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Review Article

Repurposing of Antiplatelet Agent: Cilostazol for the Treatment of Alcohol-Related Liver Disease

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Alcohol-related liver disease (ALD) is a serious global health concern, characterized by liver inflammation and progressive fibrosis. There are no Food and Drug Administration-approved drugs, thus effective treatments are needed. Severe alcoholic hepatitis (AH) is the most severe manifestation of ALD, with a 28-day mortality rate ranging from 20% to 50%. For decades, pentoxifylline, an antiplatelet agent, has been used off-label for the treatment of severe AH owing to its tumor necrosis factor-α inhibition properties. However, the STOPAH trial did not reveal the survival benefit of pentoxifylline. Consequently, pentoxifylline is no longer recommended as the first-line therapy for severe AH. In contrast, cilostazol is widely used as an antiplatelet agent in cardiovascular medicine and demonstrates promising results. Cilostazol is a selective phosphodiesterase type 3 inhibitor, whereas pentoxifylline is non-selective. Recent studies using experimental models of alcohol-induced liver injury and other liver diseases have yielded promising results. Although cilostazol shows promise for hepatoprotective effects, it has not yet been evaluated in human clinical trials. In this review, we will explore the mechanism underlying the hepatoprotective effects of cilostazol, along with the pathophysiology of alcohol-induced liver injury, addressing the pressing need for effective therapeutic options for patients with ALD. **(Gut Liver, 2025;19:318-326)**

Key Words: Alcohol-related liver disease; Antiplatelet agent; Cilostazol; Pentoxifylline; Phosphodiesterase inhibitor

INTRODUCTION

Alcohol-related liver disease (ALD) is a global health problem and is associated with liver inflammation, injury, and progressive fibrosis.[1] Severe alcoholic hepatitis (AH) represents the most severe form of ALD, defined by a Maddrey Discriminant Function score over 32 or a Model for End-Stage Liver Disease score exceeding 20 in patients with recent jaundice and a history of chronic alcohol use disorder.[2] Despite a high 28-day mortality rate ranging from 20% to 50%, there remains a significant need for effective treatments.[1-3]

Pentoxifylline is a non-selective phosphodiesterase (PDE) inhibitor with vasodilating and anti-inflammatory properties.[4,5] It is used in the management of peripheral vascular disease, and the U.S. Food and Drug Administration (FDA) approved its use for the symptomatic treatment of claudication.[6] Additionally, pentoxifylline has been used off-label for the treatment of severe AH because it inhibits tumor necrosis factor (TNF)-α, a major cytokine in the pathogenesis of AH.[7] Pentoxifylline increases the concentration of cyclic adenosine monophosphate (cAMP) by blocking membrane-bound PDE.[8]

Five systematic reviews were conducted to assess the efficacy of pentoxifylline for severe AH.[1,9-13] One systematic review, which included several old randomized controlled trials that also involved moderate AH, reported significantly fewer hepatorenal syndrome cases among patients treated with pentoxifylline,[12] while another systematic review found no effect on hepatorenal syndrome.[13] Recently, the largest randomized trial, STOPAH, showed no reduction in all-cause mortality with corticosteroids or pentoxifylline

at 1 month, although non-significant mortality benefit was observed with the use of steroids at 28 days.[14]

In recent years, several new therapies targeting the pathophysiology have been under investigation through ongoing clinical trials.[15] Novel treatments aimed at addressing inflammation, oxidative stress, apoptosis, regeneration, and gut dysbiosis are being tested in AH.[16-18] Cilostazol (OPC-13013), a synthetic vasodilator and antiplatelet agent, was approved in 1988 in Japan for the treatment of occlusive peripheral arterial disease.[19] Thereafter, cilostazol was also approved by the FDA in 1999 for the treatment of intermittent claudication.[19] Over the past 20 years, it has been widely used as a potent inhibitor of platelet aggregation and thrombosis.[20] There are reports suggesting cilostazol may be more effective than pentoxifylline for intermittent claudication.[21] The antiplatelet activity of cilostazol is attributed to its inhibition of PDE.[20] Recent studies have identified 11 different families of PDE.[22] Among these, cilostazol selectively inhibits PDE3, which is predominantly expressed in platelets, vascular smooth muscle cells, cardiac myocytes, and hepatic cells.[23] In addition to its antiplatelet effect, recent studies have suggested that it has various pharmacologic effects, including anti-inflammatory, antioxidant, and antiapoptotic effects.[24-26] Cilostazol has also shown beneficial effects on alcohol-induced liver injury and nonalcoholic fatty liver disease (NAFLD) in animal models.[27-30] The pleiotropic effects of cilostazol are mediated by both cAMP-dependent and -independent pathways, including the AMP-activated protein kinase (AMPK) pathway.[28-30] However, cilostazol has not been tested in clinical trials for treating liver diseases, particularly ALD. In this review, we will explore cilostazol based on the pathophysiology of alcohol-induced liver injury and the potential of cilostazol for the treatment of ALD.

PATHOPHYSIOLOGY OF ALD

1. TNF-α-induced apoptosis

Excessive alcohol intake increases gut permeability to bacterial endotoxin. Subsequently, lipopolysaccharide binds to the TLR4/CD14/MD2 receptor complex on Kupffer cells via portal blood flow, prompting the production of inflammatory cytokines through the MyD88-dependent or TRIF/IRF-3 pathways.[31] Among these cytokines, TNF-α stands out as a potent proinflammatory cytokine primarily generated by activated macrophages (Fig. 1A). TNF-α exerts various effects mediated by TNF receptors 1 and 2, with apoptotic effects specifically medi-

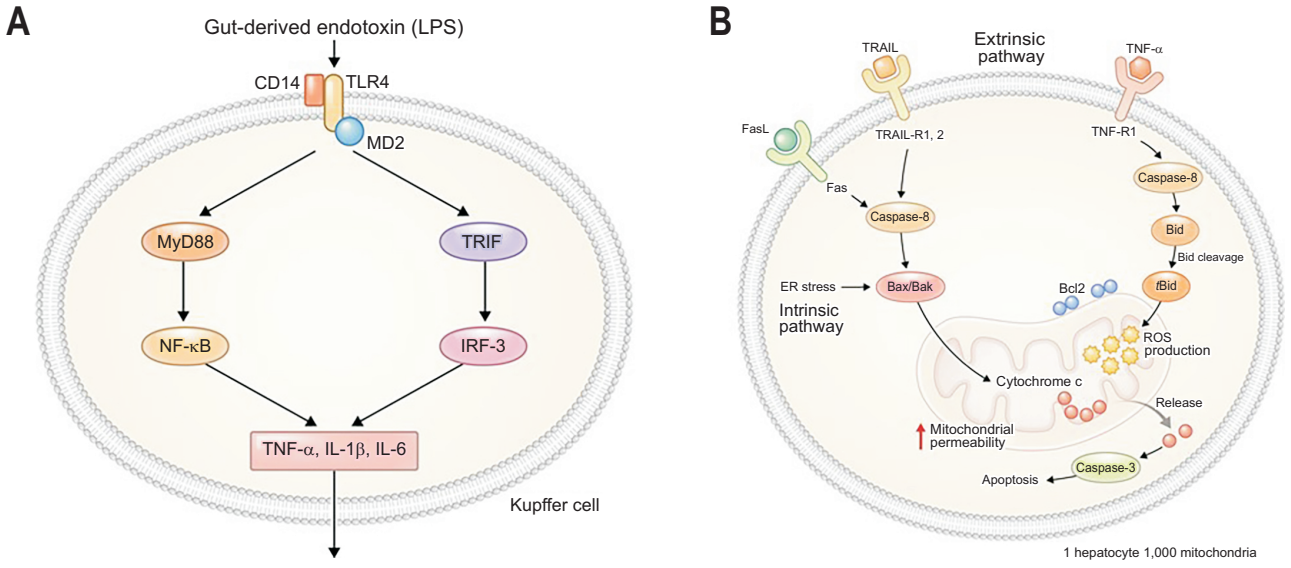

Fig. 1. TNF-α-induced apoptosis. (A) Gut-derived LPS binds to the TLR4/CD14/MD2 receptor complex on Kupffer cells, prompting the release of inflammatory cytokines through either the MyD88-dependent or TRIF/IRF-3 pathways. TNF-α is a major cytokine among them. (B) Apoptosis is a key consequence of cell injury and can occur through two pathways: the extrinsic pathway via death receptors and the intrinsic pathway via ER stress. The apoptotic effect of TNF-α is mediated solely by TNF-R1. The mitochondria are central to both pathways. Caspase-3, an executioner caspase, becomes activated following the release of cytochrome c from the mitochondria. TNF-α, tumor necrosis factor α; LPS, lipopolysaccharide; TLR4, Toll-like receptor 4; CD14, cluster of differentiation 14; MD2, myeloid differentiation 2; MyD88, myeloid differentiation primary response protein 88; TRIF, TIR domain-containing adapter-inducing interferon-β; IRF-3, interferon regulatory factor 3; IL, interleukin; TRAIL, TNF-related apoptosis-inducing ligand; ER, endoplasmic reticulum; NF-κB, nuclear factor-kappa-light chain enhancer of active B cells; tBid, truncated Bid; ROS, reactive oxygen species.

ated by TNF-R1.[32] TNF-α instigates apoptosis in hepatocytes, thereby initiating liver injury, with mitochondria playing a central role in this process. Indeed, all signaling events, either directly or indirectly, converge upon the mitochondria, the executioner in TNF-α-induced apoptosis. Caspase-3, an executioner caspase, is activated following the release of cytochrome c from the mitochondria (Fig. 1B).[33,34] Notably, serum TNF-α levels are significantly elevated in patients with fulminant hepatitis, and in those with AH, these levels correlate inversely with patient survival rates.[35,36] Chronic ethanol consumption further escalates TNF-α production, implicating TNF-α as a promising therapeutic target for AH.[32-36]

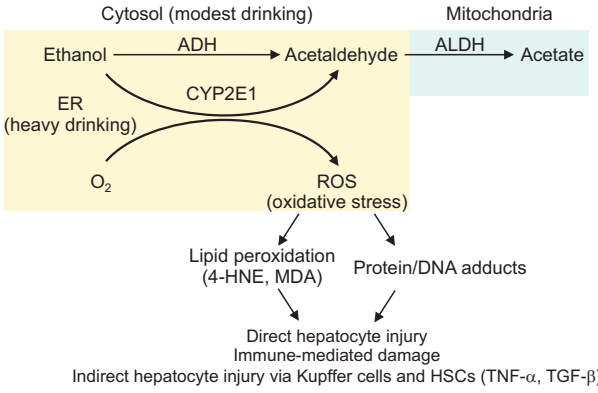

Fig. 2. Alcohol metabolism. Chronic alcohol consumption leads to the formation of ROS. ROS cause lipid peroxidation and produce protein/DNA adducts, resulting in liver injury via direct or immune-mediated mechanisms. ROS, reactive oxygen species; ADH, alcohol dehydrogenase; ALDH, aldehyde dehydrogenase; ER, endoplasmic reticulum; CYP2E1, cytochrome P450 2E1; 4-HNE, 4-hydroxynonenal; MDA, malondialdehyde; HSC, hepatic stellate cell; TNF-α, tumor necrosis factor α; TGF-β, transforming growth factor β.

2. Oxidative stress

Chronic alcohol consumption increases CYP2E1 expression, resulting in an increased acetaldehyde concentration and its accumulation in hepatocytes.[37] CYP2E1, which is located in the endoplasmic reticulum and mitochondria, participates in alcohol metabolism.[38] Its activation by chronic alcohol consumption leads to the formation of reactive oxygen species (ROS) (Fig. 2). ROS damage mitochondrial DNA and proteins, leading to alterations in protein molecule structures, lipid peroxidation, and DNA molecule damage.[39] They further lead to the accumulation of ROS, subsequently altering macromolecules causing the occurrence and progression of existing liver damage.[40] Oxidative stress is one of the important factors in ethanol-induced liver injury, and the therapeutic potential of numerous antioxidants has been explored in ALD.[40-42]

3. Cyclic adenosine monophosphate

cAMP, a key second messenger molecule, plays critical roles in metabolism, inflammation, and fibrosis in several tissues (Fig. 3A).[43-48] cAMP is synthesized from ATP (adenosine triphosphate) by adenylyl cyclase (AC) in response to various signaling molecules.[43] cAMP signaling is regulated by PDE, which degrades cAMP to AMP to terminate the signaling.[43] Increased cAMP activates various effector molecules, including protein kinase A (PKA) and the exchange proteins activated by cAMP.[43] It is clear that cAMP signaling is critical in modulating major pathogenic pathways in patients with ALD such as inflammation,

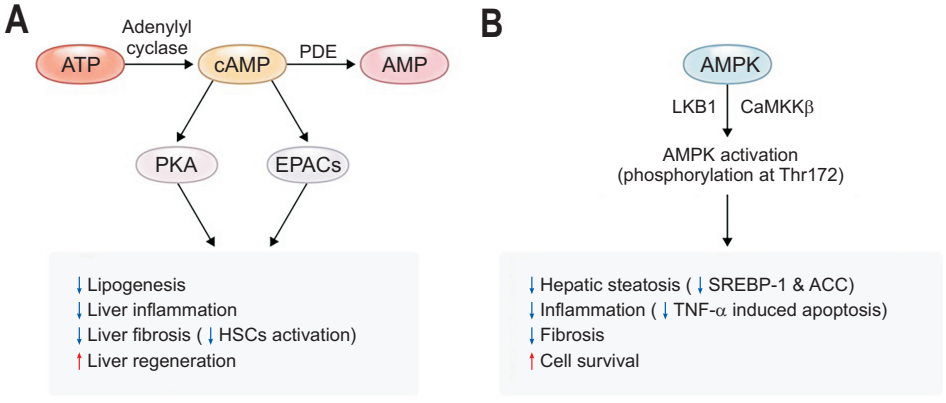

Fig. 3. cAMP and AMPK signaling pathways. (A) PDE degrades cAMP to AMP to terminate the signaling. PDE inhibitors increase cAMP levels. Increased intracellular cAMP levels attenuate inflammation, steatosis, and fibrosis, and enhance liver regeneration. (B) AMPK is activated by phosphorylation at Thr172. Upregulated AMPK activates SREBP-1 and ACC, as well as promotes hepatocyte survival. AMPK also prevents inflammation and fibrosis. cAMP, cyclic adenosine monophosphate; AMPK, adenosine monophosphate-activated protein kinase; PDE, phosphodiesterase; AMP, adenosine monophosphate; SREBP-1, sterol regulatory element-binding protein 1; ACC, acetyl-CoA carboxylase; ATP, adenosine triphosphate; PKA, protein kinase A; EPACs, exchange proteins activated by cAMP; HSC, hepatic stellate cell; LKB1, liver kianse B1; CaMKKβ, calcium/calmodulin-dependent protein kinase kinase beta; TNF-α, tumor necrosis factor α.

steatosis, fibrosis, and even liver regeneration.[43,44] Several pharmacological approaches such as the use of cAMP analogs, AC agonists, and various PDE inhibitors have been tested to study the role of cAMP signaling in both *in vitro* and *in vivo* studies.[44-46] cAMP-elevating agents invariably results in decreased proinflammatory response in monocytes and Kupffer cells.[44] cAMP signaling exerts beneficial effects on lipid metabolism and fibrosis.[47,48] Additionally, altered cAMP signaling impairs liver regeneration.[43,44] Several cAMP-elevating agents have been tested and are clinically used to treat inflammation, tissue fibrosis, asthma, and neurological disorders.[49-51] In 2011 and 2014, the FDA approved two orally available PDE4-specific inhibitors, roflumilast and apremilast, respectively.[49,50] These medications are used for treating severe chronic obstructive pulmonary disease, psoriasis, and psoriatic arthritis. Ibudilast is currently undergoing clinical trials.[51] Regarding liver diseases, PDE inhibitors have demonstrated beneficial effects in animal models of ALD. A broad-spectrum PDE inhibitor, pentoxifylline, has been used in patients with ALD owing to its anti-inflammatory activity. Many studies have reported that cilostazol increases intracellular cAMP levels.[25,28] However, despite the potential benefits of modulating cAMP signaling as an effective therapeutic strategy for ALD treatment, no human trials testing has been conducted for these inhibitors in patients with ALD.

4. AMP-activated protein kinase

AMPK plays a pivotal role in controlling cellular and organism survival during metabolic stress (Fig. 3B).[52] Moreover, it is crucial in determining cell survival or death in response to ROS, depending on the duration of oxidative stress exposure.[52] Additionally, it is crucial for maintaining mitochondrial content and quality.[53] AMPK inhibits inflammation through various mechanisms, including direct inhibition of key inflammatory proteins. Its activation by ROS can promote cell survival by inducing autophagy, mitochondrial biogenesis, and the expression of genes involved in antioxidant defense.[52,53] AMPK activated fatty acid oxidation and inhibited lipogenesis in rat hepatocytes and the livers of ethanol-fed mice. Ethanol inhibits AMPK in the liver, leading to an increased activity of sterol regulatory element-binding protein 1 (SREBP-1) and acetyl-CoA carboxylase (ACC). Consequently, hepatic lipid synthesis increases while fatty acid oxidation decreases, contributing to the development of alcoholic fatty liver disease.[54] Ethanol treatment, both *in vitro* and *in vivo,* has been shown to decrease hepatic AMPK activation. Experiments with AMPK activators and inhibitors demonstrated that upregulation of AMPK promotes hepatocyte survival.[55] Therefore, AMPK represents an attractive therapeutic target for alcoholic fatty liver disease. Additionally, Wang *et al.*[56] reported that the adipokine orosomucoid alleviates adipose tissue fibrosis via the AMPK pathway.

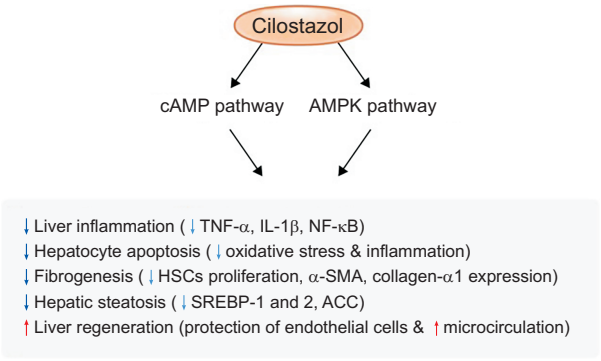

Fig. 4. Beneficial effects of cilostazol in experimental models. The effects are mediated via cAMP-dependent and -independent pathways, including the AMPK pathway. cAMP, cyclic adenosine monophosphate; AMPK, adenosine monophosphate-activated protein kinase; TNF-α, tumor necrosis factor α; IL, interleukin; NF-κB, nuclear factor-kappa-light chain enhancer of active B cells; HSC, hepatic stellate cell; α-SMA, alpha-smooth muscle actin; SREBP-1, sterol regulatory element-binding protein 1; ACC, acetyl-CoA carboxylase.

BENEFICIAL EFFECTS OF CILOSTAZOL ON LIVER INJURY MODELS

1. Attenuation of liver inflammation

The beneficial effects of cilostazol are summarized in Fig. 4. Cilostazol has been shown to decrease liver TNF-α, interleukin-1β, and nuclear factor- kappa-light chain enhancer of active B cells levels in thioacetamide-induced liver damage.[57] It also decreased TNF-α levels in the common bile duct-ligated rats.[58] Furthermore, cilostazol significantly suppressed lipopolysaccharide-stimulated TNF-α production in RAW264.7 murine macrophages exposed to ethanol and in the liver of binge-drinking mice.[29] Additionally, cilostazol has been shown to reduce levels of aspartate aminotransferase (AST) and alanine aminotransferase (ALT), and to improve liver histology.[57] Chronic ethanol exposure typically decreases in cAMP levels.[44] Cilostazol has been demonstrated to increase intracellular cAMP levels in both *in vivo* and *in vitro* studies.[25,28,59] Therefore, the anti-inflammatory effect of cilostazol was postulated to be mediated by the cAMP signaling pathway. However, Lee and Eun[29] demonstrated that the anti-inflammatory effect of cilostazol is mediated by the AMPK pathway and not by the cAMP signaling pathway. This result is consistent with the findings of Park *et al.*[26]

2. Inhibition of oxidative stress and apoptosis

Ethanol increases intracellular ROS levels in primary cultured hepatocytes.[27] Oxidative stress plays an essential role in ethanol-induced liver injury.[40] Cilostazol significantly inhibits ROS production in a dose-dependent manner.[27] Consistently, cilostazol prevents the ethanol-induced increase in intracellular 4-hydroxynonenal levels.[27] Mitochondrial permeability transition serves as a critical regulatory mechanism for cytochrome c release. Cilostazol has been shown to effectively mitigate ethanol-induced mitochondrial dysfunction in primary cultured hepatocytes, thereby preventing the release of cytochrome c from mitochondria into cytosol.[27] The Bax/Bcl-2 families are important regulators of the mitochondria-dependent apoptotic pathway.[33] Ethanol increases proapoptotic Bax levels but decreases antiapoptotic Bcl-2 levels.[60] Cilostazol inhibits ethanol-induced increase in cleaved caspase-3 (activated caspase-3).[27] These results collectively indicate that cilostazol exerts hepatoprotective effects by ameliorating oxidative stress, increasing cell viability, preserving mitochondrial function, and inhibiting apoptosis.[27] The antiapoptotic effect of cilostazol was also demonstrated by Lee *et al.*, who showed that cilostazol restores cell viability dose-dependently and inhibits apoptosis on ethanol-treated hepatocytes. Lee *et al.*[30] suggested that the hepatoprotective effect of cilostazol is mediated by the AMPK pathway and not the cAMP signaling pathway.

3. Attenuation of fibrogenesis

Several strategies have been developed to attenuate liver fibrosis, with one important signaling pathway involved being the cAMP pathway.[43,46] Increases in cAMP levels produce antifibrotic effects by inhibiting fibroblast function and extracellular matrix (ECM) protein synthesis.[61] Hence, the cAMP pathway is a potential target to mitigate fibrosis. In 1999, Shimizu *et al.*[62] first reported that OPC-13013 (cilostazol) suppresses hepatic stellate cell (HSC) activation via the cAMP signaling pathway. Cilostazol has been shown to reduce fibrogenesis in a thioacetamide-induced liver fibrosis model.[63] It modulates various processes in the liver related to oxidative stress, inflammation, apoptosis, ECM, collagen deposition, as well as the cAMP pathway.[63] Compared to clopidogrel, only cilostazol attenuates liver fibrosis, suggesting it may have distinct antifibrotic mechanisms in addition to its antiplatelet action.[64] This finding is consistent with the results of an *in vitro* study, in which cilostazol attenuated HSC proliferation and the expression of α-SMA and collagen α1, indicating the direct effect of cilostazol on HSCs.[59,64]

4. Improvement of hepatic steatosis

The effects of aspirin, ticlopidine, and cilostazol on suppressing NAFLD have been observed, with cilostazol found to be the most effective agent.[28] The authors suggested this discrepancy may be attributed to the drugs' effects on cAMP activation. The cAMP/PKA signaling pathway plays a major role in activating the cAMP-response element-binding protein (CREB) in hepatocytes.[28] In the liver, the cAMP/CREB signaling pathway regulates the expression of the key genes involved in glucose and lipid metabolism.[28] Previous studies have shown that cilostazol has beneficial effects on glucose metabolism *in vitro* and *in vivo*.[65] Additionally, cilostazol attenuated TNF-α-induced chronic inflammation in adipose tissue through the suppression of TNF-α production by macrophages, leading to an amelioration of systemic insulin resistance in obese diabetic mice.[66] AMPK phosphorylates key metabolic enzymes and transcriptional regulators, including fatty acid synthase, SREBP-1, SREBP-2, and ACC, which are associated with controlling lipid biosynthesis.[65] Cilostazol has been found to activate AMPK in vascular smooth muscle and endothelial cells.[67] Furthermore, it activates AMPK and ameliorates lipid imbalances in patients with NAFLD.[65] Several studies have shown promise for cilostazol in improving hepatic steatosis.[68,69] Considering the common mechanisms underlying the development of hepatic steatosis, cilostazol may also be effective in alcoholic fatty liver disease.

5. Enhancement of liver regeneration and others

Cilostazol enhances liver regeneration after major hepatectomy.[70,71] It increases angiogenesis-related genes, including endothelial nitric oxide synthase mRNA.[72] The increased intracellular cAMP levels in the cilostazol-treated animals may have contributed to the protection of endothelial cells, improvement of the hepatic microcirculation, and preservation of hepatocellular integrity.[71,72] In another study, cilostazol alleviated hepatic ischemic/reperfusion injury in rats by protecting against hepatocyte injury and improving liver function.[73-75] Moreover, cilostazol improved cholestatic liver injury by significantly decreasing AST, ALT, gamma-glutamyl transpeptidase, and T-bilirubin levels.[58]

CONCLUSIONS

FDA-approved drugs for ALD are currently unavailable. For decades, pentoxifylline and glucocorticoids have been used off-label for the treatment of severe AH. Pentoxifylline is no longer recommended as a first-line treatment based on the results of the STOPAH trial. High-dose glu-

cocorticoids remain the only medical treatment option, but they are contraindicated in cases of gastrointestinal bleeding or active infection and must be used with caution due to their various side effects.

Experimental studies on alcohol-induced or other liver injury models have demonstrated the beneficial pharmacological effects of cilostazol, including anti-inflammatory, antioxidant, antiapoptotic, and antifibrotic effects. Cilostazol has also shown beneficial effects on hepatic steatosis in an NAFLD animal model. The pleiotropic effects of cilostazol are mediated by both cAMP-dependent and -independent pathways, including the AMPK pathway. Therefore, cilostazol may be a promising candidate for ALD, particularly AH.

Despite this scientific evidence, it is unfortunate that cilostazol has yet to be tested in clinical trials. The greatest advantage of cilostazol is its established safety profile from decades of use in cardiovascular medicine. We hope that well-designed clinical studies of cilostazol, either alone or in combination with other drugs, will be conducted for ALD.

CONFLICTS OF INTEREST

S.U.K. has served as an advisory committee member for Gilead Sciences, GSK, Bayer, Novo Nordisk, and Eisai. He is a speaker for Gilead Sciences, GSK, Bayer, Eisai, Abbive, EchoSens, MSD, Bristol-Myers Squibb, Hanhwa, Yuhan, Samil, PharmaKing, Celltrion, and Bukwang. He has also received research grants from Abbive and Bristol-Myers Squibb. And S.U.K. is an editorial board member of the journal but was not involved in the peer reviewer selection, evaluation, or decision process of this article. No other potential conflicts of interest relevant to this article were reported.

AUTHOR CONTRIBUTIONS

Conceptualization; Investigation: J.R.E., S.U.K. Data curation; Visualization: J.R.E., S.U.K. Drafting of the manuscript: J.R.E. Critical revision of the manuscript for important intellectual content: J.R.E., S.U.K.

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