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EDITORIAL

# Peroxisome proliferator-activated receptor agonists: A new hope towards the management of alcoholic liver disease

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## Abstract

In this editorial, we examine a paper by Koizumi *et al*, on the role of peroxisome proliferator-activated receptor (PPAR) agonists in alcoholic liver disease (ALD). The study determined whether elafibranor protected the intestinal barrier and reduced liver fibrosis in a mouse model of ALD. The study also underlines the role of PPARs in intestinal barrier function and lipid homeostasis, which are both affected by ALD. Effective therapies are necessary for ALD because it is a critical health issue that affects people worldwide. This editorial analyzes the possibility of PPAR agonists as treatments for ALD. As key factors of inflammation and metabolism, PPARs offer multiple methods for managing the complex etiology of ALD. We assess the abilities of PPARα, PPARγ, and PPARβ/δ agonists to prevent steatosis, inflammation, and fibrosis due to liver diseases. Recent research carried out in preclinical and clinical settings has shown that PPAR agonists can reduce the severity of liver disease. This editorial discusses the data analyzed and the obstacles, advantages, and mechanisms of action of PPAR agonists for ALD. Further research is needed to understand the efficacy, safety, and mechanisms of PPAR agonists for treating ALD.

**Key Words:** Alcoholic liver disease; Peroxisome proliferator-activated receptors; Peroxisome proliferator-activated receptors agonists; Liver fibrosis; Inflammation; Metabolic

regulation; Hepatoprotection



**Core Tip:** Peroxisome proliferator-activated receptors (PPARs) are a family of nuclear receptors, including PPARα, PPARγ, and PPARβ/δ. They regulate vital factors in the development of alcoholic liver disease (ALD), like lipid metabolism, inflammation, and fibrosis. PPAR agonists have the potential to manage ALD. In recent preclinical and clinical trials, PPAR agonists have revealed their potency to eliminate liver steatosis, improve insulin receptor sensitivity, and diminish inflammation and fibrosis. However, to confirm their effectiveness and reveal side effects, larger clinical trials in ALD must be conducted. This article, therefore, raises the need for further study and debate on the application of PPAR agonists for ALD management.

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## INTRODUCTION

Alcoholic liver disease (ALD) remains one of the biggest problems in hepatology, affecting millions of people and causing considerable population mortality and disability[1]. Dealing with the multiple facets of ALD, from simple steatosis to alcoholic hepatitis and cirrhosis, requires research from various perspectives[2]. The global burden of ALD is overwhelming, with alcohol-related cirrhosis constituting approximately 50% of all cirrhosis deaths globally in 2023[3]. Modern management of ALD is mainly based on alcohol withdrawal and supportive measures, which are relatively ineffective if used alone for managing the progression of the disease[4]. In this setting of restricted therapeutic intervention for ALD, peroxisome proliferator-activated receptor (PPAR) agonists have taken the preventive spotlight in promising to address the pivotal pathophysiological processes of ADL and neurodegenerative diseases[5,6]. PPARs include a group of nuclear protein receptors involved in the processes that determine the metabolism, inflammation, and differentiation of cells[7]. Given that PPAR agonists are the only agents known to modify multiple signaling pathways that simultaneously play a role in ALD, the compound might change the face of hepatoprotection and disease remediation[5]. Thus, this editorial intends to review the literature regarding PPAR agonists used in ALD therapy, including studies of their action mechanisms, current data, and prospective future advances in disease treatment and medicine. We will discuss PPARα, PPARγ and PPARβ/δ, the three subtypes that are promising therapeutic targets in ALD[8]. This review details how PPAR agonists affect hepatic lipid metabolism, inflammation, and fibrosis – the hallmarks of ALD progression[9]. In light of the growing body of information from PPAR agonist clinical trials and animal studies, this article aims to provide a comprehensive overview of the opportunities and difficulties of targeting ALD with PPAR agonists. We will examine the drug discovery process and the obstacles to bridging the gap between promising preclinical results and clinical treatments. We hope to stimulate discussion of the potential for PPAR agonists to transform the treatment of ALD.

## ALCOHOL-ASSOCIATED LIVER DISEASE AND THE THERAPEUTIC POTENTIAL OF PPAR AGONISTS

Acquired liver problems from long-term alcohol use include simple steatosis, fibrotic hepatitis, protein-rich ascitic fluid leading to cirrhosis, and hepatocellular cancer[10]. Factors contributing to acute and chronic alcohol consumption include elevated lipogenesis, decreased fatty acid oxidation, and increased inflammation and free radicals, resulting in hepatocyte injury and fibrosis over time[10]. Therapeutic interventions for ALD remain limited mainly to alcohol abstinence with supportive treatment[11]. Thus, a deeper understanding of potential drug targets, especially the PPARs, is needed[12]. There are three PPAR isoforms: α, which is primarily hepatic and plays roles in fatty acid oxidation and lipoprotein metabolism; γ, also called adipogenic, which is prevalent in adipose tissue and seems critical to the determination of adipocyte sensitivity[13]; and β/δ, which is found everywhere and affects energy balance and inflammation[14].

Musso *et al*[15] reported that PPARs have potential to tackle multiple pathophysiological mechanisms of ALD. PPARα activation enhances hepatic fatty acid oxidation and suppresses lipogenesis processes, which could alleviate fat accumulation in the liver[16]. Montagner *et al*[17] believed PPARγ agonists could also improve insulin sensitivity and have potent anti-inflammatory properties, thus slowing progression to nonalcoholic steatohepatitis and subsequent cirrhosis. PPARδ agonists may reduce acute hepatic inflammation[18]. Of the three isoforms, particular attention has been paid to PPARγ, which controls glucose and lipid metabolism by regulating gene expression in response to synthetic and natural ligands [19]. Chronic alcohol administration was reported to impair *PPAR* gene expression (particularly PPARγ) and function, implying a role for PPARγ in ALD pathogenesis and suggesting that increasing PPARγ activity by using PPARγ agonists

may help treat ALD[13].

PPAR agonists have shown evidence for restoring metabolic homeostasis, reducing infection, and attenuating fibrosis in ALD[15]. PPAR agonists promise not simply to cope with symptoms but potentially reverse the underlying pathological tactics driving ALD development. PPARα agonists have provided promising results in managing ALD in animal models. Pirinixic acid (WY14643) treatment was associated with a decrease in hepatic triglycerides and inflammation in a mouse model of ALD[20]. Fenofibrate protects against liver steatosis by promoting hepatic fatty acid β-oxidation and decreasing hepatic insulin resistance[21]. Studies on PPARγ agonists, particularly thiazolidinediones, have been centered around metabolic dysfunctions. In rats, rosiglitazone reduced alcohol-induced liver injury by downregulating oxidative stress and inflammation[22]. Pioglitazone has produced improvement in liver histology (mainly on steatosis, inflammation and ballooning) and enhanced insulin sensitivity in nonalcoholic fatty liver disease (NAFLD) (NCT00063622, NCT00227110 and NCT00994682)[23]. Although the mechanism by which PPARγ agonists treat ALD is not clear, these drugs have anti-inflammatory properties and contribute to better insulin sensitivity. In a mouse model of ALD, the PPARβ/δ agonist, cardarine (GW501516), has been shown to attenuate hepatic lipid deposition and inflammation[24].

Activators of multiple types of PPARs, known as pan-PPAR agonists, have garnered significant attention due to their potential to affect various aspects of liver disease simultaneously. Elafibranor, a dual PPARα/δ agonist, was found to diminish fibrosis and improve liver histology in two studies of the treatment of NAFLD[25]. In a study by Koizumi *et al* [26], elafibranor has shown promise as a therapeutic agent for managing ALD by addressing both liver and intestinal health. The research demonstrated that elafibranor not only reduced the progression of liver fibrosis but also helped maintain intestinal barrier function in a mouse model of ALD[26]. It has been proven that the pan-PPAR agonist IVA337 works by removing fatty deposits from the liver, decreasing inflammation, and potentially preventing or alleviating the consequences of liver disease by interacting with all three PPAR subtypes: α, γ, and δ[27]. Likewise, saroglitazar, a dual PPARα/γ agonist, has been found to ameliorate lipid profile and hepatic fat accumulation and significantly improve liver enzymes in NAFLD patients[28]. In a clinical trial (NCT03008070), the PPAR agonist lanifibranor reduced steatosis, ballooning and fibrosis. There are no clinical studies to date that focus on the effects of PPARβ/δ agonists on ALD, which constitutes a research gap. Though the number of clinical trials concerning PPAR agonists on the fatty liver is ever-increasing, the scientific community has yet to make clear-cut conclusions on their efficacy against ALD due to conflicting outcomes[5]. Further work should continue with large-scale randomized controlled trials to measure the effects of PPAR agonists for ALD patients. Research should also be done to determine the impact of selective and non-selective PPAR modulators in this condition.

## MECHANISMS OF PPAR AGONISTS IN ALD

To harness the potential of PPARα, PPARγ and PPARβ/δ agonists for the treatment of ALD, it remains crucial to know how these affect key aspects of the disease process, such as liver metabolism, inflammation and injury[29]. PPARα agonists influence lipid metabolism in the liver, which is helpful in managing steatosis in ALD[30]. Activation of PPARα promotes fatty acid metabolism in the liver by increasing gene expression of critical enzymes such as acyl-CoA oxidase and carnitine palmitoyltransferase-1[31]. Additionally, these agonists decrease the activity of the gene regulator sterol regulatory element-binding protein 1c, decreasing the production of new fat[32]. These dual effects can help lower liver triglyceride levels, which may reverse fatty liver caused by alcohol consumption[33].

While PPARγ agonists are commonly known for increasing the body's insulin sensitivity, they also provide numerous benefits in the context of ALD[34]. The anti-inflammatory effects of these agonists are particularly noteworthy. They can reduce the production of pro-inflammatory cytokines and inhibit the activity of nuclear factor-kappaB, a transcriptional factor that plays an essential role in inflammation[35]. This is especially relevant in alcoholic hepatitis, in which the harm to the liver is primarily caused by inflammatory cytokines[36]. Furthermore, PPARγ activation in hepatic stellate cells has been proven to promote their reversion to a quiescent state, probably attenuating fibrosis development in ALD[37].

PPARβ/δ agonists, the least studied in the context of ALD, are emerging as potential therapeutic agents due to their effects on infection and maintaining muscle function[38]. By enhancing fatty acid oxidation in hepatocytes, PPARβ/δ activation enhances the effects of PPARα agonists in reducing steatosis[39]. Additionally, PPARβ/δ agonists have set up effective anti-inflammatory responses, suppressing the expression of inflammatory mediators by Kupffer cells and modulating macrophage polarization toward an anti-inflammatory phenotype[40]. These outcomes collectively contribute to hepatoprotection in ALD by mitigating metabolic and inflammatory insults.

PPAR subtypes may synergistically interact in ALD management[29]. Though each PPAR subtype has therapeutic potential, activating all of them may provide greater benefits. Preclinical evidence on the efficacy of PPAR agonists in ALD is incredible and developing. In a rodent model of persistent alcohol feeding, PPARα agonists like fenofibrate have been demonstrated to reduce hepatic steatosis, oxidative pressure, and inflammation[21]. Similarly, pioglitazone and other PPARγ agonists have been examined for their efficacy in reducing alcohol-induced liver damage, decreasing steatosis, and improving insulin sensitivity[41]. Emerging information on PPARβ/δ agonists advocates their potential in mitigating alcohol-induced liver injury and fibrosis, even though similar research is needed to elucidate their function in ALD[42]. For instance, dual PPARα/γ agonists have shown promise in preclinical models of ALD, demonstrating more suitable efficacy than single PPAR agonists in lowering steatosis, infection, and fibrosis[43]. Clinical trials are currently underway to assess the effectiveness and safety profiles of twin and pan-PPAR agonists in the therapy of ALD[44].

## POTENTIAL BENEFITS OF PPAR AGONISTS IN ALD TREATMENT

PPAR agonists provide the specific benefit of addressing a pair of metabolic disorders associated with ALD: Metabolic dysregulation and inflammation/fibrosis. By enhancing fatty acid oxidation, decreasing lipogenesis, and improving insulin sensitivity, PPAR agonists have the capacity to reverse hepatic steatosis[30]. The anti-inflammatory properties of PPAR agonists, especially PPARγ and PPARβ/δ agonists, may be necessary to mitigate hepatic inflammation in alcoholic hepatitis[35]. This may lessen the need for corticosteroids, which are currently the mainstay of treatment for severe alcoholic hepatitis but which are associated with significant side effects[36]. Emerging proof indicates that PPAR agonists, particularly PPARγ activators, might also attenuate hepatic fibrosis by modulating hepatic stellate cell activation[37]. This antifibrotic impact can be beneficial in preventing or slowing the progression of cirrhosis in ALD patients. In addition to hepatic benefits, PPAR agonists may improve cardiovascular risk profiles and raise insulin sensitivity, which are particularly important given the metabolic comorbidities regularly associated with ALD[34]. The mechanisms of action of PPAR agonists suggest possible synergies with different therapeutic techniques in ALD, such as antioxidants or gut-focused interventions, perhaps leading to more effective treatment[2].

## CHALLENGES AND LIMITATIONS OF PPAR AGONISTS IN TREATING ALD

Exploring PPAR agonists to treat ALD is an intriguing avenue of study with huge potential and challenges that must be overcome to see the light of day and serve an actual patient. Among the obstacles to the diagnosis and treatment of ALD patients is the fact that patients present a broad spectrum of disease stages, ranging from simple fatty liver to severe cirrhosis of the liver[45]. Since points on this spectrum differ greatly, it is difficult to devise a standard treatment for all. We need to determine which patients and disease stages will most likely benefit from PPAR agonists. While PPAR agonists have been used safely for other conditions, their long-term safety in ALD patients, especially those with advanced liver damage, needs to be carefully studied[25]. There are concerns about potential heart risks with some PPAR agonists and the possibility of further liver toxicity in an organ already struggling with alcohol damage.

There are various challenges to the introduction of PPAR agonists for the treatment of ALD. Drugs often require sizable and extended clinical trials in a complex clientele. Doctors could prescribe existing PPAR agonists for ALD off-label, which could affect the process of seeking formal approval[46]. We understand, in a general sense, how PPAR agonists act, but on a molecular level there remains much to be learned regarding the mechanisms by which these drugs assist the liver battered by alcohol. Lastly, long-term pharmacological maintenance therapy for a chronic disease like ALD may be rather expensive[47]. On the other hand, currently there are not many options at all for ALD treatment, especially in the case of advanced disease.

While total abstinence from alcohol remains the foundation of ALD management, drugs like steroids for severe alcoholic hepatitis have significant limitations in terms of both effectiveness and side effects[36]. PPAR agonists offer a more targeted, mechanism-based treatment option that could fill a significant gap in ALD care. To provide the best opportunities and minimize the concerns associated with PPAR agonists in ALD treatment, constant endeavors from the research community, physicians, and drug regulators are warranted.

## FUTURE DIRECTIONS

As we stand at the frontier of PPAR agonist studies in ALD management, future investigations and clinical programs must focus on precision medicine approaches, identifying biomarkers that predict responsiveness to specific PPAR agonists in ALD patients. Large-scale clinical trials are needed to establish safety and efficacy across ALD populations, including monitoring liver function, cardiovascular effects, and potential drug-alcohol interactions. Exploring synergistic effects with antioxidants, anti-inflammatory agents, or gut-focused interventions could lead to more effective combination therapies. Further research into tissue-specific PPAR modulators tailored for ALD could enhance therapeutic efficacy with fewer side effects. It has, however, been essential to get to know the molecular changes that are important in hepatic alcohol-injury as well as the chances of epigenetic alterations that might be brought by the activation of PPARs [48]. In clinical practice, such biomarkers should be investigated to identify ALD patients who are likely to derive the most benefit from PPAR agonist therapy, depending on the stage of the disease, the patient's metabolic abnormalities, and genetic predispositions. Use of biomarkers, such as metabolites and liver function indicators, may improve safety and efficacy standardization[49]. Introducing PPAR agonists into the drug treatment of ALD, perhaps together with antioxidants or drugs aimed at changes in gut permeability, could be beneficial[2].

## CONCLUSION

The use of PPAR agonists in treating ALD offers a novel approach. Investigation of PPARα, PPARγ, and PPARβ/δ agonists has shown that they can tackle metabolic, inflammatory, and fibrotic aspects of ALD. Their multi-target nature matches the complex process of ALD. Studies have suggested their efficacy, but clinical benefits are not proven. PPAR agonists may target the disease more precisely than existing treatments. These benefits are not limited to the liver but may also correct common metabolic problems in ALD. However, PPAR agonists face challenges such as safety issues,

drug-alcohol interactions, and treatment complications. As we advance, large-scale clinical trials may be necessary. Combining PPAR agonists with other therapies may provide better treatment options. Developing PPAR agonists to treat ALD will require researchers, clinicians, regulatory bodies, and policymakers to work together. In conclusion, PPAR agonists can revolutionize ALD management, but this will require the collaboration of experts from different fields.

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## FOOTNOTES

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