Seladelpar Treatment Resulted in Correlated Decreases in Serum IL-31 and Pruritus in Patients With Primary Biliary Cholangitis (PBC): Post-hoc Results From the Phase 3 Randomized, Placebo-Controlled ENHANCE Study

TOP-063

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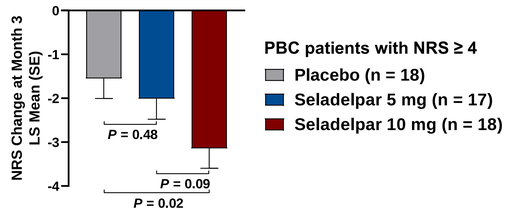
EASL CONGRESS Vienna, Austria 21–24 June 2023

BACKGROUND AND AIMS

- Pruritus is a debilitating symptom impacting the quality of life for many people living with PBC and remains a high unmet need
- The underlying mechanisms responsible for pruritus in PBC are not well understood
- Interleukin-31 (IL-31) is a cytokine reported to be mechanistically relevant to pruritus and its treatment, including in individuals with cholestasis
- Treatment with seladelpar, a selective PPAR-delta agonist, is associated with significant improvement in patients with moderate to severe pruritus (NRS ≥ 4)[1,2]

Significant Improvement in Pruritus in PBC Patients[1]



- Our aim was to evaluate the effect of seladelpar on serum IL-31 and its association with pruritus in patients with PBC

METHODS

- IL-31 levels were quantified in serum samples from the ENHANCE study of seladelpar[1] (EudraCT 2018-001171-20) in PBC patients who received daily oral doses of placebo (n = 55), seladelpar 5 mg (n = 53) or 10 mg (n = 53) for 3 months
- Serum IL-31, bile acids and their correlation with patient-reported pruritus numerical rating scale (NRS, 0-10) were assessed

RESULTS

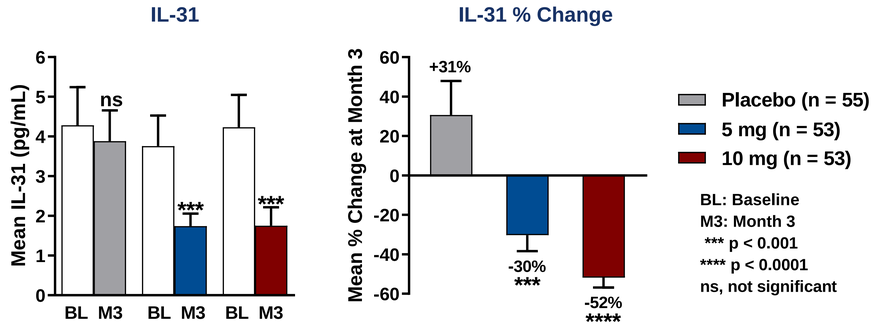
Demographic and Baseline Characteristics

Mean (SD)	Placebo n = 55	Seladelpar 5 mg n = 53	Seladelpar 10 mg n = 53	Total N = 161
Female, n (%)	54 (98%)	48 (91%)	50 (94%)	152 (94%)
Age, years	56 (7)	56 (9)	57 (10)	56 (9)
Duration of PBC, years	8.9 (6.2)	9.3 (6.2)	8.9 (7.1)	9.0 (6.5)
AMA Positive, n (%)	49 (89%)	49 (92%)	47 (89%)	145 (90%)
Concomitant UDCA, n (%)	54 (98%)	50 (94%)	49 (92%)	153 (95%)
UDCA Dose, mg/kg/day	15 (2)	15 (4)	14 (3)	15 (3)
Pruritus, NRS (0-10)	2.7 (2.5)	2.8 (2.6)	2.5 (2.5)	2.7 (2.5)
Moderate to severe (NRS ≥ 4)	6.1 (1.3)	6.3 (1.5)	6.0 (1.4)	6.1 (1.4)
Moderate to severe (NRS ≥ 4), n (%)	15 (28%)	15 (29%)	14 (26%)	44 (28%)
ALP (37-116 U/L)*	282 (105)	281 (126)	263 (96)	275 (109)
ALT (6-41 U/L)	41 (20)	46 (24)	42 (20)	43 (21)
AST (9-34 U/L)	35 (14)	38 (18)	38 (14)	37 (15)
GGT (7-38 U/L)	200 (153)	202 (162)	208 (154)	203 (155)
Total Bilirubin (0.1 - 1.1 mg/dL)	0.67 (0.27)	0.70 (0.31)	0.65 (0.28)	0.67 (0.29)
Direct Bilirubin (0-0.2 mg/dL)	0.19 (0.12)	0.20 (0.15)	0.18 (0.12)	0.19 (0.13)

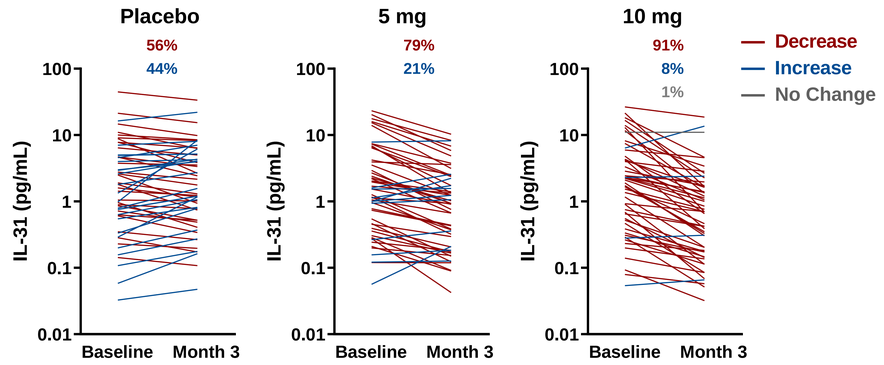
* Normal range

RESULTS

Seladelpar Reduces Serum IL-31 Levels

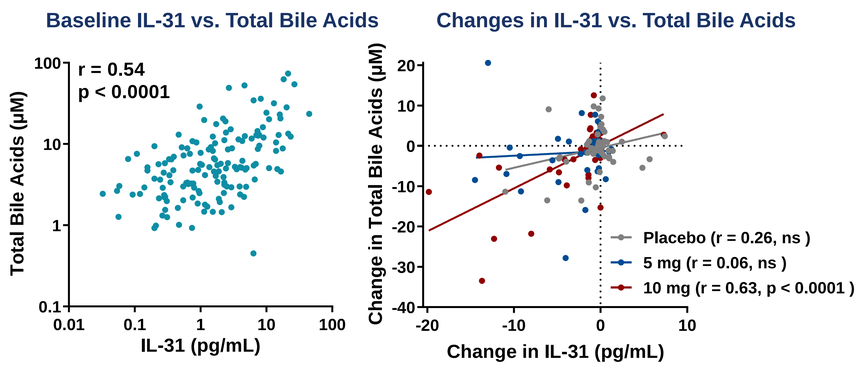


Change in IL-31 per Patient



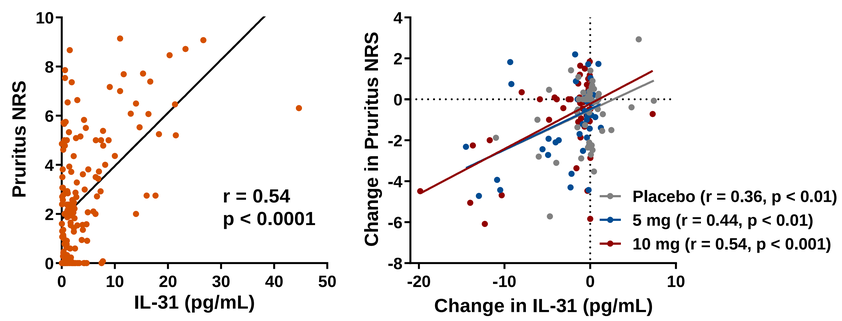
- Seladelpar treatment substantially decreased IL-31 levels in patients with PBC

Serum IL-31 Correlates with Bile Acids



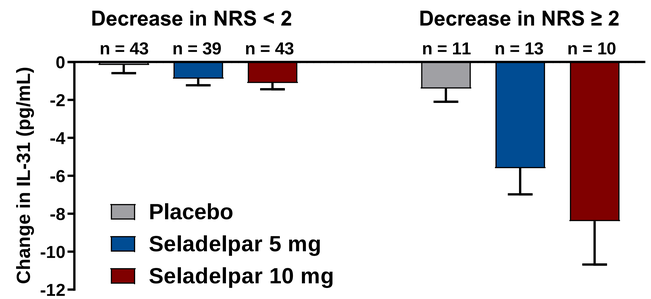
- Baseline IL-31 correlated with total bile acids
- A strong and significant correlation between changes in serum IL-31 and total bile acids was observed with seladelpar 10 mg treatment

Serum IL-31 Correlates with Pruritus NRS



- Baseline IL-31 levels positively correlated with pruritus NRS
- A significant and strong correlation was maintained between changes in IL-31 and pruritus NRS

Changes in IL-31 by Decrease in Pruritus NRS



- Patients with a clinically meaningful improvement in pruritus NRS (≥ 2 decrease) demonstrated greater dose-dependent reduction in IL-31 compared to those without pruritus improvement

CONCLUSIONS

- Seladelpar dose-dependently decreased IL-31 levels in patients with PBC
- Reduction in serum IL-31 correlated with pruritus improvement
- Serum IL-31 correlated with total bile acids and changes in total bile acids with seladelpar 10 mg treatment
- These results suggest that IL-31 may have a role in pruritus in patients with PBC
- IL-31 should be considered as a biomarker for anti-pruritic effects of seladelpar
- IL-31 may also be a component of the multifactorial causes of pruritus in PBC

REFERENCES

1. Hirschfield GM, Shiffman ML, Gulamhusein A, Kowdley KV, Vierling JM, Levy C, Kremer AE, et al. Seladelpar efficacy and safety at 3 months in patients with primary biliary cholangitis: ENHANCE, a phase 3, randomized, placebo-controlled study. *Hepatology* 2023, doi:10.1097/HEP.0000000000000039.
2. Kremer AE, Mayo MJ, Hirschfield G, Levy C, Bowlus CL, Jones DE, Steinberg A, McWherter CA, Choi Y-J. Seladelpar improved measures of pruritus, sleep, and fatigue and decreased serum bile acids in patients with primary biliary cholangitis. *Liver Int. 2022*; 42: 112–23.