Efficacy and Safety of Ustekinumab for Chronic Pouchitis: A Prospective Open-label Multicenter Study

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BACKGROUND & AIMS: **Seventeen percent of patients with ulcerative colitis that undergo proctocolectomy with pouch surgery will develop chronic pouchitis. We evaluated the efficacy of ustekinumab for these patients.**

METHODS: **We performed a prospective study of patients with chronic pouchitis receiving ustekinumab intravenously at baseline (~6 mg/kg) and 90 mg ustekinumab subcutaneously every 8 weeks thereafter. The Modified Pouchitis Disease Activity Index (mPDAI) was assessed at baseline and weeks 16 and 48. The primary endpoint was the proportion of patients achieving steroid-free remission (mPDAI <5 and reduction by ≥2 points) at week 16. Secondary endpoints included the proportion of patients achieving remission at week 48, the proportion of patients achieving response (reduction of mPDAI by ≥2 points) at weeks 16 and 48, and change in mPDAI.**

RESULTS: **We enrolled 22 patients (59% male; median age, 42.2 years). Remission was achieved in 27.3% at week 16 and 36.4% at week 48. Response was achieved in 54.5% both at weeks 16 and 48. The median mPDAI decreased from 8 (interquartile range [IQR], 7–10) to 7 (IQR, 4–9) at week 16 ($P = .007$) and 4 (IQR, 1.75–7.25) at week 48 ($P < .001$). The clinical mPDAI subscore decreased from 3.5 (IQR, 2–4) to 2 (IQR, 1–3) at week 16 ($P = .009$) and 1 (IQR, 0–2.25) at week 48 ($P = .001$). The endoscopic mPDAI subscore decreased from 5.5 (IQR, 4–6) to 4 (IQR, 3–6) at week 16 ($P = .032$) and 3 (IQR, 1.75–4.25) at week 48 ($P = .001$).**

CONCLUSION: **Ustekinumab was efficacious in one-half of the patients suffering from chronic pouchitis. Ustekinumab should therefore be positioned in the treatment algorithm of chronic pouchitis. (ClinicalTrials.gov Number NCT04089345)**

Keywords: Biological; Chronic pouchitis; IL-12/23; Ulcerative Colitis.

Restorative proctocolectomy with ileal pouch-anal anastomosis (IPAA) is considered the procedure of choice in patients with ulcerative colitis (UC) refractory to medical therapy or with dysplasia or cancer.[1] The most common complication after IPAA is the development of pouchitis.[2] Pouchitis is clinically characterized by variable symptoms including increased stool frequency and fluidity, bloody stools, abdominal cramping pain, urgency, and fecal incontinence.[1] On top, endoscopic and histological inflammation is crucial to make the diagnosis. When symptoms occur for less than 4 weeks, this is considered acute pouchitis. When symptoms persist for 4 or more weeks, this is considered chronic pouchitis. Relapsing pouchitis is defined as 3 or more episodes of pouchitis in a 1-year period.[3] The conventional treatment for pouchitis is antibiotics, with ciprofloxacin and/or metronidazole being most commonly prescribed.[4,5] However, acute antibiotic-responsive pouchitis may evolve into chronic antibiotic-refractory pouchitis over time, which is more difficult to treat. Up to 80% of patients with UC with an IPAA will experience pouchitis symptoms at any time, with

Abbreviations used in this paper: **Anti-TNF, anti-tumor necrosis factor; CD, Crohn's disease; CRP, C-reactive protein; EQ-5D-5L, EuroQol – 5 dimensions – 5 levels; IL, interleukin; IPAA, ileal pouch-anal anastomosis; IQR, interquartile range; mPDAI, Modified Pouchitis Disease Activity Index; PDAI, Pouchitis Disease Activity Index; TL, trough level; UC, ulcerative colitis.**

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approximately 17% of patients developing chronic antibiotic-refractory pouchitis.[6–8]

Both anti-tumor necrosis factor (anti-TNF) agents and vedolizumab have been proposed for the treatment of chronic pouchitis.[4,9–12] However, vedolizumab is the only biological agent that has been approved in Europe for the treatment of chronic pouchitis based on a placebo-controlled randomized trial.[13] Furthermore, many other therapies, such as corticosteroids and other advanced therapies, have demonstrated limited short- and/or long-term efficacy in the management of chronic pouchitis.[4,10]

Ustekinumab is a human monoclonal antibody directed against the p40 subunit of both interleukin (IL)-12 and IL-23. It has been approved for the treatment of moderately to severely active Crohn's disease (CD) and UC. Little is known about the role of ustekinumab in the treatment of chronic pouchitis. Retrospective data suggest that ustekinumab can effectively and safely induce remission in subjects with chronic pouchitis, but prospective data are lacking.[14,15]

In this exploratory study, we prospectively evaluated the efficacy and safety of ustekinumab for the treatment of chronic pouchitis.

What You Need to Know

Background

Seventeen percent of patients with ulcerative colitis that undergo proctocolectomy with pouch surgery will develop chronic pouchitis. We evaluated the efficacy and safety of ustekinumab for this patient population.

Findings

Ustekinumab was efficacious in one-half of the patients suffering from chronic pouchitis after 4 months and 1 year. No new safety signals were observed during the study.

Implications for patient care

Ustekinumab should be positioned in the treatment algorithm of chronic pouchitis.

Methods

Trial Design and Oversight

This study included a 16-week induction phase and a 32-week maintenance phase, representing 48 weeks of treatment with ustekinumab. The study was conducted from June 2020 through August 2022 at 3 Belgian sites. The ethics committees of the respective hospitals approved the protocol (S63085). All patients provided written informed consent.

Patients

Adult patients (≥18 years of age) with UC were eligible if they had undergone a proctocolectomy and IPAA at least 1 year before screening, and if they had either relapsing pouchitis (≥3 recurrent episodes within 1 year prior to screening, each treated with ≥2 weeks of antibiotic therapy), pouchitis refractory to ≥4 weeks maintenance antibiotic therapy, or pouchitis refractory to anti-TNF or vedolizumab therapy for ≥12 weeks. Pouchitis was defined as a Modified Pouchitis Disease Activity Index (mPDAI) ≥5 and a minimum endoscopic subscore of 2 (outside the staple or suture line).[16]

Stable doses of 5-aminosalicylic acids and immunomodulators were maintained from baseline through week 48. Oral corticosteroids were maintained at a stable dose until week 4 with a mandatory and complete tapering by week 8. Previous treatment with IL-12 or IL-23 antagonists was prohibited. Previous anti-TNF and vedolizumab therapy needed to be discontinued at least 30 days before baseline. Other conventional therapies also needed to be discontinued at least 30 days before baseline. Among the exclusion criteria were CD of the pouch, pouch strictures, cuffitis, current malignancy or history of malignancy, and active infections (including tuberculosis).

Open-label Therapy

During the induction phase, patients received a single weight-range-based (~6 mg/kg) intravenous infusion of ustekinumab at baseline (260 mg for a body weight below 55 kg, 390 mg for a body weight of 55–85 kg, and 520 mg for a body weight above 85 kg) and 1 subcutaneous injection of 90 mg ustekinumab at week 8. The first 4 weeks, ciprofloxacin 500 mg twice a day was added as bridging therapy. For patients who previously did not tolerate quinolone therapy, metronidazole 500 mg 3 times a day was allowed. From week 4 until week 16, no antibiotic therapy was allowed.

During the maintenance phase, patients received subcutaneous injections of 90 mg ustekinumab every 8 weeks. A maximum of 2 antibiotic courses with ciprofloxacin or metronidazole for 2 weeks were allowed for the treatment of flares from week 16 onwards. Dose escalation of ustekinumab was not allowed.

Assessments and Endpoints

The Pouchitis Disease Activity Index ([PDAI], with scores ranging from 0 to 18 and higher scores indicating more severe disease) and mPDAI (ie, the PDAI excluding the histologic subscore, with scores ranging from 0 to 12 and higher scores indicating more severe disease) were assessed at baseline, week 16, and 48[16,17] (Supplementary Table 1). Concentrations of fecal calprotectin were evaluated at baseline and weeks 16 and 48. Serum C-reactive protein (CRP) levels were

evaluated at all visits during the induction and maintenance period.

The primary endpoint was the proportion of patients achieving steroid-free remission (mPDAI <5 and a reduction by ≥ 2 points from baseline) at week 16. Secondary endpoints were the proportion of patients achieving steroid-free remission at week 48, the proportion of patients achieving response (a reduction of mPDAI by ≥ 2 points from baseline) at week 16 and 48, and the change in mPDAI, mPDAI clinical and endoscopic subscore, PDAI, PDAI histologic subscore, CRP, fecal calprotectin, and quality of life at week 16 and 48 compared with baseline. Quality of life was measured using the EQ-5D-5L (EuroQol – 5 dimensions – 5 levels) questionnaire.

Pharmacokinetics and Immunogenicity

Serum ustekinumab concentrations were quantified at week 16 using a validated enzyme-linked immunosorbent assay with a lower limit of quantification of 0.50 μg/mL. Anti-ustekinumab antibodies were quantified in serum samples with undetectable ustekinumab by using a drug-sensitive bridging enzyme-linked immunosorbent assay. The relationship between exposure and response at week 16 was assessed.

Statistical Analysis

Because chronic pouchitis is a rare condition, we aimed to include approximately 20 patients spread across all three participating centers in this exploratory study.

All statistical analyses were performed using Prism version 8 (GraphPad Software). Patients who discontinued the treatment were regarded as treatment failures (non-responder imputation). Continuous variables were reported using median and interquartile range (IQR) and were compared using Wilcoxon rank-sum testing (per-protocol analysis). Categorical variables were expressed as proportions and compared using Fisher exact and χ^2 testing as appropriate. Comparison between patient groups was done with nonparametric unpaired Mann-Whitney U tests. A P-value $<$ .05 was considered statistically significant.

All authors had access to the study data and reviewed and approved the final manuscript.

Results

Patients

Twenty-four patients were assessed for eligibility, and 22 patients (9 female; median age, 42.2 years) were enrolled. Two patients failed the screening process, one due to an anal stenosis and one due to concurrent biologic use for a rheumatological disorder. One center enrolled 18 patients and the other 2 centers enrolled 2 patients each. Of those 22 patients, 21 (95%) remained in the study until week 16, and 14 (64%) until week 48. All patients who discontinued ustekinumab did so for lack of efficacy, except for one patient who withdrew consent for practical reasons. Four patients required antibiotic treatment for a flare during the maintenance phase. One patient required 2 antibiotic courses; the other 3 patients required one antibiotic course. Baseline demographics and clinical characteristics are depicted in Table 1. Twelve patients (54.5%) had previously been treated with biologics or small molecules (anti-TNF, n = 9; vedolizumab, n = 7; tofacitinib, n = 1) for pouchitis.

Efficacy

Primary and secondary endpoints. At week 16, the percentage of patients achieving steroid-free remission was 27.3%. The percentage of patients in steroid-free remission at week 48 was 36.4%. The response rate was 54.5% at both week 16 and week 48. One patient lost response after week 16, whereas another patient gained response by week 48.

The median total mPDAI significantly decreased from 8 (IQR, 7–10) at baseline to 7 (IQR, 4–9) at week 16 (P = .007) and 4 (IQR, 1.75–7.25) at week 48 ($P < .001$). The clinical mPDAI subscore significantly decreased from 3.5 (IQR, 2–4) at baseline to 2 (IQR, 1–3) at week 16 (P = .009) and 1 (IQR, 0–2.25) at week 48 (P = .001). The endoscopic mPDAI subscore significantly decreased from 5.5 (IQR, 4–6) at baseline to 4 (IQR, 3–6) at week 16 (P = .032) and 3 (IQR, 1.75–4.25) at week 48 (P = .001) (Figure 1).

The total PDAI significantly decreased from 12 (IQR, 9–13) at baseline to 8 (IQR, 6–10) at week 16 (P = .005)

Table 1. Baseline Disease Characteristics (N = 22)

Characteristics	Data
Male	13 (59)
Age at treatment initiation, years	42.2 (32.2–52.3)
Time since colectomy, years	8.2 (3.1–16.4)
Previous therapies prior to colectomy	
Anti-TNF	15 (68.2)
Vedolizumab	5 (22.7)
Tofacitinib	3 (13.6)
Previous therapies for pouchitis	
5-ASA (topical/systemic)	6 (27.3)
Steroids (topical/systemic)	17 (77.3)
Immunomodulators	8 (36.3)
Anti-TNF	9 (40.9)
Vedolizumab	7 (31.8)
Tofacitinib	1 (4.5)
Concomitant therapy during induction	
Steroids (topical/systemic)	3 (13.6)
Immunomodulators	1 (4.5)

Note: Data are presented as number (%) or median (interquartile range).
Anti-TNF, Anti-tumor necrosis factor; 5-ASA, 5-aminosalicylate.

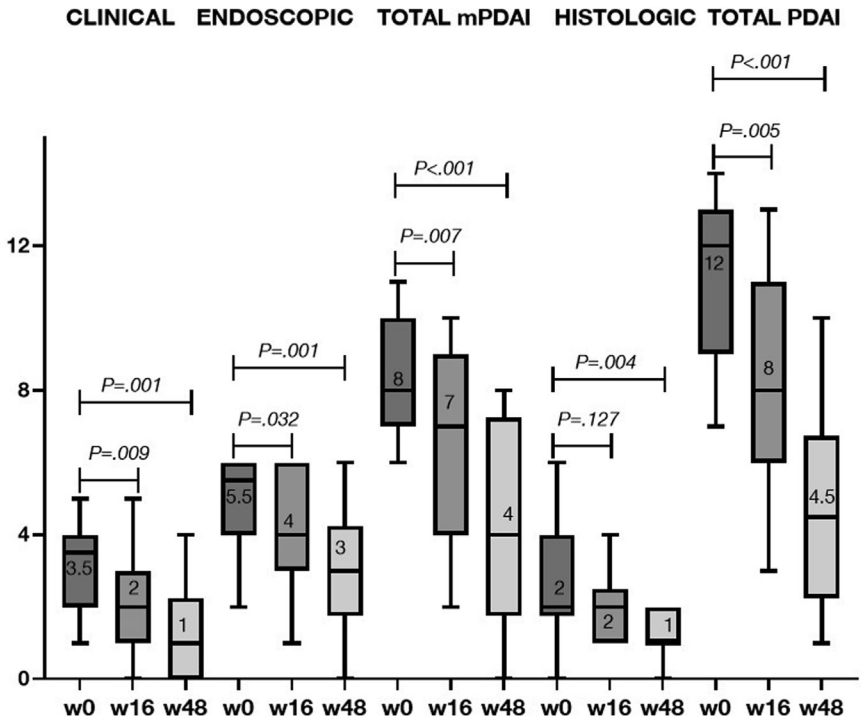

Figure 1. mPDAI and PDAI evolution. N at w0 = 22; n at w16 = 21; n at w48 = 14.

and 4.5 (IQR, 2.25–6.75) at week 48 ($P < .001$). The histologic PDAI subscore did change numerically from baseline to week 16 (2 [IQR, 1.75–4]) and 2 [IQR, 1–2.5) respectively; $P = .127$), but significantly decreased to 1 (IQR, 1–2) at week 48 ($P = .004$) (Figure 1).

Fecal calprotectin levels did not significantly decrease from baseline (357 [IQR, 199–666] mg/kg) to week 16 (175 [IQR, 91–593] mg/kg; $P = .63$) and week 48 (129 [IQR, 63–333] mg/kg; $P = .17$). Also, CRP levels did not significantly decrease from baseline (4.1 [IQR, 1.9–7.2] mg/L) to week 16 (3.7 [IQR, 1.8–9.5] mg/L; $P = .82$) and week 48 (2.45 [IQR, 1.33–4.43] mg/L; $P = .09$) (Figure 2).

Pharmacokinetics and immunogenicity. The median ustekinumab trough level (TL) at week 16 was 1.37 (IQR, 0.88–3.38) μg/mL. Three patients had undetectable levels at week 16, but no anti-drug antibodies were detected. Ustekinumab TLs were numerically though not significantly different between patients in remission and those not in remission at week 16 (2.22 [IQR, 1.31–6.01] μg/mL vs 1.19 [IQR, 0.79–2.19] μg/mL; $P = .112$) (Figure 3*A*). However, the difference in TL between patients in response and not in response at week 16 was significantly different (1.85 [IQR, 1.21–3.98] vs 1.16 [IQR, 0.50–1.64]; $P = .049$) (Figure 3*B*). When considering the optimal ustekinumab TL of 1.3 μg/ml at steady-state,[18] a significant higher proportion of patients in remission and response was seen with TL above 1.3 μg/ml at week 16 ($P = .038$ and $P = .044$ respectively) (Figure 4).

Covariates

Multiple variables were analyzed to evaluate their potential relationship with response or remission. These variables included age, sex, body mass index, time since colectomy, and prior use of advanced therapies for pouchitis. None of the variables were predictive of response or remission. Also, the type of pouchitis (relapsing pouchitis vs pouchitis refractory to biologics vs pouchitis refractory to antibiotics) was not significantly associated with response or remission. Three patients with primary sclerosing cholangitis were included. None of them were in remission, but one of them had a

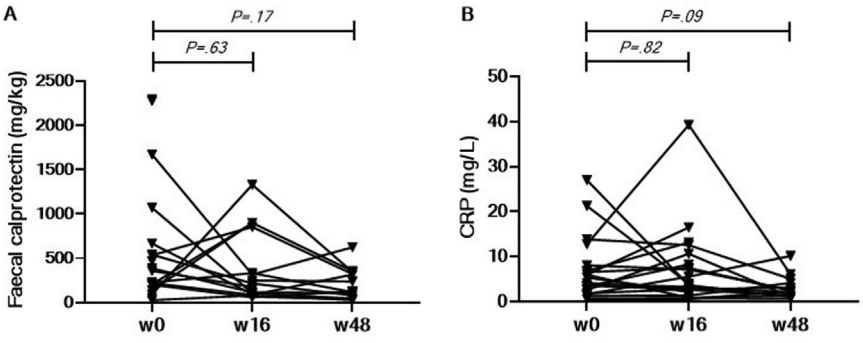

Figure 2. Fecal calprotectin (*A*) and CRP evolution (*B*). (*A*) n at w0 = 19; n at w16 = 17; n at w48 = 13. (*B*) n at w0 = 22; n at w16 = 21; n at w48 = 14. Normal reference values: ≤250 mg/kg for fecal calprotectin and ≤5 mg/L for CRP.

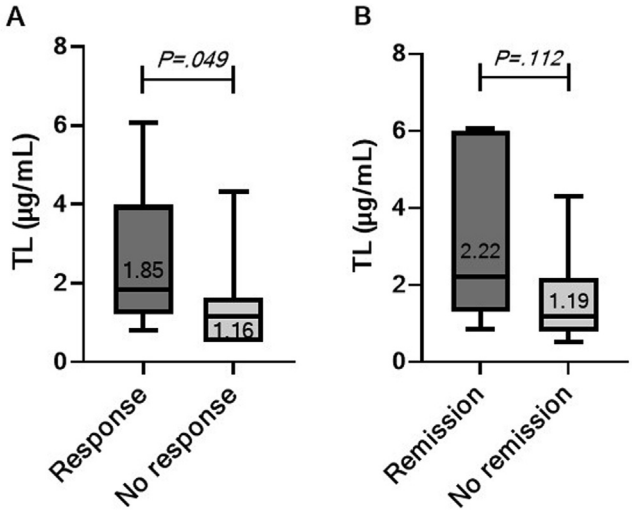

Figure 3. TLs at week 16 compared between patients with or without response (*A*) and remission (*B*) at week 16 (n = 21).

response at both week 16 and 48. Two patients underwent proctocolectomy and IPAA due to UC-related dysplasia. None of them were in remission, but one had a response at both week 16 and 48.

Quality of Life

The evolution of the patients' quality of life from baseline to week 16 and 48 is depicted in Figure 5. Statistically significant improvement was noted at week 48 for the EQ-5D-5L usual activities score ($P = .0071$), but the EQ-5D-5L mobility score worsened significantly at week 16 ($P = .036$). The visual analogue scale of health significantly increased from 57.5 (IQR, 41.3–70) at baseline to 60 (IQR, 55–77) at week 16 ($P < .0001$) and 71.5 (IQR, 68.5–79.5) at week 48 ($P < .0001$).

Safety

No new safety signals were observed during the study. Three serious adverse events were recorded including hospitalization for subobstruction, worsening pouchitis, and choledocholithiasis. None of these were considered related to ustekinumab.

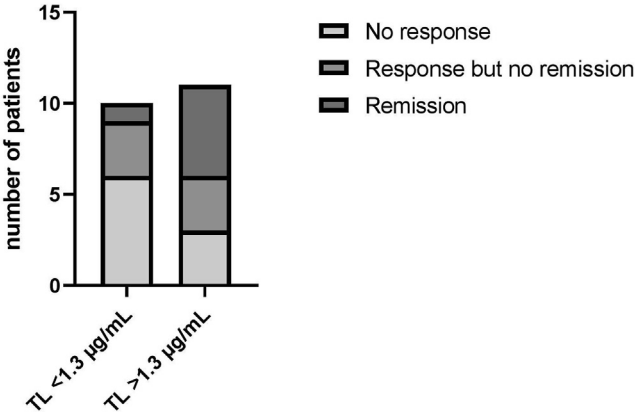

Figure 4. Number of patients in remission, response but no remission, and no response with a TL below or above 1.3 µg/mL (n = 21).

Discussion

Chronic pouchitis is a rare condition, accompanied with debilitating symptoms and with few medical treatment options. If patients fail to respond to medical treatment, the only treatment option remaining is the placement of an ileostomy with or without a pouchectomy.

In this open-label pilot study, we investigated the treatment of chronic pouchitis patients with ustekinumab. We observed a steroid-free remission rate of 27.3% at week 16 and 36.4% at week 48. More than one-half of the patients had a response at week 16 and 48.

A meta-analysis of Rocchi et al evaluated the efficacy of ustekinumab in chronic refractory pouchitis. In this analysis, clinical remission rate was 10% after 8 to 52 weeks, and clinical response rate was 63% after 4 to 12 weeks. Large heterogeneity of therapy protocols/outcome definitions was a significant limitation, making comparison with our study results rather difficult.[19]

Three retrospective studies evaluated the efficacy of ustekinumab in the treatment of chronic pouchitis. The first study, conducted by Weaver et al, included 9 patients with chronic pouchitis.[14] Clinical remission was defined as a return to baseline symptoms; clinical response was defined as any improvement in symptoms. At month 3, 88% of patients demonstrated a clinical response, but none were in clinical remission. From the 6 patients in the study at month 6, 83% demonstrated a clinical response, but still none were in clinical remission. Only 4 patients reached the 12-month mark, with 3 patients in clinical response and 1 patient in clinical remission. There were no endoscopic data available from these patients. The second study by Ollech et al included 24 patients with chronic pouchitis.[15] The median time to the clinic visit following ustekinumab initiation was 52 (IQR, 34–125) days. One-half of the patients (12/24) had a significant clinical response based on the physician's clinic note. Thirteen patients had pouchoscopies available post-ustekinumab treatment. In these patients, the median endoscopic mPDAI subscore decreased from 5 (IQR, 3–6) to 4 (IQR, 2–5) ($P = .016$). Likewise, among these 13 patients, 9 (69%) had an ulcerated surface area >10% before ustekinumab treatment; after treatment with ustekinumab, only 4 patients (31%) still had an ulcerated surface area of >10%.

Dalal et al assessed the outcomes of standard and intensified dosing of ustekinumab in patients with chronic pouch disorders.[20] A retrospective cohort of 46 patients was included, but only 6 patients were diagnosed with chronic pouchitis. Clinical response, determined by the inflammatory bowel disease provider's assessment 8 to 16 weeks after ustekinumab induction, was seen in 80.4% of patients, 50.0% underwent dose intensification after a median of 223 days, and 63.6% had clinical response 8 to

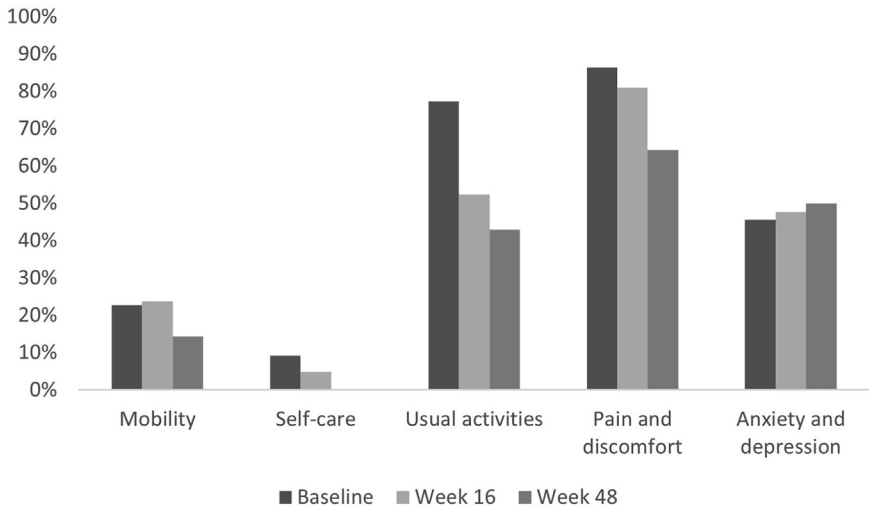

Figure 5. Proportion of patients reporting 'some problems' by EQ-5D-L dimension, at baseline, week 16 and 48. 'Some problems' = level 2 + 3 + 4 + 5.

16 weeks after dose intensification. In our study, we observed an association between ustekinumab TLs and response rates, suggesting that dosing should be tailored to the individual patient to optimize outcomes.

Only one randomized placebo-controlled trial, the EARNEST study, has been performed in patients with chronic pouchitis evaluating the efficacy of vedolizumab.[13] Remission (mPDAI $\leq$4 and a reduction by $\geq$2 points from baseline) at week 14 and 34 was seen in 31% and 35% of patients, respectively. Response (reduction of mPDAI by $\geq$2 points from baseline) at week 14 and 34 was seen in 63% and 51% of patients, respectively. Remission and response rates were significantly higher in the vedolizumab group compared with the placebo group and are comparable with our remission and response rates. Vedolizumab is the first treatment that received marketing authorization in Europe for active chronic pouchitis.

We here present the first prospective study evaluating ustekinumab for chronic pouchitis. Despite the multi-refractory patient population included, efficacy results are comparable with the EARNEST study and the previous retrospective studies evaluating ustekinumab for chronic pouchitis. However, mucosal inflammation remains present, even in the patients in steroid-free remission, and might explain the lack of a significant decrease in fecal calprotectin and CRP levels. Quality of life significantly improved from baseline to week 16 and week 48. The EQ-5D-5L mobility score worsened significantly at week 16, but the small sample size makes interpretation of the EQ-5D-5L evolution difficult.

A strength of the present prospective study is the standardized evaluation of the clinical and endoscopic outcomes. The small sample size and the lack of a control group are the main limitations of this study. Also, the per-protocol analysis of the (m)PDAI, CRP, fecal calprotectin, and quality of life evolution might create bias.

Managing patients with chronic pouchitis remains a challenge for the treating gastroenterologist. With these study results, we might position ustekinumab next to vedolizumab in the treatment algorithm of chronic pouchitis. Performing a randomized controlled trial to further investigate ustekinumab for chronic pouchitis seems unnecessary with these study results, the known efficacy rates of ustekinumab in both UC and CD, the known low remission rates of placebo in the EARNEST study, and the challenges that come with performing a randomized controlled trial. The efficacy of ustekinumab in chronic pouchitis patients who have preoperatively already been exposed to ustekinumab, remains unclear and is—until further data—not recommended. Because higher proportions of patients in steroid-free remission and response was seen with TLs above 1.3 μg/ml, we suggest TL measurement in patients with a loss of response and dose-escalation if necessary.

In this prospective open-label pilot study in patients with chronic pouchitis, therapy with ustekinumab showed a clinical and endoscopic effect in slightly more than one-half of the patients, and a remission in approximately one-third of the patients. This was, however, not associated with significant changes in inflammatory biomarkers. Larger studies should provide additional evidence for further positioning ustekinumab in the treatment algorithm of chronic pouchitis.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Clinical Gastroenterology and Hepatology* at www.cghjournal.org, and at https://doi.org/10.1016/j.cgh.2024.04.030.

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Edouard Louis (Data curation: Supporting; Project administration: Supporting; Writing – review & editing: Supporting)
Olivier Dewit (Data curation: Supporting; Project administration: Supporting; Writing – review & editing: Supporting)
Catherine Reenaers (Data curation: Supporting; Writing – review & editing: Supporting)
Ganel Schops (Data curation: Supporting; Project administration: Equal; Writing – review & editing: Supporting)
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Bram Verstockt (Conceptualization: Supporting; Data curation: Supporting; Writing – review & editing: Supporting)
João Sabino (Data curation: Supporting; Writing – review & editing: Supporting)
Séverine Vermeire (Conceptualization: Supporting; Data curation: Supporting; Funding acquisition: Supporting; Writing – review & editing: Supporting)
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Conflicts of interest
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Data Availability
Deidentified individual participant data underlying this article will be shared indefinitely upon reasonable request to the corresponding author. The data will be shared through a secure file transfer system for person-to-person email communication.

Supplementary Table 1. The PDAI

Criteria	Score	Subtotal
Clinical		
Stool frequency		
Usual postoperative stool frequency	0	
1–2 stools/day >postoperative usual	1	
3 or more stools/day > postoperative usual	2	
Rectal bleeding		
None or rare	0	
Present daily	1	
Fecal urgency or abdominal cramps		
None or rare	0	
Occasional	1	
Usual	2	
Fever (temperature >37.8 °C)		
Absent	0	
Present	1	
Endoscopic inflammation		
Edema	1	
Granularity	1	
Friability	1	
Loss of vascular pattern	1	
Mucus exudates	1	
Ulceration	1	
Acute histologic inflammation		
Polymorphic nuclear leukocyte infiltration		
Mild	1	
Moderate + crypt abscess	2	
Severe + crypt abscess	3	
Ulceration per low power field (mean)		
<25%	1	
25-50%	2	
>50%	3	

PDAI, Pouch Disease Activity Index.