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LETTER TO THE EDITOR

Dual peroxisome proliferator-activated receptor α/δ agonists: Hope for the treatment of alcohol-associated liver disease?

Xin-Yang Zhang, Qin-Jun-Jie Chen, Feng Zhu, Min Li, Dan Shang

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Abstract

In this letter, we review the article "Effects of elafibranor on liver fibrosis and gut barrier function in a mouse model of alcohol-associated liver disease". We focus specifically on the detrimental effects of alcohol-associated liver disease (ALD) on human health. Given its insidious onset and increasing incidence, increasing awareness of ALD can contribute to reducing the prevalence of liver diseases. ALD comprises a spectrum of several different disorders, including liver steatosis, steatohepatitis, fibrosis, cirrhosis, and hepatocellular carcinoma. The pathogenesis of ALD is exceedingly complex. Previous studies have shown that peroxisome proliferator-activated receptors (PPARs) regulate lipid metabolism, glucose homeostasis and inflammatory responses within the organism. Additionally, their dysfunction is a major contributor to the progression of ALD. Elafibranor is an oral, dual PPARα and δ agonist. The effectiveness of elafibranor in the treatment of ALD remains unclear. In this letter, we emphasize the harm of ALD and the burden it places on society. Furthermore, we summarize the clinical management of all stages of ALD and present new insights into its pathogenesis and potential therapeutic targets. Additionally, we discuss the mechanisms of action of PPARα and δ agonists, the significance of their antifibrotic effects on ALD and future research directions.

Key Words: Alcohol-associated liver disease; Fibrosis; Antifibrotic effect; Elafibranor; Peroxisome proliferator-activated receptor

Core Tip: Alcohol-associated liver disease (ALD) is a common disease with an annually increasing incidence. It is the primary cause of cirrhosis and mortality due to hepatopathy in patients from many regions worldwide. Chronic liver damage resulting from prolonged excessive alcohol consumption can lead to liver fibrosis, which may progress to cirrhosis and hepatocellular carcinoma. Strengthening awareness of the risks associated with ALD, abstaining from alcohol, and implementing early intervention are fundamental to the management of ALD.

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TO THE EDITOR

In the recent issue of the *World Journal of Gastroenterology*, Koizumi *et al*[1] published an interesting article "Effects of elafibranor on liver fibrosis and gut barrier function in a mouse model of alcohol-associated liver disease". This research elucidated the antifibrotic effect of elafibranor (EFN), a dual peroxisome proliferator-activated receptor (PPAR) α/δ agonist, in a mouse model of alcohol-associated liver disease (ALD). Preventing, alleviating, and even reversing liver fibrosis have long been popular research topics in the field of chronic liver diseases. However, previous studies have focused predominantly on viral liver disease and metabolic dysfunction-associated steatotic liver disease (MASLD), with relatively less attention given to ALD. The research conducted by Koizumi *et al*[1] is highly recommended for reading because of its significant contributions to public awareness of the harms of ALD and to the field of antifibrotic therapy for ALD. Currently, 43% of the global population engages in alcohol consumption, and 5.1% suffers from alcohol use disorder (AUD)[2]. Chronic excessive alcohol consumption increases the mortality rate associated with liver disease by 260-fold[3], and approximately 35% of individuals with AUD are at risk of developing different stages of ALD[4]. ALD is a leading cause of liver-related morbidity and mortality. ALD encompasses a spectrum of diseases ranging from asymptomatic hepatic steatosis to steatohepatitis with or without fibrosis, advanced cirrhosis, and even hepatocellular carcinoma (HCC)[5]. Although alcohol consumption is responsible for 48% of all cirrhosis-related deaths and 10% of all liver cancers[6] and ALD is a prevalent condition with an annually increasing incidence, its insidious onset often leads to a delayed diagnosis, which consequently results in the inability to receive timely treatment. Moreover, public awareness and understanding of ALD are still inadequate. This letter seeks to increase the awareness of ALD by health care professionals and to provide novel insights into its clinical management.

ALCOHOL METABOLISM

Alcohol consumption disrupts hepatic metabolic homeostasis and is a fundamental cause of ALD. Alcohol is predominantly absorbed into the bloodstream through the small intestine, subsequently reaching the liver *via* the circulatory system. In the liver, it is metabolized within hepatocytes through an oxidative pathway involving alcohol dehydrogenases. Alcohol dehydrogenases oxidize most of the ingested alcohol in the liver, resulting in the formation of the toxic metabolite acetaldehyde[7]. Subsequently, acetaldehyde is swiftly converted into the less toxic acetate by aldehyde dehydrogenases. Acetate is then further metabolized into water and carbon dioxide, which are efficiently eliminated from the body. The toxic metabolite acetaldehyde, along with excess reactive oxygen species generated during this metabolic process, leads to hepatocyte injury. The accumulation of these toxic substances disrupts endoplasmic reticulum homeostasis within hepatocytes, a phenomenon referred to as endoplasmic reticulum stress. This disruption activates the unfolded protein response signaling pathway, which may subsequently induce inflammation and apoptosis[8]. If the hepatocyte response to stress is inadequate, multiple cell death pathways, including apoptosis, necroptosis, pyroptosis, and ferroptosis, are activated. A meta-analysis conducted by Rehm *et al*[9] demonstrated that even minimal levels of alcohol consumption with an increased risk of mortality related to liver cirrhosis. Furthermore, among individuals consuming equivalent amounts of alcohol, women are at a higher risk of developing liver cirrhosis compared to men. Thus, alcohol consumption is entirely detrimental to the liver. Total abstinence from alcohol is the fundamental and indispensable first step in the treatment of ALD and is imperative for all patients.

MANAGEMENT OF ALD

The clinical management of ALD can be broadly divided into two parts, as described below.

Treatment for AUD

AUD is a mental disorder characterized by compulsive alcohol consumption, ranging from mild to severe. Individuals with AUD continue to drink despite being fully aware of its detrimental effects on various aspects of their lives and remain unable to control their behavior[10]. Current treatment strategies for AUD encompass a combination of pharmacological, behavioral, and psychological treatments[11]. However, the options for pharmacological treatments are limited due to the associated potential damage to the liver. The goals of treatment for patients with ALD comorbid AUD are to achieve total abstinence from alcohol and to prevent relapse. In most patients, mild-to-moderate ALD will resolve after alcohol consumption ceases[12]. Even in advanced stages of ALD, including decompensated cirrhosis and severe liver failure, sustaining alcohol abstinence significantly improves patient outcomes[13].

Treatment for liver disease itself

ALD, a heterogeneous disease, often coexists with other liver diseases, including viral liver disease and MASLD. ALD ranges from steatosis to progressive steatohepatitis, with or without fibrosis, to the end-stage liver disease of cirrhosis and its associated complications. The treatment for each stage of ALD primarily focuses on symptomatic treatment and the management of associated complications. Currently, no approved drugs are available for the treatment of ALD. Several clinical trials are underway with the goal of slowing ALD progression and improving patient outcomes. Next, we provide an overview of the characteristics of each stage of ALD, along with the corresponding potential therapeutic targets and clinical trials.

Hepatic steatosis and steatohepatitis: As mentioned previously, alcohol is metabolized mainly in the liver *via* an oxidation pathway. Hepatocyte injury resulting from alcohol metabolism leads to hepatocyte steatosis and even death. Protecting hepatocytes from injury, preventing hepatocyte death and promoting liver regeneration are viewed as potential therapeutic strategies. Granulocyte colony stimulating factor can mobilize hematopoietic stem cells; in severe alcoholic hepatitis (AH), it regulates the inflammatory response by promoting granulopoiesis and aiding in immune cell differentiation, while also promoting liver regeneration. IL-22, the prime anti-inflammatory cytokine, protects the liver and promotes regeneration. An ongoing multicenter clinical trial is investigating the efficacy of IL-22Fc in treating acute and chronic liver failure, including severe AH (CTR20212657)[14]. Total abstinence from alcohol generally results in histological normalization in patients with steatosis. However, chronic excessive alcohol consumption can perpetuate a state of chronic inflammation in the liver, termed alcoholic steatosis hepatitis (ASH), ultimately leading to the development of liver fibrosis. ASH requires substantial attention, given that it progresses to cirrhosis at an annual rate of approximately 10%[15].

AH: AH is a severe form of acute liver inflammation that poses a significant risk of mortality due to acute liver failure and multi-organ dysfunction, with the most severe cases associated with a short-term mortality rate of up to 80%[11]. Currently, corticosteroids are the prime recommended therapeutic approach for AH. Early liver transplantation constitutes a viable therapeutic option for sever AH. Inflammation serves as a pivotal factor in the progression of ALD. Multiple cell types and inflammatory mediators contribute to the inflammatory processes underlying ALD. Therefore, modulating the inflammatory response is a potential therapeutic strategy for mitigating ALD. Given that various immune cells (such as Kupffer cells, neutrophils and natural killer cells) and inflammatory mediators [including tumor necrosis factor-α, toll-like receptor 4 (TLR4), and IL-1β] participate in both liver injury and liver regeneration, a comprehensive treatment approach is needed. This approach should go beyond merely suppressing or promoting inflammatory responses[8]. Excessive alcohol consumption disrupts the gut microbiota and impairs intestinal barrier function, leading to the translocation of large amounts of gut-derived lipopolysaccharides into the liver, which activates TLR4 signaling in hepatic macrophages[16]. Subsequently, the activation of the lipopolysaccharides-TLR4-nuclear factor-κB signaling pathway leads to a proinflammatory response in individuals with ALD. Therefore, TLR4 antagonists are potential therapeutic agents for AH. Hyaluronic acid of 35 kD (HA35) has been shown to inhibit TLR4 signaling pathway in Kupffer cells in ALD mouse models[17].

Hepatic fibrosis and cirrhosis: As ASH progresses, patients face the risk of hepatic fibrosis progressing to cirrhosis and eventually liver cancer. The development of fibrosis affects the quality of life and prognosis of patients with chronic liver disease. Reducing the degree of liver fibrosis is of significant clinical importance, especially in reversing progressive liver fibrosis. In contrast to steatosis, the reduction in fibrosis after abstinence is not uniform; some patients still progress to cirrhosis or liver failure even while maintaining abstinent[18]. Preventing, alleviating, and even reversing liver fibrosis are crucial therapeutic strategies for ALD. In clinical practice, currently, no specific treatments are available for liver fibrosis. Existing medications focus on anti-inflammatory pathways and/or improving lipid metabolism to alleviate liver fibrosis. Given the lack of effective treatments for ALD patients at the liver fibrosis stage, increasing public awareness of the risks associated with ALD and focusing on prevention, beginning with a total abstinence from alcohol, are crucial.

PPAR, a transcription factor of the nuclear receptor superfamily, mediates the transcriptional regulation of various physicological processes, including inflammation, lipid metabolism, atherosclerosis, glucose homeostasis, and energy homeostasis[19,20]. The three isoforms of PPARs, PPARα, PPARδ, and PPARγ, are distributed variably across different tissues[21,22]. Although these PPARs exhibit anti-inflammatory activities, their specific effects on the organism's metabolism differ. Based on these data, various clinical trials of dual/pan PPAR agonists for the treatment of MASLD are

currently ongoing. Presently, two drugs are the most noteworthy for the treatment of liver fibrosis. As previously mentioned, Koizumi *et al*[1] demonstrated that EFN, a dual PPARα/δ agonist, has an antifibrotic effect on ALD model mice; however, further clinical trials are needed to verify whether it has antifibrotic effects on patients with ALD. In past research, despite the EFN trial advancing to phase III, it was terminated in 2020 due to its failure to achieve the primary endpoint of metabolic dysfunction-associated steatohepatitis resolution without worsening of fibrosis. Lanifibranor, a pan PPARα/δ/γ agonist, was initially discovered for its capacity to prevent skin and lung fibrosis; subsequently, it was explored for treating liver fibrosis[23-25]. A large-scale (about 1000 patients) phase III clinical trial assessing the efficacy and safety of lanifibranor in adults with metabolic dysfunction-associated steatohepatitis and fibrosis stages 2-3 (NCT04849728) is currently in progress[26]. The results have not yet been published.

HCC: Around 8%-20% of individuals who engage in chronic heavy drinking will develop alcohol-related cirrhosis, and among these patients, approximately 2% will go on to develop HCC[8]. Compared to patients with HCC from other etiologies, those with alcohol-related HCC are more likely to receive a diagnosis at a more advanced stage[27]. For unresectable HCC, combination immunotherapy has emerged as a new trend. In the absence of contraindications, regimens incorporating immune checkpoint inhibitors should be strongly considered as the preferred first-line treatment; for example, atezolizumab combined with bevacizumab. In the past decade, a growing body of evidence has revealed a link between PPAR signaling and the progression of HCC. As a result, PPAR modulators may become potential therapeutic options for HCC in clinical settings. However, contradictory research findings have limited the extensive adoption of PPAR modulators for HCC treatment.

CONCLUSION

ALD is a common disease with an annually increasing incidence. It is the primary cause of cirrhosis and mortality due to hepatopathy in patients from many regions worldwide. Furthermore, the incidence of the disease is notably higher in developed countries. ALD includes an array of liver disorders, ranging from simple steatosis to more severe forms of pathological liver changes, including alcohol-associated steatohepatitis, cirrhosis, and HCC. Alcohol consumption is entirely detrimental to the liver. Most patients with ALD also have comorbid AUD, and thus it is necessary to promote the implementation of an integrated multidisciplinary treatment model, including that of hepatologists and psychologist, to provide comprehensive management of these patients. In conclusion, strengthening awareness of the risks associated with ALD, abstaining from alcohol, and implementing early interventions are fundamental to the management of ALD. Once the disease advances to the cirrhosis stage, preventing and treating liver fibrosis become exceedingly difficult due to the scarcity of effective medications and the generally poor outcomes of available treatments.

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REFERENCES

1 **Koizumi A**, Kaji K, Nishimura N, Asada S, Matsuda T, Tanaka M, Yorioka N, Tsuji Y, Kitagawa K, Sato S, Namisaki T, Akahane T, Yoshiji H. Effects of elafibranor on liver fibrosis and gut barrier function in a mouse model of alcohol-associated liver disease. *World J Gastroenterol* 2024; **30**: 3428-3446 [PMID: 39091710 DOI: 10.3748/wjg.v30.i28.3428]

2 **Devarbhavi H**, Asrani SK, Arab JP, Nartey YA, Pose E, Kamath PS. Global burden of liver disease: 2023 update. *J Hepatol* 2023; **79**: 516-537 [PMID: 36990226 DOI: 10.1016/j.jhep.2023.03.017]

3 **Hagström H**, Thiele M, Roelstraete B, Söderling J, Ludvigsson JF. Mortality in biopsy-proven alcohol-related liver disease: a population-based nationwide cohort study of 3453 patients. *Gut* 2021; **70**: 170-179 [PMID: 32220902 DOI: 10.1136/gutjnl-2019-320446]

4 **Stein E**, Cruz-Lemini M, Altamirano J, Ndugga N, Couper D, Abraldes JG, Bataller R. Heavy daily alcohol intake at the population level predicts the weight of alcohol in cirrhosis burden worldwide. *J Hepatol* 2016; **65**: 998-1005 [PMID: 27392424 DOI: 10.1016/j.jhep.2016.06.018]

5 **Prince DS**, Nash E, Liu K. Alcohol-Associated Liver Disease: Evolving Concepts and Treatments. *Drugs* 2023; **83**: 1459-1474 [PMID: 37747685 DOI: 10.1007/s40265-023-01939-9]

6 **World Health Organization**. Global status report on alcohol and health 2018. [cited 15 July 2024]. Available from: https://iris.who.int/handle/10665/274603

7 **Edenberg HJ**, McClintick JN. Alcohol Dehydrogenases, Aldehyde Dehydrogenases, and Alcohol Use Disorders: A Critical Review. *Alcohol Clin Exp Res* 2018; **42**: 2281-2297 [PMID: 30320893 DOI: 10.1111/acer.13904]

8 **Wu X**, Fan X, Miyata T, Kim A, Cajigas-Du Ross CK, Ray S, Huang E, Taiwo M, Arya R, Wu J, Nagy LE. Recent Advances in Understanding of Pathogenesis of Alcohol-Associated Liver Disease. *Annu Rev Pathol* 2023; **18**: 411-438 [PMID: 36270295 DOI: 10.1146/annurev-pathmechdis-031521-030435]

9 **Rehm J**, Taylor B, Mohapatra S, Irving H, Baliunas D, Patra J, Roerecke M. Alcohol as a risk factor for liver cirrhosis: a systematic review and meta-analysis. *Drug Alcohol Rev* 2010; **29**: 437-445 [PMID: 20636661 DOI: 10.1111/j.1465-3362.2009.00153.x]

10 **Reus VI**, Fochtmann LJ, Bukstein O, Eyler AE, Hilty DM, Horvitz-Lennon M, Mahoney J, Pasic J, Weaver M, Wills CD, McIntyre J, Kidd J, Yager J, Hong SH. The American Psychiatric Association Practice Guideline for the Pharmacological Treatment of Patients With Alcohol Use Disorder. *Focus (Am Psychiatr Publ)* 2019; **17**: 158-162 [PMID: 32021585 DOI: 10.1176/appi.focus.17205]

11 **Singal AK**, Shah VH, Malhi H. Emerging targets for therapy in ALD: Lessons from NASH. *Hepatology* 2024; **80**: 223-237 [PMID: 36938877 DOI: 10.1097/HEP.0000000000000381]

12 **Bataller R**, Arab JP, Shah VH. Alcohol-Associated Hepatitis. *N Engl J Med* 2022; **387**: 2436-2448 [PMID: 36577100 DOI: 10.1056/NEJMra2207599]

13 **Arab JP**, Addolorato G, Mathurin P, Thursz MR. Alcohol-Associated Liver Disease: Integrated Management With Alcohol Use Disorder. *Clin Gastroenterol Hepatol* 2023; **21**: 2124-2134 [PMID: 36858144 DOI: 10.1016/j.cgh.2023.02.017]

14 **Mackowiak B**, Fu Y, Maccioni L, Gao B. Alcohol-associated liver disease. *J Clin Invest* 2024; **134** [PMID: 38299591 DOI: 10.1172/JCI176345]

15 **Poulsen LI**, Siersbæk M, Mandrup S. PPARs: fatty acid sensors controlling metabolism. *Semin Cell Dev Biol* 2012; **23**: 631-639 [PMID: 22273692 DOI: 10.1016/j.semcdb.2012.01.003]

16 **Saikia P**, Bellos D, McMullen MR, Pollard KA, de la Motte C, Nagy LE. MicroRNA 181b-3p and its target importin α5 regulate toll-like receptor 4 signaling in Kupffer cells and liver injury in mice in response to ethanol. *Hepatology* 2017; **66**: 602-615 [PMID: 28257601 DOI: 10.1002/hep.29144]

17 **Parker R**, Aithal GP, Becker U, Gleeson D, Masson S, Wyatt JI, Rowe IA; WALDO study group. Natural history of histologically proven alcohol-related liver disease: A systematic review. *J Hepatol* 2019; **71**: 586-593 [PMID: 31173814 DOI: 10.1016/j.jhep.2019.05.020]

18 **Nagy LE**, Ding WX, Cresci G, Saikia P, Shah VH. Linking Pathogenic Mechanisms of Alcoholic Liver Disease With Clinical Phenotypes. *Gastroenterology* 2016; **150**: 1756-1768 [PMID: 26919968 DOI: 10.1053/j.gastro.2016.02.035]

19 **Cariou B**, Hanf R, Bruckert E, Darteil R, Hum D, Staels B. O78 Le GFT505, premier co-agoniste PPAR α/δ, a une double action favorable sur les paramètres lipidiques et glucidiques chez les sujets pré-diabétiques. *Diabetes Metab* 2011; **37**: A19-A20 [DOI: 10.1016/s1262-3636(11)70566-3]

20 **Lamas Bervejillo M**, Ferreira AM. Understanding Peroxisome Proliferator-Activated Receptors: From the Structure to the Regulatory Actions on Metabolism. *Adv Exp Med Biol* 2019; **1127**: 39-57 [PMID: 31140170 DOI: 10.1007/978-3-030-11488-6_3]

21 **Wagner N**, Wagner KD. The Role of PPARs in Disease. *Cells* 2020; **9** [PMID: 33126411 DOI: 10.3390/cells9112367]

22 **Ahmed W**, Ziouzenkova O, Brown J, Devchand P, Francis S, Kadakia M, Kanda T, Orasanu G, Sharlach M, Zandbergen F, Plutzky J. PPARs and their metabolic modulation: new mechanisms for transcriptional regulation? *J Intern Med* 2007; **262**: 184-198 [PMID: 17645586 DOI: 10.1111/j.1365-2796.2007.01825.x]

23 **Ruzehaji N**, Frantz C, Ponsoye M, Avouac J, Pezet S, Guilbert T, Luccarini JM, Broqua P, Junien JL, Allanore Y. Pan PPAR agonist IVA337 is effective in prevention and treatment of experimental skin fibrosis. *Ann Rheum Dis* 2016; **75**: 2175-2183 [PMID: 26961294 DOI: 10.1136/annrheumdis-2015-208029]

24 **Avouac J**, Konstantinova I, Guignabert C, Pezet S, Sadoine J, Guilbert T, Cauvet A, Tu L, Luccarini JM, Junien JL, Broqua P, Allanore Y. Pan-PPAR agonist IVA337 is effective in experimental lung fibrosis and pulmonary hypertension. *Ann Rheum Dis* 2017; **76**: 1931-1940 [PMID: 28801346 DOI: 10.1136/annrheumdis-2016-210821]

25 **Boyer-Diaz Z**, Aristu-Zabalza P, Andrés-Rozas M, Robert C, Ortega-Ribera M, Fernández-Iglesias A, Broqua P, Junien JL, Wettstein G, Bosch J, Gracia-Sancho J. Pan-PPAR agonist lanifibranor improves portal hypertension and hepatic fibrosis in experimental advanced chronic liver disease. *J Hepatol* 2021; **74**: 1188-1199 [PMID: 33278455 DOI: 10.1016/j.jhep.2020.11.045]

26 **Kamata S**, Honda A, Ishikawa R, Akahane M, Fujita A, Kaneko C, Miyawaki S, Habu Y, Shiiyama Y, Uchii K, Machida Y, Oyama T, Ishii I. Functional and Structural Insights into the Human PPARα/δ/γ Targeting Preferences of Anti-NASH Investigational Drugs, Lanifibranor, Seladelpar, and Elafibranor. *Antioxidants (Basel)* 2023; **12** [PMID: 37627519 DOI: 10.3390/antiox12081523]

27 **Costentin CE**, Mourad A, Lahmek P, Causse X, Pariente A, Hagège H, Dobrin AS, Becker C, Marks B, Bader R, Condat B, Héluwaert F, Seitz JF, Lesgourgues B, Denis J, Deuffic-Burban S, Rosa I, Decaens T; CHANGH Study Group. Hepatocellular carcinoma is diagnosed at a later stage in alcoholic patients: Results of a prospective, nationwide study. *Cancer* 2018; **124**: 1964-1972 [PMID: 29589878 DOI: 10.1002/cncr.31215]

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