7-1-2022

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Crohn's & Colitis 360, XXXX, **4**, 1–10
https://doi.org/10.1093/crocol/otac030
Advance access publication 2 August 2022
Observations and Research

Treatment Patterns and Standardized Outcome Assessments Among Patients With Inflammatory Conditions of the Pouch in a Prospective Multicenter Registry

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Background: Much of our understanding about the natural history of pouch-related disorders has been generated from selected populations. We designed a geographically diverse, prospective registry to study the disease course among patients with 1 of 4 inflammatory conditions of the pouch. The primary objectives in this study were to demonstrate the feasibility of a prospective pouch registry and to evaluate the predominant treatment patterns for pouch-related disorders.

Methods: We used standardized diagnostic criteria to prospectively enroll patients with acute pouchitis, chronic antibiotic-dependent pouchitis (CADP), chronic antibiotic refractory pouchitis (CARP), or Crohn's disease (CD) of the pouch. We obtained detailed clinical and demographic data at the time of enrollment, along with patient-reported outcome (PRO) measures.

Results: We enrolled 318 patients (10% acute pouchitis, 27% CADP, 12% CARP, and 51% CD of the pouch). Among all patients, 55% were on a biologic or small molecule therapy. Patients with CD of the pouch were more likely to use several classes of therapy ($P < .001$). Among patients with active disease at the time of enrollment, 23% with CARP and 40% with CD of the pouch were in clinical remission at 6 months after enrollment.

Conclusions: In a population where most patients had refractory inflammatory conditions of the pouch, we established a framework to evaluate PROs and clinical effectiveness. This infrastructure will be valuable for long-term studies of real-world effectiveness for pouch-related disorders.

Lay Summary

The PROP-RD study evaluated the disease course among patients with inflammatory conditions of the pouch. Among patients with active disease at the time of enrollment, 23% with chronic antibiotic refractory pouchitis and 40% with Crohn's disease of the pouch were in clinical remission at 6 months after enrollment.

Key Words: Crohn's disease of the pouch, ileal pouch-anal anastomosis, pouchitis, real-world effectiveness

INTRODUCTION

Although restorative proctocolectomy with ileal pouch-anal anastomosis (IPAA) is often depicted as a curative surgery for patients with medically refractory ulcerative colitis (UC),[1] many short- and long-term complications can occur. Symptoms of acute and chronic pouchitis affect up to 80% of patients after IPAA with a negative impact on quality of life.[2–4] In addition, 10% of patients undergoing IPAA will ultimately be diagnosed with Crohn's disease (CD) of the pouch.[5] Despite concerns about the potentially increasing incidence

Received for publication: June 23, 2022. Editorial Decision: July 24, 2022

of pouch-related disorders,[6] our ability to reliably predict these outcomes at the time of IPAA and to counsel patients regarding effective preventive and/or treatment strategies is limited.

Much of our understanding regarding the natural history of inflammatory conditions of the pouch has been generated from selected, mostly single-center populations.[7–11] Although these studies have provided the foundation for clinical care and research in this field, analyses of select populations have inherent limitations, including a limited ability to adequately evaluate the epidemiology of pouchitis and to perform studies of therapy utilization and effectiveness. The heterogeneity that exists between studies is also a significant concern, including in clinical definitions between studies.[5,12,13]

To improve our understanding of the disease course among patients with inflammatory conditions of the pouch, we created A Prospective Registry for the Study of Outcomes and Predictors of Pouchitis and Pouch-Related Disorders (the PROP-RD study). In this initial analysis from the PROP-RD study, our primary aim was to demonstrate the feasibility of enrolling patients in a prospective registry to study pouch-related disorders using standardized diagnostic criteria and outcome assessments. We also aimed to investigate the predominant treatment patterns for patients with each of 4 inflammatory conditions of the pouch at the time of enrollment into the PROP-RD study. In these analyses, we evaluated the demographics and clinical characteristics of patients with inflammatory conditions of the pouch, including patient-reported outcomes (PROs).

METHODS

Study Design

We enrolled patients with a confirmed diagnosis of acute pouchitis, chronic antibiotic-dependent pouchitis (CADP), chronic antibiotic refractory pouchitis (CARP), or CD of the pouch into a prospective registry using standardized criteria (Table 1). These diagnostic criteria were developed prior to enrollment, and were agreed upon by all investigators after review of available literature and existing diagnostic criteria for each of the 4 inflammatory conditions of the pouch. At the time of enrollment, the treating physician selected relevant diagnostic criteria utilized in their assessment, and this was recorded alongside other applicable clinical and demographic information. Enrollment was not restricted by a predefined disease activity score. Patients were enrolled from 1 of 8 academic medical centers with expertise in the care of patients with inflammatory bowel disease (IBD) and pouch-related disorders (Supplementary Table S1). Patients were recruited from standard-of-care clinic visits or via telephone consent if identified prior to a clinic visit by their treating physician. Patients completed electronic follow-up via a secure portal at 3, 6, and 12 months after enrollment.

Outcomes of Interest

The utilization of therapies for the treatment of pouch-related conditions was evaluated at the time of enrollment into PROP-RD, including antibiotics, probiotics, glucocorticoids (oral and rectal/topical formulations), aminosalicylates (oral and rectal/topical formulations), biologic therapies (infliximab, adalimumab, certolizumab, infliximab, golimumab, ustekinumab, or vedolizumab), and oral small molecules/immunomodulators (tofacitinib, methotrexate, and thiopurines). In the assessment of treatment patterns among patients with inflammatory conditions of the pouch, we evaluated clinical remission at 6 months after enrollment, defined by the clinical portion of the modified Pouchitis Disease Activity Index (mPDAI).[14] In this analysis, clinical remission was defined as a clinical mPDAI score of <2[15] with both the bowel frequency and urgency subscores <1. Multiple other secondary analyses are detailed in Supplementary Methods.

Covariates

We evaluated demographic factors such as sex, race/ethnicity, and age, as well as clinical factors that may increase the risk of development of pouchitis or other inflammatory conditions of the pouch including smoking status,[16,17] the use of nonsteroidal anti-inflammatory drugs,[16] *Clostridioides difficile* infection prior to IPAA,[18] and primary sclerosing cholangitis.[19]

TABLE 1. Diagnostic criteria for patients with inflammatory conditions of the pouch enrolled in PROP-RD.

Acute pouchitis	Acute onset of symptoms within the past 4 weeks Endoscopic evaluation
Chronic antibiotic-dependent pouchitis	Episodes occurring at least 4 times per year, requiring recurrent courses of antibiotics or continuous antibiotic therapy, with symptoms being responsive to antibiotic therapy Endoscopic evaluation
Chronic antibiotic refractory pouchitis	Lack of response to standard antibiotic therapy Requirement of a longer duration of antibiotic therapy than expected, with minimal improvement in symptoms Requirement of additional therapy, including immunosuppressive therapies Endoscopic evaluation
Crohn's disease of the pouch	Presence of a fistula or fistulae after IPAA (developed at least 3 months postoperatively) Stricture involving the pouch or prepouch ileum on imaging or pouchoscopy (nonanastomotic strictures) Presence of prepouch ileitis (inflammation of the afferent limb) on imagining or pouchoscopy

Patients with acute pouchitis, chronic antibiotic-dependent pouchitis, and chronic antibiotic refractory pouchitis were evaluated for the presence of frequency, urgency, bleeding, fever, and a general sense of malaise as part of the diagnostic algorithm. Differentiating factors between the diagnostic categories are presented above. Investigators were encouraged to suggest any other diagnostic criteria utilized for each category, and these were reviewed by Principal Investigator on a monthly basis. Abbreviation: IPAA, ileal pouch-anal anastomosis.

TABLE 2. Baseline demographics and clinical characteristics of patients with inflammatory conditions of the pouch.

	Acute pouchitis *n* = 32		Chronic antibiotic-dependent pouchitis *n* = 87		Chronic antibiotic refractory pouchitis *n* = 38		Crohn's disease of the pouch *n* = 161		*P*
	Median	IQR	Median	IQR	Median	IQR	Median	IQR	
Current age	45.5	34–57.5	56	31.5–62	55	40.5–63	51	38–60	.176
	n	%	n	%	n	%	n	%	
Female sex	15	47	33	38	17	45	76	47	.558
Race									.097
White	26	81	85	98	32	84	149	93	
Black	3	9	1	1	4	11	9	6	
Other	3	9	1	1	2	6	3	2	
Hispanic ethnicity	3	9	3	3	2	5	2	1	.160
BMI									.569
Normal	17	55	39	45	16	42	59	37	
Overweight	9	29	25	29	13	34	59	37	
Obese	5	16	22	26	9	42	42	26	
Disease extent prior to surgery									.182
Proctitis	4	13	6	7	1	3	10	7	
Left sided	5	17	8	9	5	14	9	6	
Extensive colitis	14	47	53	62	21	58	107	72	
Unknown	7	23	18	21	9	25	22	15	
Indication for surgery									.857
Medically refractory colitis	30	94	76	87	33	87	146	91	
Dysplasia/colorectal cancer	1	3	5	6	1	3	7	4	
Medically refractory + dysplasia/CRC (both)	1	3	2	2	2	5	3	2	
Other indication	0	0	4	5	2	5	4	2	
Number of stages in surgery[b]									.021
I	3	9	8	9	1	3	25	16	
II	7	22	35	40	13	34	69	43	
Modified II	2	6	5	6	3	8	12	7	
III	19	59	34	39	21	55	44	27	
Unknown	1	3	5	6	0	0	11	7	
IPAA surgery was performed at the current medical center	25	78	57	66	18	47	101	63	.061
Primary sclerosing cholangitis diagnosis	3	9	9	10	3	8	10	6	.692
Clostridium difficile infection prior to IPAA	8	25	10	11	6	16	22	14	.305
Smoker at the time of colectomy	1	3	3	3	2	5	11	7	.881
Current smoker	1	3	9	11	3	8	7	5	.257
NSAIDs in the prior 2 weeks	15	47	31	36	10	27	60	37	.115
Current therapy at enrollment									
Antibiotics (*n* = 156)	19	59	61	72	19	50	57	36	<.001
Probiotics (*n* = 84)	9	28	31	36	9	24	35	22	.107
Oral steroids (*n* = 54)	3	9	14	16	8	21	29	18	.592
Topical steroids (*n* = 23)	2	6	5	6	4	11	12	7	.819
Oral 5-ASA (*n* = 8)	0	0	4	5	1	3	3	2	.441
Topical 5-ASA (*n* = 11)	2	6	3	3	3	8	3	2	.241
Thiopurine (azathioprine or mercaptopurine) (*n* = 23)	0	0	1	1	1	3	21	13	.001
Methotrexate (*n* = 15)	1	3	2	2	0	0	12	7	.121
Tofacitinib (*n* = 5)	0	0	0	0	1	3	4	2	.389

Table 2. Continued

	n	%	n	%	n	%	n	%	
anti-TNF									
Adalimumab (*n* = 32)	0	0	5	6	4	11	23	14	.038
Certolizumab (*n* = 2)	0	0	0	0	2	5	0	0	.424
Infliximab (*n* = 26)	0	0	1	1	0	0	25	16	<.001
Ustekinumab (*n* = 74)	1	3	4	5	8	21	61	38	<.001
Vedolizumab (*n* = 38)	0	0	6	7	7	18	25	16	.020

Abbreviations: 5-ASA, 5-aminosalicylate; anti-TNF, anti-tumor necrosis factor alpha; BMI, body mass index; CRC, C-reactive protein; IPAA, ileal pouch-anal anastomosis; IQR, interquartile range; NSAIDs, nonsteroidal anti-inflammatory drugs.
[a]"Other indications" not shown.
[b]A modified 2-stage procedure was defined as follows: a total abdominal colectomy with end ileostomy is completed in the first operation and after a recovery interval, a second surgery is performed including completion proctectomy and IPAA (without a diverting loop ileostomy).

Statistical Analysis

Descriptive statistics were used to summarize demographic and clinical characteristics at the time of enrollment. Continuous variables are described using means and SD, although medians and interquartile range (IQR) are used to describe continuous variables with a nonnormal distribution. Categorical variables are reported as raw values with accompanying percentages. In comparisons across the 4 categories of inflammatory conditions of the pouch, ANOVA and Kruskal–Wallis testing were utilized as appropriate. For all analyses, 2-sided *P* values of .05 or less were considered statistically significant. All analyses were performed using SAS version 9.4 (SAS Institute).

Ethical Considerations

The study protocol was approved by the Institutional Review Board at each of the participating institutions.

RESULTS

Demographics and Clinical Characteristics at Enrollment

Between June 5, 2019 and August 3, 2020, we enrolled 318 patients with inflammatory conditions of the pouch. When evaluating the diagnoses of each enrolled patient, 32 (10%) had acute pouchitis, 87 (27%) had CADP, 38 (12%) had CARP, and 161 (51%) had CD of the pouch (Table 2). The frequency of each criteria used in diagnoses is depicted in Supplementary Table S2). Of note, diagnostic criteria were not exclusionary with a large proportion of patients meeting criteria for a diagnosis based on multiple criteria. Among patients with CD of the pouch, the most common fistulae identified were perianal (65%) and pouch-vaginal (27%) locations. The median age of patients enrolled in PROP-RD was 50 years (IQR 37–59.5) and there were 141 (44%) female patients. Retention rates, defined by completion of assessments of clinical remission were 286 (90%) at 3 months and 6 months after enrollment.

There were no significant differences across inflammatory conditions of the pouch when comparing sex, race, ethnicity, current age, or disease extent prior to surgery. Patients with acute pouchitis demonstrated the highest use of preoperative vedolizumab and tofacitinib in comparison to other inflammatory conditions of the pouch ($P < .001$ for both comparisons, Supplementary Table S3). Additionally, where available, there were no significant differences in C-reactive protein, fecal calprotectin, and hemoglobin at the time of enrollment (Supplementary Table S4). At the time of enrollment, 171 patients (54%) were being treated with a biologic or small molecule therapy. The median duration of therapy with these agents prior to enrollment was 468 days (IQR 268–962).

Disease Activity and PROs at Enrollment

In a comparison of the median clinical mPDAI scores between patients with the 4 inflammatory conditions of the pouch, there were no significant differences noted at the baseline visit ($P = .177$). One hundred eighty-nine patients (61%) had active disease with a clinical mPDAI >2 or an urgency or bowel frequency subscore >1. Among all patients, the mean number of bowel movements per day was 8.4 (SD 4.2) with a mean nightly frequency of bowel movements of 2.1 (SD 1.7). In assessment of other PROs at enrollment, 148 (48%) patients had occasional urgency, 82 (27%) reported having urgency on a usual basis, and 28 (9%) had rectal bleeding at the time of enrollment. When assessing differences in PROs between patients with active disease at the time of enrollment and those in remission, patients with active disease demonstrated a greater number of mean daily and nocturnal bowel movements in inflammatory conditions of the pouch, as well as increased stool frequency and urgency scores (Tables 3 and 4).

Among all enrolled patients, 103 (33%) underwent pouchoscopy at the time of enrollment. The median endoscopic subscore of the PDAI was 2 (IQR 1–4). Thirty percent of patients had cuffitis present on the initial pouchoscopy, 17 (17%) had a stricture at the ileoanal anastomosis, and 5 (5%) had a perianal fistula.

Clinical Remission at 6 Months After Enrollment

Among 283 patients with available data, 138 (49%) were in clinical remission at 6 months after enrollment into PROP-RD. When stratified by baseline remission status, 74% of patients in remission at enrollment remained in remission at 6 months whereas 36% of patients with active disease at enrollment achieved remission at 6 months. In examining rates of remission among the 4 inflammatory conditions of the pouch, the proportion of patients with achieving remission at 6 months (among those with active disease at enrollment) ranged from 22% of patients with CARP to 43% of patients with CD of the pouch (Supplementary Tables S5a and S5b).

TABLE 3. Clinical assessments at enrollment, stratified by disease state and baseline remission status.

	Acute pouchitis (active at baseline) *n* = 19		Acute pouchitis (remission at baseline) *n* = 13		*P*	Chronic antibiotic-dependent pouchitis (active at baseline) *n* = 50		Chronic antibiotic-dependent pouchitis (remission at baseline) *n* = 36		*P*
	Median	IQR	Median	IQR		Median	IQR	Median	IQR	
Clinical portion of the mPDAI	3	3–4	1	1–2	<.001	3	3–4	1	0–1	<.001
Current quality of life	7	5–8	8	7–9	.071	7	5–7	8	7–9	<.001
Current quality of health	6	5–8	8	7–8	.141	6	5–7	7	6–9	.001
Current energy level	6	4.5–7	7	6–8	.047	5	4–6	7	5–8	.001
	n	%	n	%		n	%	n	%	
Stool frequency										
Usual stool frequency after surgery	2	11	10	77	<.001	2	4	30	83	<.001
1–2 stools greater	3	16	3	23		3	6	6	17	
3 or more stools per day greater	14	74	0	0		45	90	0	0	
Rectal bleeding										
None or rare rectal bleeding	12	63	11	85	.101	46	92	36	100	.425
Present daily	7	37	1	8		2	4	0	0	
Don't know	0	0	1	8		2	4	0	0	
Urgency										
None	0	0	3	23	.001	7	14	17	47	<.001
Occasional	9	47	10	77		19	38	19	53	
Usual	10	53	0	0		23	46	0	0	
Don't know	0	0	0	0		1	2	0	0	
Fever in the past 24 hours										
No	19	100	13	100	>.999	48	96	33	92	.036
Yes	0	0	0	0		0	0	3	8	
Don't know	0	0	0	0		2	4	0	0	
Have you had bowel incontinence in the past 7 days										
No days	10	53	10	77	.416	27	54	34	94	.001
1 day	2	11	2	15		8	16	1	3	
2–3 days	2	11	1	8		5	10	0	0	
4–5 days	4	21	0	0		5	10	1	3	
6–7 days	1	5	0	0		5	10	0	0	
Leakage of stool or soiling of underwear in the past 7 days										
No days	6	32	7	54	.568	18	36	28	78	.001
1 day	2	11	2	15		10	20	5	14	
2–3 days	3	16	2	15		7	14	0	0	
4–5 days	5	26	2	15		4	8	1	3	
6–7 days	3	16	0	0		11	22	2	6	
	Mean	SD	Mean	SD	P	Mean	SD	Mean	SD	P
Number of daily bowel movements, last 3 days	8.7	5.2	6.0	1.6	.093	9.6	3.8	6.7	2.3	<.001
Number of nocturnal bowel movements, last 3 nights	2.6	1.7	1.5	1.0	.031	2.6	1.8	1.2	0.9	<.001

Abbreviations: IQR, interquartile range; mPDAI, modified Pouchitis Disease Activity Index.

Antibiotic Use Patterns Over the First 6 Months

Among all patients enrolled, 135 (43%) were treated with antibiotics at the time of enrollment. When evaluating the percentage of patients with CADP in remission at 6 months by initial antibiotic monotherapy utilized at enrollment, 18 (46%) patients on a fluoroquinolone and 6 (43%) patients on metronidazole were in remission (Supplementary Table S6).

TABLE 4. Clinical assessments at enrollment, stratified by disease state and baseline remission status.

	Chronic antibiotic refractory pouchitis (active at baseline) *n* = 27		Chronic antibiotic refractory pouchitis (remission at baseline) *n* = 9		*P*	Crohn's disease pouch (active at baseline) *n* = 94		Crohn's disease pouch (remission at baseline) *n* = 64		*P*
	Median	IQR	Median	IQR		Median	IQR	Median	IQR	
Clinical portion of the mPDAI	3	3–4	1	1–1	<.001	3	2–4	1	0–1	<.001
Current quality of life	7	5.5–8	8	7–9	.051	7	5–8	8	6–9	.019
Current quality of health	6	4.5–7	6	6–7	.317	6	5–8	7	6–8	.041
Current energy level	5	3.5–6	6	5–7	.099	6	4–7	7	5–8	.043
	n	%	n	%		n	%			
Stool frequency										
Usual stool frequency after surgery	1	4	7	78	<.001	11	12	53	83	<.001
1–2 stools greater	0	0	2	22		4	4	11	17	
3 or more stools per day greater	26	96	0	0		79	84	0	0	
Rectal bleeding										
None or rare rectal bleeding	23	85	8	89	>.999	81	86	59	92	.454
Present daily	2	7	1	11		11	12	5	8	
Don't know	2	7	0	0		2	2	0	0	
Urgency										
None	4	15	3	33	.061	16	17	27	42	<.001
Occasional	13	48	6	67		37	39	37	58	
Usual	10	37	0	0		40	43	0	0	
Don't know	0	0	0	0		1	1	0	0	
Fever in the past 24 hours										
No	27	100	9	100	>.999	92	98	64	100	>.999
Yes	0	0	0	0		1	1	0	0	
Don't know	0	0	0	0		1	1	0	0	
Have you had bowel incontinence in the past 7 days										
No days	16	59	8	89	.337	68	72	54	84	.548
1 day	5	19	0	0		10	11	4	6	
2–3 days	4	15	0	0		8	9	4	6	
4–5 days	1	4	1	11		4	4	1	2	
6–7 days	1	4	0	0		4	4	1	2	
Leakage of stool or soiling of underwear in the past 7 days										
No days	12	44	6	67	.312	47	50	37	58	.988
1 day	6	22	0	0		13	14	15	23	
2–3 days	4	15	3	33		17	18	7	11	
4–5 days	3	11	0	0		5	5	3	5	
6–7 days	2	7	0	0		12	13	2	3	
	Mean	SD	Mean	SD	P	Mean	SD	Mean	SD	P
Number of daily bowel movements, last 3 days	12.2	6.7	7.6	1.9	.050	8.5	4.0	6.8	2.5	.003
Number of nocturnal bowel movements, last 3 nights	3.3	2.7	1.6	1.2	.071	2.1	1.8	1.5	1.1	.031

Abbreviations: IQR, interquartile range; mPDAI, modified Pouchitis Disease Activity Index.

Biologic and Other Immunosuppressive Medication Use Over the First 6 Months

Among patients with CARP, 21 (62%) were treated with a biologic therapy at enrollment. There were 13 patients with active CARP at enrollment being treated with a biologic therapy, and among these patients, 3 (23%) were in clinical remission at 6 months after enrollment (Supplementary Table S7).

Seventy-six percent of patients with CD of the pouch were on a biologic therapy at enrollment, whereas 24% were treated with small molecules (20 thiopurine, 10 methotrexate, 6 tofacitinib). Among 78 patients with CD of the pouch treated with a biologic therapy who had active disease at enrollment, 31 (40%) were in clinical remission at 6 months after enrollment (Supplementary Table S7). Additionally, 2 of 4 patients (50%) with active CD of the pouch at enrollment treated with tofacitinib were in clinical remission at 6 months after enrollment (Fig. 1). Antibiotics continued to be utilized in 18 (14%) patients treated with a biologic therapy and 5 (21%) patients treated with a small molecule. A minority of patients with acute pouchitis or CADP (4% of population) demonstrated a change to a more refractory disease state (CARP or CD of the pouch) within the first 6 months after enrollment.

DISCUSSION

In this initial evaluation of the PROP-RD study, we demonstrated the feasibility of creating a prospective registry to evaluate longitudinal outcomes among patients with inflammatory conditions of the pouch using standardized diagnostic criteria. Additionally, we identified the predominant treatment patterns for inflammatory conditions of the pouch in a diverse group of IBD centers and multidisciplinary pouch clinics, allowing for standardized assessment of clinical remission at 6 months after enrollment. Perhaps most important among these initial findings, those patients with CARP and CD of the pouch demonstrated durability with the initial biologic therapy utilized at the time of enrollment, a finding which is particularly striking given the number of patients long-term biologic or small molecule therapy at the time of enrollment (with less than 50% of these patients being in clinical remission).

One of the major limitations in the study of patients with inflammatory conditions of the pouch has been the significant heterogeneity present in both clinical presentation after IPAA and the diagnostic terminology utilized in this population.[5,20–23] In this prospective registry, we used standardized diagnostic criteria that all co-investigators agreed upon prior to the initiation of the study, based on existing literature. Additionally, local investigators at each site had the opportunity to identify other diagnostic criteria where gaps in the original criteria might exist, and these "other criteria" were reviewed on a monthly interval. However, no new criteria were added over the course of the study.

The patients enrolled in the PROP-RD study are representative of those seen in tertiary care IBD centers and multidisciplinary pouch clinics. This is noted, given that 50% of patients in this study population had a diagnosis of CD of the pouch. The incidence of CD of the pouch among patients undergoing IPAA for UC is estimated to be 10%,[5] thus this population represents an over-sampling of patients with this diagnosis. However, the burden of chronic inflammatory conditions of the pouch is significant after IPAA,[2,24,25] necessitating larger prospective studies to better understand outcomes in this population. A recent retrospective evaluation by Bresteau et al demonstrated that 35% of consecutively enrolled patients undergoing IPAA went on to develop chronic pouchitis or CD of the pouch.[26] In a separate retrospective multicenter evaluation of pouch-related disorders from the Sinai-Helmsley Alliance for Research Excellence (SHARE) cohort, over 40% of patients with an IPAA treated at one of the 7 academic centers had a diagnosis of CD of the pouch.[27] However, the analysis of the SHARE cohort did not utilize standardized diagnostic criteria in the evaluation.

Although these patients are representative of those seen in tertiary care IBD centers, this was not an inception cohort. Patients were enrolled from standard-of-care visits for pouch-related disorders, and thus many historical factors related to preoperative UC history, perioperative factors, and decision-making at the time of colectomy were not

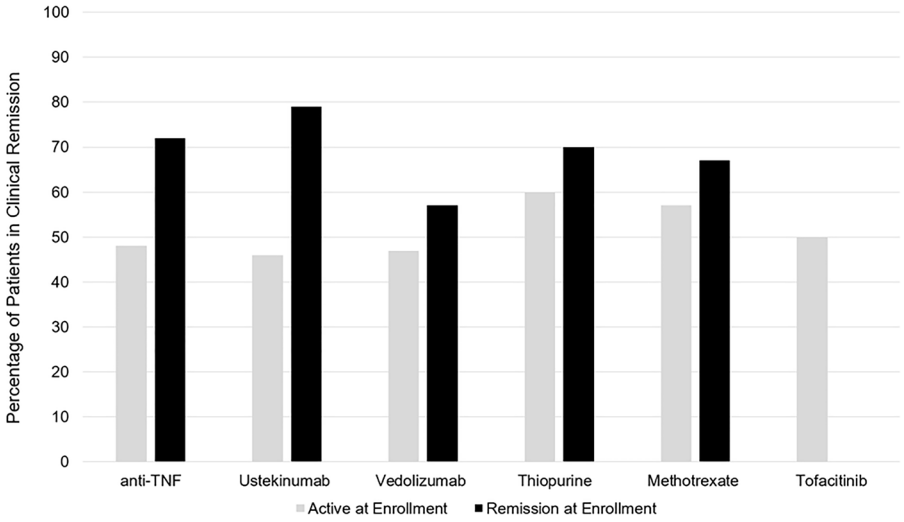

FIGURE 1. Comparison of proportion of patients with Crohn's disease of the pouch in clinical remission at 6 months after enrollment, stratified by disease activity at enrollment (remission vs active disease) and initial therapy. Abbreviation: anti-TNF, anti-tumor necrosis factor alpha. Only those patients with available data at 6 months presented.

available for analysis. For example, risk variants such as the single-nucleotide polymorphism *NOD2*insC[28] and serologic markers[12] have been associated with an increased risk for chronic inflammatory conditions of the pouch, but these risk variants could not be assessed as patients were enrolled after the development of a pouch-related disorder. Additionally, because the primary objective of the PROP-RD registry was to analyze patients with 1 of 4 inflammatory conditions of the pouch, patients without a pouch-related disorder (ie, patients with normal pouch function) were not enrolled and thus not available for comparison.

We analyzed the use of multiple biologic therapies and tofacitinib for the treatment of CARP and CD of the pouch. The majority of published data evaluating the response to biologic therapy for the treatment of chronic inflammatory conditions of the pouch has been retrospective series from single centers.[29–34] However, retrospective evaluations using a multicenter approach[35–37] and 1 randomized clinical trial[38] have also been performed. Our initial evaluations of remission with anti-tumor necrosis factor (TNF) therapies compare similarly to a recent systematic review and meta-analysis by Huguet et al where the rate of long-term remission with anti-TNF therapy for CD of the pouch was 0.57 (95% CI 0.43–0.71) and the rate of long-term remission for chronic refractory pouchitis was 0.37 (95% CI 0.14–0.62).[33]

When comparing outcomes among patients treated with ustekinumab to a recent publication by Weaver et al, the rate of clinical remission at 6 months after enrollment among patients with CD of the pouch was higher in PROP-RD (62% vs 11%), however 83% of patients in the Weaver study demonstrated a clinical response at 6 months as judged by physician assessment.[36] Additionally, Weaver et al evaluated all patients newly initiating ustekinumab whereas patients could be enrolled in PROP-RD on established therapies, perhaps leading to an enrichment of the responder population in our evaluation of ustekinumab and other therapies in the initial analyses at 6 months. Despite this, the durability findings with respect to ustekinumab have also been demonstrated in recent real-world evaluations of other patients with IBD.[39] The number of patients with CARP treated with ustekinumab in PROP-RD was smaller than that of CD of the pouch, however the clinical remission rate (29%) was noteworthy given that prior studies have only assessed clinical response by physician assessment.[29,36] The proportion of patients in clinical remission treated with vedolizumab also compared favorably to recent reports of the effectiveness of this therapy in pouch-related disorders.[30,35,37] Finally, although little is known about the efficacy of tofacitinib in inflammatory conditions of the pouch,[40,41] 50% patients treated with tofacitinib for CD of the pouch were in clinical remission at 6 months after enrollment.

Fluoroquinolones and metronidazole were the predominant antibiotics utilized by patients with acute pouchitis and CADP, patterns also previously reported in analysis of administrative claims.[25] Recent evaluations have demonstrated the potential for antibiotic resistance among nonpathogenic bacteria, perhaps contributing to the development of antibiotic-dependent disease.[42] In theory, a pouch microbiome with antibiotic resistant bacteria with low inflammatory potential might prevent colonization by more inflammatory bacteria, but also establish the potential for subsequent antibiotic dependence.[42] Among patients with CADP treated with the 2 most common antibiotics at baseline however, approximately 45% were in clinical remission. Continuing to assess the impact of cycling antibiotics and other strategies to diversify antibiotic techniques in this population will be informative.

The strengths of our study include the prospective evaluation of patients with inflammatory conditions of the pouch using standardized assessments and the multicenter design representing large portions of the United States. However, our study has limitations. This was not an inception cohort, given that all patients had an existing diagnosis of 1 of 4 inflammatory conditions of the pouch. Therapy decisions were likely differential, however we did not account for physician-based factors or patient preference in the assessment of medication utilization patterns or subsequent outcomes at 6 months after enrollment. Similarly, all patients being treated with a medication were not enrolled on a new medication at baseline, and thus the assessment of clinical remission is based on 6 months after enrollment into PROP-RD and not 6 months after induction. Some differences in the 4 inflammatory conditions of the pouch may be attributed to factors not directly addressed in the study. For example, although patients with acute pouchitis demonstrated a significantly higher frequency of vedolizumab and tofacitinib use preoperatively, this likely represents a recency bias of IPAA and not a pathophysiologic link between these therapies and acute pouchitis. Additionally, although we utilized standardized assessments including the mPDAI, this has not been validated for use in patients with CD of the pouch. Finally, although pouchoscopy was performed in the majority of patients enrolled, endoscopic evaluation (with accompanying histopathology) was not required prior to enrollment.

In conclusion, in a prospective, multicenter cohort of patients with inflammatory conditions of the pouch, we demonstrated the ability to diagnose and perform objective assessments using standardized criteria. These initial efforts are informative regarding utilization patterns of therapies for pouch-related disorders, but also create a foundation for long-term studies of real-world durability and comparative effectiveness in this population. Long-term assessments of this cohort will also allow for an improved evaluation of the risk factors for disease progression and refractory disorders, perhaps allowing for earlier and standardized interventions to improve outcomes in this population.

Supplementary Data

Supplementary data is available at *Crohn's and Colitis 360* online.

Funding

This research was supported by grants from the Crohn's & Colitis Foundation [614963 (E.L.B.)] and the National Institutes of Health [K23DK127157-01 (E.L.B.) and P30DK034987 (J.G.)]. P.D. is supported by a Junior Faculty Development Award from the American College of Gastroenterology and IBD Plexus of the Crohn's and Colitis Foundation.

Conflicts of Interest

Edward L. Barnes has served as a consultant for AbbVie, Gilead, Pfizer, and Target RWE. Parakkal Deepak has served as a consultant or on an advisory board for Janssen, Pfizer, Prometheus Biosciences, Boehringer Ingelheim, AbbVie, Arena Pharmaceuticals, and Scipher Medicine Corporation. He has also received funding under a sponsored research agreement unrelated to the data in the paper from Takeda Pharmaceutical, Arena Pharmaceuticals, Bristol Myers Squibb-Celgene, and Boehringer Ingelheim. Parakkal Deepak holds the position of Associate Editor for *Crohn's & Colitis 360* and has been recused from reviewing or making decisions for the manuscript. Poonam Beniwal-Patel has received honorarium from the Takeda speaker's bureau. Laura Raffals has served on an advisory board for Janssen. Laura Raffals holds the position of Associate Editor for *Crohn's & Colitis 360* and has been recused from reviewing or making decisions for the manuscript. Marla Dubinsky has served as a consultant or has received advisory board fees from AbbVie, Arena, BMS, Eli Lilly, Gilead, Janssen, Pfizer, Prometheus Labs, and Takeda. She has received grant support from Janssen and AbbVie. She also has the following relationships: Licenser of software: Takeda; Co-Founder, Equity ownership and board of director for Trellus Health. Shannon Chang has served as a consultant for AbbVie, BMS, and Pfizer. Raymond K. Cross has participated in advisory boards for AbbVie, Bristol Myers Squibb, Janssen, and Pfizer and has served as a consultant for Eli Lilly. Millie D. Long has served as a consultant for AbbVie, UCB, Takeda, Janssen, Pfizer, Salix, Valeant, and Target Pharmasolutions and has received research support from Pfizer and Takeda. Hans H. Herfarth has served as a consultant for Alivio, AMAG, BMS, ExeGI Finch, Gilead, Janssen, Lycera, Merck, Otsuka, Pfizer, PureTech, and Seres and has received research support from Pfizer and Artizan Biosciences. Maia Kayal, Peter D.R. Higgins, Jennifer I. Barr, Joseph Galanko, and Yue Jiang have no relevant disclosures.

Data Availability

Raw data may be available for further analysis. Please direct any questions regarding data availability and analytic methods to the corresponding author.

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