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Novel intervention for alcohol-associated liver disease

Novel intervention for ALD

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Abstract

An article by Koizumi A and colleagues clarified that elafibranor, a dual peroxisome proliferator activated receptor α/δ (PPAR α/δ) agonist, reduced inflammation and fibrosis in alcohol-associated liver disease (ALD). This editorial aims to discuss the findings presented in the article. ALD is a global health problem, and no effective drugs had been approved by the Food and Drug Administration (FDA) to cure it. Thus, finding targeted therapies is of great urgency. Herein, we focus on the pathogenesis of ALD and the role of PPAR α/δ in its development. Consistent with the conclusion of their article, we think that elafibranor may be a promising therapeutic option for ALD, due to its pivotal involvement in the pathogenesis of the disease. However, its treatment dose, timing, and side effects need to be further investigated in future studies.

Key Words: Alcohol-associated liver disease; Elafibranor; Peroxisome proliferator activated receptor α/δ ; Therapy; Pathogenesis

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Core Tip: Alcohol-associated liver disease (ALD) remains a significant global health challenge. The peroxisome proliferator-activated receptors α and δ (PPAR α/δ) play a crucial role in the pathogenesis of ALD. Elafibranor, a dual PPAR α/δ activator, shows promise as a potential therapeutic agent for ALD.

INTRODUCTION

Alcohol-associated liver disease (ALD) represents a global health concern, accounting for about 47% of liver disease-related deaths worldwide[1]. ALD is caused by excessive alcohol consumption. Definitions of heavy drinking is established by National Institute on Alcohol Abuse and Alcoholism (NIAAA) and Centers for Disease Control and Prevention (CDC), while criteria for low-risk drinking is made by World Health

Organization (WHO). As detailed in Table 1, for women, consumption exceeding 56 g of alcohol per day or 112 g per week is considered heavy drinking, while less than 20 g per day and 140 g per week is categorized as low-risk. For men, heavy drinking is defined as more than 70 g per day or 210 g per week, with low-risk thresholds set at less than 40 g per day and 280 g per week.

Alcohol-associated liver disease includes a spectrum of conditions ranging from simple steatosis to steatohepatitis and finally to cirrhosis. In some cases, this progression culminates in hepatocellular carcinoma. Although it has severe public health implications, there are currently no therapies approved by the Food and Drug Administration (FDA) for ALD treatment[2]. Consequently, it is crucial to investigate and develop therapies targeting the underlying mechanisms of ALD. The study “Effects of elafibranor on liver fibrosis and intestinal barrier function in a mouse alcoholic liver disease model” by Koizumi A *et al.* offers valuable insights for the development of effective treatment options for ALD[3].

PATHOGENESIS OF ALCOHOL-ASSOCIATED LIVER DISEASE

Potential pathogenesis of alcohol-associated liver disease is diverse[4], as depicted in Figure 1. Hepatocyte death and regeneration are key factors in the progression of ALD[5]. Programmed cell death mechanisms include apoptosis, pyroptosis, necroptosis, autophagy and ferroptosis[6, 7], all of which contribute to the disease process. Oxidative and endoplasmic reticulum stress driven by ethanol metabolism can trigger these cell death pathways in ALD.

Inflammatory response is crucial to the development of ALD. A complex interplay of immune cells and factors drive the inflammation associated with ALD. Macrophages and neutrophils significantly exacerbate ALD by producing inflammatory mediators and reactive oxygen species[8]. T cells are implicated in a profibrotic capacity[9]. And B cells promote the deposition of antibody and the activation of complement, which contribute to liver damage[10]. Elevated levels of cytokines such as TNF- α , IL-1, IL-6, IL-10, IL-22, and TGF- β have been observed in ALD patients, exerting both

protective and damaging effects on the disease[11]. Chemokines like CXCL8 and CCL20 play a critical role in attracting inflammatory cells to the liver, thus amplifying hepatic inflammation and fibrosis[12].

The gut-liver axis also plays a role in ALD. Chronic alcohol consumption increases gut permeability by downregulating junction proteins[13]. And then microbes were translocated into the bloodstream. Alcohol also affects intestinal flora imbalance. It leads to a decrease in microbial diversity, an increase in pathogenic bacteria such as *Candida*, and a reduction in beneficial bacteria. These would affect the production of virulence factors such as cytolysin, and further affecting the progression of ALD[14].

Long-term drinking can seriously damage adipose tissue function, resulting in metabolic dysregulation, thereby promoting the development of ALD[15]. Alcohol stimulates lipolysis in adipose tissue, leading to an increase in circulating free fatty acids. These acids play a crucial role in the development of hepatic steatosis and further trigger inflammatory pathways[16]. Moreover, long-term drinking elevates the secretion of adipose-derived hormones such as visfatin and leptin, which enhance fibrotic and inflammatory processes within the liver[15].

Other potential pathogenesis, such as mitochondrial functionality, also plays a role. High-risk drinking negatively affects mitochondrial regeneration, and escalates oxidative stress, ultimately resulting in cell death[17].

INVOLVEMENT OF PPAR α / δ IN ALCOHOL-ASSOCIATED LIVER DISEASE PATHOGENESIS

PPAR α , a ligand-activated transcription factor, is widely present in organs such as the liver, heart and adipose tissue[18]. It can regulate glucolipid metabolism, inflammation responses and cell death. PPAR α modulates β -oxidation, lipid transport, as well as bile acid metabolism[19]. These metabolism activities are vital to ALD development. Loss of PPAR α is linked to severe hepatic steatosis[20]. Regarding inflammation, another critical pathogenesis of ALD, PPAR α mainly acts through trans-inhibition, that is, antagonizing regulatory factors such as AP-1, and STAT, thereby inhibiting the

expression of pro-inflammatory genes[21]. Moreover, PPAR α has been reported to induce autophagy[22], which also influences ALD progression. In addition, PPAR α activation can reduce the levels of 4-Hydroxynonenal (4-HNE), a lipid peroxide that contributes to ALD by inhibiting the activation of NF- κ B [23].

Similar to PPAR α , PPAR δ is expressed and functions in multiple tissues. In the liver, it mitigates liver fibrosis by interfering the transformation of profibrogenic myofibroblasts[24]. Notably, PPAR δ expression is found to be lower in patients with severe hepatic steatosis[25], suggesting its potential role in protecting against steatosis. And intestinal PPAR δ can enhance mucosal defense capabilities and helps prevent dysbiosis[26].

Elafibranor, bezafibrate, and pemafibrate are all PPAR agonists[27]. Both bezafibrate and pemafibrate are PPAR α agonists used to treat hypertriglyceridemia. However, pemafibrate is a more selective PPAR α agonist, offering greater specificity and fewer side effects compared to bezafibrate. Elafibranor, a dual agonist of PPAR α/δ , exhibits superior efficacy in regulating glucose and lipid metabolism, as well as in reducing inflammation and fibrosis. Consequently, elafibranor shows greater potential in the treatment of alcoholic fatty liver disease. Although still an experimental drug[28], elafibranor's promising effects justify further investigation.

ALCOHOL CESSATION THERAPIES

It is well established that abstaining from alcohol can significantly benefit patients with ALD. However, these patients often struggle to quit drinking on their own. Alcohol cessation medications, such as disulfiram, naltrexone, and acamprosate, can be helpful in supporting their efforts. These medications, however, are primarily approved for use in alcohol use disorder (AUD)[29], and ALD patients do not always meet the criteria for AUD. Additionally, these medications can cause adverse effects like liver and kidney function damage. And unlike the PPAR activator elafibranor, these medications do not have the capacity to reverse the inflammation and fibrosis that have already developed in the liver.

FUTURE OF ELAFIBRANOR

Elafibranor is a dual agonist of PPAR α and PPAR δ . It has been found to have therapeutic effects on primary biliary cholangitis and non-alcoholic fatty liver disease[30, 31], which share some pathogenic mechanisms with ALD. However, its efficacy in treating ALD has not yet been clarified. Given the beneficial roles of both PPAR α and PPAR δ in ALD, and the ability of elafibranor to activate these receptors, it is conceivable that elafibranor could significantly ameliorate ALD. Thus, investigating elafibranor's impact on ALD presents an interesting area of research. The study conducted by Koizumi A *et al.* has provided evidence that elafibranor effectively reduces liver steatosis, inflammation, and fibrosis in ALD.

CONCLUSION

ALD is a common disease with a poor prognosis. Finding targeted therapies for the disease can improve patient outcomes and their life quality. According to the research conducted by Koizumi A *et al.*, elafibranor represents a promising therapeutic candidate. However, further investigation into elafibranor's application in ALD treatment is needed. This includes determining optimal therapeutic dosages and evaluating potential side effects specific to ALD.

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