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LETTER TO THE EDITOR

Elafibranor: A promising therapeutic approach for liver fibrosis and gut barrier dysfunction in alcohol-associated liver disease

Chun-Han Cheng, Wen-Rui Hao, Tzu-Hurng Cheng

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Abstract

This article discusses the recent study written by Koizumi *et al*. Alcohol-associated liver disease (ALD) is a major cause of liver-related morbidity and mortality, which is driven by complex mechanisms, including lipid accumulation, apoptosis, and inflammatory responses exacerbated by gut barrier dysfunction. The study explored the therapeutic potential of elafibranor, a dual peroxisome proliferator-activated receptor alpha/delta agonist. In clinical trials, elafibranor has shown promise for the treatment of other liver conditions; however, its effects on ALD remain unclear. The authors' findings indicate that elafibranor significantly reduced liver fibrosis and enhanced gut barrier integrity in patients with ALD. These positive effects of elafibranor are mediated through multiple pathways. Elafibranor promotes lipid metabolism, reduces oxidative stress, and inhibits inflammatory responses by restoring gut barrier function. Specifically, it improves hepatocyte function by enhancing autophagic and antioxidant capacity, and it mitigates inflammation by suppressing the lipopolysaccharide/toll-like receptor 4/nuclear factor kappa B signaling pathway. These findings indicate that elafibranor has promising clinical applications. In addition, the study highlights elafibranor's potential as a therapeutic agent for liver diseases, particularly ALD. This article underscores the importance of understanding the mechanistic pathways underlying ALD and suggests directions for future research aimed at elucidating the benefits and limitations of elafibranor.

Key Words: Elafibranor; Liver fibrosis; Gut barrier function; Alcohol-associated liver disease; Peroxisome proliferator-activated receptor agonists

Core Tip: This article highlights the major findings of the study written by Koizumi *et al*. The study demonstrated the potential of elafibranor, a peroxisome proliferator-activated receptor agonist, in mitigating liver fibrosis and improving gut barrier integrity in a mouse model of alcohol-associated liver disease. These findings underscore the promising therapeutic potential of elafibranor and its relevance in advancing treatment strategies for liver diseases linked to chronic alcohol consumption.

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TO THE EDITOR

Elafibranor, a peroxisome proliferator-activated receptor (PPAR) agonist, has attracted considerable interest for its therapeutic potential in liver diseases, particularly alcohol-associated liver disease (ALD). Recent research by Koizumi *et al*[1] has investigated elafibranor's effects on liver fibrosis and gut barrier function in ALD models, providing valuable insights into its potential role in managing ALD pathogenesis. ALD encompasses a range of liver conditions, from hepatic steatosis to cirrhosis, exacerbated by chronic alcohol consumption and posing significant global health challenges. This article critically evaluates the findings of Koizumi *et al*'s study[1], emphasizing elafibranor's potential to improve liver health and gut barrier integrity. Experimental evidence suggests that PPAR agonists, like elafibranor, offer a multifaceted approach to addressing ALD by targeting both liver fibrosis and gastrointestinal complications. The study's insights into elafibranor's mechanisms provide promising new avenues for treating liver fibrosis and associated gut dysfunctions. In this article, we discuss the clinical implications of these findings, address potential challenges, and propose future research directions to enhance elafibranor's translational impact in ALD treatment.

CURRENT UNDERSTANDING OF ALD

ALD encompasses a range of liver conditions, from hepatic steatosis (fatty liver) to more severe forms like alcoholic hepatitis and cirrhosis. Chronic alcohol consumption disrupts hepatic lipid metabolism, induces oxidative stress, and triggers inflammatory responses - all of which contribute to fibrosis and liver dysfunction. Despite the high morbidity and mortality associated with ALD, effective treatment options are limited, highlighting the need for new therapeutic approaches. The pathogenesis of ALD involves interconnected mechanisms, including lipid accumulation, activation of inflammatory pathways, and progressive fibrosis. Recent research has underscored the critical role of the gut-liver axis "a bidirectional relationship between the gut and liver" in the progression of ALD. Chronic alcohol intake disrupts gut barrier integrity, increasing intestinal permeability and allowing bacterial endotoxins, such as lipopolysaccharide (LPS), to enter the portal circulation. These endotoxins activate toll-like receptors (TLRs) on hepatic cells, especially TLR4, which triggers the nuclear factor kappa B (NF-κB) signaling pathway. This pathway promotes inflammation and fibrogenesis within the liver, exacerbating liver injury[2,3]. Also, metabolic dysfunction-associated steatotic liver disease (MASLD) and primary biliary cholangitis (PBC) are linked to the pathogenesis of ALD, with each condition potentially worsening liver damage. MASLD, characterized by hepatic fat accumulation and metabolic disturbances, shares key mechanisms with ALD, including lipid dysregulation and increased oxidative stress, which together amplify hepatic inflammation and fibrosis[4,5]. Likewise, PBC can worsen ALD by promoting cholestasis (bile flow impairment) and intensifying hepatic inflammation, thereby accelerating liver injury[6,7]. Recognizing the interplay among these conditions supports a multifaceted approach to ALD treatment, targeting the complex liver dysfunction seen in MASLD and PBC. The role of PPARδ in intestinal cells is especially relevant within the ALD and gut-liver axis context. PPARδ, highly expressed in intestinal epithelial cells, helps maintain gut barrier integrity. In ALD, downregulation of PPARδ impairs the proliferation of intestinal epithelial cells, weakens the gut barrier, and enhances inflammatory responses from macrophages, which further worsens gut permeability and fuels the inflammatory cascade[1,8]. Elafibranor, a dual PPARα/δ agonist, shows promise in reducing liver fibrosis and restoring gut barrier function in ALD. By upregulating PPARδ activity, elafibranor improves lipid metabolism, reduces oxidative stress, and strengthens the intestinal barrier. This improvement reduces endotoxemia, thereby diminishing LPS-induced hepatic inflammation by inhibiting the LPS/TLR4/NF-κB pathway[9]. Furthermore, elafibranor's anti-inflammatory effects extend to modulating cytokine profiles, which may further protect against liver inflammation and fibrosis. Targeting both hepatic and extrahepatic factors, including the gut-

liver axis, elafibranor offers a promising therapeutic strategy for ALD. Understanding the mechanisms of elafibranor and other PPAR agonists in ALD is essential for optimizing their use in treating this complex disease. Future studies should explore how these agents affect different stages of ALD, MASLD, and PBC, which will be critical for developing comprehensive treatment strategies. Evaluating the long-term safety and efficacy of these treatments across diverse patient populations also remains a priority for advancing ALD management[1,10].

EXPLORING ELAFIBRANOR'S MECHANISMS IN ALD

Elafibranor has emerged as a promising therapeutic candidate for ALD. Research highlights its ability to modulate hepatic lipid metabolism, reduce inflammation, and promote fibrosis resolution in experimental ALD models. By activating PPARα and PPARδ, elafibranor enhances fatty acid oxidation and reduces hepatic triglyceride accumulation, which are essential for alleviating steatosis, a key feature of ALD[10,11]. This dual agonist action not only addresses metabolic dysregulation but also exerts anti-inflammatory effects by suppressing NF-κB signaling and lowering the expression of pro-inflammatory cytokines, thus mitigating hepatic inflammation and injury[8,9]. Elafibranor also impacts liver fibrosis through the modulation of fibrogenic pathways. It downregulates fibrosis-promoting factors such as transforming growth factor-beta 1 and alpha-smooth muscle actin while enhancing matrix metalloproteinase activity to support extracellular matrix remodeling and fibrosis regression[1,7]. In addition, recent studies emphasize elafibranor's role in restoring gut barrier function and inhibiting the LPS/TLR4/NF-κB inflammatory pathway, both critical in ALD progression. Elafibranor improves gut-liver axis integrity by upregulating tight junction proteins and reducing gut-derived endotoxin translocation to the liver, thereby decreasing inflammation in the liver. This effect on the gut-liver crosstalk is particularly important in ALD, where compromised gut barrier function can exacerbate hepatic inflammation and fibrosis[2,3]. Overall, elafibranor's multifaceted mechanisms - encompassing metabolic regulation, anti-inflammatory effects, and fibrosis modulation - position it as a strong therapeutic candidate for ALD. Future research should focus on exploring its clinical efficacy and safety profiles to optimize treatment strategies for ALD patients.

CLINICAL IMPLICATIONS AND FUTURE DIRECTIONS

While previous studies have highlighted elafibranor's potential to improve liver steatosis and fibrosis in ALD mouse models, systematic clinical data remain limited. Key challenges include optimizing dosing regimens, establishing long-term safety profiles, and identifying patient subsets most likely to benefit from treatment. Future research should focus on integrating elafibranor into comprehensive ALD management protocols, exploring synergistic effects with other therapies, and employing biomarkers to effectively monitor treatment responses[1,4,6]. This article critically assesses elafibranor's promise as an ALD therapeutic agent, highlighting its complex mechanisms of action and discussing future directions for enhancing its clinical impact. Recent studies emphasize elafibranor's role in modulating hepatic lipid metabolism and reducing inflammation, both essential in mitigating hepatic steatosis and inflammation[1,6]. Moreover, elafibranor's capacity to attenuate liver fibrosis - through mechanisms involving fibrogenesis markers and matrix remodeling - underscores its potential to reverse advanced liver damage[1,9]. Strategic integration of elafibranor within multidisciplinary ALD treatment frameworks, supported by ongoing refinements in therapeutic strategies and rigorous patient outcome monitoring, will be critical to unlocking its full potential[5,11]. Further research should explore the relationship between elafibranor's hepatic effects and its broader impact on systemic metabolism, particularly regarding gut barrier function and immune modulation pathways[4,8]. In summary, while challenges remain in optimizing its clinical application, elafibranor is positioned as a promising therapeutic option for ALD, with strong preclinical support and active translational research efforts[1,6].

CONCLUSION

In conclusion, the investigation into elafibranor's effects on liver fibrosis and gut barrier function in an ALD mouse model, as reported in recently, underscores its promising therapeutic potential[1]. By targeting multiple pathways central to ALD pathogenesis including hepatic lipid metabolism, inflammation, and fibrosis-elafibranor offers a multifaceted approach to mitigating disease progression. This robust preclinical evidence establishes a solid foundation for advancing to clinical trials to evaluate elafibranor's efficacy and safety in human ALD patients. Future studies should focus on refining treatment protocols, identifying biomarkers that can signal treatment response, and exploring potential synergies with existing therapies[4,6]. Additionally, incorporating elafibranor into comprehensive ALD management strategies including lifestyle modifications and alcohol cessation programs could significantly enhance patient outcomes and help reduce the global burden of ALD-related complications. This article advocates for continued collaboration among researchers, clinicians, and pharmaceutical developers to accelerate the translation of preclinical insights into effective therapies for ALD[8,11]. Addressing the unmet medical needs in ALD management, elafibranor represents a promising step forward in achieving better clinical outcomes and improving the quality of life for individuals affected by this condition worldwide.

FOOTNOTES

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