Hepatoprotective effects of semaglutide, elafibranor and resmetirom in the non-obese CDAA-HFD rat model of advanced MASH with progressive fibrosis

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Background & Aim

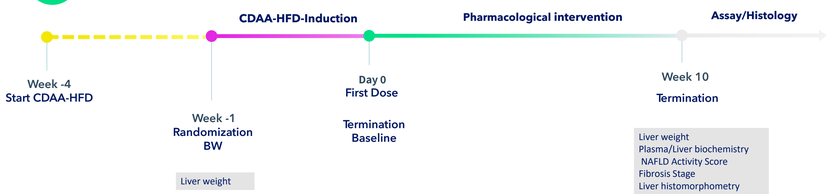
Semaglutide (GLP-1 receptor agonist), elafibranor (dual PPAR-α/δ agonist), and resmetirom (THR-β agonist) have demonstrated therapeutic benefits in clinical trials for metabolic dysfunction-associated steatohepatitis (MASH). Resmetirom has recently been FDA approved as the first drug treatment for MASH.

The present study aimed to compare metabolic, biochemical and histological outcomes of semaglutide, elafibranor and resmetirom monotherapy in the non-obese choline-deficient L-amino-acid defined high-fat diet (CDAA-HFD) rat model of advanced MASH with progressive fibrosis.

Methods

Male Sprague-Dawley rats (SPD RjHan:SD, Charles River) were fed CDAA-HFD (45 kcal% fat, 0.1% methionine, 1% cholesterol, 28 kcal% fructose) for 4 weeks prior to treatment start. The animals were randomized into treatment groups based on body weight. A baseline group (n=12) was terminated at the study's start. CDAA-HFD fed rats (n=12-14 per group) were administered either semaglutide (SC, 30 nmol/kg), elafibranor (PO, 30 mg/kg), resmetirom (PO, 3 mg/kg), or vehicle (IP) for 10 weeks. Terminal endpoints included plasma biomarkers, liver biochemistry, NAFLD Activity Score (NAS), Ishak fibrosis score, and quantitative liver histology.

1 Study Outline



Group no.	Group	Animal model	Number of animals	Administration route	Dosing frequency	Dose
1	**Baseline**	CDAA-HFD	12	NA	NA	NA
2	**Vehicle**	CDAA-HFD	14	IP	TIW	NA
3	**Semaglutide**	CDAA-HFD	14	SC	QD	30 nmol/kg
4	**Elafibranor**	CDAA-HFD	12	PO	QD	30 mg/kg
5	**Resmetirom**	CDAA-HFD	12	PO	QD	3 mg/kg

2 Metabolic and biochemical parameters

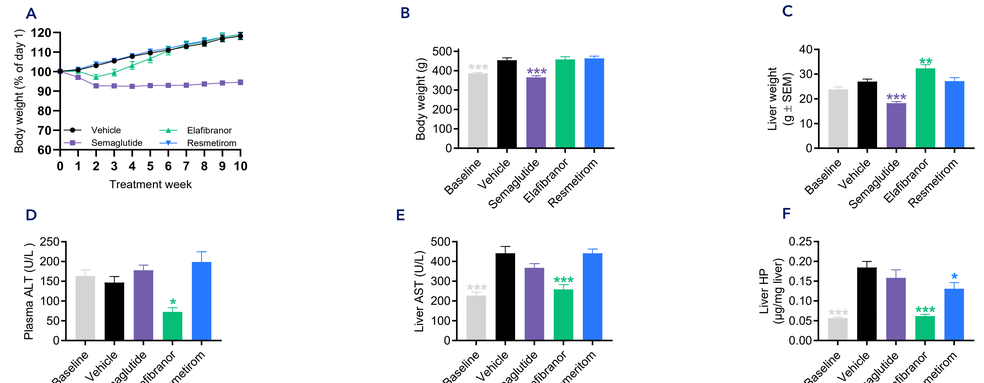


Figure 1. **(A)** Body weight change relative to baseline (Day 0). **(B)** Terminal body weight (g). **(C)** Terminal liver weight (g). **(D)** Terminal plasma alanine aminotransferase (ALT, U/L). **(E)** Terminal plasma aspartate aminotransferase (AST, U/L) **(F)** Terminal liver hydroxyproline (HP, µg/mg). *p<0.05, **p<0.01, ***p<0.001 compared to CDAA-HFD Vehicle group (Dunnett's test one-factor linear model).

3 NAFLD Activity Score and Fibrosis Score (Ishak)

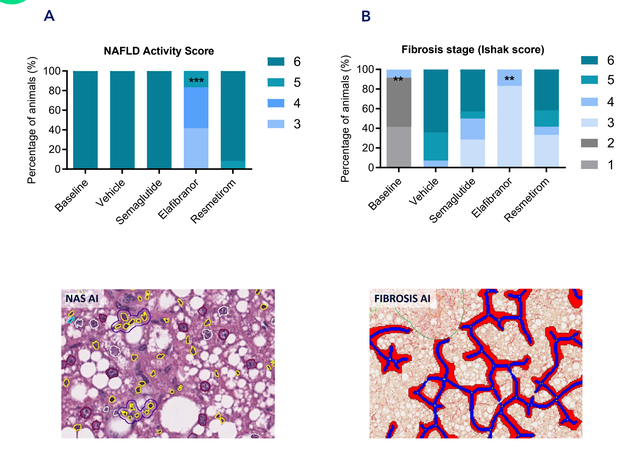


Figure 2. Histopathological scores were determined by Gubra Histopathological Objective Scoring Technique (GHOST) deep learning-based image analysis. **(A)** NAFLD Activity Score (NAS). **(B)** Fibrosis Stage.). **p<0.01, ***p<0.001 compared to CDAA-HFD Vehicle group (one-sided Fisher's exact test with Bonferroni correction). Bottom panels: Representative HE and PSR photomicrographs used for GHOST evaluation.

4 Quantitative histological markers of steatosis, inflammation and fibrogenesis

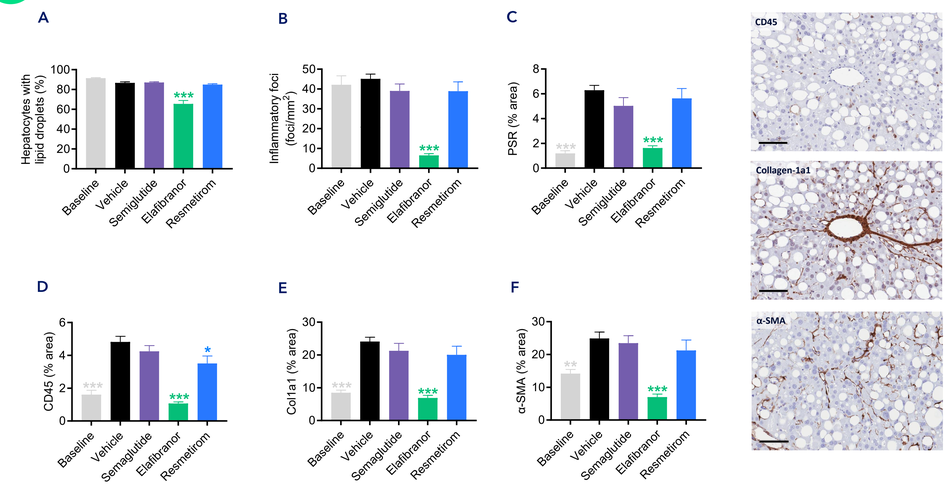


Figure 3. Histomorphometric assessments were performed by GHOST deep learning-based image analysis on scoring-associated variables and conventional IHC image analysis. **(A)** % hepatocytes with lipid droplets. **(B)** Number of inflammatory foci. **(C)** % area of PSR. **(D)** % area of galectin-3. **(E)** % area of collagen-1a1. **(F)** % area of alpha-smooth muscle actin (α-SMA). Mean ± SEM. **p<0.01, ***p<0.001 compared to CDAA-HFD Vehicle group (Dunnett's test one-factor linear model). Right panels: Representative galectin-3, collagen 1a1 and α-SMA photomicrographs for elafibranor treatment group (scale bar, 100 µm).

Conclusion

- The CDAA-HFD rat shows advancing fibrosis with consistent development of cirrhosis
- Only semaglutide reduces body weight in the CDAA-HFD rat
- Semaglutide improves hepatomegaly while elafibranor increases liver weight
- Only elafibranor improves transaminases and liver hydroxyproline levels
- Only elafibranor improves NAS and Ishak fibrosis score
- Only elafibranor improves quantitative histological markers of steatosis, inflammation and fibrosis

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