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EDITORIAL

Role of cenicriviroc in the management of nonalcoholic fatty liver disease

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Abstract

Nonalcoholic fatty liver disease (NAFLD) is the commonest chronic liver disease in high-income countries and is associated with increased morbidity and mortality. Macrophages appear to play an important role in the development and progression of hepatic fibrosis in patients with NAFLD. Accordingly, modulation of macrophage trafficking might represent an attractive therapeutic strategy in this population. Cenicriviroc is an oral inhibitor of the chemokine ligand 2/C-C chemokine receptor 2 pathway, which plays an important role in the hepatic recruitment of the macrophages. Preclinical studies and a phase 2b study in humans suggest that this agent might hold promise in the management of NAFLD.

Key words: Cenicriviroc; Macrophages; Nonalcoholic fatty liver disease; Fibrosis; Nonalcoholic steatohepatitis

Core tip: Macrophages appear to play an important role in the development and progression of hepatic fibrosis in patients with nonalcoholic fatty liver disease (NAFLD). Accordingly, modulation of macrophage trafficking might represent an attractive therapeutic strategy in this population. Cenicriviroc is an oral inhibitor of the chemokine ligand 2/C-C chemokine receptor 2 pathway, which plays an important role in the hepatic recruitment of the macrophages. Preclinical studies and a phase 2b study in humans suggest that this agent might hold promise in the management of NAFLD.

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INTRODUCTION

The prevalence of nonalcoholic fatty liver disease (NAFLD)

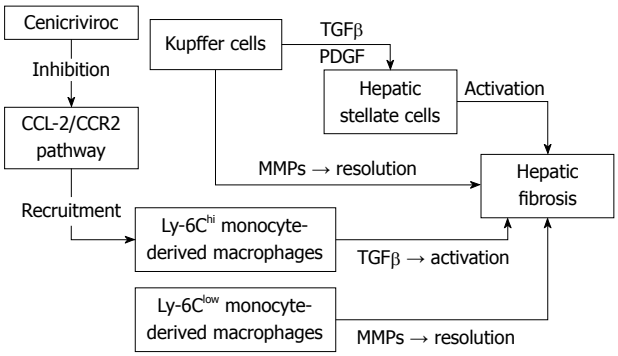

Figure 1 Molecular pathway through which cenicriviroc acts. TGFβ: Transforming growth factor β; PDGF: Platelet-derived growth factor; MMPs: Matrix metalloproteinases; CCL-2/CCR2: Chemokine (C-C motif) ligand 2/ C-C chemokine receptor 2.

is increasing worldwide and NAFLD has become the most predominant liver disease in Western countries due to the pandemic of obesity, metabolic syndrome and type 2 diabetes[1]. The histopathological spectrum of NAFLD ranges from isolated steatosis to nonalcoholic steatohepatitis (NASH) and cirrhosis, and NAFLD is associated with increased risk for hepatocellular carcinoma (HCC)[2].

The mainstay of treatment of NAFLD is weight loss through diet and exercise[2]. However, many patients cannot achieve or sustain weight loss[2]. Accordingly, pharmacotherapy is required in a considerable proportion of patients with NAFLD, particularly those with advanced fibrosis, who are at higher risk for liver-related complications[2,3].

Hepatic macrophages play an important role in the pathogenesis of acute and chronic liver injury[4,5]. Hepatic macrophages are a heterogenous population, consisting of Kupffer cells (KCs) and monocyte-derived macrophages (MoMF), which are recruited from the circulation to the liver[4,5]. KCs activate hepatic stellate cells (HSCs) through the production of pro-fibrotic cytokines transforming growth factor β (TGFβ) and platelet-derived growth factor (PDGF)[4,5]. On the other hand, KCs also secrete matrix metalloproteinases (MMPs), resulting in resolution of fibrosis[4,5]. Therefore, hepatic macrophages appear to exert both pro- and anti-fibrotic functions[4,5]. In cases of hepatic injury, Ly-6C^{hi} monocytes differentiate into proinflammatory macrophages, which interact with HSCs to promote fibrosis through the production of TGFβ[4,5]. The chemokine (C-C motif) ligand (CCL) 2/C-C chemokine receptor 2 (CCR2) pathway plays an important role in the hepatic recruitment of the Ly-6C^{hi} monocytes[4,5]. On the other hand, a recent study showed that phagocytosis of cellular debris facilitates a phenotypic switch from Ly-6C^{hi} macrophages to Ly-6C^{low} macrophages[4,5]. The Ly-6C^{low} monocyte is the main source of MMPs and promotes fibrosis resolution[4,5] (Figure 1).

CENICRIVIROC IN NAFLD

Given the important role of hepatic macrophages in the pathogenesis of liver fibrosis, targeting these cells might represent a promising approach in the management of NAFLD. Krenkel *et al*[6] recently reported an increased number of CCR2$^+$ macrophages in patients with NASH and either advanced fibrosis (stage 3) or cirrhosis (stage 4). It was also shown that cenicriviroc (CVC), an oral CCR2/CCR5 antagonist, prevents macrophage trafficking and hepatic infiltration by CCR2$^+$ MoMFs and might therefore be useful in the prevention and/or resolution of hepatic fibrosis in patients with NAFLD[6].

Several animal studies evaluated the antifibrotic potential of CVC. Kruger *et al*[7] administered CVC 10 mg/(kg•d) or 30 mg/(kg•d) for 4 wk and 20 mg/(kg•d) or 30 mg/(kg•d) for 14 wk in mice fed with a choline-deficient, L-amino acid- defined, high-fat diet (CDAHFD). A second group of mice was fed with standard chow and did not receive CVC. At 4 and 14 wk, livers were harvested for histology and flow cytometric analyses of intrahepatic cells. Serum alanine transaminase (ALT) and aspartate transaminase (AST) levels were normal in the standard chow group but were elevated in CDAHFD-fed, untreated control mice. In contrast, the CDAHFD-fed mice that were treated with CVBC 10 mg/(kg•d) and 30 mg/(kg•d) for 4 wk experienced a reduction in ALT levels. Moreover, after 4 wk of high-dose CVC treatment, a significant decrease in the number of intrahepatic Ly6-C^{high} macrophages was observed relative to the vehicle control. The intrahepatic CCR2$^+$ macrophages also decreased with 4 wk of CVC treatment whereas CCR5$^+$ macrophages were not affected. Therefore, CVC appears to have greater affinity for CCR2 than for CCR5 in mice. Kruger *et al*[7] also noticed a significant decrease in hepatic fibrosis in mice that received high-dose CVC treatment for 14 wk compared with vehicle controls. In another study, CVC reduced monocyte/macrophage recruitment at doses > 20 mg/(kg•d) in a mouse model of thiaglycalate-induced peritonitis[8]. At these doses, CVC also prevented hepatic fibrosis in a rat model of thioacetamide-induced liver fibrosis and in a mouse model of diet-induced NASH. A reduction in NAFLD activity score (NAS) and in plasma ALT levels was also observed with CVC treatment[8]. In another animal model of carbon tetrachloride-induced acute liver injury, mice received CVC or a vehicle control solution orally before the administration of carbon tetrachloride and after 12 h and 24 h[9]. CVC treatment reduced the number of F4/80 positive macrophages in the liver, particularly in the periportal and necrotic areas. Reductions in ALT levels and in the necrotic area at 36 h were also observed[9].

Recently, the results of the CENTAUR study were published[10]. This was a phase 2b, double-blind, placebo-controlled, multinational study that randomized 289 patients with NASH, NAS ⩾ 4 with ⩾ 1 in each component and stage 1-3 liver fibrosis to receive CVC 150 mg per os once daily or placebo. After 1 year of treatment, the primary endpoint (⩾ 2-point improvement in NAS with ⩾ 1-point reduction in either lobular inflammation or hepatocellular ballooning and no worsening of fibrosis) in the intent-to-treat population was achieved in a similar proportion of subjects on CVC and placebo

(16% *vs* 19%, respectively; $P = 0.52$). Resolution of steatohepatitis and no worsening of fibrosis, a key secondary outcome, was also observed in similar rates in the 2 groups (8% *vs* 6%, respectively; $P = 0.49$). However, improvement in fibrosis by $\geqslant$ 1 stage and no worsening of steatohepatitis, another key secondary outcome, was observed in more patients on CVC than placebo (20% *vs* 10%, respectively; $P = 0.02$). Patients with higher NAS, prominent hepatocellular ballooning, higher fibrosis stage, mild or no portal inflammation and with higher body mass index showed greater improvements with CVC treatment. The levels of biomarkers of systemic inflammation (high-sensitivity C-reactive protein, interleukin-6 and 1β, and fibrinogen) and of monocyte activation (sCD14) decreased in patients treated with CVC. On the other hand, CCL-2 and -4 increased in CVC-treated patients, confirming CCR2 and CCR5 blockade by CVC. Importantly, safety and tolerability of CVC were comparable to placebo[10]. AURORA, a phase Ⅲ study, will evaluate the effects of CVC on hepatic fibrosis in 2000 patients with NASH and is expected to be completed in 2019[11].

CONCLUSION

Cenicriviroc appears to represent a promising tool in the management of patients with NAFLD. However, larger studies are needed to clearly define the safety and efficacy of this novel agent in this highly prevalent disease.

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