Glucocorticoids in Alcoholic Hepatitis

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Alcoholic hepatitis is a major health and economic burden worldwide. Glucocorticoids (GCs) are the only first-line drugs recommended to treat severe alcoholic hepatitis (sAH), with limited short-term efficacy and significant side effects.

glucocorticoid receptor glucocorticoid resistance mineralocorticoid receptor alcoholic hepatitis

1. Introduction

Alcohol is the most consumed xenobiotic worldwide. Alcoholic liver disease (ALD) is among the most common liver diseases, and more than 2 million people had alcohol-associated cirrhosis in the US in 2017 [1]. There was a greater than three-fold increase in deaths from alcoholic cirrhosis in the United States between 1999 and 2019 [2]. The consumption of alcohols and alcohol-related deaths increased significantly during the COVID-19 pandemic [3]. ALD is the leading cause of alcohol-related deaths, with 29, 504 deaths due to ALD in the US in 2020 [3]. Severe alcoholic hepatitis (sAH) is defined as a modified Maddrey's discriminant function (MDF) score greater than or equal to 32 or a Model for End-Stage Liver Disease (MELD) score greater than 20 [1]. sAH is associated with the development of acute-on-chronic liver failure and multiorgan failure [4]. Marked steatohepatitis, jaundice, cholestatic liver injury, and impaired liver regeneration are hallmarks of sAH, which causes high mortality [5][6]. Moreover, many patients with AH may progress to alcoholic cirrhosis and liver cancer. Patients with alcoholic cirrhosis incur nearly double the per-person health care costs compared to those with non-alcoholic cirrhosis [7]. An analysis of a 2007–2014 national inpatient sample shows that among 159,973 ALD hospitalizations in the USA, 83.7% and 18.4% had a primary diagnosis of alcohol-associated cirrhosis and AH, respectively [8]. Native Americans (OR = 1.88) and Asian/Pacific Islanders (OR = 2.02) with AH had significantly higher in-hospital mortality compared with non-Hispanic whites [8]. In a health care claims analysis of over 15,000 commercially insured adults hospitalized with AH between 2006 and 2013 in the USA, the total costs were nearly USD 145,000 per patient, and about two-thirds of hospitalized sAH patients died within 5 years after the initial hospitalization [9]. In 2016, AH-related and alcoholic-cirrhosis-related hospitalizations accounted for USD 1.15 billion and USD 7.67 billion in the USA, respectively [10]. Therefore, ALD, and sAH in particular, is a major health and economic burden worldwide [1]. Currently, there is no FDA-approved drug treatment specifically for sAH. Glucocorticoids (GCs) have been widely used in the treatment of sAH for decades due to their putative anti-inflammatory and liver-protective effects, with limited short-term benefits but no long-term effects [11][12]. Currently, GCs (prednisolone 40 mg/day or methylprednisolone 32 mg/day) are the only first-line drugs recommended in the US and Europe for sAH [6][13]. sAH patients with MDF score > 32

and with no signs of infection, pancreatitis, gastrointestinal bleed, or acute renal failure are eligible to receive GCs [6]. Patients with an improvement in the Lille score (<0.45 on day 7), an indicator of liver and kidney functions, are considered responders to GCs, and their treatment will continue. Patients without an improvement in the Lille score (>0.45 on day 7) are considered non-responders to GCs, and the GC therapy will be stopped [6]. A recent study indicates that the Lille score at day 4 can be used to predict the response to GC therapy in patients with sAH [14]. Although there have been various recent clinical studies regarding GC therapy of sAH, no review dedicated to GC therapy of sAH has been published in the last 5 years.

2. Efficacy of GCs in sAH Therapy

There have been various clinical studies regarding the efficacy of GCs in the treatment of sAH, with variable results and conclusions. In a multicenter, double-blind, randomized trial to evaluate the effect of treatment of sAH with prednisolone or pentoxifylline (a phosphodiesterase inhibitor and antioxidant), prednisolone tended to reduce the 28-day mortality with an odd ratio of 0.72 (95% CI, 0.52 to 1.01; p = 0.06), whereas pentoxifylline was ineffective [15]. In a retrospective, international multicenter cohort study across four continents published in 2021, corticosteroid use significantly decreased the 30-day mortality by 41%, with no difference in the type of corticosteroids used (prednisone, prednisolone, or methylprednisolone) [16]. Corticosteroid had no benefit in sAH patients with MELD score > 51 [16]. In a meta-analysis of individual patient data from 11 randomized controlled trials comparing corticosteroids, pentoxifylline, or their combination in patients with sAH, corticosteroid treatment significantly decreased the risk of death within 28 days compared with controls or pentoxifylline; however, GC's survival benefits disappeared after 6 months of treatment [17]. It is noteworthy that the short- and medium-term outcome (before 6 months) is mainly determined by the severity of liver injury at baseline and the early improvement in hepatic function, whereas the long-term outcome (after 6 months) can be greatly influenced by alcohol consumption [18]. In contrast to the reported short-term benefits, a recent meta-analysis of 16 randomized clinical trials with an overall high risk of bias found no significant benefits or harms of GC treatments in sAH patients [19]. The combination of GCs with other therapies, such as pentoxifylline, S-adenosil-L-methionine, or N-acetylcysteine, did not further reduce the mortality in sAH [20][21][22]. However, dual therapy with GC and pentoxifylline significantly decreased the incidences of hepatorenal syndrome or acute kidney injury and the infection risk [21], and dual therapy with GC and S-adenosil-L-methionine significantly increased the GC therapy response and decreased the occurrence of the hepatorenal syndrome [22]. The summary of recent studies of biomarkers of GC responsiveness/non-responsiveness in sAH patients suggests that only select sAH patients with moderately severe AH may benefit from GC therapy.

3. GC Resistance/Non-Responsiveness (GCR) as a Limiting Factor in sAH Therapy

Unfortunately, GCR is common in sAH and sepsis [23][24]. Both sAH and sepsis feature hyperinflammation and multiorgan dysfunction. In fact, sepsis is a leading cause of death in sAH [25][26]. An increased risk of infections by systemic GC treatment is a major side effect that may offset its benefit in AH [15][27][28][29][30]. In contrast, the hepatic

protein levels of GR decrease in patients with sepsis, and hepatic GR deficiency worsens liver failure and mortality in mice with sepsis due to hyperinflammation and heightened cholestatic liver injury [31]. Neutrophil dysfunction plays a key role in liver injury and increased infection in AH [32]. In particular, neutrophils interact with cholangiocytes to cause cholestatic changes in AH [33], and neutrophils produce reactive oxygen species to aggravate AH [34]. The large Steroids or Pentoxifylline for Alcoholic Hepatitis (STOPAH) study discovered that the baseline inflammatory biomarker neutrophil-to-lymphocyte ratio (NLR) predicts GC responsiveness in sAH; prednisolone increases the 90-day survival if NLR is 5–8 but increases the risk of day 7 infection and AKI if NLR > 8 [35]. A comparative clinical study of 246 sAH patients indicates that the probability of infection after GCs is drastically lower in GC responders (Lille score < 0.45) than non-responders [30]. Nonresponse to GCs is the key factor in the development of infection and prediction of survival in sAH patients [30]. sAH patients who are resistant to GR-mediated anti-inflammatory and liver-protective effects will have an elevated risk of the prednisolone-MR-mediated side effects, such as AKI [35]. Additionally, high blood levels of keratin-18 fragments, generated by caspase cleavage during apoptosis [36], strongly predict good GC response in sAH patients [37]. In sAH patients, the presence of bridging liver fibrosis is the strongest negative prognostic marker, whereas marked neutrophil infiltration is associated with more favorable outcomes [38]. In this regard, high neutrophil infiltration is associated with a more acute liver injury but less severe fibrosis/cirrhosis in sAH patients [34]. Likewise, the blood levels of keratin-18 fragments negatively correlate with liver fibrosis in sAH patients [37]. A high NLR of 5–8 indicates marked neutrophilia and hepatic infiltration of neutrophils in sAH patients. In contrast, an NLR > 8 will indicate an uncontrolled severe inflammation and cholestasis that likely cause GCR. Additionally, sAH patients with elevated blood ferritin, an indicator of iron overload and cirrhosis [39], do not respond well to GC therapy [40]. A recent histological study of 225 AH patients shows that bridging fibrosis or cirrhosis is present in 81.8% of AH patients [41]. Thus, as blood biomarkers of good GC responsiveness in sAH, high keratin-18 fragments, low ferritin, and NLR of 5–8 will indicate acute severe, but still controllable, inflammation and apoptosis without prominent fibrosis/cirrhosis and GCR, which is consistent with the known potent anti-inflammatory and anti-apoptotic effects of GC/GR on the liver [42][43].

In addition to blood biomarkers, blood transcriptomics and urinary metabolomics have been studied for GC responsiveness in sAH patients. RNA-sequencing and flow-cytometry analyses of peripheral blood mononuclear cells of sAH patients show that GC non-responders have higher baseline levels of CD4 and CD8 T cells and NK cells, and their blood transcriptomes are not altered by GC therapy, indicating a GC resistance [44]. Additionally, a urine metabolomics study in Indian sAH patients shows that nine urinary metabolites linked to mitochondrial functions significantly discriminate GC non-responders, with markedly elevated baseline urinary acetyl-L-carnitine being the most predictive for GC non-responders and non-survivors [45]. An increase in urinary acylcarnitine excretion is associated with L-carnitine deficiency in renal and metabolic diseases [46]. Unfortunately, the blood levels of carnitine were not determined in that study [45]. L-carnitine is required for normal mitochondrial β oxidation of fatty acids, and L-carnitine is a “nutritional modulator” of the GR by acting as a GR-agonist-like compound [47]. Interestingly, the baseline hepatic transcriptome correlates with urinary acylcarnitines in these sAH patients [45]. The association of L-carnitine disorder with sAH severity and GCR warrants further investigation.

4. Mechanisms of GR Deficiency and GCR in sAH

Although short-term alcohol exposure may increase GR responsiveness, several distinct mechanisms ultimately lead to decreased GR responsiveness in sAH. The recent study found that GR was strongly activated by binge alcohol in mouse liver to protect against liver dysfunction and injury [48]. Ethanol treatment has been shown to induce the GR-target gene GILZ in the cultured human lung epithelial cells via increasing nuclear translocation of GR [49]. Thus, hepatic GR may be activated by ethanol or its metabolites to protect against steatohepatitis in the early stage of AH. In contrast, hepatic GR signaling is markedly impaired in sAH patients; however, the underlying mechanism of the defects of GR signaling in sAH remains poorly understood. There are many (more than 100) GR mutations in the general population that may contribute to the intrinsic GCR [50]. The common GR 9β SNP rs6198, which causes stabilization and increased translation of the GRβ mRNA to decrease GC response, is associated with poor efficacy of GC therapy in patients with childhood acute lymphoblastic leukemia [51]. Additionally, the common GR polymorphism rs41423247 (BclI) located in the intron2-3 with GC hypersensitivity is associated with better responses to GC's protective effects on postoperative posttraumatic stress disorder symptoms in cardiac surgery patients and inflammatory bowel disease [52][53]. So far, there are no published pharmacogenetic studies on the effects of various mutations/SNPs of GR on the GC responsiveness in sAH patients. The putative inhibition of HSD11β1 by the accumulated BAs will hinder the activation of the endogenous GCs, resulting in impaired hepatic GR signaling in sAH. Interestingly, Indian, but not French, sAH patients who were non-responsive to GC therapy had decreased hepatic GR proteins [54]. Thus, the decrease in hepatic GR proteins is an important mechanism of acquired GCR; however, other mechanisms of GCR also exist. sAH patients are highly susceptible to sepsis, and sepsis is a leading cause of death in sAH [25][26]. A recent study indicates that decreases in the DNA binding of GR play a key role in global GCR in sepsis [55]. Combined GCR and hyperlactatemia due to defective gluconeogenesis contributes to immunodeficiency, hyperinflammation, and lethal shock in sepsis [55]. Ethanol markedly inhibits gluconeogenesis from lactate due to decreased free NAD+ during the oxidation of ethanol and the resultant decreases in the concentration of pyruvate and the rate of pyruvate carboxylase reaction [56]. A prominent feature of alcohol abuse is the disruption of the intestinal barrier, dysbiosis, and increase in circulating endotoxins [57]. The increase in circulating toxins, specifically lipopolysaccharide (LPS), plays a vital role in potentiating ethanol hepatotoxicity and/or GCR in sAH and sepsis [55][58][59]. sAH patients with high blood levels of LPS do not respond to GC therapy [59]. LPS stimulates the release of TNF from Kupffer cells, and TNF causes GCR in hepatocytes [60]. Therefore, increases in circulating LPS and TNF and decreases in hepatic HSD11β1 activity, GR proteins, and DNA binding of GR likely play major roles in the markedly impaired GR signaling and GCR in sAH. The combination of GCR and inhibition of gluconeogenesis from lactate by ethanol may help explain sepsis as a leading cause of death in sAH patients [25][26].

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