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

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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, alters multiple pathophysiologic pathways in NASH mouse models. Here we evaluate seladelpar and its combinations with the GLP-1 R agonist liraglutide or the AS1 inhibitory 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, Harshem, DK). Prior to treatment, mice with histologically confirmed steatosis (score 2-4) and fibrosis (stage 1-4) were randomized into groups, and then treated daily for 12 weeks. Seladelpar, liraglutide, selonsertib and a together (OCA, comparator) were tested alone or were combinations of seladelpar with liraglutide or selonsertib or their effects on fibrosis and NASH pathology. Deuterated water (D2O) 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.

12-Week Seladelpar treatment in a diet-induced obese 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
- Broadened reduction in fibrosis markers such as collagen expression, protein synthesis and content
- Seladelpar is the only agent that reduced liver hydroxyproline content
- 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.