A 4-week mouse model allows the rapid evaluation of resmetirom and tirzepatide benefits on metabolic dysfunction-associated steatohepatitis

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Background and Aims: There is currently no marketed drug for the treatment of metabolic dysfunction-associated steatohepatitis (MASH). To expedite preclinical drug development, we have developed a mouse model fed a high fat/cholesterol/choleic acid diet with cyclodextrin in drinking water (HFCC+CDX diet) to promote hepatocyte cholesterol loading, liver inflammation and MASH within 4 weeks. For future head-to-head comparison or drug combinations studies with incretin-based therapies, we evaluated the efficacy of resmetirom, a thyroid hormone receptor-β agonist, and tirzepatide, a dual gastric inhibitory polypeptide receptor and glucagon-like peptide-1 receptor agonist.

Method: Male, 8-week-old, C57BL6/J mice were fed the HFCC+CDX diet for 4 weeks. After 2 weeks of diet, animals were randomized based on their plasma transaminases levels and body weight. Mice were kept on the same diet and were treated once daily with vehicle, resmetirom 3 mg/kg p.o. or tirzepatide 3µg/kg s.c. for 2 weeks. At the end of the treatment period, blood and liver samples were collected for biochemistry and histology analysis.

Results: Resmetirom did not alter plasma transaminases levels but significantly reduces plasma total cholesterol and LDL-cholesterol levels (-27% and -37% respectively, both p<0.001 vs. vehicle). This LDL-lowering effect was associated with higher LDL-receptor (+39%) and lower apolipoprotein B (-17%) hepatic gene expression (both p<0.01). Resmetirom reduced hepatic triglycerides content (-25%, p<0.01) and significantly reduced NAFLD activity score through lower inflammation score (p<0.01), as well as lower IL-6 and IL-1β hepatic gene expression (both p<0.05). Resmetirom also showed anti-fibrotic effects as shown by a significantly lower % Sirius Red labelling. As expected, tirzepatide induced body weight loss, leading to a 13% lower body weight after 2 weeks of treatment, as compared to vehicle (p<0.001). Although it did not alter plasma transaminases levels significantly, tirzepatide significantly lowered the hepatic gene expression of IL-1β and IL-6 (both p<0.05 vs. vehicle). It also reduced liver triglycerides content by 18% and hepatic inflammation score (p<0.05 vs. vehicle).

Conclusion: Resmetirom and tirzepatide both improve MASH in our 4-week diet-induced mouse model. This preclinical model will be useful to expedite preclinical drug development for the treatment of MASH.