Seladelpar Improves Hepatic Steatohepatitis and Fibrosis in a Diet-Induced and Biopsy-Confirmed Mouse Model of NASH

BACKGROUND

Seladelpar, a selective PPARδ agonist, is in clinical development for the treatment of nonalcoholic steatohepatitis (NASH) and primary biliary cholangitis. Unlike the selective tissue distributions of PPARα and PPARγ, PPARδ is ubiquitously expressed. Seladelpar exerts peripheral and hepatic effects through regulation of lipid metabolism, energy expenditure, and inflammation, and by reducing hepatic fibrosis. The efficacy of seladelpar on hepatic lipids, inflammation, and fibrosis was evaluated in a diet-induced and biopsy-confirmed NASH mouse model.

METHODS

Male C57BL/6J mice were fed a diet high in fat, fructose, and cholesterol for 43 weeks to induce NASH. Mice (n=11-12/group) with biopsy confirmed histologic steatosis (score 2) and fibrosis (stage 2) were randomized into vehicle, seladelpar (10 mg/kg), or obeticholic acid (OCA, 30 mg/kg, comparator) groups and treated daily for 12 weeks. Biochemical and liver histological parameters were assessed. Liver fibrogenesis was evaluated by LC/MS-MS analysis of the guanidine-soluble (less cross-linked ECM) fraction after D2O (heavy water) labeling for 7 days.

RESULTS

Liver Fibrosis

Liver Steatosis

Inflammation

Liver Fibrosis Markers

Liver Steatosis Morphometric Analysis

Hepatic Fat Fraction (%)

% Change from Baseline

Hepatic Fat Fraction

% Change from Baseline

NAFLD Activity Score (NAS)

Liver Inflammation

NAS

Hepatocellular Ballooning

Lobular Inflammation

Streallpear Improves Hepatic Steatohepatitis and Fibrosis

Inflammation

Liver Steatosis Morphometric Analysis

Liver Inflammation RNAseq Analysis

Liver Fibrosis RNAseq Analysis

Liver Steatosis RNAseq Analysis

CONCLUSION

In a diet-induced obesity mouse model of NASH, seladelpar treatment for 12 weeks

- Improved NASH pathology
- Significantly reduced liver fibrotic markers
- Profoundly decreased hepatic fat
- Decreased NAS
  - Improvement of steatosis score
  - Mean decrease of 2.1 points
  - Complete resolution of hepatocellular ballooning
  - Reduction in inflammatory markers
  - Eliminate bridging fibrosis
- Decreased liver collagen I synthesis (fibrogenesis)

Phase 2b NASH study is ongoing

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