Comparison of Seladelpar and Combinations with Liraglutide or Selonsertib for Improvement of Fibrosis and NASH in a Diet-Induced and Biopsy-Confirmed Mouse Model of NASH

FRI-329

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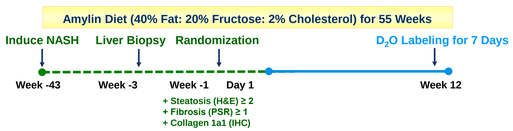
BACKGROUND AND AIMS

Complete resolution of non-alcoholic steatohepatitis (NASH) is challenging due to the multifactorial etiology of this complex disease. Combining therapies with complementary mechanisms of action may achieve better outcomes. Seladelpar, a potent PPAR delta agonist, attenuates multiple pathophysiologic pathways in NASH mouse models. Here we evaluate seladelpar and its combinations with the GLP-1-R agonist liraglutide or the ASK1 inhibitor selonsertib in a diet-induced and biopsy-confirmed mouse model of NASH.

METHODS

Male C57BL/6J mice were fed a diet high in fat, fructose and cholesterol for 43 weeks (Gubra, Hørsholm, DK). Prior to treatment, mice with histologically confirmed steatosis (score ≥ 2) and fibrosis (stage ≥ 1) were randomized into groups and then treated daily for 12 weeks. Seladelpar, liraglutide, selonsertib and obeticholic acid (OCA, comparator) were tested alone as were combinations of seladelpar with liraglutide or selonsertib for their effects on fibrosis and NASH pathology. Deuterated water (D_2O) was administered to allow measurement of hepatic collagen fractional synthesis rate (FSR). Biochemical (ALT, AST, total triglycerides (TG) and total cholesterol (TC) and hydroxyproline), liver histological (NAFLD Activity Score (NAS) and fibrosis) and RNAseq analyses were performed.



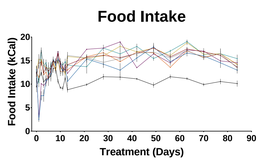
Treatment Groups

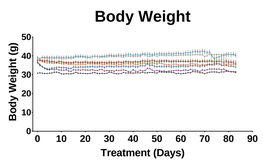
- NASH Vehicle
- Liraglutide (0.2 mg/kg, BID, SC)
- Selonsertib (30 mg/kg, BID, PO)
- OCA (30 mg/kg, QD, PO)
- Seladelpar (10 mg/kg, QD, PO)
- Seladelpar + Liraglutide
- Seladelpar + Selonsertib
- CHOW Vehicle

Combination treatment used the same dose as single treatment.
Data are presented as Mean ± SE; P-values: * < 0.05; ** < 0.01; *** < 0.001; **** < 0.0001
Statistical significance (P-value < 0.05) between groups are presented by different letters (a,b,c,d,e)

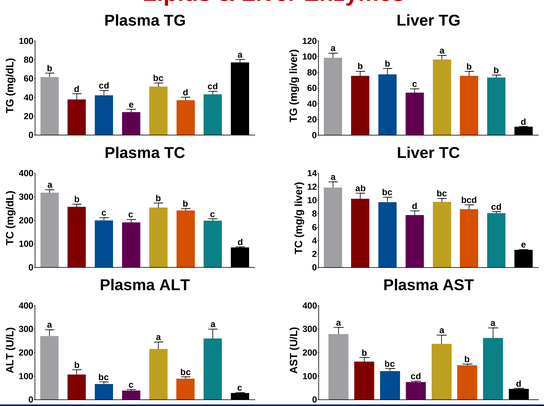
RESULTS

Food Intake & Body Weight



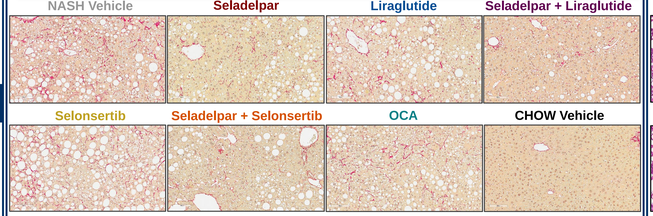


Lipids & Liver Enzymes

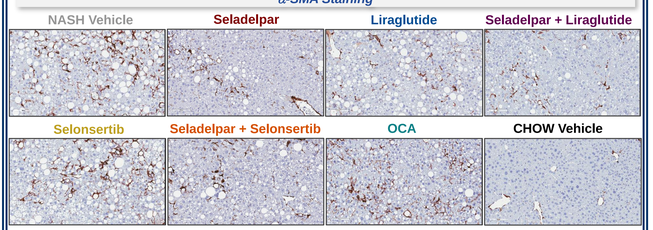


Liver Fibrosis

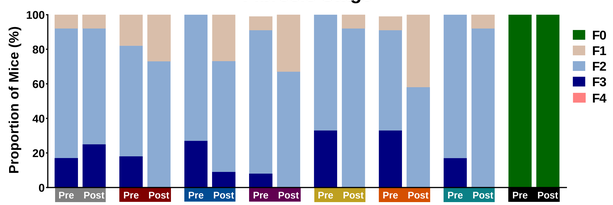
Sirius Red Staining



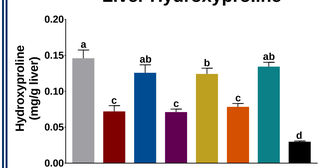
α-SMA Staining



Fibrosis Stage

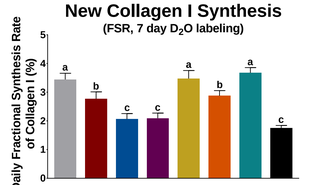


Liver Hydroxyproline

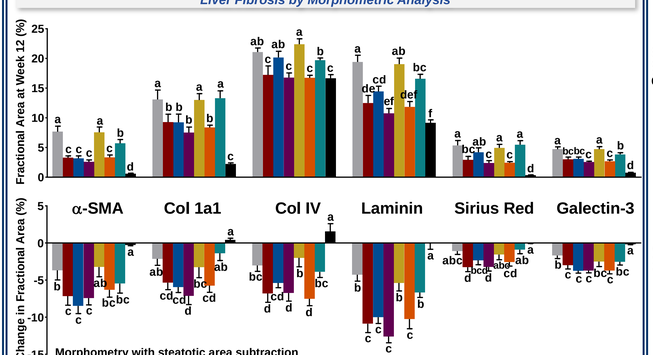


New Collagen I Synthesis

(FSR, 7 day D_2O labeling)

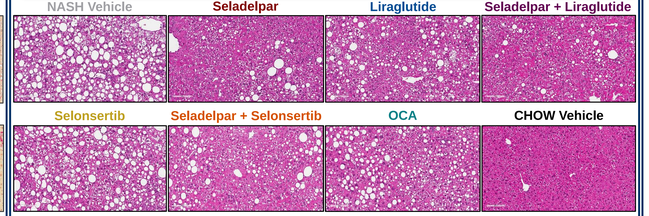


Liver Fibrosis by Morphometric Analysis



Liver Steatosis

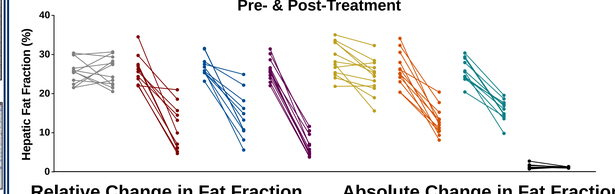
Haemotoxylin & Eosin Staining



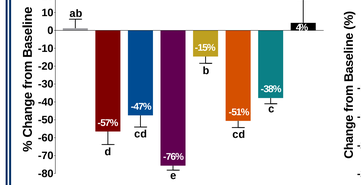
Liver Fat by Morphometric Analysis

Liver Fat Fraction

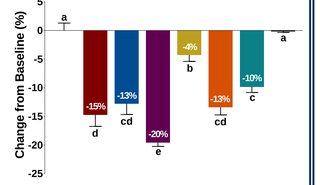
Pre- & Post-Treatment



Relative Change in Fat Fraction

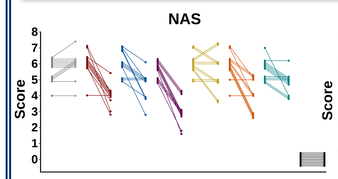


Absolute Change in Fat Fraction

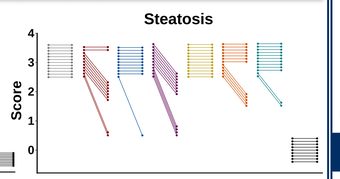


NAFLD Activity Score (NAS)

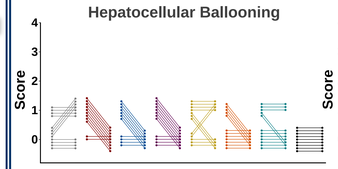
NAS



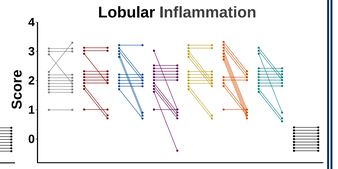
Steatosis



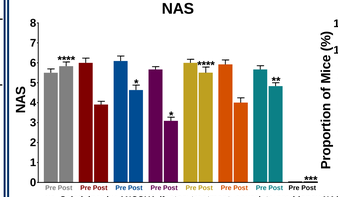
Hepatocellular Ballooning



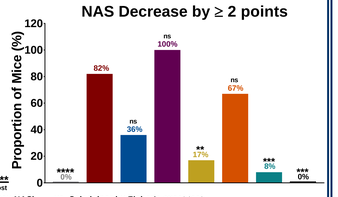
Lobular Inflammation



NAS



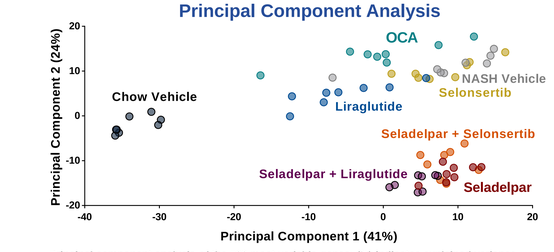
NAS Decrease by ≥ 2 points



Pathway Analysis

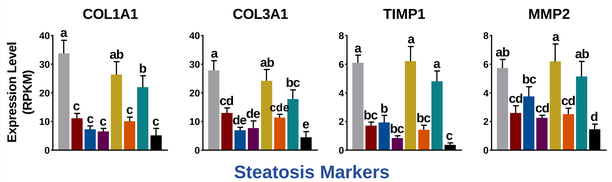
RNAseq Analysis

Principal Component Analysis

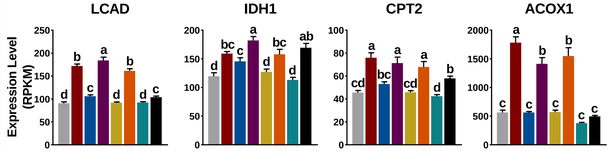


Principal component analysis of the 500 most variable genes; (%) indicates explained variance

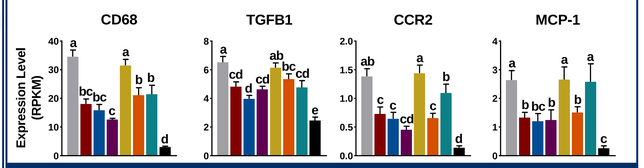
Fibrosis Markers



Steatosis Markers



Inflammation Markers



CONCLUSION: Seladelpar for NASH

12-Week Seladelpar treatment in a diet-induced obesity mouse model of NASH:

- More pronounced decrease in hepatic fat fraction than liraglutide, selonsertib or OCA
- Led to a decreased NAS
- Resolved established bridging fibrosis
- Broadest reduction in fibrosis markers such as collagen expression, protein synthesis and content
- Seladelpar is the only agent that reduced liver hydroxyproline content

12-Week Seladelpar + Selonsertib treatment in the mouse NASH model:

- Similar effects to seladelpar alone

12-Week Seladelpar + Liraglutide treatment in the mouse NASH model:

- Caused a greater decrease in hepatic fat fraction than either agent alone
- Principal component analysis of RNA expression suggests differentiated mechanisms of action between the two agents

This study confirms the anti-NASH and anti-fibrotic effects of seladelpar and also provides a rationale for combination with seladelpar and a GLP-1 receptor agonist.

Phase 2b NASH study is ongoing
NCT03551522