Seladelpar, a PPAR-delta agonist, improves inflammatory lipid mediators in the serum metabolome in patients with primary biliary cholangitis (PBC)

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BACKGROUND & AIM

- Primary biliary cholangitis (PBC) is a progressive autoimmune liver disease characterized by chronic inflammation and cholestasis due to damaged intrahepatic bile ducts
- Seladelpar is a potent, selective peroxisome proliferator-activated receptor-delta (PPARδ) agonist being developed for PBC
- In recent phase 2 and phase 3 studies in patients with PBC, seladelpar significantly improved biochemical markers associated with cholestasis, liver injury and risk for disease progression, and it also reduced lipids associated with cardiovascular risk
- We undertook an untargeted serum metabolomic study to further investigate mechanisms underlying the beneficial effects of seladelpar

METHODS

- A phase 3, double-blind, randomized, placebo-controlled study in patients with PBC (ENHANCE: NCT03602560)
- Eligible patients had a diagnosis of PBC:
  - Inadequate response or intolerant to UDCA
  - Alkaline phosphatase (ALP) ≥ 1.67x ULN and bilirubin ≤ 2 x ULN
- Randomization and analysis timepoint
  - 1:1:1 to placebo, seladelpar 5 or 10 mg
  - Analyzed samples at baseline and after once daily oral dose for 12 weeks
- Untargeted analysis of serum metabolomics
  - The metabolome of each patient was analyzed using LC-MS on fasting serum samples collected at Day 1 and after 12 weeks of treatment with placebo, seladelpar 5 or 10 mg (Metabolon, Inc.)

RESULTS

Demographics and Serum Biochemistry

Demographics	Placebo (n = 55)	Seladelpar 5 mg (n = 52)	Seladelpar 10 mg (n = 53)
Female, n (%)	54 (98%)	47 (90%)	50 (94%)
Age, years	56 (7)	56 (9)	57 (10)
BMI, kg/m²	29 (6)	28 (5)	28 (7)
White, n (%)	49 (89%)	49 (94%)	46 (87%)
AMA-positive, n (%)	49 (89%)	48 (92%)	47 (89%)
UDCA received, n (%)	54 (98%)	49 (94%)	49 (92%)

Biochemistry	Day 1	Week 12	Day 1	Week 12	Day 1	Week 12
ALP (U/L)	282 (105)	281 (116)	282 (126)	179 (56)	263 (96)	147 (56)
ALT (U/L)	41 (20)	43 (23)	47 (24)	35 (18)	42 (20)	38 (26)
AST (U/L)	35 (14)	36 (16)	39 (18)	35 (16)	38 (14)	38 (19)
GGT (U/L)	200 (153)	203 (177)	204 (163)	141 (112)	208 (154)	134 (111)
Bilirubin (mg/dL)	0.7 (0.3)	0.7 (0.3)	0.7 (0.3)	0.7 (0.3)	0.6 (0.3)	0.6 (0.3)
TC (mg/dL)	233 (53)	231 (53)	215 (45)	209 (45)	231 (56)	221 (55)
LDL-C (mg/dL)	137 (42)	136 (42)	120 (36)	113 (33)	129 (43)	120 (45)
HDL-C (mg/dL)	73 (22)	72 (23)	75 (22)	77 (25)	75 (22)	80 (22)
TG (mg/dL)	117 (55)	116 (44)	101 (48)	96 (42)	125 (77)	101 (55)
Albumin (g/dL)	4.2 (0.2)	4.2 (0.3)	4.1 (0.3)	4.2 (0.3)	4.1 (0.3)	4.2 (0.3)
Total protein (g/dL)	7.6 (0.6)	7.5 (0.6)	7.4 (0.4)	7.4 (0.4)	7.5 (0.6)	7.6 (0.6)
Urea (mg/dL)	15.4 (3.9)	14.7 (3.8)	15.5 (4.6)	15.8 (4.0)	14.9 (4.9)	15.7 (4.5)
Creatinine (mg/dL)	0.7 (0.1)	0.7 (0.1)	0.7 (0.2)	0.7 (0.2)	0.8 (0.2)	0.8 (0.2)

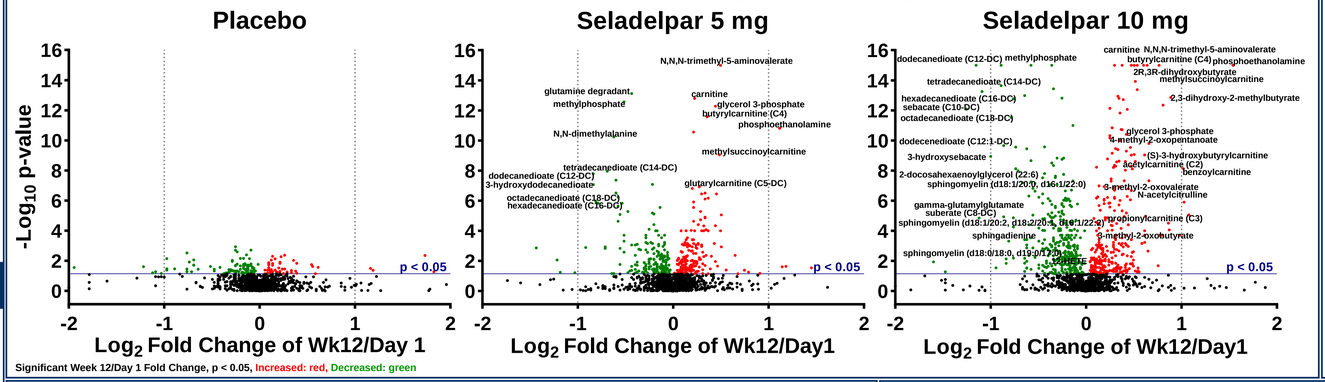
Mean (SD)

Metabolites with Significant Change after 12 Weeks

Untargeted Metabolomic Analysis of Human Serum From PBC Patients			
A total of 1474 Metabolites Identified (1171 Named and 303 Unnamed)			
Day 1 vs. Week 12	**Placebo**	**Seladelpar 5 mg**	**Seladelpar 10 mg**
Total Biochemicals, p ≤ 0.05	98	316	583
Biochemicals (↑|↓)	33 | 65	159 | 157	269 | 314

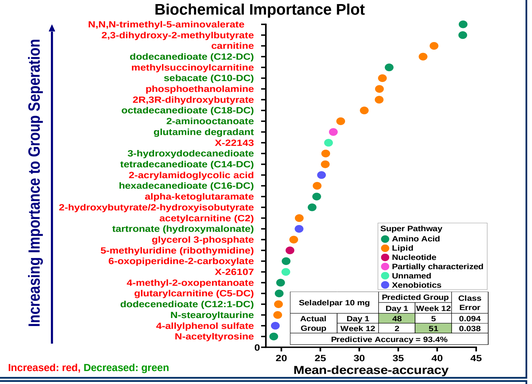
RESULTS

Seladelpar Results in Dose-Dependent and Highly Significant Changes in Serum Metabolites



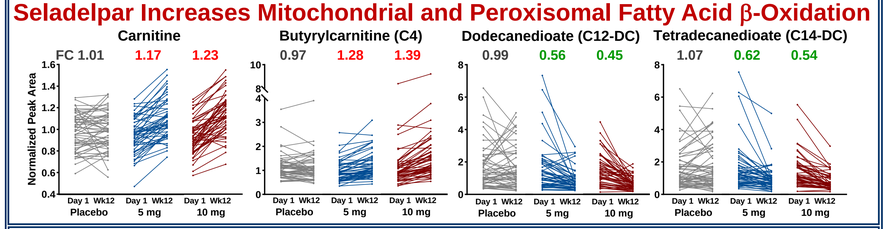
Significant Week 12/Day 1 Fold Change, p < 0.05, Increased: red, Decreased: green

Random Forest

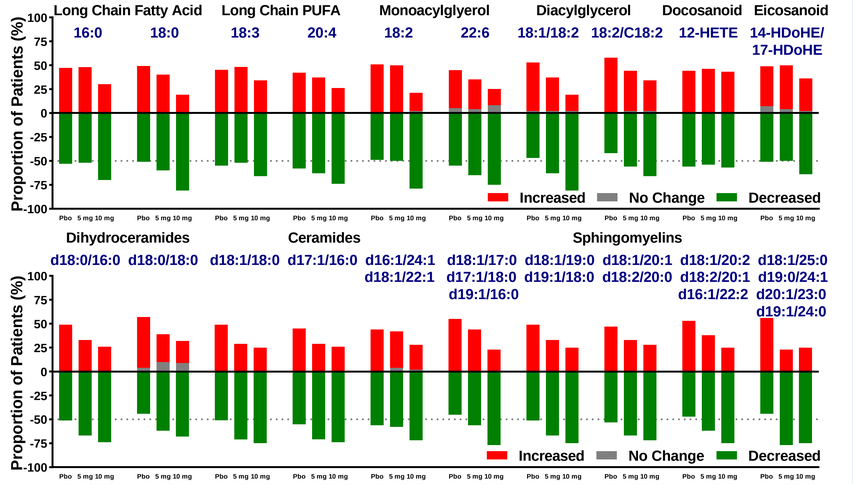


Increased: red, Decreased: green

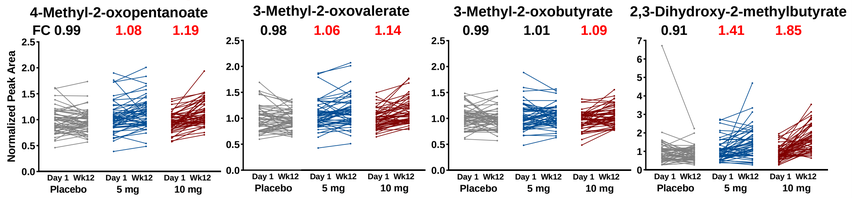
Seladelpar Increases Mitochondrial and Peroxisomal Fatty Acid β-Oxidation



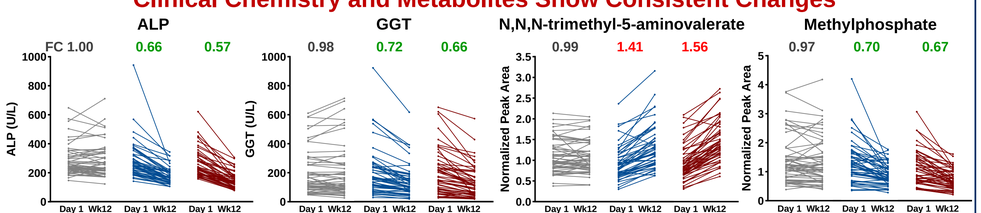
Seladelpar Decreases Fatty Acids and Inflammatory Lipid Mediators



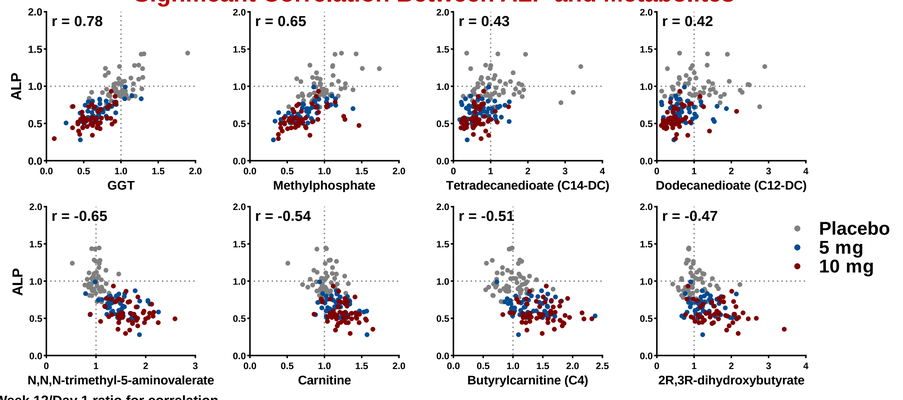
Seladelpar Increases Branched Amino Acid Metabolites



Clinical Chemistry and Metabolites Show Consistent Changes



Significant Correlation Between ALP and Metabolites*



* Week 12/Day 1 ratio for correlation

CONCLUSION

- Seladelpar treatment in patients with PBC resulted in broad changes in serum metabolomics
- Seladelpar increased mitochondrial and peroxisomal fatty acid β-oxidation indicated by increases in carnitine and acylcarnitines and decreases in dicarboxylates
- Seladelpar significantly reduced serum levels of inflammatory lipid mediators including long-chain fatty acids, mono- and diacylglycerols, eicosanoids, ceramides, and sphingomyelins
- Untargeted global serum metabolomics provided mechanistic insight into metabolic pathways altered by seladelpar treatment of patients with PBC
- These results suggest novel aspects by which the action of seladelpar may improve measures of cholestasis and liver function in patients with PBC