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Seladelpar treatment reduces IL-31 and pruritus in patients with primary biliary cholangitis

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Abstract

Background and Aims: Pruritus is a debilitating symptom for many people living with primary biliary cholangitis (PBC). In studies with seladelpar, a selective peroxisome proliferator-activated receptor-delta agonist, patients with PBC experienced significant improvement in pruritus and reduction of serum bile acids. Interleukin-31 (IL-31) is a cytokine known to mediate pruritus, and blocking IL-31 signaling provides relief in pruritic skin diseases. This study examined the connection between seladelpar's antipruritic effects and IL-31 and bile acid levels in patients with PBC.

Approach and Results: IL-31 levels were quantified in serum samples from the ENHANCE study of patients with PBC receiving daily oral doses of placebo (n = 55), seladelpar 5 mg (n = 53) or 10 mg (n = 53) for 3 months, and for healthy volunteers (n = 55). IL-31 levels were compared with pruritus using a numerical rating scale (NRS, 0–10) and with bile acid levels. Baseline IL-31 levels closely correlated with pruritus NRS ($r = 0.54$, $p < 0.0001$), and total ($r = 0.54$, $p < 0.0001$) and conjugated bile acids (up to 0.64, $p < 0.0001$). Decreases in IL-31 were observed with seladelpar 5 mg (−30%, $p = 0.0003$) and 10 mg (−52%, $p < 0.0001$) versus placebo (+31%). Patients with clinically meaningful improvement in pruritus (NRS ≥ 2 decrease) demonstrated greater dose-dependent reductions in IL-31 compared to those without pruritus improvement (NRS < 2 decrease). Strong correlations were observed for the changes between levels of IL-31 and total bile acids ($r = 0.63$, $p < 0.0001$) in the seladelpar 10 mg group.

Conclusions: Seladelpar decreased serum IL-31 and bile acids in patients with PBC. The reductions of IL-31 and bile acids correlated closely with each

Abbreviations: ALP, alkaline phosphatase; AST, aspartate aminotransferase; ELF, enhanced liver fibrosis; FXR, farnesoid X receptor; GCA, glycocholic acid; IL-31, Interleukin-31; NRS, numerical rating scale; PBC, primary biliary cholangitis; PPAR, peroxisome proliferator-activated receptor; UDCA, ursodeoxycholic acid.

Trial registration: ClinicalTrials.gov number: NCT03602560.

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other and pruritus improvement, suggesting a mechanism to explain seladelpar's antipruritic effects.

INTRODUCTION

Primary biliary cholangitis (PBC) is a rare, slowly progressive, female-predominant liver disease characterized by immune-mediated destruction of small intrahepatic bile ducts followed by the development of chronic cholestasis.[1] If untreated, patients with PBC have a higher risk of cirrhosis and its complications, liver failure, and death.[2] Along with fatigue, pruritus is one of the most common presenting symptoms in patients with PBC.[3,4] Treatments for cholestatic pruritus are currently limited, and active pruritus can cause sleep deprivation, exacerbate fatigue, and impact the quality of life for patients living with PBC. The currently approved first-line [ursodeoxycholic acid; ursodeoxycholic acid (UDCA)] and second-line therapies (obeticholic acid) improve biochemical markers of PBC associated with disease progression, but fail to address key symptoms, including pruritus, associated with the disease. In the absence of efficacious therapy acceptable to patients, pruritus remains a high unmet need for patients with PBC.[5]

Seladelpar is a potent and selective peroxisome proliferator-activated receptor (PPAR)-delta agonist in development for the treatment of patients with PBC. In studies with patients with PBC having insufficient response to UDCA, seladelpar 10 mg demonstrated significant improvements in biochemical markers of cholestasis as well as significant reductions in patient-reported pruritus measurements in those patients with moderate-to-severe pruritus.[6–8] Seladelpar treatment also improved sleep disturbance and fatigue, as measured by the 5-D itch and PBC-40 questionnaires.[6]

A variety of pruritogenic molecules have been suggested to play a role in the pruritus experienced by patients with PBC, but the precise mechanism remains elusive. Individual bile acids, or sets of them, may be components of an ensemble of pruritogenic or pruritus-sensitizing signaling molecules, although serum bile acids are not always correlated with itch.[9] Nevertheless, bile acids can initiate signaling through G protein-coupled receptors such as MRGPRX4, which has been localized to human dorsal root ganglia–associated sensory neurons as well as a variety of other cells.[10,11] Autotaxin, a lysophosphatidic acid–forming enzyme, is associated with the severity of cholestatic itch and is lowered by certain but not all antipruritic treatments.[9,12,13]

Interleukin-31 (IL-31) is a pruritogenic cytokine produced by immune cells such as monocytes, mast cells, macrophages, fibroblasts, eosinophils, basophils, and, especially, T-helper 2 cells.[14–16] IL-31 has a role in neurite outgrowth and branching and in transmitting pruritic signals through a heterodimeric receptor composed of IL-31 receptor A and oncostatin M receptor β on keratinocytes and dorsal root ganglia neurons.[17–19] Higher levels of IL-31 or IL-31 receptor A have been reported in the tissue and serum of patients with pruritic skin diseases such as atopic dermatitis.[16] Recent studies with nemolizumab, a humanized antibody against IL-31 receptor A, demonstrated significant decreases in pruritus and improvement of sleep disturbance and quality of life in patients with atopic dermatitis,[20–22] but its effects on itch in PBC have not been reported. However, elevated levels of IL-31 have been reported in patients with cholestatic diseases such as PBC, primary sclerosing cholangitis, and intrahepatic cholestasis of pregnancy.[23–25] Furthermore, Xu and colleagues[23] demonstrated that farnesoid X receptor (FXR) agonists, which are known to cause itch when treating patients, resulted in increases in levels of IL-31 in humans and in mice with humanized livers.

In this study, we evaluated the association of levels of IL-31, type 2 cytokines, and bile acids with pruritus experienced by patients with PBC being treated with seladelpar or placebo. IL-31 and bile acid levels were also assessed in comparison with age-matched, sex-matched, and BMI-matched healthy volunteers. This report demonstrates that IL-31, a known pruritogenic mediator, can be reduced in patients with PBC by a therapeutic intervention that concomitantly improves pruritus. Our findings both shed light on the potential mediators for cholestatic itch and provide important information on novel therapeutic approaches.

METHODS

Study design, patients, and treatment

The ENHANCE study [ClinicalTrials.gov (NCT03602560) and EU Clinical Trials Registry (EudraCT2018-001171-20)][8] was a multicenter, randomized, double-blind, placebo-controlled phase 3 study of seladelpar in patients with PBC with an inadequate response or intolerance to UDCA. Patients (18–72 years old) with a diagnosis of PBC, elevated alkaline phosphatase (ALP) level (ALP $\geq$ 1.67 times the upper limit of normal), and total bilirubin $\leq$ 2 times the upper limit of normal were eligible to participate

in the study. Enrolled patients were stratified by ALP level (< 350 U/L or ≥ 350 U/L) and pruritus numerical rating scale (NRS) (< 4 or ≥ 4) and randomly assigned to a treatment group to receive once-daily dosing of an oral placebo, seladelpar 5 mg, or 10 mg. The study protocol was approved by appropriate local and national Institutional Review Boards or independent ethics committees, and the trial was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines. All patients provided written informed consent before study procedures. The detailed methodology and results of the ENHANCE study have been described in full elsewhere.[8] This analysis evaluated 161 patients with PBC with available serum samples (placebo, n = 55; seladelpar 5 mg, n = 53; seladelpar 10 mg, n = 53) at baseline and study end point (month 3) to investigate the treatment effects of seladelpar on IL-31 and its association with pruritus NRS, bile acids, and other laboratory measures.

To compare baseline IL-31 and bile acid levels in patients with PBC with healthy volunteers, serum samples were collected from healthy volunteers (n = 55) who were prospectively recruited by matching age, sex, and BMI to the patients with PBC in the ENHANCE study (BioCollections Worldwide, Inc.).

To confirm the findings in the ENHANCE study, we evaluated the effect of seladelpar on IL-31, bile acids, and pruritus in a separate population enrolled in an open-label phase 2 study with patients with PBC (NCT02955602; EudraCT # 2016-002996-91).[7]

Pruritus numerical rating scale (NRS)

Patients reported an NRS each evening for the previous 24 hours on a scale of 0 (no itching) to 10 (worst imaginable itching) using a daily electronic diary. Pruritus NRS at baseline and study endpoint (month 3) were determined by means of all daily recorded scores during the run-in period (up to 14 days) and the week prior to the month 3 visit, respectively. Changes in IL-31 levels associated with clinically meaningful improvement in pruritus NRS (≥2 decrease) as defined by Reich and colleagues[26] were evaluated.

Cytokine measurements

Serum IL-31 and other known pruritic cytokines such as IL-4, IL-13, and IL-33 were quantified by Simoa ultrasensitive immunoassays using Simoa HD-1 Analyzer and single-molecule array technology (Rules-Based Medicine, Austin, TX, USA). Capture antibody-conjugated paramagnetic beads were incubated with standards, serum samples or controls, and biotinylated detection antibodies. The beads were then washed and incubated with streptavidin β-galactosidase. After the final wash, the beads were loaded into the Simoa Disc with the enzyme substrate resorufin β-galactopyranoside. The concentration of IL-31, IL-4, IL-13, or IL-33 in each sample was calculated by interpolating from a standard curve. The lower limits of quantitation for IL-31, IL-4, IL-13, and IL-33 were 0.03 pg/mL, 0.022 pg/mL, 0.36 pg/mL, and 0.19 pg/mL, respectively.

Autotaxin measurement

Serum autotaxin levels were measured using a human ENPP-2/Autotaxin Quantikine ELISA kit (R&D Systems, Inc., USA) according to the manufacturer's instructions.

Bile acid measurements

Serum bile acids in samples at baseline and month 3 in ENHANCE and in those from healthy volunteers were analyzed quantitatively by liquid chromatography tandem mass spectrometry (Metabolon, Durham, NC, USA). Fifteen primary and secondary bile acids and glycine and taurine conjugates were measured: cholic acid, glycocholic acid (GCA), taurocholic acid, chenodeoxycholic acid, glycochenodeoxycholic acid, taurochenodeoxycholic acid, deoxycholic acid, glycodeoxycholic acid, taurodeoxycholic acid, lithocholic acid, glycolithocholic acid, taurolithocholic acid, UDCA, glycoursodeoxycholic acid, and tauroursodeoxycholic acid.

Statistical analyses

JMP statistical software (version 17; SAS Institute, Cary, NC, USA) was used for statistical analysis. Graphs were created in PRISM (version 9; GraphPad, San Diego, CA, USA). Descriptive statistics were used to summarize clinical data. Paired *t*-tests were used to detect differences for a given patient between baseline and month 3 for each treatment group. One-way ANOVA followed by a post hoc Student *t*-test was used to evaluate the difference between treatment groups. Pearson's correlation coefficients (*r*) using multivariate analysis were used to evaluate correlations between IL-31 and pruritus NRS, autotaxin, and bile acids.

RESULTS

Baseline characteristics

Of the 161 patients with PBC evaluated at the study end point (month 3), 55 received placebo, 53 received seladelpar 5 mg, and 53 received seladelpar 10 mg. Demographics and baseline characteristics are

TABLE 1 Demographics and baseline characteristics of patients with primary biliary cholangitis

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, y	56 (7)	56 (9)	57 (10)	56 (9)
BMI, kg/m^2	29 (6)	28 (5)	28 (7)	29 (6)
White, n (%)	49 (89)	50 (94)	46 (87)	144 (90)
Duration of PBC, y	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)
UDCA received, n (%)	54 (98)	50 (94)	49 (92)	153 (95)
UDCA daily dose, mg/kg	15 (2)	15 (4)	14 (3)	15 (3)
Pruritus, NRS	2.7 (2.5)	2.8 (2.6)	2.5 (2.5)	2.7 (2.5)
NRS≥4	6.1 (1.3)	6.3 (1.5)	6.0 (1.4)	6.1 (1.4)
NRS≥4, n (%)	15 (28)	15 (29)	14 (26)	44 (28)
ALP (U/L)	282 (105)	281 (126)	263 (96)	275 (109)
ALT (U/L)	41 (20)	46 (24)	42 (20)	43 (21)
AST (U/L)	35 (14)	38 (18)	38 (14)	37 (15)
GGT (U/L)	200 (153)	202 (162)	208 (154)	203 (155)
Total bilirubin (mg/dL)	0.67 (0.27)	0.70 (0.31)	0.65 (0.28)	0.67 (0.29)
Direct bilirubin (mg/dL)	0.19 (0.12)	0.20 (0.15)	0.18 (0.12)	0.19 (0.13)
Albumin (g/dL)	4.2 (0.2)	4.1 (0.3)	4.1 (0.3)	4.1 (0.3)
ELF score	9.6 (1.0)	9.7 (0.9)	10.0 (1.0)	9.8 (1.0)
Cirrhosis, n (%)	5 (9)	6 (11)	6 (11)	17 (11)

Abbreviations: ALP, alkaline phosphatase; ALT, alanine aminotransferase; AMA, antimitochondrial antibody; AST, aspartate aminotransferase; ELF, enhanced liver fibrosis; GGT, gamma-glutamyl transferase; NRS, numerical rating scale; PBC, primary biliary cholangitis; UDCA, ursodeoxycholic acid.

summarized in Table 1 and were generally well-balanced between treatment groups. Patients were mostly females (94%) living with PBC for 9 years, a mean (SD) age of 56 (9) years, 90% antimitochondrial antibody-positive, 95% on UDCA, BMI of 29 (6) kg/m^2, and 28% with moderate-to-severe pruritus (NRS ≥ 4, mean (SD), NRS = 6.1 (1.4)). The number of patients with cirrhosis was limited in this study (11%, n = 17), with few suffering from moderate-to-severe pruritus (Placebo, n = 3; 5 mg, n = 2; 10 mg, n = 1). The 55 healthy volunteers were matched to patients with PBC in this study: a female proportion of 95% (52 females and 3 males), a mean age of 56 (5) years, and a BMI of 29 (3) kg/m^2.

Patients with PBC had 31-fold higher serum concentrations of IL-31 compared to those of healthy volunteers (Figure 1A). Patients with PBC in our study also demonstrated elevated serum bile acid levels at baseline compared to healthy volunteers (Figure 1B). Serum levels of IL-31 correlated positively with total bile acids ($r = 0.56$, $p < 0.0001$, Figure 1C).[23]

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

At baseline, there were no significant differences in serum IL-31 levels between treatment groups ($p = 0.8962$). Mean changes from baseline to month 3 for serum IL-31 levels among treatment groups are presented in Figure 2A. Seladelpar treatment resulted in substantial decreases in mean IL-31 levels from baseline to month 3: seladelpar 5 mg (3.8 to 1.7 pg/mL, $p = 0.0002$), 10 mg (4.2 to 1.7 pg/mL, $p = 0.0003$) compared to placebo (4.3 to 3.9 pg/mL, $p = 0.28$). A robust dose-dependent percentage decrease in IL-31 levels was observed with the seladelpar treatments (Figure 2B): seladelpar 5 mg (−30%, $p = 0.0003$) and 10 mg (−52%, $p < 0.0001$) compared to placebo (+31%). Changes in IL-31 for individual patients are presented in Figure 2C. After 3 months of seladelpar treatment, 79% of patients in the 5 mg and 91% of patients in the 10 mg groups had decreased IL-31 levels compared to mixed responses in the placebo group (56% decrease and 44% increase). Seladelpar treatment lowered serum ALP (placebo: −4.2%; seladelpar 5 mg: −35.9%; seladelpar 10 mg: −44.3%, respectively)[8] and changes in IL-31 and ALP were also correlated in the seladelpar treatment groups (placebo $r = 0.11$, $p = 0.4179$; 5 mg $r = 0.56$, $p < 0.0001$; 10 mg $r = 0.40$, $p = 0.0028$). Seladelpar treatment did not result in changes in other type 2 cytokines, IL-4, IL-13, and IL-33, known to be involved in the production of IL-31 in other diseases such as atopic dermatitis. (Supplemental Figures 1A-C, http://links.lww.com/HEP/I187).[27]

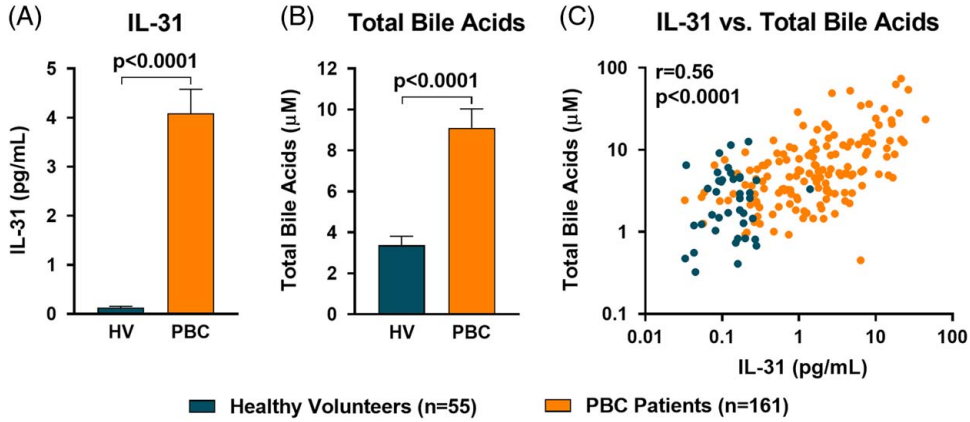


FIGURE 1 Serum IL-31 and total bile acid levels in healthy volunteers and patients with PBC. (A) Patients with PBC had higher levels of serum IL-31 than healthy volunteers. (B) Patients with PBC had higher levels of total bile acids than healthy volunteers. (C) Serum IL-31 levels were significantly correlated with total bile acids in healthy volunteers and patients with PBC. Data are presented as means ± SE. Abbreviations: HV, healthy volunteers; PBC, primary biliary cholangitis.

Correlation of itch intensity and serum IL-31 levels with seladelpar treatment

At baseline, serum IL-31 levels were closely correlated with pruritus NRS ($r = 0.54$, $p < 0.0001$, Figure 3A). A significant, dose-ordered association was maintained between the changes in IL-31 and pruritus NRS in the seladelpar treatment groups and placebo group (Figure 3B): placebo ($r = 0.36$, $p = 0.0080$), seladelpar 5 mg ($r = 0.44$, $p = 0.0011$), and seladelpar 10 mg ($r = 0.54$, $p < 0.0001$). Patients having clinically meaningful improvement in pruritus (NRS ≥ 2 decrease)[26] had greater dose-dependent reductions in serum IL-31 levels compared to those without pruritus improvement (NRS < 2 decrease) (Figure 3C). Baseline levels of IL-31 were 1.7- to 2.2-fold greater in those patients treated with seladelpar

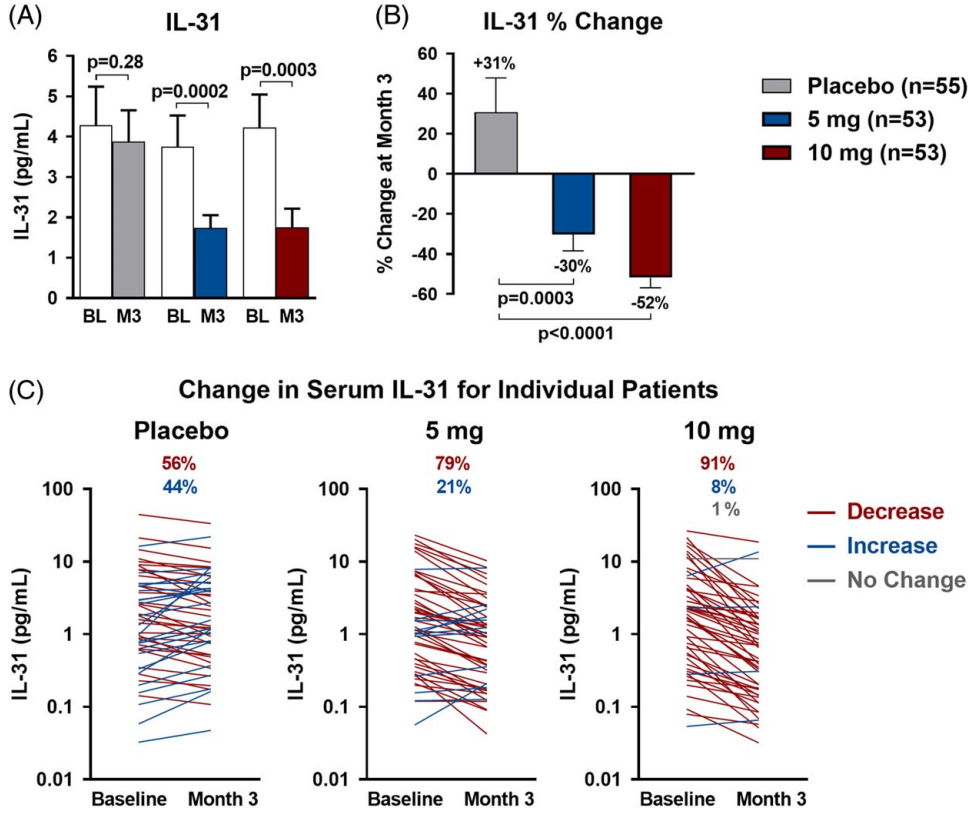
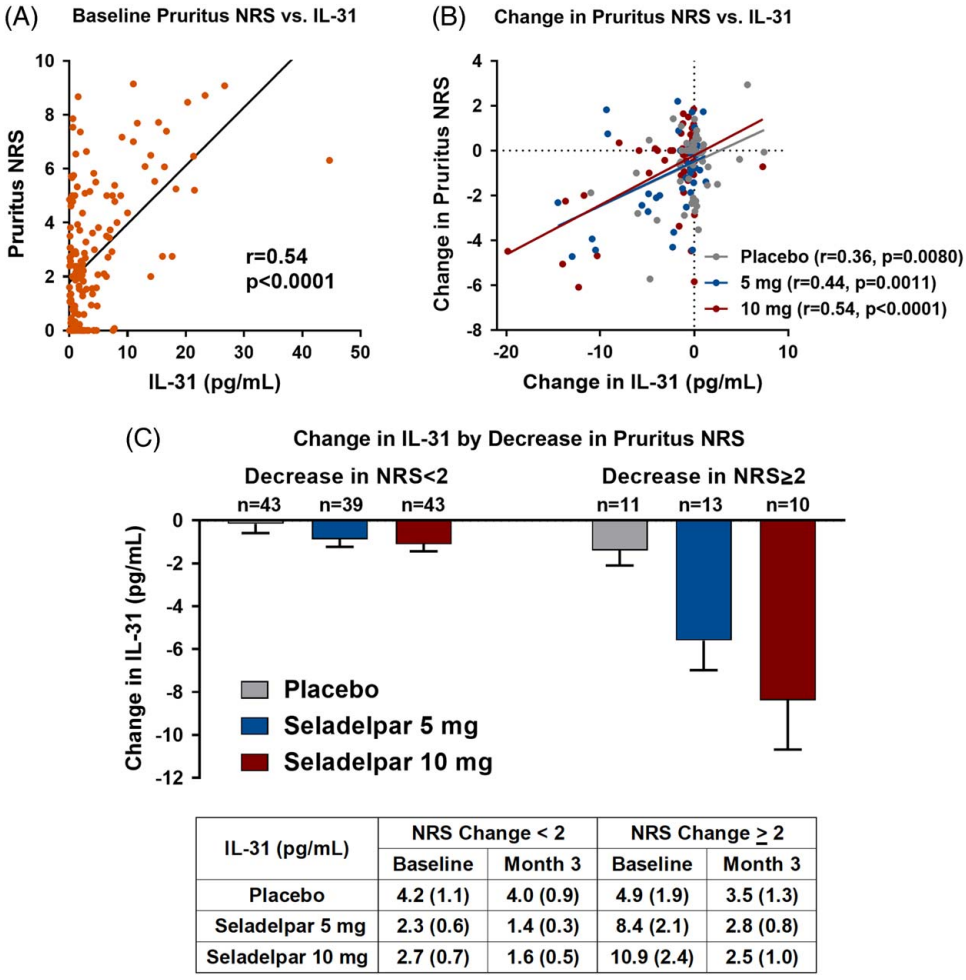


FIGURE 2 Changes in serum IL-31 levels from baseline to month 3. (A) Significant reduction in serum IL-31 levels by seladelpar treatment for 3 months. (B) Mean % change in serum IL-31 levels from baseline to month 3. (C) Individual patient IL-31 levels at baseline and month 3: the majority of patients in the seladelpar 10 mg decreased IL-31 levels after 3 months of treatment. BL: baseline, M3: month 3. Data are presented as means ± SE.



IL-31 (pg/mL)	NRS Change < 2		NRS Change ≥ 2	
	Baseline	Month 3	Baseline	Month 3
Placebo	4.2 (1.1)	4.0 (0.9)	4.9 (1.9)	3.5 (1.3)
Seladelpar 5 mg	2.3 (0.6)	1.4 (0.3)	8.4 (2.1)	2.8 (0.8)
Seladelpar 10 mg	2.7 (0.7)	1.6 (0.5)	10.9 (2.4)	2.5 (1.0)

FIGURE 3 Serum IL-31 levels were correlated with pruritus NRS. (A) A close correlation between IL-31 and pruritus NRS was observed at baseline. (B) Correlation between changes in IL-31 and pruritus NRS was maintained. (C) Decrease in serum IL-31 levels was associated with improvement in pruritus. Data are presented as means ± SE. Abbreviation: NRS, numerical rating scale.

with pruritus improvement (NRS ≥ 2 decrease) than in patients on placebo. In patients without improvement (NRS < 2 decrease), baseline IL-31 levels were 2.0- to 4.7-fold less than patients treated with seladelpar who improved (Bottom of Figure 3C).

Treatment effects of seladelpar on serum IL-31 levels and pruritus in an open-label phase 2 study

To confirm the findings in the ENHANCE study, we evaluated the effect of seladelpar on IL-31, bile acids, and pruritus in a separate population enrolled in an open-label phase 2 study with patients with PBC. Seladelpar treatment in this study had previously demonstrated improvements of pruritus, sleep disturbance, and fatigue measured by visual analog scale (0–100), 5-D itch, and PBC-40 questionnaires at 1 year.[6] Similar to ENHANCE, we found substantial decreases in serum IL-31 levels with seladelpar treatment. A correlation of serum IL-31 and pruritus measured by visual analog scale was also observed at baseline. An improvement of pruritus measured by visual analog scale was correlated with a decrease in serum IL-31 levels with 1 year of seladelpar 10 mg treatment (Supplemental Figure 2, http://links.lww.com/HEP/I187).

Correlation between serum IL-31 levels and circulating bile acids

The correlations of serum IL-31 with serum bile acids at baseline and with the change from baseline to month 3 are shown in Table 2. There were no correlations between serum IL-31 levels and any of the unconjugated bile acids at baseline. Serum IL-31 levels were significantly and closely correlated with taurine-conjugated or glycine-conjugated bile acids ($p < 0.0001$) at baseline: taurocholic acid ($r = 0.64$), taurochenodeoxycholic acid ($r = 0.54$),

TABLE 2 Correlations between serum IL-31 levels and bile acids at baseline and change from baseline at month 3 in patients with primary biliary cholangitis

	Correlation with serum IL-31: baseline			Correlation with serum IL-31: Change from baseline at month 3					
	Median (IQR)	All patients (N = 161)		Placebo (n = 55)		Seladelpar 5 mg (n = 53)		Seladelpar 10 mg (n = 53)	
Bile acids	**(μM)**	**Coefficient (r)**	***p*-value**	**Coefficient (r)**	***p*-value**	**Coefficient (r)**	***p*-value**	**Coefficient (r)**	***p*-value**
Unconjugated									
CA	0.04 (0.01, 0.13)	−0.01	0.89	0.00	0.98	0.01	0.96	0.03	0.82
CDCA	0.14 (0.06, 0.34)	−0.05	0.54	−0.01	0.97	0.15	0.29	−0.01	0.95
DCA	0.26 (0.13, 0.42)	−0.12	0.12	−0.03	0.81	−0.04	0.79	0.00	0.99
LCA	0.05 (0.02, 0.10)	−0.11	0.16	−0.04	0.77	−0.08	0.60	0.10	0.46
Taurine-conjugated									
TCA	0.18 (0.07, 0.56)	**0.64**	**< 0.0001**	**0.46**	**0.0004**	−0.20	0.16	**0.62**	**< 0.0001**
TCDCA	0.29 (0.12, 0.68)	**0.54**	**< 0.0001**	**0.29**	**0.029**	0.01	0.93	**0.39**	**0.0042**
TDCA	0.09 (0.04, 0.22)	**0.52**	**< 0.0001**	0.26	0.062	**0.31**	**0.027**	**0.29**	**0.035**
TLCA	0.01 (0.01, 0.03)	**0.39**	**< 0.0001**	0.01	0.95	0.01	0.93	0.25	0.085
Glycine-conjugated									
GCA	0.96 (0.44, 2.47)	**0.52**	**< 0.0001**	0.26	0.057	−0.03	0.82	**0.67**	**< 0.0001**
GCDCA	1.54 (0.82, 3.38)	**0.45**	**< 0.0001**	0.10	0.46	0.17	0.23	**0.49**	**0.0002**
GDCA	0.64 (0.30, 1.16)	**0.31**	**< 0.0001**	0.03	0.83	**0.28**	**0.045**	0.27	0.056
GLCA	0.08 (0.03, 0.17)	0.12	0.12	0.04	0.76	0.06	0.65	0.23	0.10
Total bile acids									
TBA	5.18 (2.92, 10.66)	**0.54**	**< 0.0001**	0.26	0.068	0.06	0.66	**0.63**	**< 0.0001**
UDCA, unconjugated									
UDCA	1.99 (0.75, 5.06)	−0.07	0.39	0.02	0.87	−0.07	0.61	−0.04	0.77
UDCA, taurine-conjugated									
TUDCA	0.27 (0.13, 0.72)	**0.49**	**< 0.0001**	**0.44**	**0.0009**	0.23	0.10	**0.38**	**0.0048**
UDCA, glycine-conjugated									
GUDCA	7.10 (3.82, 16.15)	**0.40**	**< 0.0001**	**0.35**	**0.0097**	0.24	0.088	**0.51**	**< 0.0001**
Total bile acids + UDCAs									
TBA+UDCAs	16.76 (9.71, 32.37)	**0.43**	**< 0.0001**	**0.33**	**0.020**	0.14	0.34	**0.55**	**< 0.0001**

Correlation between serum IL-31 and bile acids are significant ($p < 0.05$), both coefficient and *p*-value are bolded.

Abbreviations: CA, cholic acid; CDCA, chenodeoxycholic acid; DCA, deoxycholic acid; GCA, glycocholic acid; GCDCA, glycochenodeoxycholic acid; GDCA, glycodeoxycholic acid; GLCA, glycolithocholic acid; GUDCA, glycoursodeoxycholic acid; LCA, lithocholic acid; TBA, total bile acids; TCA, taurocholic acid; TCDCA, taurochenodeoxycholic acid; TDCA, taurodeoxycholic acid; TLCA, taurolithocholic acid; TUDCA, tauroursodeoxycholic acid; UDCA, ursodeoxycholic acid.

total bile acids ($r = 0.54$), GCA ($r = 0.52$), taurodeoxycholic acid ($r = 0.52$), tauroursodeoxycholic acid ($r = 0.49$), glycochenodeoxycholic acid ($r = 0.45$), total bile acids including unconjugated and conjugated UDCA ($r = 0.43$), glycoursodeoxycholic acid ($r = 0.40$), taurolithocholic acid ($r = 0.39$), glycodeoxycholic acid ($r = 0.31$) (Supplemental Figure 3, http://links.lww.com/HEP/I187). As for the observations at baseline, treatment for 3 months led to no significant correlations between changes in serum IL-31 levels and unconjugated bile acids. In marked contrast, strong and significant correlations between changes in serum IL-31 levels and changes in GCA ($r = 0.67$, $p < 0.0001$), total bile acids ($r = 0.63$, $p < 0.0001$), and taurocholic acid ($r = 0.62$, $p < 0.0001$) were seen with the seladelpar 10 mg treatment for 3 months.

Seladelpar 10 mg treatment led to a significant decrease in total bile acids ($p = 0.035$), which was attributed to the significant reductions in the major glycine-conjugated primary bile acids glycochenodeoxycholic acid ($p = 0.033$) and GCA ($p = 0.030$) (Supplemental Figure 4, http://links.lww.com/HEP/I187).

Effect of seladelpar treatment on serum autotaxin levels

Autotaxin has been associated with pruritus in PBC.[9] Various antipruritic therapies, including cholestyramine, rifampicin, nasobiliary drainage, and ileal bile acid transporter inhibitors, also reduce the serum level of this enzyme.[9,28,29] In our study, we also found that baseline serum autotaxin levels were correlated with pruritus as well as serum IL-31 and total bile acids. However, seladelpar treatment did not result in decreases in autotaxin levels (Supplemental Figure 5, http://links.lww.com/HEP/I187).

DISCUSSION

In the absence of effective and well-tolerated treatment options, treatment for pruritus remains a high unmet medical need in patients with PBC. In this study, we demonstrate that the improvement in pruritus from seladelpar treatment in patients with PBC is correlated with reductions in the known pruritogenic cytokine IL-31. We importantly demonstrate elevated baseline levels of IL-31 in patients, an association between reductions in IL-31 and seladelpar treatment, as well as an association between pruritus improvement and reductions in IL-31. The reduction in IL-31 levels is associated with improvements in bile acid levels. Seladelpar treatment did not, however, correlate with other related type 2 cytokines nor with autotaxin.

In studies, seladelpar treatment in these patients resulted in a robust improvement in pruritus and associated symptoms,[6–8] but the mechanism by which this PPAR-delta agonist ameliorates pruritus is not well-understood. IL-31 is a known critical mediator in pruritic skin diseases such as atopic dermatitis.[20] Two studies,[23,24] including ours, have reported elevation of serum IL-31 levels among patients with PBC compared to healthy subjects. Of importance, FXR agonists, which are known to improve cholestatic markers (eg., ALP) while causing or worsening pruritus in patients with PBC,[30] dose-dependently increased serum IL-31 in clinical studies in NASH, PBC, and primary sclerosing cholangitis, and in mice with humanized livers.[23] Clearly, cholestatic markers, IL-31 and pruritus can diverge with certain treatments.

In the current study, the majority of patients treated with seladelpar 10 mg demonstrated a remarkably uniform reduction in IL-31. We have observed close and significant correlations between IL-31 levels and severity of pruritus measured by NRS at baseline and changes at month 3 with seladelpar 10 mg treatment. These correlations were comparable to that of other pruritic diseases, such as prurigo nodularis, for which IL-31 has been therapeutically validated.[31–33] Pruritus NRS data were collected by patients using daily electronic diaries, which are the preferred method for accurately recording robust pruritus data, and this difference in methodology may explain why a report did not observe a correlation between pruritus and serum IL-31 in patients with PBC.[24]

Therapies to reduce bile acids such as bile acid sequestrants, nasobiliary drainage, inhibitors of ileal bile acid transporter, and the pan-PPAR agonist bezafibrate have demonstrated relief of pruritus in patients with PBC,[34–36] thus demonstrating a connection between bile acids and pruritus. Receptor-mediated effects of bile acids through FXR and G protein-coupled receptors are compelling in this regard, and these may represent components of itch signaling. Alternatively, bile acids can cause oxidative stress and mitochondrial injury in hepatocytes, leading to inflammation. Other components of the hepatobiliary system are also impacted by bile acids, although the mechanisms of the impact of cholestatic levels of bile acids on the liver are also still subject to debate.[37]

At baseline, IL-31 in our study was clearly correlated with total bile acids and a variety of taurine-conjugated and glycine-conjugated bile acids but not with unconjugated bile acids. This correlation is maintained after the changes due to treatment with seladelpar in which both IL-31 and conjugated bile acids are decreased. This may suggest that conjugated bile acids, despite being considered less toxic, are more proximal to the regulation of IL-31 release.

We measured autotaxin levels in the patients with PBC in our study and found that they are correlated with pruritus, total bile acids, and serum IL-31 levels at baseline. However, seladelpar did not lower the serum

levels of autotaxin. This is concordant with the results of the BEZURSO (PBC) and FITCH (PBC and primary sclerosing cholangitis) studies of bezafibrate, where this pan-PPAR agonist reduced pruritus but did not reduce serum autotaxin levels.[36,38,39]

IL-31 has been reported to affect itch by directly acting on sensory neurons or adjacent keratinocytes, both of which possess high affinity IL-31 receptors.[18,40] *In vitro* and *in vivo* evidence indicates that IL-31 can lengthen and cause branching of such neurons.[17] Our finding that the type 2 cytokines IL-4, IL-13, and IL-33 are not affected by seladelpar suggests that the role of IL-31 in PBC itch is different than that seen in skin diseases. In cholestatic itch, IL-31 is putatively derived from the liver,[23] and it may not respond to IL-4, IL-13, and IL-33 as it is known to do in T-helper type 2 cells in dermatological diseases. Furthermore, the observation that agonists of the bile acid receptor FXR both cause itch and increase IL-31 suggests a connection between cholestasis, the levels of bile acids, IL-31, and itch. Seladelpar improved cholestasis while lowering bile acids and IL-31, presenting a plausible explanation for its observed improvement of pruritus. This reinforces that IL-31 may serve as a pruritogenic mediator in both skin and cholestatic diseases but may originate from different sources.

Whether IL-31, bile acids, and autotaxin act independently or coordinately by mutual potentiation is unknown. It seems clear that there are multiple likely components of pruritus signaling in cholestatic disease. Considering the well-established role of IL-31 and its receptor in itch, our findings suggest that IL-31 is also a component of the etiology of pruritus in patients with PBC and an addressable target in its treatment. Hopefully, IL-31 will be a guide for an improved understanding of cholestatic liver diseases and facilitate therapeutic interventions in alleviating pruritus.

DATA AVAILABILITY STATEMENT

Data are available from the corresponding authors upon reasonable request.

AUTHOR CONTRIBUTIONS

Yun-Jung Choi, Jeff D. Johnson, Charles A. McWherter, and Andreas E. Kremer contributed to the study concept and study design. Yun-Jung Choi was responsible for data collection and data analysis. Andreas E. Kremer, Marlyn J. Mayo, Gideon M. Hirschfield, Cynthia Levy, Christopher L. Bowlus, and David E. Jones were investigators in the ENHANCE study. All authors interpreted data, reviewed and revised drafts of the manuscript, and approved the final manuscript for submission.

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CONFLICTS OF INTEREST

Andreas E. Kremer consults, advises, is on the speakers' bureau, and received grants from Gilead and Intercept. He consults, advises, is on the speakers' bureau for AbbVie, Advanz, Bayer, CymaBay, Eisai, Falk, GlaxoSmithKline, MSD, Novartis, and Roche. He consults and advises Beiersdorf, Escient, FMC, Guidepoint, Medscape, Mirum, Myr, and Viofor. He is on the speakers' bureau for AOP Orphan, Bristol Myers Squibb, CMS, Janssen, Lilly, Newbridge, Viofor, and Zambon. Marlyn J. Mayo consults and is on the speakers' bureau for Intra-Sana Laboratories. She consults and received grants from TARGET. She advises and received grants from CymaBay, GlaxoSmithKline, and Ipsen. She advises and received grants from Mallinckrodt. She received grants from GENFIT, Intercept, and Mirium. Gideon M. Hirschfield consults for and is on the speakers' bureau for GlaxoSmithKline, Intercept, and Ipsen. He consults for Advanz, CymaBay, Escient, Gilead, Kowa, Mirum, and Pliant. Cynthia Levy consults, advises, and received grants from CymaBay, GlaxoSmithKline, Intercept, and Ipsen. She consults and received grants from Calliditas and Mirium. She consults for Escient and Kowa Research Institute. She received grants from Cara, Escient, Gilead, HighTide, TARGET, and Zydus. She has other interests with AASLD. Christopher L. Bowlus consults and received grants from CymaBay, GlaxoSmithKline, Ipsen, and Mirum. He consults for BiomX, Eli Lilly, Invea Therapeutics, Shire, and Trevi. He received grants from Bristol Myers Squibb, Boston Scientific, Calliditas, Chemomab, COUR Pharmaceuticals, Eli Lilly, GENFIT, Gilead, Hanmi, Intercept, Novartis, Novo Nordisk, Pliant, Takeda, TARGET, and Viking. David E. Jones consults, is on the speakers' bureau, and received grants from Intercept. He consults and is on the speakers' bureau for Ipsen. He consults for CymaBay, Kowa, and Umecrine. He is on the speakers' bureau for Falk and GlaxoSmithKline. Jeff D. Johnson consults for CymaBay. Charles A. McWherter is employed by and owns stock in CymaBay. Yun-Jung Choi is employed by CymaBay.

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