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Ustekinumab Is Effective for the Treatment of Chronic Antibiotic-Refractory Pouchitis

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Abstract

Background—Chronic antibiotic-refractory pouchitis (CARP) occurs in up to 15% of patients with ulcerative colitis (UC) following proctocolectomy with ileal pouch-anal anastomosis (IPAA).

Aim—To investigate the effectiveness of ustekinumab in the treatment of CARP.

Methods—This was a retrospective single-center study of UC patients with an IPAA, who subsequently developed CARP and received ustekinumab with standard Crohn's disease (CD) dosing between 2016 and 2018. Patients with CD of the pouch were excluded. Demographic, clinical, and endoscopic data were collected. Outcomes included a change in the endoscopic subscore of the Pouchitis Disease Activity Index (PDAI), change in the ulcerated surface area, clinical response, and the number of bowel movements per 24 h.

Results—Twenty-four patients with CARP were included for analysis. Median follow-up time was 12.9 months (IQR 7.9–16). Twelve patients (50%) had a clinical response with the median number of bowel movements within 24 h decreasing from 8 (IQR, 5–12) to 6 (IQR, 5–8) $P = 0.002$. Thirteen patients had pouchoscopies available post-ustekinumab treatment. In these patients, the median endoscopic subscore of the PDAI decreased from 5 (IQR, 3–6) to 4 (IQR, 2–5), $P = 0.016$. Likewise, among these thirteen patients, nine (69%) had an ulcerated surface area > 10% before ustekinumab treatment; after treatment with ustekinumab, only four patients (31%) still had an ulcerated surface area of > 10%.

Conclusions—This is the largest study of ustekinumab treatment for patients with chronic antibiotic-refractory pouchitis. We found that ustekinumab therapy led to the improvement in clinical and endoscopic endpoints.

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Author's contribution JEO, DTR, and SRD conceived and designed the study. JEO, LG, RW, AI, KEJ, and NCK contributed to the acquisition of data. JEO, DTR, SRD, RW, RDC, AS, JP, and NH contributed to the analysis and interpretation of data. All authors were involved in drafting the article or revising it critically for important intellectual content. All authors approved the final manuscript to be submitted.

Compliance with ethical standards

Conflict of interest JEO, RW, KEJ, AI, NKC, and NH have no relevant disclosures.

Keywords

Pouchitis; Ustekinumab; Ileal pouch-anal anastomosis; PDAI

Introduction

Colectomy is required in up to 30% of patients with ulcerative colitis (UC) due to medically refractory disease or development of dysplasia/cancer [1, 2]. In these situations, restorative proctocolectomy with ileal pouch-anal anastomosis (IPAA) is the usual surgery of choice. However, pouchitis may occur in up to 80% of patients and is associated with a significantly impaired quality of life due to symptoms of urgency, diarrhea, multiple bowel movements per day, and incontinence [3, 4].

A variety of conditions may cause symptoms of diarrhea and urgency after IPAA [4, 5]. Clinical symptoms correlate poorly with endoscopic disease, and thus, it is essential to perform pouchoscopy to establish pouchitis as the cause of symptoms, assess the severity, and rule out other conditions such as cuffitis [5, 6].

The conventional treatment for confirmed pouchitis is antibiotics such as ciprofloxacin and metronidazole [7]. Up to 15% of patients, however, develop chronic pouchitis and either become dependent on antibiotics for symptom relief or have continuous symptoms despite chronic antibiotic therapy [7–9]. With no approved treatments for chronic antibiotic-refractory pouchitis, a significant unmet medical need exists.

Ustekinumab is a human monoclonal antibody against the p40 subunit shared by both IL-12 and IL-23. It was shown to be effective for the treatment of moderate-to-severe Crohn's disease (CD). [10]. Recent studies have also demonstrated its efficacy in inducing remission in patients with UC [15], but its utility in the treatment of pouchitis remains unclear.

Our study aimed to evaluate the effectiveness and safety of ustekinumab for the treatment of chronic antibiotic-refractory pouchitis.

Methods

Patient Selection

This was a retrospective single-center study including patients with UC who had undergone a total proctocolectomy with IPAA, subsequently developed chronic antibiotic-refractory pouchitis, and received ustekinumab with standard CD dosing (one 90-mg IV loading dose infusion followed by 90-mg injections every eight weeks). Patients with CD of the pouch were excluded. Patients were defined as having chronic antibiotic-refractory pouchitis when pouch inflammation was confirmed on pouchoscopy, and patients had over four weeks of pouch symptoms; such as increased stool frequency, urgency, tenesmus, and fecal seepage, despite standard courses (> 1 month) of antibiotic treatment. At our institution, pouch inflammation is classified as "CD of the pouch" only when satisfying one of the following criteria: 1) discrete ulcerations in the pre-pouch ileum, 2) de novo perianal disease that is not suspected to be a technical complication of pouch creation, or 3) histopathological presence

of granulomas in the pouch biopsies. All eligible patients seen at the University of Chicago IBD center between 2016 and 2018 were included in the study if they had a minimal follow-up time of 3 months. Patients had their UC diagnosis confirmed by review of their prior clinical and pathologic records including their colectomy pathology report. Patients were excluded if they had a pre- or postoperative diagnosis of CD.

Data Collection

Patients' demographic, clinical, and endoscopic data were collected by a comprehensive review of their electronic medical records. The following baseline characteristics were collected: age at inclusion, gender, disease duration, UC extent based on the Montreal classification, and smoking status. Pouchoscopies performed before and following ustekinumab initiation were recorded. At our institution, pouchoscopies are performed using a standard operating protocol. These reports include detailed descriptions of the mucosa as well as high-definition images of the different areas of the pouch—specifically, the pre-pouch ileum, the pouch inlet, forward view of the pouch, and a retroverted view of the pouch. Based on these images and descriptions, the reviewer computed the PDAI and ulcer location and area to capture endoscopic data in a standardized manner. Due to the nature of the histologic reports and clinical data available to us, we could not give clinical and histologic subscores of the PDAI. For clinical data, we used bowel movements (BM) over 24 h which was captured in clinic visits and physician global assessment for the outcome of clinical improvement, both of which were collected at the last clinic visit before initiation of ustekinumab and at the first clinic visit following the loading dose of ustekinumab. Exposure to other treatments (antibiotics, mesalamines, immunomodulators, steroids, and biologics) before and after surgery was also recorded. Previous infections including clostridium difficile infection (CDI) and cytomegalovirus infection were recorded as well. All patients gave informed consent to receive ustekinumab. The institutional ethics review board approved the study.

Outcomes

The change in the endoscopic subscore of the PDAI[11], as well as the change in the ulcerated surface area after treatment with ustekinumab, was assessed in patients with follow-up pouchoscopies. The ulcerated surface area of the pouch (including the inlet) was calculated based on the endoscopic image. Patients were divided into three categories (patients who had < 10% of their pouch ulcerated, patients who had 10–30% of the pouch ulcerated, and patients who had > 30% of their pouch ulcerated).

Physician global assessment and the number of BM per 24 h, before and after treatment with ustekinumab, were reported for all patients.

Statistical Analysis

Descriptive statistics for demographic and clinical characteristics include median (IQR) for continuous variables and frequency distributions for categorical data. Nonparametric testing was performed with the Wilcoxon matched-pair signed-rank test. A two-sided p value of < 0.05 was determined to be statistically significant. All analyses were performed with GraphPad Prism version 8.00 for Windows (GraphPad Software, La Jolla, California, USA).

Results

Patient Characteristics

A total of 24 patients met the inclusion criteria. The median age was 35.6 years (IQR 26.6–41.5), 10 (42%) of which were females. Twenty-one (87.5%) of patients had never smoked, and two patients (8.3%) had a concurrent diagnosis of primary sclerosing cholangitis (PSC). Before colectomy, 21 patients (87.5%) had extensive colitis. Fourteen patients (58.3%) and 16 patients (66.7%) were preoperatively treated with biologics and immunomodulators, respectively. Previous treatment for pouchitis included antibiotics (ciprofloxacin or metronidazole) in all patients, biologics other than ustekinumab in 12 patients (50%), and immunomodulators in six patients (25%). Median time from the start of ustekinumab treatment to pouchoscopy was 7.4 months (IQR 4.6–10.6). Median follow-up duration was 12.9 months (IQR 7.9–16). Over the follow-up period, five patients stopped treatment with ustekinumab, two patients had their pouch excised, and three patients were switched to other therapies. Twenty patients were still on ustekinumab at the end of the follow-up period. The baseline demographic and clinical characteristics of the whole cohort and of the subgroup with follow-up endoscopic data are presented in Table 1.

Endoscopic Outcomes

Detailed pouchoscopy reports were available for all the patients in the study before receiving ustekinumab. At the time of pre-ustekinumab pouchoscopy, 33% of patients had pouch inlet ulcers, and 88% of patients had ulcerations in the pouch. Following the initiation of ustekinumab, pouchoscopies were performed in 13 patients. In these patients, the median endoscopic subscore of the PDAI decreased from 5 (IQR, 4–6) to 4 (IQR, 2–5) post-treatment ($P = 0.016$) (Fig. 1, Panel A). Likewise, among these thirteen patients, nine (69%) had an ulcerated surface area > 10% before ustekinumab treatment; after treatment with ustekinumab, only four patients (31%) still had an ulcerated surface area of > 10% (Fig. 1, Panel B). No subject achieved a PDAI endoscopic subscore of 0 (complete endoscopic normalization of the pouch).

For the particularly refractory group of patients who had already received treatment for pouchitis with immunomodulatory and biologic drugs (Eight patients), before treatment with ustekinumab and in whom we had follow- up endoscopic data, the endoscopic subscore of the PDAI decreased from a median of 6 to a median of 4. Likewise, four patients had an ulcerated surface area of over 10% before ustekinumab treatment, while only one patient still had an ulcerated surface area of over 10% after treatment with ustekinumab.

Clinical Outcomes

Clinical follow-up data were available for all patients. Half of the patients (12/24) had a significant clinical response based on the physician's clinic note. Median BM over 24 h decreasing from 8 (IQR, 5–12) to 6 (IQR, 5–8) $P = 0.002$ (Fig. 1, Panel C). The median time to the clinic visit following ustekinumab initiation was 52 days IQR (34–125).

Discussion

In this retrospective cohort of patients with chronic antibiotic-refractory pouchitis, we observed favorable endoscopic and clinical responses to ustekinumab. More than half of our patients had also been treated with biologics or immunomodulators; thus, ustekinumab demonstrated efficacy in a highly resistant cohort of patients.

A recent multicenter retrospective study reported the effectiveness of ustekinumab for CD of the pouch in 56 patients [12]. The authors of this study concluded that ustekinumab is an effective treatment for chronic pouchitis and CD of the pouch. The study's strength lies in its large number of patients and its multicenter design. However, the majority (84%) of patients in this study had a diagnosis of CD of the pouch, and only nine patients (16%) had chronic antibiotic-refractory pouchitis. The authors do not specify the criteria they used to diagnose patients as having CD of the pouch. The primary outcome of the study was clinical remission based on physician assessment. When endoscopic data were available, patients were described as being in endoscopic remission or endoscopic response by clinicians performing pouchoscopies in the different institutions. There were no data on the dosing of ustekinumab, and it is probable that the study included patients from 2013 onward (before ustekinumab approval for use in CD) that a variety of dosing regimens was used.

In our single-center study, we reported standardized endoscopic outcome measures, as endoscopic healing of the pouch is considered to be a preferred outcome. Reported measures in our study included the endoscopic subscore of the PDAI, as this is the most widely used metric for reporting endoscopic findings in pouchitis [11]. We also described the ulcerated surface area before and after ustekinumab treatment as this measure was found to have the highest interobserver reliability when grading pouchitis severity in a recent large prospective study and it was recommended that it be part of any future endoscopic score of pouchitis [13]. We believe that using objective endpoints in trials of pouchitis is essential due to the poor correlation between clinical and endoscopic findings in such patients [5].

Ustekinumab has known efficacy in patients with CD[10] and has recently been shown to be effective in inducing remission in patients with UC [15]; therefore, it is plausible that patients with pouchitis will respond to such therapy. However, previous studies have suggested that biologic therapy might be more effective in the treatment of CD of the pouch when compared to chronic antibiotic-refractory pouchitis [14]. Our results using CD dosing showed that ustekinumab is effective in chronic antibiotic-refractory pouchitis without a CD like phenotype as well.

Limitations to our study include its retrospective nature with its inherent risk of bias, and while our results are exploratory due to the small sample size, we believe that our ability to characterize clinical and endoscopic findings is a strength.

We used objective outcomes such as endoscopic disease activity and characterized the severity of pouch inflammation using measures which have been shown to have high interobserver reliability [13]. However, none of the physicians were blinded to the treatment or evaluations, and so, treatment effects and endoscopic objectivity might have been biased.

We also applied the standard treatment regimen for CD to our pouchitis patients; further studies are needed to identify the optimal dose and schedule for pouchitis.

In conclusion, we report on the largest experience with ustekinumab treatment of patients with chronic antibiotic-refractory pouchitis and demonstrate that ustekinumab improves both clinical and endoscopic endpoints. Prospective studies are warranted to confirm these findings.

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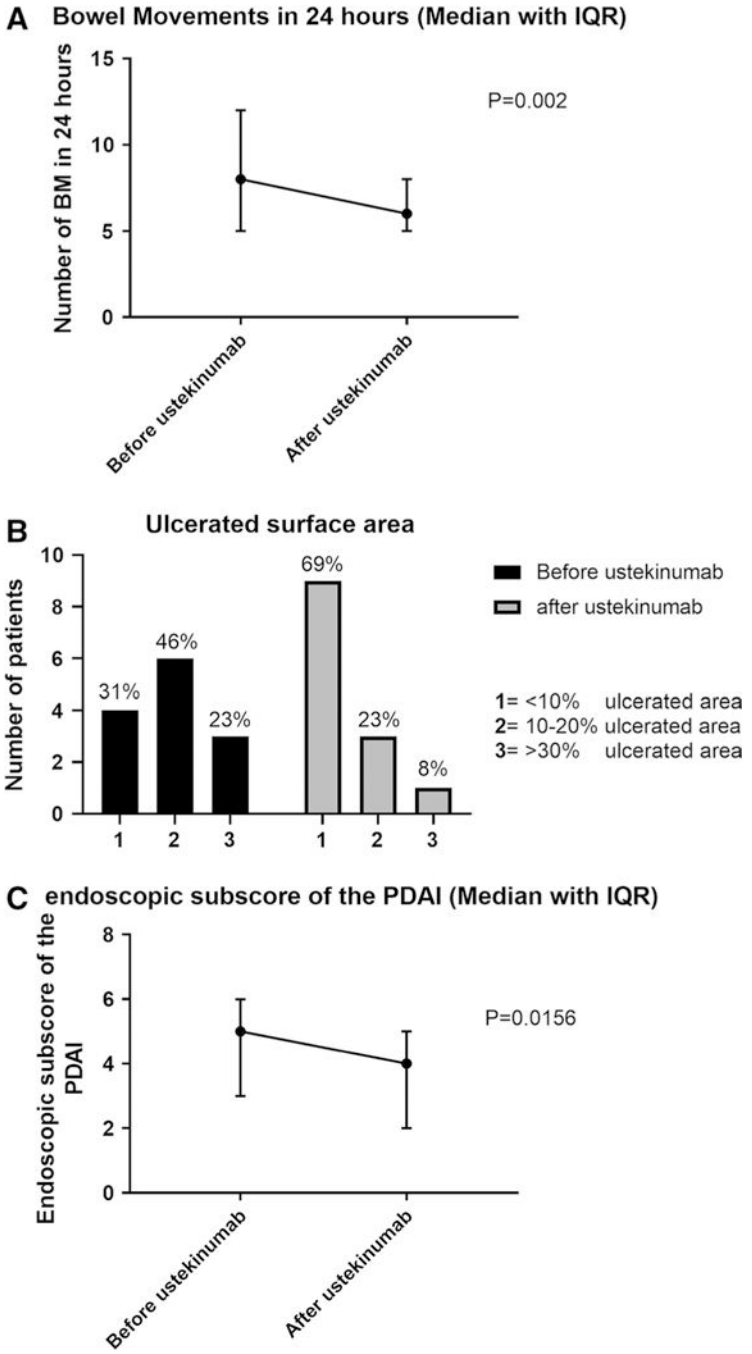

Fig. 1.

Panel A. Endoscopic subscore of the PDAI prior and post- ustekinumab treatment of pouchitis (median + IQR). Panel B. Ulcerated surface area (%) prior and post-ustekinumab treatment of pouchitis. Panel C. Change in bowel movements in 24 h (Median + IQR)

Table 1

Patient demographics

	n = 24 (%) whole cohort	n = 13 (%) cohort with endoscopic follow-up
Female	10 (42)	5 (38)
Median age at first ustekinumab dose (IQR)	35.6 (26.6–41.5)	31.1 (27.4–39.3)
Smoking status		
Current smoker	1 (4.2)	1 (8)
Ex-smoker	2 (8.3)	0 (0)
Never	21 (87.5)	12 (92)
Median BMI (IQR)	24.4 (23–27)	25 (23–27)
PSC	2 (8.3)	2 (15)
Caucasian	20 (83)	11 (85)
Extensive colitis prior to colectomy	21 (87.5)	12 (92)
Treatment prior to colectomy		
Mesalamine	12 (50)	7 (54)
Immunomodulator	16 (66.7)	11 (85)
Azathioprine	15 (62.5)	10 (77)
MTX	1(4.2)	1(8)
Biologics	14(58.3)	8(62)
Infliximab	14 (58.3)	8 (62)
Adalimumab	2 (8.3)	1 (8)
Vedolizumab	1 (4.2)	0 (0)
Antibiotics	35 (21.3)	3 (23)
Prednisone	13 (54.1)	8 (62)
Treatment after colectomy		
Mesalamine	6 (25)	3 (23)
Immunomodulator	6 (25)	4 (31)
Azathioprine	6 (25)	4(31)
Biologics	12 (50)	6 (46)
Infliximab	6 (25)	3 (23)

	n = 24 (%) whole cohort	n = 13 (%) cohort with endoscopic follow-up
Adalimumab	9 (37.5)	4 (31)
Vedolizumab	4 (16.7)	3 (23)
Certolizumab pegol	3 (12.5)	2 (15)
Antibiotics	24 (100)	13 (100)
Prednisone	13 (54.2)	9 (69)
Budesonide	16 (66.7)	8 (62)
Rifaximine	2 (8.3)	2 (15)
VSL	6 (25)	1 (8)
Biologic naïve prior to UST infusion	4 (16)	3 (23)
Median PDAI prior to UST infusion	5(3–6)	5 (4–6)
Median follow-up period—months (IQR)	12.6 (5.2–10.76)	16.9 (15–18.7)