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Patient-focused drug development in primary sclerosing cholangitis: Insights on patient priorities and involvement in clinical trials

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Abstract

Background: According to the new AASLD Practice Guidance, all patients with primary sclerosing cholangitis (PSC) should be considered for participation in clinical trials. However, PSC's rarity has posed challenges to characterizing patient interest in trial participation and identifying predictors of patient willingness to participate in drug trials.

Methods: PSC Partners Seeking a Cure developed the "Our Voices" survey to inform the development of the Externally-Led Patient-Focused Drug Development Forum, an FDA initiative to capture patient experiences and perspectives on drug development.

Results: Of 797 survey respondents from over 30 countries, 536 (67%) identified slowing disease progression as the most important outcome. Eighty-nine percent identified their hepatologist/gastroenterologist as someone they would approach for advice about trials. Although 61% reported being willing to participate in drug trials, only 26% had ever been asked to participate. Notable barriers to trial involvement included unknown long-term risks (71%), long travel times to the study center (32%), and a liver biopsy requirement (27%). On multivariable logistic regression, pruritus (OR 1.62, 95% CI: 1.09–2.40, $p = 0.017$) was positively associated with willingness to participate in disease-modifying therapy trials, while jaundice (OR 0.34, 95% CI: 0.19–0.61, $p < 0.001$) and inflammatory bowel disease (OR 0.64, 95% CI: 0.42–0.98, $p = 0.038$) were negatively associated. Pruritus (OR 2.25, 95% CI: 1.50–3.39, $p < 0.001$) was also independently associated with willingness to participate in symptom treatment trials.

Abbreviations: AASLD, American Association for the Study of Liver Disease; AIH, autoimmune hepatitis; ASA, aminosalicylic acid; CCA, cholangiocarcinoma; EASL, European Association for the Study of the Liver; EL-PFDD, Externally-Led Patient-Focused Drug Development; ERCP, endoscopic retrograde cholangiopancreatography; IBD, inflammatory bowel disease; MRCP, magnetic resonance cholangiopancreatography; PROMs, patient-reported outcome measures; PSC, primary sclerosing cholangitis.

Conclusions: Most patients with PSC report interest in participating in clinical trials, but few have been asked to participate. Referral of patients with PSC by their hepatologist/gastroenterologist to clinical trials and patient education on trial participation are vital to closing the gap between trial interest and participation. Pruritus may serve as a key indicator of patient interest in trial participation.

INTRODUCTION

Primary sclerosing cholangitis (PSC) is a chronic inflammatory liver disease that causes bile duct strictures and leads to life-threatening complications, including bacterial cholangitis, cholangiocarcinoma, and cirrhosis. Currently, there are no disease-modifying treatments proven to alter the natural history of PSC except for liver transplantation. Furthermore, ~25% of patients will develop PSC recurrence within 5 years of transplantation.[5–7] The treatments for most clinical symptoms other than cholestatic pruritus are not effective. While patient-reported outcome measures (PROMs) for pruritus that are PSC-specific[8] and disease-agnostic[9] have been developed. However, there is an absence of validated PSC-specific PROMs for nonpruritus symptoms.

Recently, new PSC practice guidance documents have been released by the American Association for the Study of Liver Disease (AASLD) and the European Association for the Study of the Liver (EASL). Given the absence of proven disease-modifying therapies, AASLD recommends that all patients with PSC be considered for participation in clinical trials.[10] Similarly, EASL recognizes that clinical trials for PSC are usually concentrated in experienced centers and suggests that patients should be offered the chance to enter into such trials.[11] However, little is known regarding predictors of and barriers to clinical trial involvement from the patient's perspective. The Externally-Led Patient-Focused Drug Development (EL-PFDD) program is an FDA initiative to ensure that patient experiences, needs, and priorities are captured and meaningfully incorporated into drug development and evaluation.[12,13] Quantitative and qualitative data from EL-PFDD initiatives across numerous disciplines and diseases have been used to highlight the patient's voice, identify unmet clinical needs based on patient concerns, and develop PROMs.[14–16] An EL-PFDD Forum for patients with PSC was conducted in October 2020 and generated data through a patient survey to better characterize the patients with PSC experience and therapeutic priorities.[17] Using these data, we sought to characterize interest in clinical trial participation, identify barriers to trial involvement, and discover factors associated with willingness to participate in trials.

METHODS

PSC Partners developed the 40-question "Our Voices" survey as part of the PSC EL-PFDD Forum, which was distributed to patients enrolled in the PSC Partners Patient Registry starting in July 2020. The Registry was established by PSC Partners in collaboration with the National Institutes of Health Office of Rare Disease Research and currently has over 2500 patients. The primary goal of the registry is to facilitate and accelerate clinical research in PSC through direct patient-reported data collection. The registry is patient-driven, web-based, and de-identified in accordance with the NIH standards for privacy and confidentiality.[18] It is reviewed and approved annually by a central institutional review board. The survey was also made available through an external website to patients not enrolled in the Registry. The survey included demographics, disease status, concurrent diagnoses, medications, clinical trial enrollment, and quality-of-life measures. Adult patients 18 years or older who completed the survey before the EL-PFDD Forum were included in this study. Institutional review board approval was obtained from the UCSF Human Research Protection Program.

Outcomes and covariates

Identifying patient willingness to participate in clinical trials for disease-modifying therapy was the primary outcome of this study, while patient willingness to participate in clinical trials targeting PSC symptoms was the secondary outcome. Other patient attributes and opinions related to clinical trials, including important trial outcomes, barriers to clinical trial involvement, past/current trial participation, and the proportion of patients who reported ever being approached about a clinical trial, were also characterized. All answers to survey questions used for data analyses in this study were closed-ended, with options predominantly being binary yes/no. The exceptions were the question asking for the most

important clinical outcome to participants (3 possible options), the questions on barriers to clinical trial participation (rank top 5 choices), and preferred sources for advice about clinical trials (rank top three choices).

Statistical analysis

Baseline patient demographics and covariates are reported as frequencies and percentages. Univariable analyses were performed using chi-squared or Fisher exact tests. Multivariable logistic regression was employed to adjust for potential confounders. Patients who reported having undergone liver transplantation and patients who reported receiving treatment for decompensated liver disease (eg, paracentesis, lactulose/rifaximin treatment, variceal bleeding) were excluded from the logistic regression models evaluating interest in clinical trial participation, as posttransplant patients and patients with decompensated liver disease would typically not be considered candidates for clinical trials. Covariates included in logistic regression models were those that were either identified a priori as potentially being related to the primary or secondary outcomes or those that were associated with the outcomes on univariable analysis. Covariates deemed to be on the causal pathway between another variable and the outcomes being studied were excluded from multivariable logistic regression; in all cases, these excluded covariates were therapies (eg, pruritus medications, antidepressants) for symptoms that were included in the models (eg, pruritus, depression). The sample sizes for the multivariable models exceeded the 10:1 events (the number of the less frequent outcomes) per variable rule of thumb commonly used to avoid overfitting.[19,20] Statistical significance was defined as $p < 0.05$ for all analyses. Statistical analyses were performed using SAS version 9.4 (Cary, NC, USA) and R version 4.3 (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

A total of 797 adults completed the Our Voices survey before the Patient-Focused Drug Development Meeting on October 23, 2020. Patients from over 30 countries completed the survey. Most patients lived in the United States (76%), with Canada (11%), the United Kingdom (3%), Australia (2%), and Norway (1%) being the next most represented countries of origin. Demographics and clinical characteristics are shown in Table 1. Most patients were between 26 and 59 years of age, with 45.5% of patients self-identifying as male and 85.7% as non-Latino White. Most patients (59%) had ulcerative colitis and 15.7% had Crohn's disease. Autoimmune hepatitis overlap was present in 9.9% of patients, and 17.8% reported being diagnosed with cirrhosis. In terms of liver transplantation status, 16.3% of patients received a deceased-donor liver transplant, 6.9% received a living-donor liver transplant, and 4.3% were listed for transplantation. Almost all patients reported receiving a magnetic resonance cholangiopancreatography (95.5%); most patients also underwent a liver biopsy (70.9%). Most patients reported having at least 1 endoscopic retrograde cholangiopancreatography (61.0%), with 32.5% undergoing stenting during endoscopic retrograde cholangiopancreatography and 42.4% reporting ever receiving antibiotics for treatment of bacterial cholangitis. Interventions for complications of cirrhosis (variceal banding, treatment with lactulose and/or rifaximin, paracentesis, and TIPS placement) occurred in 13% or fewer of respondents. The most common PSC-related therapy in the study population was ursodiol (52.9%). Vancomycin treatment (7.2%) was relatively uncommon. Patients reported taking medications for various PSC-related symptoms, including pruritus (18.8%), nausea (15.2%), depression (14.9%), and pain (13.9%).

Patient responses regarding clinical trial characteristics are displayed in Table 2. Overall, 67.3% of patients identified slowing progression of PSC as the single most important outcome for drug development. Most patients (59.5%) reported that they would be willing to participate in drug clinical trials; 57.3% indicated the willingness to participate in a trial for disease-modifying therapy, and 44.2% indicated the willingness to participate in a trial for symptom treatment. However, only a minority of patients (27.0%) reported ever being asked to participate in a clinical trial, and 88.1% of patients had never been involved in a trial. When asked to identify the top 5 factors that might prevent them from joining a trial, uncertainty about side-effects/long-term risks (71.1%) and fear of jeopardizing current quality of life (49.1%) were highlighted. Other common responses were long travel times (31.5%), the possibility that the drug might affect the treatment of their other diseases (27.6%), liver biopsy requirement (26.7%), and potentially affecting transplantation chances (24.0%). When asked to identify the top 3 sources they would approach for advice or with questions about joining a trial, patients overwhelmingly identified their hepatologist or gastroenterologist (89.1%), followed by the clinical trial team (52.1%), family members (50.1%), their primary care doctor (28.2%), the internet (17.9%), and patient organizations (17.8%).

Factors associated with willingness to participate in drug trials

Table 3 details clinical characteristics and patient-reported symptoms stratified by willingness to participate in trials for disease-modifying therapy after excluding patients who underwent liver transplantation and patients with decompensated liver disease; these patients were significantly less likely to be willing to

TABLE 1 Clinical characteristics

Characteristics	Study participants (n = 797)
Age, n (%)	
18–25 y	81 (10.2)
26–39 y	243 (30.5)
40–59 y	313 (39.3)
60 and older	160 (20.1)
Gender, male	361 (45.5)
Race, n (%)	
White, non-Latino	683 (85.7)
White, Latino	58 (7.3)
Asian	15 (1.9)
Black	13 (1.7)
Mixed	10 (1.3)
Indigenous	1 (0.1)
Prefer not to answer or leave blank	17 (2.1)
Comorbidities, n (%)	
Autoimmune hepatitis overlap	79 (9.9)
Ulcerative colitis	470 (59.0)
Crohn's	125 (15.7)
Cirrhosis	142 (17.8)
Cholangiocarcinoma	19 (2.4)
Transplant status, n (%)	
Listed for transplantation	34 (4.3)
Transplanted, deceased donor	130 (16.3)
Transplanted, living donor	55 (6.9)
Tests/interventions at or since diagnosis, n (%)	
MRI/MRCP	761 (95.5)
MR elastography	190 (23.8)
Fibroscan	423 (53.1)
Liver biopsy	565 (70.9)
ERCP	486 (61.0)
ERCP with stenting	259 (32.5)
Antibiotics for cholangitis	338 (42.4)
Lactulose or rifaximin treatment	102 (12.8)
Paracentesis	84 (10.5)
Variceal banding	108 (13.6)
TIPS	26 (3.3)
Current PSC-related therapies, n (%)	
Ursodiol	422 (52.9)
Chronic antibiotics	56 (7.0)
Vancomycin	57 (7.2)
Pain medications	111 (13.9)
Pruritus medications	150 (18.8)
Nausea medications	121 (15.2)
Antidepressants	119 (14.9)
AIH overlap medications	57 (7.2)
Posttransplant medications	155 (19.4)
Encephalopathy medications	33 (4.1)
Current IBD therapies, n (%)	
5-ASA	234 (29.4)
Steroids	54 (6.8)
Immunosuppressants	89 (11.2)
Biologics	116 (14.6)

Note: Data are n (%).
Abbreviations: AIH, autoimmune hepatitis; ASA, aminosalicylic acid; ERCP, endoscopic retrograde cholangiopancreatography; IBD, inflammatory bowel disease; MRCP, magnetic resonance cholangiopancreatography; PSC, primary sclerosing cholangitis.

participate in disease-modifying trials (RR 0.37, 95% CI: 0.28–0.49, $p < 0.001$ and RR 0.64, 95% CI: 0.49–0.82, $p < 0.001$, respectively) and as discussed in the Methods section would not be typical clinical trial candidates. Among patients with compensated liver disease without a history of liver transplantation, pruritus was positively associated with willingness to participate in disease-modifying drug trials (RR 1.26, 95% CI: 1.00–1.59, $p = 0.050$). Factors negatively associated with willingness to participate in disease-modifying drug trials were inflammatory bowel disease (IBD) (RR 0.89, 95% CI: 0.80–0.99, $p = 0.034$) and jaundice (RR 0.47, 95% CI: 0.29–0.76, $p = 0.002$).

Table 4 details clinical characteristics and patient-reported symptoms stratified by the willingness to participate in trials for symptom treatment, also after excluding patients who underwent liver transplantation and patients with decompensated liver disease. Patients willing to participate in symptom treatment trials experienced more symptoms (median 6[3-9] vs. 4,[1-7] $p < 0.001$) than those not willing to participate, and almost all patient-reported symptoms were associated with the willingness to participate, as were treatment with pain medications (RR 2.52, 95% CI: 1.56–4.08, $p < 0.001$), pruritus medications (RR 1.77, 95% CI: 1.24–2.51, $p = 0.001$), nausea medications (RR 1.80, 95% CI: 1.15–2.81, $p = 0.009$), and antidepressants (RR 1.51, 95% CI: 0.99–2.28, $p = 0.051$). History of antibiotic treatment for bacterial cholangitis was a non–symptom-related factor positively associated with willingness to participate in symptom treatment trials (RR 1.29, 95% CI: 1.02–1.64, $p = 0.037$), while there was a trend towards IBD being negatively associated with willingness to participate in symptom treatment trials (RR 0.91, 95% CI: 0.82–1.01, $p = 0.088$).

Two multivariable logistic regression models are displayed in Table 5. After adjusting for age, gender, and ursodiol treatment, pruritus (OR 1.62, 95% CI: 1.09–2.40, $p = 0.017$), jaundice (OR 0.34, 95% CI: 0.19–0.61, $p < 0.001$), and IBD (OR 0.64, 95% CI: 0.42–0.98, $p = 0.038$) were significantly associated with the primary outcome of the study, willingness to participate in disease-modifying drug trials.

Regarding the secondary outcome, pruritus (OR 2.14, 95% CI: 1.44–3.20, $p < 0.001$) was positively

TABLE 2 Clinical trial characteristics

Characteristics	Study participants (n = 797)
Most important outcome for patients, n (%)	
Slowing progression of PSC	536 (67.3)
Reducing risk of CCA	144 (18.1)
Reducing symptoms	78 (9.8)
Trial participation, n (%)	
Ever asked to be in the clinical trial	215 (27.0)
Current clinical trial participant	26 (3.3)
Past clinical trial participant	74 (9.3)
Never participated in trial	702 (88.1)
Willing to participate in drug trial	474 (59.5)
Willing to participate in the trial of disease-modifying therapy	457 (57.3)
Willing to participate in trial for symptom treatment	352 (44.2)
Top 5 factors that might prevent patients from joining a trial, n (%)	
Unknown side-effects or long-term risks	567 (71.1)
Fear of jeopardizing current quality of life	391 (49.1)
Long travel time to the study center	251 (31.5)
Possibility that drug may affect the treatment of their other diseases	220 (27.6)
A liver biopsy	213 (26.7)
Participation might affect the chance for transplantation	191 (24.0)
Too much time off work	178 (22.3)
Worried about receiving placebo	170 (21.3)
General fear of the unknown	143 (17.9)
Frequent/long study visits	137 (17.2)
Other invasive procedures such as endoscopy	128 (16.1)
Too much disruption to family life	116 (14.6)
Lack of access to study results	112 (14.1)
Difficulty communicating with the trial team	104 (13.0)
Not understanding or trusting the consent	66 (8.3)
Don't understand role in trial	56 (7.0)
Too many blood draws	43 (5.4)
Concerns about future access to trial medication	36 (4.5)
Total study duration is too long	26 (3.3)
Top 3 sources who patients would approach for advice or with questions about joining a clinical trial, n (%)	
Hepatologist/gastroenterologist	710 (89.1)
Clinical trial team	415 (52.1)
Family	399 (50.1)
Primary care doctor	225 (28.2)
Internet	143 (17.9)
Patient organization	142 (17.8)
Other provider	49 (6.1)

Notes: Data are n (%).
Abbreviation: CCA, cholangiocarcinoma; PSC, primary sclerosing cholangitis.

associated with willingness to participate in symptom treatment trials after adjusting for other PSC-related symptoms, IBD, history of antibiotic treatment for cholangitis, and ursodiol treatment. There was a trend towards liver pain being positively associated with willingness to participate in symptom treatment trials (OR 1.49, 95% CI: 0.93–2.37, $p = 0.097$).

DISCUSSION

Patient advocacy organizations play a crucial role in patient-focused drug development through efforts to define unmet patient needs, advocate for patients in policy development and clinical services, and shape and co-produce PSC research.[11] The PSC Partners EL-PFDD Forum and the "Our Voices" survey brought together the voices of 797 patients from over 30 countries in the largest-ever patient survey for this rare disease. The results of this survey are particularly timely given recent AASLD and EASL guidance recommending that all patients with PSC be considered for clinical trials. Despite this recommendation, only 27% of participants reported ever being asked to consider enrolling in a trial. Notably, most patients (60%) expressed that they were willing to participate in a trial. As patients overwhelmingly identified their hepatologist/gastroenterologist as whom they would approach with questions about joining a clinical trial (89%), addressing the substantial gap between interest in clinical trial participation and actual clinical trial enrollment falls first and foremost upon PSC specialists.

Our data also identified several covariates associated with interest in drug trial participation following multivariable adjustment. Pruritus was the only patient-reported symptom positively associated with willingness to participate in both disease-modifying and symptom treatment trials, with robust ORs for both outcomes. This suggests that pruritus is a highly impactful symptom, and its presence could be used to flag patients who are particularly interested in participating in trials. This is consistent with evidence associating pruritus with substantial impairments in quality of life in patients with PSC.[21] Jaundice was negatively associated with the willingness to participate in disease-modifying therapy trials. We speculate that the presence of jaundice is a sign of more advanced liver disease or other medical complications, which may decrease the patient's ability or willingness to participate in trials. Concurrent IBD was also negatively associated with willingness to participate in disease-modifying therapy trials. This may reflect a population of patients with IBD with active disease who have greater nonhepatic symptom burden, which may also decrease motivation to participate in PSC trials. Additionally, patients with jaundice and active IBD often meet trial exclusionary criteria, influencing how they are approached about potential trials. The impact of

TABLE 3 Clinical characteristics and symptoms, stratified by willingness to participate in trial for disease-modifying therapy

Characteristics	Not willing to participate (n = 191)	Willing to participate (n = 354)	*p*
Age	—	—	0.670
18–25 y	25 (13.1)	40 (11.3)	—
26–39 y	62 (32.5)	109 (30.8)	—
40–59 y	65 (34.0)	139 (39.3)	—
60 and older	39 (20.4)	66 (18.6)	—
Male gender	82 (42.9)	157 (44.6)	0.750
White, non-Latino	175 (95.6)	330 (94.8)	0.495
Autoimmune hepatitis overlap	16 (8.4)	33 (9.3)	0.713
Inflammatory bowel disease	147 (77.0)	242 (68.4)	0.034
Cirrhosis	18 (9.4)	44 (12.4)	0.292
History of receiving ERCP	103 (53.9)	178 (50.3)	0.417
History of antibiotics treatment for cholangitis	55 (28.8)	125 (35.3)	0.123
Current PSC-related therapies			
Ursodiol	96 (50.3)	203 (57.3)	0.113
Chronic antibiotics	6 (3.1)	22 (6.2)	0.121
Vancomycin	19 (9.9)	25 (7.1)	0.238
Pruritus medications	30 (15.7)	78 (22.0)	0.077
Number of symptoms experienced	4 (1–9)	5 (2–8)	0.452
Symptoms			
Fatigue	129 (67.5)	242 (68.4)	0.844
Insomnia	105 (55.0)	176 (49.7)	0.241
Anxiety	92 (48.2)	157 (44.4)	0.393
Joint pain	73 (38.2)	145 (41.0)	0.533
Depression	79 (41.4)	140 (39.5)	0.680
Weakness	64 (33.5)	134 (37.9)	0.314
Abdominal pain	69 (36.1)	127 (35.9)	0.954
Pruritus	64 (33.5)	149 (42.1)	0.050
Liver pain	65 (34.0)	132 (37.3)	0.450
Brain fog	61 (31.9)	131 (37.0)	0.237
Other pain	49 (25.7)	98 (27.7)	0.611
Nausea/ vomiting	55 (28.8)	94 (26.6)	0.575
Anorexia	51 (26.7)	98 (27.7)	0.806
Night sweats	59 (30.9)	87 (24.6)	0.112
Jaundice	31 (16.2)	27 (7.6)	0.002

Note: Data are n (%).
Abbreviations: ERCP, endoscopic retrograde cholangiopancreatography; PSC, primary sclerosing cholangitis.

TABLE 4 Clinical characteristics and symptoms, stratified by the willingness to participate in the trial for symptom treatment

Characteristic	Not willing to participate (n = 283)	Willing to participate (n = 262)	*p*
Age	—	—	0.505
18–25 y	35 (12.4)	30 (11.5)	—
26–39 y	85 (30.0)	86 (32.8)	—
40–59 y	102 (36.0)	102 (38.9)	—
60 and older	61 (21.6)	44 (16.8)	—
Male gender	129 (45.7)	110 (42.1)	0.398
White, non-Latino	260 (94.5)	245 (95.7)	0.464
Autoimmune hepatitis overlap	23 (8.1)	26 (9.9)	0.464
Inflammatory bowel disease	211 (74.6)	178 (67.9)	0.088
Cirrhosis	31 (11.0)	31 (11.8)	0.747
History of receiving ERCP	145 (51.2)	136 (51.9)	0.875
History of antibiotic treatment for cholangitis	82 (29.0)	98 (37.4)	0.037
Current PSC-related therapies			
Ursodiol	147 (51.9)	152 (58.0)	0.155
Vancomycin	26 (9.2)	18 (6.9)	0.321
Pain medications	21 (7.4)	49 (18.7)	< 0.001
Pruritus medications	41 (14.5)	67 (25.6)	0.001
Nausea medications	27 (9.5)	45 (17.2)	0.009
Antidepressants	33 (11.7)	46 (17.6)	0.051
Number of symptoms experienced	4 (1–7)	6 (3–9)	< 0.001
Symptoms			
Fatigue	175 (61.8)	196 (74.8)	0.001
Insomnia	141 (49.8)	140 (53.4)	0.399
Anxiety	117 (41.3)	132 (50.4)	0.034
Joint pain	98 (34.6)	120 (45.8)	0.008
Depression	107 (37.8)	112 (42.7)	0.240
Weakness	84 (29.7)	114 (43.5)	0.001
Abdominal pain	89 (31.4)	107 (40.8)	0.022
Pruritus	79 (27.9)	134 (51.1)	< 0.001
Liver pain	82 (29.0)	115 (43.9)	< 0.001
Brain fog	83 (29.3)	109 (41.6)	0.003
Other pain	60 (21.2)	87 (33.2)	0.002
Nausea/vomiting	65 (23.0)	84 (32.1)	0.017
Anorexia	58 (20.5)	91 (34.7)	< 0.001
Night sweats	67 (23.7)	79 (30.2)	0.088
Jaundice	35 (12.4)	23 (8.8)	0.175

Data are n (%).
Abbreviations: ERCP, endoscopic retrograde cholangiopancreatography; PSC, primary sclerosing cholangitis.

TABLE 5 Logistic regression models

Covariate	OR	95% CI	*p*-value
A: Willingness to participate in disease-modifying therapy trial			
Age[a]	1.00	0.82–1.22	0.962
Male gender	1.15	0.80–1.66	0.464
IBD	0.64	0.42–0.98	0.038
Ursodiol treatment	1.22	0.84–1.75	0.293
Pruritus	1.62	1.09–2.40	0.017
Jaundice	0.34	0.19–0.61	< 0.001
B: Willingness to participate in trial for symptom treatment			
IBD	0.81	0.54–1.20	0.290
History of antibiotic treatment for cholangitis	1.26	0.86–1.84	0.243
Ursodiol treatment	1.16	0.80–1.66	0.436
Fatigue	1.22	0.78–1.91	0.388
Anxiety	1.02	0.69–1.53	0.913
Joint pain	0.97	0.61–1.54	0.886
Weakness	1.14	0.69–1.88	0.615
Abdominal pain	0.76	0.46–1.26	0.290
Pruritus	2.14	1.44–3.20	< 0.001
Liver pain	1.49	0.93–2.37	0.097
Brain fog	1.16	0.74–1.83	0.512
Other pain	1.38	0.80–2.36	0.247
Nausea/vomiting	0.71	0.41–1.22	0.215
Anorexia	1.47	0.86–2.50	0.158
Night sweats	0.81	0.52–1.28	0.369

[a]Ordinal variable: 18–25 y, 26–39 y, 40–59 y, > 60 y.
Abbreviation: IBD, inflammatory bowel disease.

jaundice and IBD was somewhat unexpected and warrants further investigation.

Almost all patient-reported PSC symptoms were positively associated with the willingness to participate in symptom treatment trials, suggesting the need for drug development to address the PSC symptom burden. No validated PSC-specific PROMs currently exist and are urgently needed for use in clinical trials. PSC Partners is leading efforts to develop validated PROMs that can measure meaningful changes in symptom frequency and severity of key symptoms.

Patients identified multiple potential barriers to clinical trial involvement. While liver biopsy is not required for diagnosis, liver histology continues to be a primary end point in clinical trials as there are currently no established noninvasive surrogate end points for PSC.[22,23] This highlights the unmet clinical need to identify and validate noninvasive surrogate biomarkers of PSC disease activity. Other barriers revolving around time constraints (eg, long travel time to the study center, too much time off work, frequent/long study visits) are starting to be addressed through the adoption of telehealth or at-home study visits. Addressing these logistical factors may also facilitate enrollment of disadvantaged patients and/or those of lower socioeconomic status, as this group is often underrepresented among clinical trial participants.[24]

Strengths of this study include the international patient enrollment, which was done through direct patient outreach by PSC Partners, which enabled a large sample size for this rare disease and avoided center-specific or provider-specific biases. A limitation of this study is sampling bias, as only 45% of responders identified as male, while ~two-thirds of patients with PSC are male.[25] The respondents of the "Our Voices" survey may therefore differ from the general PSC population, including the possibility that they may have more positive attitudes towards clinical trial involvement or may be more likely to experience a greater number of PSC-related symptoms. However, rates of PSC-related comorbidities in our study, including autoimmune hepatitis overlap and IBD, were consistent with the reported literature,[10] supporting population validity. Furthermore, though there was a high percentage of non-Latino White patients, this proportion was consistent with a large cohort of adults with PSC,[26] suggesting that the diversity initiative undertaken by PSC Partners for enrollment was reasonably successful. Recall and nonresponse biases are always possible in survey-based studies, though our analyses focused on active symptoms at the time of survey completion, and there were minimal (< 1%) missing data for any given survey question, suggesting that these biases were limited in our study.

In summary, there is a substantial gap that exists between patient interest in clinical trial involvement and trial referral by providers. Given the almost universal trust by patients in their hepatologist or gastroenterologist, PSC specialists must be responsible for closing this gap. Pruritus appears to be a highly influential PSC symptom, and its presence may predict patient willingness to enroll in clinical trials. Key potentially modifiable barriers to trial involvement include invasive procedures, time constraints, and patient communication and education.

AUTHOR CONTRIBUTIONS

Michael Li: conceptualization, data curation, formal analysis, methodology, writing (original draft). Ruth-Anne Pai, Joanne Hatchett, Sarah Curup Callif: conceptualization, data curation, methodology, writing (review and editing). Rachel Gomel and Mary Vyas: conceptualization, data curation, writing (review and editing). Christopher L. Bowlus: conceptualization, writing (review and editing). Jennifer C. Lai: conceptualization, methodology, supervision, writing (review and editing).
Michael Li and Ruth-Anne Pai are co-first authors.

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CONFLICTS OF INTEREST

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