammatory mediators that play critical roles in the pathogenesis of ALD in patients and can be used for the treatment of ALD, which will take years to complete. The immunosuppressive drug prednisolone or other steroids will likely continue to be used for the treatment of severe AH despite the controversial reports on their application in these patients. Indeed, prednisolone is currently included as a standard therapy for severe AH in several clinical trials registered at ClinicalTrials.gov (Table 1). The side effects of steroid therapy are related to inhibition of liver regeneration and promotion of bacterial infection, which can be overcome by IL-22 treatment. Thus, clinical trials examining IL-22 plus steroids for the treatment of patients with severe AH are warranted (Fig. 1).

Acknowledgments

The work described here from Dr. Bin Gao’s laboratory was supported by the intramural program of NIAAA, NIH.

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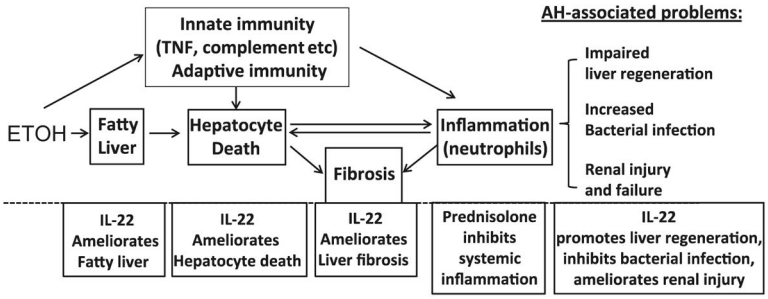

Fig. 1.

Rationale for using IL-22 plus steroids for the treatment of severe AH: severe AH is associated with many problems in the liver plus systemic inflammation, increased bacterial infection, and renal failure. Prednisolone treatment inhibits systemic inflammation but may increase the risk of bacterial infection. IL-22 treatment exerts many beneficial effects in the liver, such as amelioration of fatty liver, hepatocyte death, liver fibrosis, and promotion of liver regeneration. IL-22 treatment also inhibits bacterial infection and ameliorates renal injury (two deleterious conditions that are often associated with severe AH)

Table 1

Ongoing clinical trials using drugs for the treatment of AH registered at ClinicalTrials.gov

AH target(s)	Drug type(s)	Trial design	Title/trial number
Gut microbiota	Probiotics	Probiotic *Lactobacillus rhamnosus* GG versus placebo	Novel therapies in moderately severe acute AH (NTAH-moderate)/ NCT01922895
IL-1 and inflammation	IL-1 blocker (rilonacept) immunosuppressive agent (mycophenolate)	Rilonacept + prednisolone or mycophenolate + prednisolone versus prednisolone	A safety and efficacy study of mycophenolate mofetil and rilonacept in patients with AH/ NCT01903798
TNF and inflammation	Immunosuppressive agent and a nonspecific TNF inhibitor (pentoxifylline)	Prednisolone versus pentoxifylline	Short-term survival in patients with severe AH treated with steroid versus pentoxifylline/ NCT01455337
IL-1 TNF Gut barrier	IL-1 blocker (anakinra) TNF inhibitor (pentoxifylline), nutritional supplement (zinc sulfate)	Anakinra + pentoxifylline + zinc sulfate versus methylprednisolone	Efficacy study of anakinra, pentoxifylline, and zinc compared to methylprednisolone in severe acute AH/NCT01809132
LPS	Hyperimmune bovine colostrum enriched with anti-LPS antibodies	Prednisolone + Imm 124-E versus prednisolone + placebo	Safety and efficacy of IMM 124-E for patients with severe AH (TREAT)/NCT01968382
Cell death	Caspase inhibitor (emricasan, also known as IDN-6556 and PF-03491390)	IDN-6556 versus placebo	Study of IDN-6556 in patients with severe AH and contradictions to steroid therapy/NCT01912404
			Pharmacokinetic and pharmacodynamic study of IDN-6556 in ACLF/NCTO1937130
Bone marrow	Granulocyte colony stimulating factor (G-CSF); or G-CSF + erythropoietin (EPO)	G-CSF versus placebo; or G-CSF + EPO versus placebo	Efficacy of G-CSF in the management of steroid non-responsive severe AH/ NCT01820208
			G-CSF in acute liver failure and AH/NCT01341951
			Efficacy of G-CSF and erythropoietin for patients with acute-on-chronic liver failure/ NCT01383460