Resmetirom protects against diet-induced MASLD and reduces atherosclerosis development in obese LDLR-/-.Leiden mice

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1. Introduction

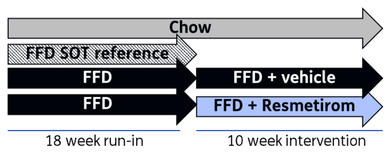
Resmetirom (Rezdiffra) is a potent lipid-lowering drug (thyroid hormone receptor-β agonist) and the first approved drug for MASLD. Clinical trials have revealed its remarkable efficacy in reducing plasma LDL cholesterol levels, suggesting its potential impact on mitigating obesity-related cardiovascular disease (CVD), the foremost contributor to mortality among MASLD patients.

2. Study aims and design

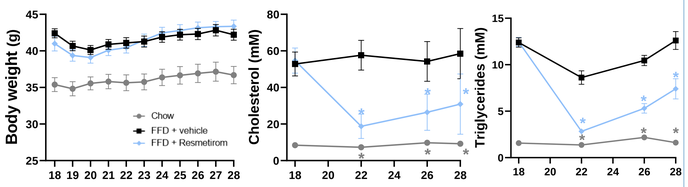
The study aimed to assess resmetirom's impact on CVD progression (atherosclerosis) on top of its positive effects on MASLD-associated liver fibrosis.

Ldlr-/-.Leiden mice were initially fed a fast-food diet (FFD) for 18 weeks to induce early MASLD and atherosclerosis. After this period, one group was terminated as a start-of-treatment reference (FFD SOT). The rest continued on FFD and received either vehicle or 3 mg/kg Resmetirom for an additional 10 weeks before termination at t=28 weeks. Chow-fed mice served as a healthy reference group.

LDLr$^{-/-}$.Leiden mice
(n=8 chow mice;
n=15 FFD mice/grp)

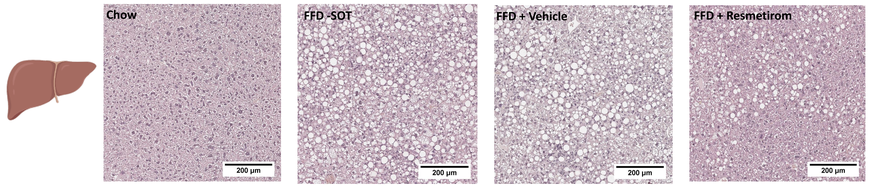


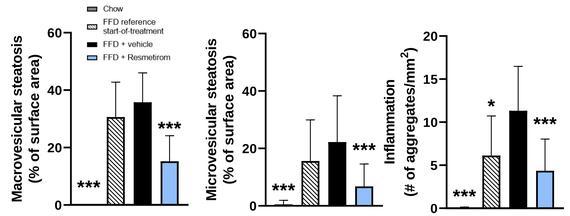
3. Resmetirom improved metabolic risk factors independent of BW effects



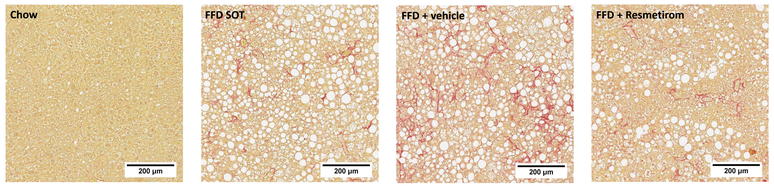
Resmetirom reduced FFD-induced increased in plasma lipids cholesterol and triglycerides in absence of an effect on body weight (BW).

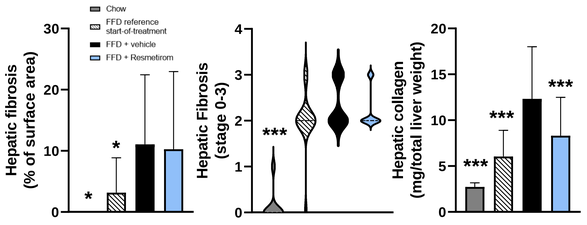
4. Resmetirom reduced MASLD/MASH development





Resmetirom reduced FFD-induced macro- and microvesicular steatosis, as well as liver inflammation, reaching levels below those observed in the FFD start-of-treatment reference group.



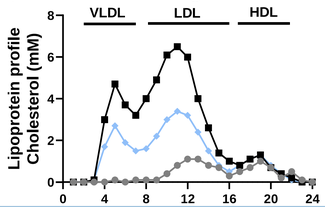


Resmetirom didn't impact fibrosis area (SR) but did decrease the number of animals progressing to stage 3 fibrosis. It also significantly reduced hepatic collagen compared to FFD, aligning with clinical Phase 3 trial results.

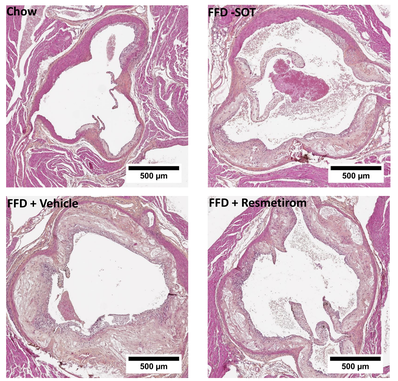
5. Resmetirom improved atherogenic-lipid particles

The Ldlr-/-.Leiden mouse model mimics both human NASH and CVD through diet-induced conditions. While the LDLR alteration isn't the direct cause of NAFLD/NASH, it effectively mirrors human lipid trafficking and vascular complications affecting vessels inside and outside the liver.

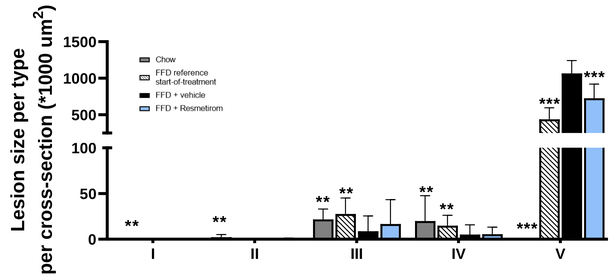
Consistent with the plasma lipid lowering, the FFD-induced increase in atherogenic (V)LDL lipoprotein-particles were attenuated after 10 weeks of resmetirom treatment, in line with the LDL-cholesterol lowering by resmetirom in the clinical Phase 3 trial.



6. Resmetirom attenuated atherosclerosis



In line with the strong reduction in circulating lipids, resmetirom significantly reduced the FFD-induced atherosclerosis lesion area compared to FFD + vehicle.



Lesion severity analysis according to the American Heart Association (AHA) scoring system reveals that resmetirom exhibits its most significant impact on the lesion area of severe type V lesions.

7. Conclusion

Resmetirom reduced MASLD/MASH and lowered plasma LDL-cholesterol, consistent with Phase 3 MAESTRO-NASH trial findings, highlighting the relevance of the Ldlr-/-.Leiden mouse model.
Additionally, it reduced atherosclerosis progression alongside its positive effects on the liver. Since obesity-related CVD remains a top cause of death in MASH patients, our findings emphasize resmetirom's clinical potential as a promising therapy for MASH.

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