Saroglitazar Attenuates Hepatic Inflammation, Oxidative Stress and Fibrosis in Models of NAFLD/NASH

Abstract

Nonalcoholic fatty liver disease (NAFLD) and nonalcoholic steatohepatitis (NASH) affects millions of patients worldwide. In these conditions, excessive lipid deposition in the hepatocytes induces inflammatory changes, ROS generation and mitochondrial dysfunction that lead to activation of hepatic stellate cells and development of fibrosis. PPARα agonists are known to affect liver lipids and show pleiotropic benefits. Saroglitazar is a novel PPARα/γ agonist having predominant PPARα alpha-activity. In earlier studies, saroglitazar lowered liver dysfunction markers and prevented accumulation of lipid in choline-deficient high-fat diet fed CCl4 mice. It also reduced the expression of pro-inflammatory and pro-fibrotic marker genes and histologically showed suppression of steatosis, ballooning, inflammation and fibrosis. In present study the role of saroglitazar in preventing NASH, NAFLD and liver fibrosis has been evaluated using HepG2 cells, co-culture of stellate cells with HepG2 cells and Carbon tetrachloride (CCl4), i.e., induced liver fibrosis in Sprague Dawley (SD) rats. HepG2 cells were treated with palmitic acid (PAS) (0.75 mM) for 16 hr to induce lipid overload. PAS significantly (P <0.001) decreased the expressions of various antioxidant genes (SOD1, SOD2, GPX and CAT) and caused induction of inflammatory marker (TNFα, IL6, IL10) these effects were blocked/ reversed by saroglitazar (10 μM). Saroglitazar treatment also reversed (P <0.001) PA-mediated changes in mitochondrial dysfunction and reduction in ATP production, and abrogated phosphorylation of NFκB. PA-mediated induction of fibrotic genes in stellate cells (Fibronectin) co-cultured with HepG2 was rectified by saroglitazar treatment. Saroglitazar also abrogated the formation of focal adhesion points and reorganization of cytoskeletal actin in activated stellate cells. Effect of saroglitazar on hepatic fibrosis was assessed in SD rats following administration of CCl4, intraperitoneally for a period of 6 weeks. Treatment with saroglitazar (0.4 and 4 mg/kg p.o.) showed dose-dependent reduction in CCl4-induced liver fibrosis as indicated by reduction in hydroxyproline levels and histological improvements in fibrosis shown by HE and Masson’s Trichrome staining of liver tissues. The effect of saroglitazar was better than one shown by pioglitazone (10 mg/kg) and fenofibrate (100 mg/kg p.o.) in this study.

Conclusions: Study has revealed anti-inflammatory & anti-fibrotic effects of saroglitazar in hepatic cells and animal model of NASH/hepatic fibrosis. Saroglitazar appears to be a promising drug for the treatment of NASH.

Background

Saroglitazar is a dual PPARα/γ agonist that has shown insulin sensitizing and lipid lowering effects along with improved metabolic profile in various preclinical and clinical studies. Saroglitazar is approved in India for treatment of diabetic dyslipidemia and hypertriglyceridemia in patients with type 2 diabetes not adequately controlled by statins. In earlier studies conducted in choline-deficient high-fat diet-fed CCl4 mouse model, both prophylactic and curative saroglitazar (3 mg/kg) treatment regimens improved liver injury markers, serum alanine aminotransferase and aspartate aminotransferase. Saroglitazar prevented / reduced the accumulation of lipids in hepatocytes. Saroglitazar reduced the expression of inflammatory and pro-fibrotic marker genes such as TNFα, MCP-1, MMP-1, TGF-β, COL1A1 and α-SMA. Liver histology revealed the suppression/reversal of steatosis, ballooning, inflammation and fibrosis in animals treated with saroglitazar. In an observational study in NASH patients, saroglitazar was reported to reduce liver fat content, which supports preclinical observations. Liver appears to be primary site of action for saroglitazar as tissue distribution studies have also revealed highest concentrations of saroglitazar in liver tissue.

Conclusions

- Saroglitazar treatment rectifies lipid-mediated injury, inflammation, oxidative stress and impaired mitochondrial function
- Saroglitazar showed reduction in hepatic fibrosis as revealed by Masson’s Trichrome staining & total NASH score
- Saroglitazar may be reducing the fibrosis by preventing the activation of stellate cells and abrogating the release of inflammatory, pro-fibrogenic factors from PA-treated hepatocytes.
- Thus saroglitazar shows anti-inflammatory, antioxidant and antifibrotic effects in both in-vitro and in-vivo models and appears to be a promising drug for the treatment of NASH.

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