The pan-PPAR agonist lanifibranor decreases portal pressure in models of both hepatic and prehepatic portal hypertension

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Introduction

Portal hypertension (PHT) can cause severe complications in patients with advanced chronic liver disease (ACLD). Studies have indicated that the pan-peroxisome proliferator-activated receptor (pan-PPAR) agonist lanifibranor reduces portal pressure in preclinical models of ACLD. However, as lanifibranor simultaneously improves the underlying fibrosis, the effect on PHT might be secondary. In contrast, the partial portal vein ligation (PPVL) model, a model of non-fibrotic PHT, allows us to investigate the effect of lanifibranor on the extra-hepatic vascularization.

Aim

In this study, we aimed to investigate the method of action of lanifibranor on PHT. More specifically, the effect of lanifibranor on hepatic and splanchnic angiogenesis and liver sinusoidal endothelial cell (LSEC) dysfunction was explored, since these play a major role in the pathogenesis of PHT.

Method

Mice with prehepatic PHT (PPVL) and fibrotic mice with PHT (common bile duct ligation; CBDL) received daily lanifibranor (10mg/kg or 30mg/kg) or vehicle in a therapeutic setting for 7 or 14 days, respectively. The effect of lanifibranor on PHT, angiogenesis and LSEC was evaluated by analyzing hepatic and systemic hemodynamics, serum, hepatic and mesenteric histology, and hepatic, mesenteric and LSEC gene expression levels. Vascular corrosion casts of the venous mesenteric and hepatic vasculature were analyzed using scanning electron microscopy (SEM).

Conclusions

Lanifibranor improves PHT, independently from fibrosis reduction, potentially through reducing the venous mesenteric vascular expansion and the mesenteric blood flow and ameliorating LSEC function.

References

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Results

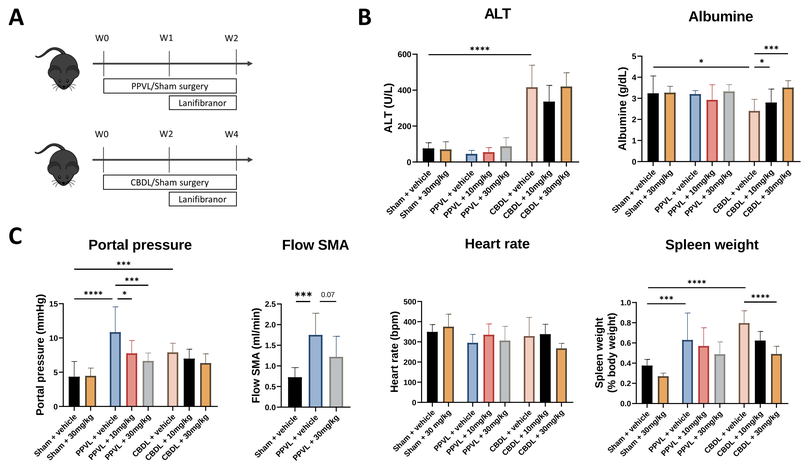

Figure 1. PPVL and CBDL mice received daily lanifibranor or vehicle for 7 or 14 days respectively (A). In CBDL mice, high-dose lanifibranor treatment restored the serum albumin to a level comparable to the sham-operated mice. ALT remained unchanged (B). Lanifibranor reduced the portal pressure by 30-35% compared to vehicle-treated PPVL mice, without affecting heart rate (C). The portal pressure was increased to a lesser extent in the CBDL model and was decreased non-significantly by 12-20% upon lanifibranor administration. Superior mesenteric artery (SMA) blood flow was significantly increased in vehicle-treated PPVL mice but tended to decrease in PPVL mice treated with lanifibranor. Lanifibranor significantly alleviated splenomegaly in both models (C).

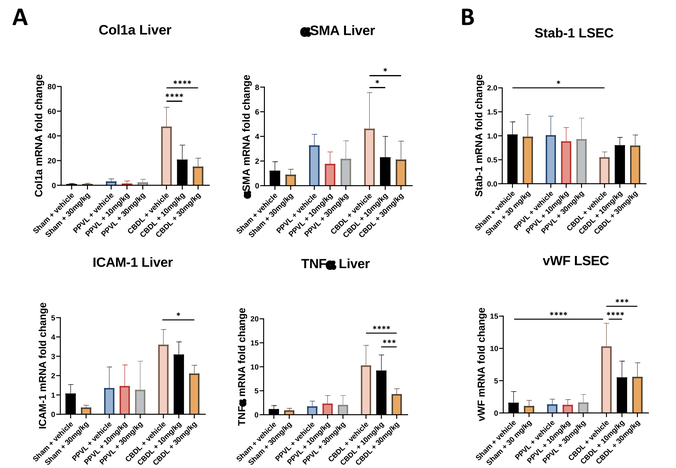

Figure 2. Hepatic mRNA levels of inflammatory and fibrotic markers and cell adhesion molecules were significantly reduced in lanifibranor-treated CBDL mice compared to vehicle-treated CBDL mice. No hepatic injury was observed in PPVL mice (A). LSEC dysfunction was improved by lanifibranor treatment in CBDL mice (B).

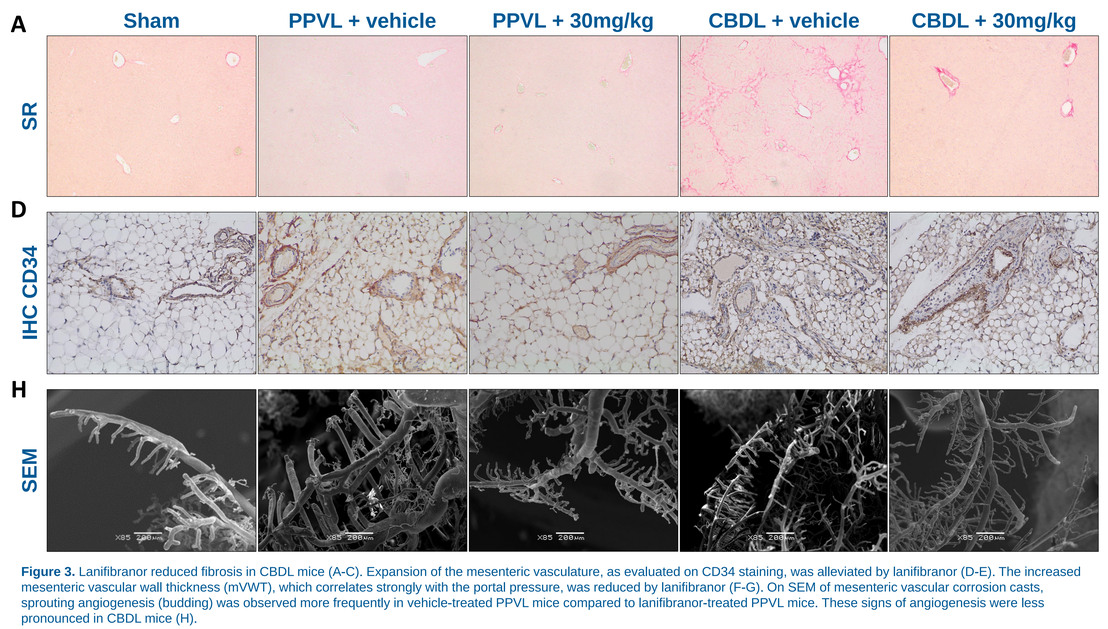

Figure 3. Lanifibranor reduced fibrosis in CBDL mice (A-C). Expansion of the mesenteric vasculature, as evaluated on CD34 staining, was alleviated by lanifibranor (D-E). The increased mesenteric vascular wall thickness (mVWT), which correlates strongly with the portal pressure, was reduced by lanifibranor (F-G). On SEM of mesenteric vascular corrosion casts, sprouting angiogenesis (budding) was observed more frequently in vehicle-treated PPVL mice compared to lanifibranor-treated PPVL mice. These signs of angiogenesis were less pronounced in CBDL mice (H).