

Maralixibat, an Ileal Bile Acid Transporter Inhibitor, Reduces Cholestatic Pruritus in PSC: Real-World Experience

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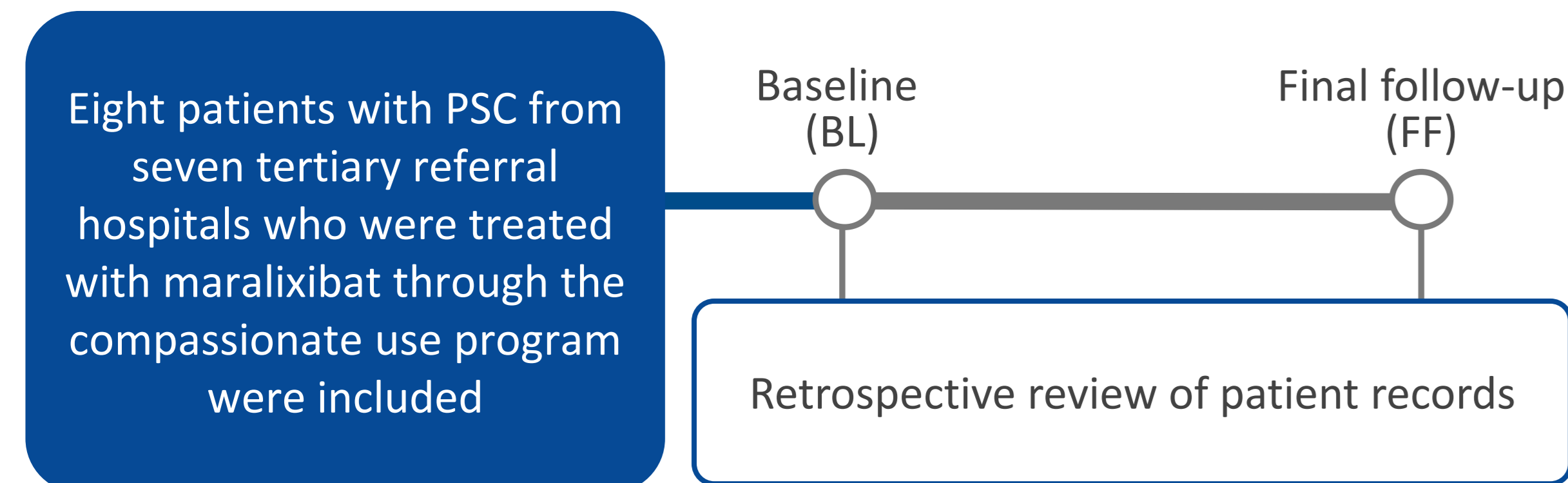
Introduction

- Primary sclerosing cholangitis (PSC) is a progressive autoimmune liver disease that scars the bile ducts and can lead to cirrhosis or cancer.¹⁻³
 - Common symptoms include pruritus, fatigue, and jaundice.^{1,2,4}
- Pruritus is present in up to 91% of patients with PSC and can be severe and debilitating, leading to reduced quality of life.^{4,5}
- In one survey, 49% of patients with PSC used ≥2 antipruritic medications, but 75% reported only partial or no relief.⁴
- Maralixibat (MRX) is a minimally absorbed ileal bile acid transporter (IBAT) inhibitor that reduces enterohepatic bile acid recirculation and significantly reduces pruritus and serum bile acid (sBA) levels.^{6,7} It is approved for^{8,9}:
 - Treatment of cholestatic pruritus in patients with Alagille syndrome ≥3 months of age in the US and ≥2 months of age in the EU.
 - Treatment of cholestatic pruritus in patients with progressive familial intrahepatic cholestasis (PFIC) ≥12 months of age in the US and treatment of PFIC in patients ≥3 months of age in the EU.
- Participants with PSC who received maralixibat treatment demonstrated significant reductions in pruritus and sBA levels, and treatment was well tolerated.¹⁰

Objective

- To report on the efficacy, safety, and tolerability of maralixibat in eight patients with PSC who received maralixibat through the compassionate use program.

Methods



- Pruritus was assessed using the five-point Clinician Scratch Scale (CSS), for which 0 = none, 1 = rubbing or mild scratching when undistracted, 2 = active scratching without abrasions, 3 = abrasions, and 4 = cutaneous mutilations, hemorrhage, scarring.⁷
 - A ≥1-point reduction in CSS is considered clinically meaningful.

Abbreviations

AIH, autoimmune hepatitis; ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BID, twice daily; BL, Baseline; CSS, Clinician Scratch Scale; FF, final follow-up; GGT, gamma-glutamyl transferase; IBAT, ileal bile acid transporter; IBD, inflammatory bowel disease; MRX, maralixibat; NA, not applicable; NR, not reported; PFIC, progressive familial intrahepatic cholestasis; PSC, primary sclerosing cholangitis; QD, once daily; sBA, serum bile acid.

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Results

Table 1. Demographic and Clinical Characteristics

Parameter	All cases (N=8)
Sex, female, n (%)	4 (50)
Age, median (min, max), y	
At PSC diagnosis	22.5 (4.5, 43.0)
At first presentation of pruritus	29.5 (4.0, 43.0)
At initiation of MRX	34.0 (7.0, 44.0)
Type of PSC, n (%)	
PSC/AIH overlap	3 (50) ^a
Large duct PSC	8 (100)
Small duct PSC	4 (80) ^b
History of PSC symptoms, n (%)	
Fatigue	7 (71) ^a
Jaundice	6 (75)
Ulcerative colitis	4 (50)
Crohn's disease	3 (43)
IBD indeterminate	1 (14) ^a
AIH overlap	1 (14) ^a
Compensated cirrhosis	1 (14) ^a
Decompensated liver cirrhosis ^c	0
Antipruritic medications prior to starting MRX, n (%)	
Rifampicin	2 (25)
Cholestyramine	4 (50)
Antihistamines	5 (63)
Ursodeoxycholic acid, n (%)	8 (100)
Liver transplant waitlist status before initiation of MRX, n (%)	
NA – the patient is not undergoing evaluation for liver transplantation	6 (75)
Referred or presently undergoing assessment for liver transplantation	1 (13)
On the liver transplant waitlist	1 (13)

^aData were available for seven patients. ^bData were available for five patients. ^cDefined as gastrointestinal bleeding or ascites requiring treatment with diuretics.

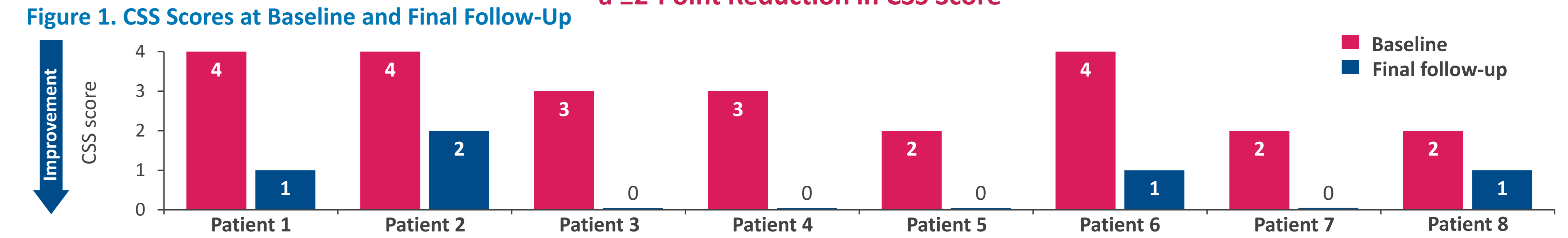
- Six adult patients and two pediatric patients were included in the study.

Table 2. Initial and Final Doses of Maralixibat

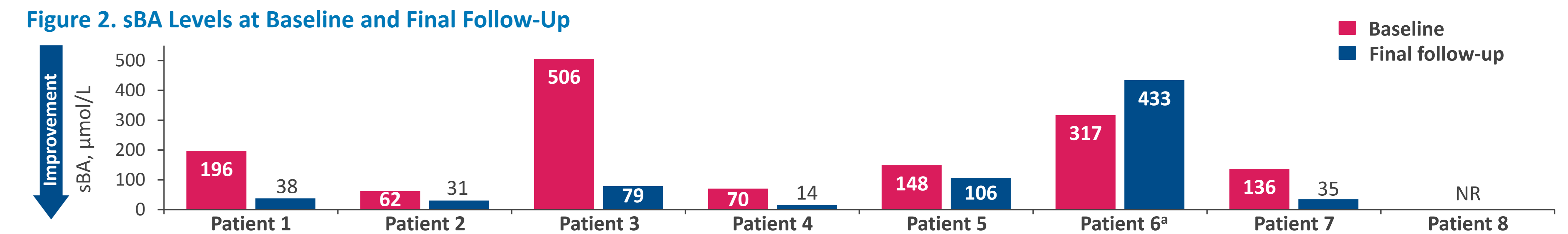
Patient	Initial dose	Final dose
1	245 µg/kg QD	380 µg/kg QD
2	380 µg/kg BID	380 µg/kg BID
3	190 µg/kg QD	380 µg/kg QD
4	190 µg/kg QD	190 µg/kg QD
5	190 µg/kg QD	190 µg/kg QD
6	190 µg/kg QD	380 µg/kg QD
7	190 µg/kg QD	380 µg/kg QD
8	190 µg/kg BID	85 µg/kg BID

- The median (min, max) duration of maralixibat treatment was 7.5 (4.0, 11.0) months.

All Patients Showed Complete or Near-Complete Resolution of Pruritus, With Seven of Eight Having a ≥2-Point Reduction in CSS Score



Most Patients Showed Reductions in sBA Levels



^aPatient 6 had history of chronically elevated transaminases with substantial fluctuations.

- Among the six patients who showed reductions in sBA after maralixibat treatment, the median (min, max) sBA levels were 142 (62, 506) µmol/L at Baseline and 37 (14, 106) µmol/L at final follow-up.

Table 3. Key Laboratory Parameters at Baseline and Final Follow-Up

Parameter	Patient 1		Patient 2		Patient 3		Patient 4		Patient 5		Patient 6		Patient 7		Patient 8	
	BL	FF	BL	FF	BL	FF	BL	FF	BL	FF	BL	FF	BL	FF	BL	FF
Total bilirubin, ^a mg/dL	3.3	2.4	5.3	2.6	2.3	1.7	0.5	1.1	3.2	1.6	11.9	13.2	3.6	3.5	0.6	NR
ALT, U/L	88	233	137	118	154	242	112	87	144	148	116	408	118	101	42	53
AST, U/L	76	177	91	79	109	137	85	68	181	135	155	577	88	68	28	53
ALP, U/L	230	584	640	635	718	673	348	348	407	367	847	1275	757	729	227	249
GGT, U/L	NR	NR	NR	NR	129	NR	377	321	290	218	821	540	379	266	131	NR

^aAn increase in total bilirubin was observed in two patients. The increase in Patient 4 stayed within the reference range (0.5 mg/dL at BL to 1.1 mg/dL at FF), while Patient 6 already had high levels at BL (11.9 mg/dL at BL to 13.2 mg/dL at FF).

- Diarrhea occurred in two patients; one had moderate to severe symptoms requiring dose adjustments and later discontinued treatment, while the other had mild, transient diarrhea.
- Transplant status: Of the two patients listed for transplant, one remained on the waitlist, and the other received a transplant several months after stopping treatment following proctocolectomy with ileal pouch-anal anastomosis.
- Liver enzymes: While mild liver enzyme elevations were observed, determining hepatotoxicity is challenging in cholestatic liver diseases, such as PSC, where liver tests often fluctuate. Although increases in liver enzymes have been reported with IBAT inhibitors, this effect is thought to be unrelated to direct toxicity, given their minimal systemic absorption.

Conclusions

- All patients had clinically meaningful reductions in CSS scores, with four patients experiencing complete resolution of pruritus.
- Substantial reductions in sBA levels were observed following maralixibat treatment in most patients.
- These results suggest a potential role for IBAT inhibitors for the treatment of pruritus in PSC.