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LETTER TO THE EDITOR

Elafibranor, a dual PPARα and PPARδ agonist, reduces alcohol-associated liver disease: Lessons from a mouse model

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Abstract

Metabolic dysfunction-associated steatotic liver disease (MASLD) is a highly prevalent liver pathology in need of novel pharmacological treatments to complement lifestyle-based interventions. Nuclear receptor agonists have been under scrutiny as potential pharmacological targets and as of today, resmetirom, a thyroid hormone receptor b agonist, is the only approved agent. The dual PPAR α and δ agonist elafibranor has also undergone extensive clinical testing, which reached the phase III clinical trial but failed to demonstrate a beneficial effect on MASLD. As alcohol-associated liver disease and MASLD can be interconnected, whether elafibranor might be affective against liver disease caused by alcohol consumption is worth investigating. Writing recently in the *World Journal of Gastroenterology*, Koizumi *et al* reported using a mouse model of alcohol-associated liver disease and found that hepatic steatosis, liver fibrosis, and hepatocyte apoptosis were alleviated by administration of elafibranor. Although preclinical in nature, these data support the potential beneficial action of elafibranor in alcohol-induced MASLD, warranting the testing of this molecule in patients with steatotic liver disease caused by alcohol consumption.

Key Words: PPAR nuclear receptors; Elafibranor; Steatotic liver disease; Alcohol-associated liver disease; Liver fibrosis

Core Tip: Metabolic dysfunction-associated steatotic liver disease needs novel pharmacological treatments. Elafibranor, a PPAR agonist, remains a promising molecule against steatotic liver disease caused by alcohol consumption. Koizumi *et al* reported, in *World Journal of Gastroenterology*, on their use of a mouse model of alcohol-associated liver disease which indicated that hepatic steatosis, liver fibrosis, and hepatocyte apoptosis were alleviated by administration of elafibranor. These data support the potential beneficial action of elafibranor, warranting clinical testing.

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TO THE EDITOR

Metabolic dysfunction-associated steatotic liver disease (MASLD) is defined as a steatotic liver disease (SLD) associated to at last one cardiometabolic risk factor[1]. It is the most prevalent liver pathology worldwide, affecting almost 30% of the adult population[2]. MASLD is projected to further increase its burden in the coming years due to the aging of the population and the ever-increasing incidence of obesity[3].

MASLD pathologies were, until recently, identified as non-alcoholic fatty liver disease [or non-alcoholic steatohepatitis (NASH)]. MASLD is defined by the absence of harmful alcohol intake. Yet, SLD also develops upon excessive alcohol consumption, and pharmacological treatments for alcohol-associated liver disease (ALD) are still being sought.

MASLD progression, leading to metabolic dysfunction-associated steatohepatitis (MASH) characterized by moderate to advanced fibrosis (F2 to F3 stages), has been the object of intensive investigation to identify potential pharmacological agents to be used along with diet and exercise. In the search for therapeutic options for MASLD, nuclear receptors, including THR, and PPARα and δ as molecular targets are under intense scrutiny. As of today, only resmetirom, an orally administered selective agonist of THR-β, has proven its efficacy in the treatment of MASH and has recently obtained conditional approval for marketing[4].

The discovery of a dual PPARα and PPARδ agonist, termed GFT505 and later elafibranor[5], also raised substantial hopes to target MASH, with promising preclincal and clinical early phase results[5]. Following these initial promises, a multicenter double-blind and placebo-controlled phase III study (Resolve-IT) evaluating the safety and efficacy of elafibranor *vs* placebo in a cohort of participants with NASH did not lead to statistically significant improved primary endpoints at an interim analysis. It consisted of the resolution of NASH without worsening of the stage 2 and 3 fibrotic state as compared to the placebo group. Hence, the study was terminated[6].

Elafibranor works through activation of PPARα and δ targets in multiple cell types and biological processes involved in the pathophysiology of cholestatic liver disease, including cholestasis (impairment of bile flow in the liver), bile toxicity, inflammation and fibrosis, and bile acid output. Elafibranor has also been the subject of clinical investigation as a treatment for primary biliary cholangitis, and the efficacy and safety in this disease was shown[7].

Writing in the *World Journal of Gastroenterology*, Koizumi *et al*[8] added a new exploratory aspect to the potential pharmacological action of elafibranor in liver disease by studying its pharmacological effect on experimentally induced ALD in a preclinical mouse model. ALD in mice was induced by continuously feeding mice a liquid Lieber-DeCarli diet containing 2.5% ethanol in conjunction with three weekly intraperitoneal injections of hepatotoxic carbon tetrachloride (CCl_4), a well-known inducer of hepatotoxicity and liver fibrosis[9].

Simultaneous addition of elafibranor by daily gavage at a low or high dose (3 and 10 mg/kg of body weight, respectively) improved several pathological parameters observed during the development of SLD. It decreased aspartate aminotransferase and alanine aminotransferase activity, lowered serum triglycerides, lowered liver fat accumulation, and increased lipolysis and fatty acid oxidation.

Elafibranor also: (1) Prevented ALD-induced apoptosis, as measured by the TUNEL assay showing decreased apoptosis; (2) Allowed recovery of hepatocyte proliferation as measured by Ki67 immunostaining; and (3) Improved autophagy, which is strongly impaired in ALD animals. These biochemical improvements resulted in lowered scores of fibrosis and an overall relief from liver inflammation as demonstrated by decreased infiltration of Kupfer cells in the hepatic parenchyma, lowered activation of NF-kB signaling, and reduced expression levels of proinflammatory genes *Tnfa*, *Il1b*, *Il6*, and *Ccl2* (encoding monocyte chemoattractant protein 1). Importantly, elafibranor also ameliorated the intestinal barrier function by reinstating the expression of tight junction genes and proteins Zo1, occludin, and claudin 2 and alleviating ALD-induced apoptosis, as observed in the liver.

In summary (Figure 1), the investigation of Koizumi *et al*[8], using a set of well-designed and informative experimental approaches, supported the notion that elafibranor may have a potential to ameliorate ALD. A small drawback of the study was that the experimental model was boosted by multiple CCl_4 injections. Hence, it is difficult to discern the specific contribution to liver pathology caused by CCl_4 or the administered ethanol. In this respect, follow-up studies inducing ALD in rodents by administration of the Lieber-DeCarli ethanol-supplemented diet (without CCl4 administration) would prove informative[10]. Also, the induction of ALD and therapeutic treatment by elafibranor were simultaneous, while translational use in humans would occur once the symptoms of ALD had occurred. Finally, it must not be discounted that in most patients with SLD caused by alcohol consumption, alcohol might not be the only

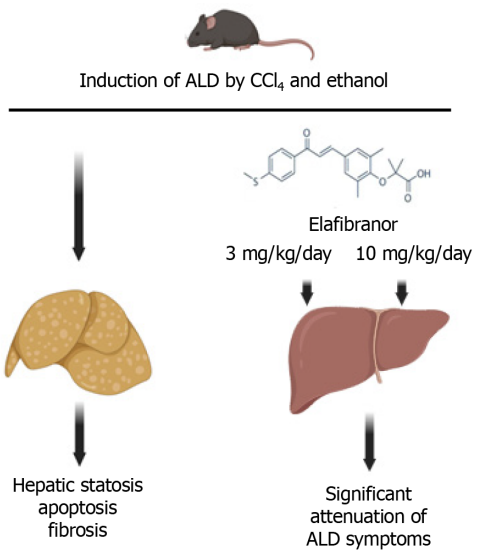

Figure 1 Schematic diagram of study protocol inducing alcohol-associated liver disease and beneficial effects of elafibranor on liver steatotic disease. ALD: Alcohol-associated liver disease; CCl_4: Carbon tetrachloride.

contributor, with other nutritional of lifestyle habits contributing to the manifestation of the pathology. Further studies in animal models may be warranted to fully define the positive effects of elafibranor on ALD. As the efficacy and safety profiles of elafibranor have been already proven in humans, clinical testing on patients suffering from ALD may be feasible to potentially define elafibranor as a treatment for the disease.

FOOTNOTES

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