Improvements in Pruritus, Serum Bile Acids, and Total Bilirubin Following Treatment With Maralixibat in Patients With Primary Sclerosing Cholangitis

Poster Mo1627

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Introduction

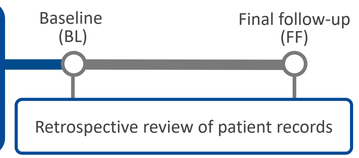
- Primary sclerosing cholangitis (PSC) is a progressive, autoimmune, cholestatic liver disease characterized by scarring and destruction of intrahepatic and extrahepatic bile ducts that can lead to fibrosis, cirrhosis, hepatocellular carcinoma, or bile duct cancer.[1-3]
  - Key clinical manifestations include fatigue, brain fog, anxiety, difficulty sleeping, pruritus, pain, and jaundice.[1,2,4,5]
- Pruritus is present in up to 91% of patients with PSC and can be severe and debilitating, leading to reduced quality of life.[1,4,6]
- Nearly half of patients with PSC take ≥2 antipruritic medications, but 75% of patients experience partial or no relief with these treatments.[4]
- Maralixibat (MRX) is a minimally absorbed ileal bile acid transporter (IBAT) inhibitor that prevents enterohepatic bile acid recirculation and is approved for[7,8]:
  - Treatment of cholestatic pruritus in patients with Alagille syndrome (ALGS) ≥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.
- In other cholestatic diseases, such as ALGS and PFIC, patients who received maralixibat demonstrated significant reductions in pruritus and sBA levels.[9,10]
- In an open-label pilot study (CAMEO), participants with PSC who received maralixibat demonstrated significant reductions in pruritus and sBA levels, and treatment was well tolerated.[11]

Objective

- To report on the efficacy, safety, and tolerability of maralixibat in 7 patients with PSC who received maralixibat through the compassionate use program.

Methods

7 patients with PSC from 5 tertiary referral hospitals who were treated with maralixibat through the compassionate use program were included



- Pruritus was assessed using the 5-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.[10]
  - A ≥1-point reduction in CSS is considered clinically meaningful.

Results

Table 1. Demographic and Clinical Characteristics

Parameter	All cases (N=7)
Sex, female, n (%)	4 (57.1)
Age at PSC diagnosis, median (min, max), y	16.0 (4.5, 43.0)
Type of PSC, n (%)	
PSC/AIH overlap	4 (57.1)
Large duct PSC	7 (100)
Small duct PSC	4 (66.7)[a]
History of PSC symptoms, n (%)	
Fatigue	6 (85.7)
Jaundice	6 (85.7)
Ulcerative colitis	4 (57.1)
Crohn's disease	2 (28.6)
IBD indeterminate	1 (14.3)
AIH overlap	1 (14.3)
Compensated cirrhosis	1 (14.3)
Decompensated liver cirrhosis[b]	0
Age at first presentation of pruritus, median (min, max), y	27.0 (4.0, 43.0)
Liver transplant waitlist status before initiation of MRX	
NA – the patient is not undergoing evaluation for liver transplantation	5 (71.4)
Referred or presently undergoing assessment for liver transplantation	1 (14.3)
On the liver transplant waitlist	1 (14.3)
Ursodeoxycholic acid, n (%)	7 (100)
Antipruritic medications prior to starting MRX, n (%)	
Rifampicin	2 (28.6)
Cholestyramine	3 (42.9)
Antihistamines	5 (72.5)
Age at initiation of MRX, median (min, max), y	34.0 (7.0, 44.0)
Duration of MRX treatment, median (min, max), mo	8.0 (4.0, 11.0)

[a]Data were available for 6 patients. [b]Defined as gastrointestinal bleeding or ascites requiring treatment with diuretics.

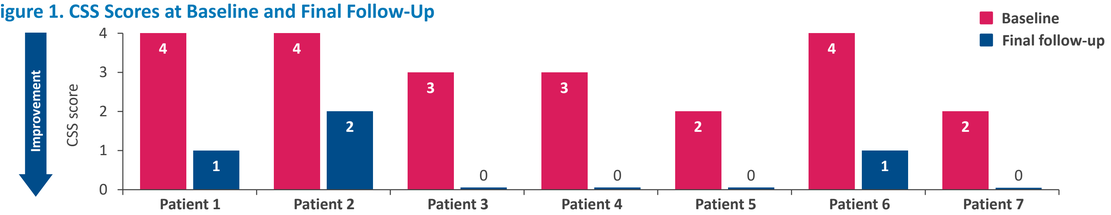
- Five adult patients and 2 pediatric patients were included in the study.

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

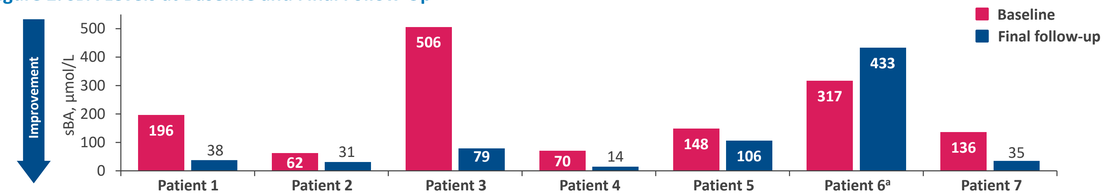
All Patients Had ≥2-Point Reduction in CSS Score, With 6 of 7 Patients Demonstrating Complete or Near Complete Resolution of Pruritus

Figure 1. CSS Scores at Baseline and Final Follow-Up



Most Patients Showed Reductions in sBA Levels

Figure 2. sBA Levels at Baseline and Final Follow-Up



[a]Patient 6 had history of chronically elevated transaminases with substantial fluctuations.

- Among the 6 patients who showed reductions in sBA after maralixibat treatment, the median (min, max) sBA levels were 142 (70, 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	
	BL	FF	BL	FF	BL	FF	BL	FF	BL	FF	BL	FF	BL	FF
Total bilirubin, 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	1.9
ALT, U/L	88	233	137	118	154	242	112	87	144	148	116	408	118	67
AST, U/L	76	177	91	79	109	137	85	68	181	135	155	577	88	301

- Diarrhea was reported in 2 patients:
  - One patient had moderate to severe diarrhea that required dose adjustment and interruptions. Diarrhea improved in frequency and achieved a tolerable pattern.
  - One patient had mild and transient diarrhea.
- The 2 patients listed or referred for liver transplant at Baseline were on the waitlist at final follow-up.
- Liver transaminases should be monitored.

Conclusions

- All patients had clinically meaningful reductions in CSS score, with 4 patients experiencing complete resolution of pruritus.
- Substantial reductions in sBA levels were observed after treatment with maralixibat in most patients.
- These results suggest a potential role for IBAT inhibitors for the treatment of pruritus in PSC.

Abbreviations

AIH, autoimmune hepatitis; ALGS, Alagille syndrome; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BID, twice daily; BL, Baseline; CSS, Clinician Scratch Scale; FF, final follow-up; 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.

Disclosures

AG is a consultant for Gilead Sciences, Intercept Pharmaceuticals, and Kezar Life Sciences. MCL has received research grants from Mirum Pharmaceuticals, Inc., and Gilead; is an advisor for Gilead, Ipsen, Advanz, Falk, and GSK; and is a speaker for Gilead, Ipsen, and Advanz. CL has received research grants through their institution from Calliditas Therapeutics, Cara Therapeutics, CymaBay Therapeutics, GENFIT, Gilead Sciences, GSK, Intercept Pharmaceuticals, Novartis, HighTide Therapeutics, Zydus Pharmaceuticals, Mirum Pharmaceuticals, Inc., Escient Pharmaceuticals, Pliant Therapeutics, and Target PharmaSolutions; has served as a consultant for CymaBay Therapeutics, GENFIT, Disc Medicine, GSK, Ipsen, Pliant Therapeutics, Mirum Pharmaceuticals, Inc., Calliditas Therapeutics, and Intercept Pharmaceuticals; serves as associate editor for *Hepatology*; and is a member of the ABIM Test and Policy committee for Transplant Hepatology. JH, DG, JC, AM, MM, TK, KE, and SL have nothing to disclose.

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