Synergy of SOAT2-inhibitor PRD001 with resmetirom in reducing MASH and fibrosis in obese Ldlr-/-.Leiden mice

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Background and Aims:
Metabolic-dysfunction associated steatohepatitis (MASH) is characterized by hepatic lipid accumulation and inflammation. Sterol *O*-acyltransferase 2 (SOAT2), formerly known as ACAT2, plays a key role in intestinal cholesterol absorption and hepatic secretion. Pharmacological inhibition of SOAT2 reduces cholesterol uptake, thereby limiting hepatic lipid accumulation and secretion. Combining a SOAT2-inhibitor with resmetirom, a thyroid hormone receptor-β (THR-β) agonist that promotes lipid oxidation, could provide complementary reductions in fat and plasma lipids. This study aimed to assess the effects of PRD001, a SOAT2-inhibitor, combined with resmetirom on MASH and liver fibrosis.

Methods:
20-week high-fat diet (HFD) fed Ldlr-/-.Leiden mice received vehicle, resmetirom (3 mg/kg), or resmetirom + PRD001 (30 mg/kg) for 12 weeks.

Results:
Resmetirom and the combination treatment reduced body weight and fat mass, while increasing lean body mass as % of body weight. Fecal neutral sterol excretion, mainly driven by cholesterol excretion, was significantly increased with resmetirom and tended to be further enhanced when combined with PRD001. Resmetirom decreased plasma lipids and apoB with a significant further decrease for both when combined with PRD001. Lipoprotein profiles confirmed that this additional decrease was primarily due to a further decrease in VLDL- and LDL-cholesterol. Hepatic triglycerides and cholesterol esters were significantly decreased as well with resmetirom and combination with PRD001 led to a significant further decrease in hepatic cholesterol ester content. Hepatic macrovesicular steatosis, microvesicular steatosis, inflammation and fibrosis were all significantly reduced upon resmetirom treatment with a further decease in macro- and microvesicular steatosis when combined with PRD001. Hepatic gene expression confirmed involvement of (lipid)metabolism, inflammation pathways and mitochondrial pathways with more significant genes when resmetirom was combined with PRD001.

Conclusion:
Using an advanced translational MASH model, we demonstrate resmetirom improved MASH and hepatic fibrosis. Adding PRD001 provided additional benefits on cholesterol excretion, plasma lipids, lipoproteins and steatosis highlighting the complementary mechanisms of PRD001 and resmetirom. Given the CVD risk in MASH patients, the observed lowering of atherogenic lipoproteins underscore substantial clinical advantages for the combination treatment.