Characterization of resmetirom in the CDAA-HFD mouse model of advanced MASH with progressive fibrosis

Authors
Jacob Nøhr-Meldgaard[1], Denise Oro[1], Henrik H. Hansen[1], Michael Feigh[1]

[1]Gubra, Hørsholm Kongevej 11B, Hørsholm, Denmark

Corresponding author:
Michael Feigh: **mfe@gubra.dk**

Background & Aim

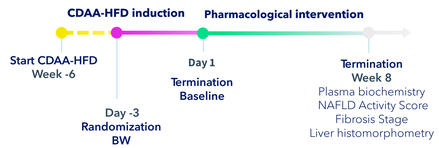
Resmetirom, a selective THR-β agonist, has been demonstrated to improve NAFLD Activity Score (NAS) and fibrosis stage in a recent phase-3 clinical trial (MAESTRO-NASH) in patients with metabolic dysfunction-associated steatohepatitis (MASH). FDA has recently granted accelerated approval for resmetirom (Rezdiffra) for the treatment of MASH patients with moderate to advanced liver fibrosis.

The present study aimed to investigate resmetirom intervention in the non-obese choline-deficient L-amino-acid defined high-fat diet (CDAA-HFD) mouse model of advanced MASH with progressive fibrosis.

Methods

C57BL/6JRj mice were fed chow or CDAA-HFD (45 kcal% fat, 0.1% methionine, 1% cholesterol, 28 kcal% fructose) for 6 prior to treatment start (i.e, after development of fibrosis). Animals were randomized into treatment groups based on body weight. A baseline group (n=12) was terminated at study start. CDAA-HFD fed mice (n=8-12 per group) were administered (PO) vehicle or resmetirom (1mg/kg) for 8 weeks. Chow-fed mice (n=8) served as normal controls. Terminal endpoints included plasma biomarkers, liver biochemistry, NAFLD Activity Score (NAS), fibrosis stage, and quantitative liver histology.

1 Study Outline



Group no.	Group	Model	Number of animals	Administration route	Dosing frequency	Dose
1	Chow	**LEAN-CHOW**	8	PO	QD	-
2	Baseline	**CDAA-HFD**	12	-	-	-
3	Vehicle	**CDAA-HFD**	12	PO	QD	-
4	Resmetirom	**CDAA-HFD**	12	PO	QD	1 mg/kg

2 Metabolic and biochemical parameters

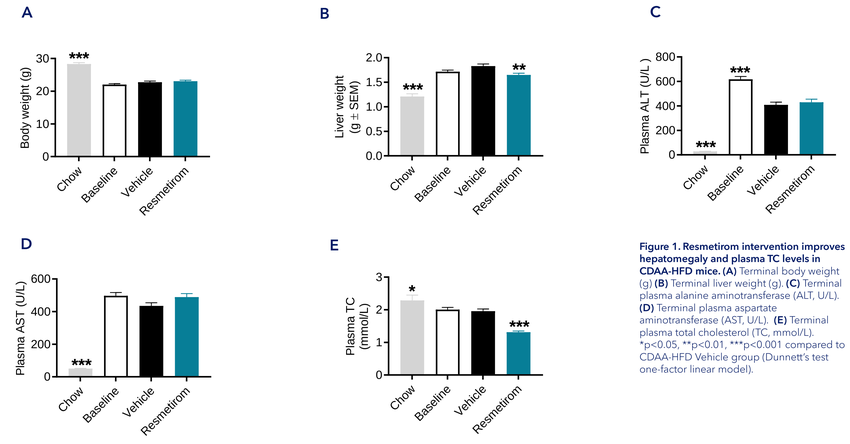


Figure 1. Resmetirom intervention improves hepatomegaly and plasma TC levels in CDAA-HFD mice. (A) Terminal body weight (g) **(B)** Terminal liver weight (g). **(C)** Terminal plasma alanine aminotransferase (ALT, U/L). **(D)** Terminal plasma aspartate aminotransferase (AST, U/L). **(E)** Terminal plasma total cholesterol (TC, mmol/L). *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 Stage

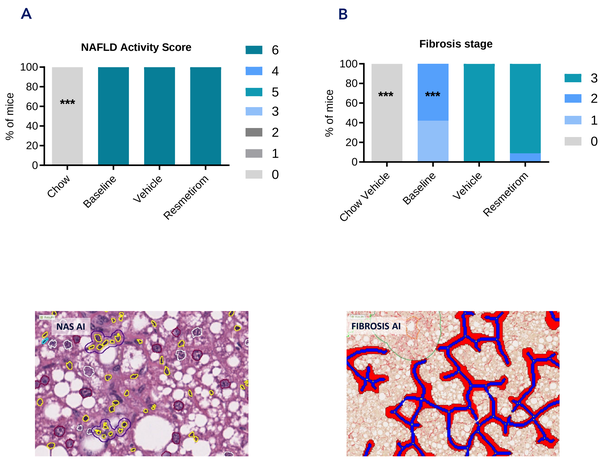


Figure 2. Resmetirom does not improve NAS or Fibrosis stage in CDAA-HFD mice. Histopathological scores were determined by Gubra Histopathological Objective Scoring Technique (GHOST) deep learning-based image analysis. **(A)** NAFLD Activity Score (NAS). **(B)** Fibrosis Stage.). ***p<0.001 compared to corresponding 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

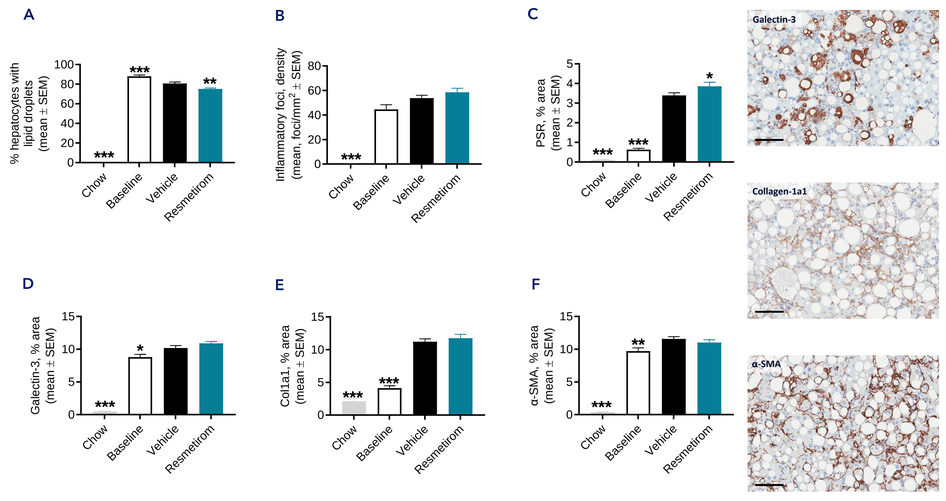


Figure 3. Resmetirom improves quantitative steatosis histology in CDAA-HFD mice. Histomorphometric assessments were performed by GHOST deep learning-based image analysis on scoring-associated variables and conventional IHC image analysis **(A)** % hepatocytes with lipid droplets. **(B)** Number of inflammatory 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<0.05, **p<0.01, ***p<0.001 compared to corresponding CDAA-HFD Vehicle group (Dunnett's test one-factor linear model). Right panels: Representative galectin-3, collagen 1a1 and α-SMA photomicrographs (scale bar, 100 µm).

Conclusion

Resmetirom treatment outcomes in CDAA-HFD mice:

+ Improved hepatomegaly and plasma total cholesterol levels
+ No effect on NAS and fibrosis scores
+ Mild beneficial effects on quantitative steatosis histology

In conclusion, resmetirom has limited therapeutic effects in the non-obese CDAA-HFD mouse model of MASH and fibrosis.

This emphasizes the importance of using translational DIO-MASH mouse models for efficacy testing of drug candidates with metabolic mode of action.

Scan the QR code to see the poster online

www.gubra.dk