Synergistic hepatoprotective effects of semaglutide and resmetirom combination therapy in the GAN diet-induced obese and biopsy-confirmed mouse model of MASH

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Background and Aims: Semaglutide (glucagon-like receptor-1 (GLP-1R) agonist) and resmetirom (THR-β receptor agonist) are both in late-stage clinical development for treatment of metabolic dysfunction-associated steatohepatitis (MASH). The present study aimed to compare metabolic, biochemical, and histological effects of semaglutide and resmetirom as mono- and combination treatment in a translational GAN diet-induced obese and biopsy-confirmed mouse model of MASH with liver fibrosis.

Method: C57BL/6JRj mice were fed the GAN diet high in saturated fat, fructose, and cholesterol for 38 weeks before treatment start. Only animals with biopsy-confirmed MASH (NAFLD Activity Score, NAS≥5) and moderate fibrosis (stage ≥F2) were included and stratified into treatment groups. GAN DIO-MASH mice (n=17-18 per group) received vehicle (SC), semaglutide (30 nmol/kg, SC), resmetirom (3 mg/kg, PO) or resmetirom (3 mg/kg, PO) + semaglutide (30 nmol/kg, SC) once daily for 12 weeks. Vehicle-dosed (SC) chow-fed controls (n=10) served as healthy controls. Within-subject comparisons (pre- vs. post-treatment) were performed for NAS and fibrosis stage. Terminal quantitative endpoints included plasma/liver biochemistry and quantitative liver histology.

Results: While resmetirom was weight-neutral, semaglutide significantly reduced body weight (28%) and combination treatment led to further weight loss (37%) in GAN DIO-MASH mice. Both monotherapies and combination treatment reduced plasma transaminases and plasma/liver markers of inflammation (MCP-1) and fibrogenesis (TIMP-1). Combination treatment improved hepatomegaly and liver lipid levels greater than individual monotherapies. NAS (pre-post) was significantly improved by semaglutide (≥2-point, 28% of mice) and resmetirom (≥2-point, 17% of mice) and combination treatment led to synergistic reductions in NAS (≥2-point, 71% of mice) largely driven by improved steatosis scores, being further supported by quantitative histology. Only semaglutide significantly reduced quantitative histological markers of inflammation (galectin-3) and fibrogenesis (α-SMA). Treatments did not improve fibrosis stage and quantitative histological markers of fibrosis (PSR, Col1a1).

Conclusion: Both semaglutide and resmetirom improve biochemical and histological hallmarks of MASH in GAN DIO-MASH mice. Further therapeutic benefits are achieved by combination treatment, demonstrating the feasibility of combined stimulation of GLP-1R and THR-β receptor function to improve outcomes in MASH.