Postoperative Outcomes in Ustekinumab-Treated Patients Undergoing Abdominal Operations for Crohn's Disease: Single-Center Series

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Introduction: The impact of ustekinumab on adverse postoperative outcomes in Crohn's disease (CD) remains largely unknown. We determined the difference in 90-day postoperative complication rates among CD patients exposed to ustekinumab within 12 weeks prior to an abdominal operation as compared to patients not exposed to biologic therapy.

Methods: A retrospective chart review of all adults with CD who underwent an abdominal operation between October 1, 2017 and December 31, 2018 at a single tertiary medical center was performed. Data collection included patient demographics, concurrent immunosuppression, serum laboratory values, operative values, and 90-day outcomes including superficial surgical site infection (sSSI), intra-abdominal sepsis, overall infectious complications, readmission, and reoperation rates. The primary outcome was the 90-day rate of intra-abdominal sepsis.

Results: Fifty-seven CD patients received ustekinumab and 277 received no biologic therapy in the 12 weeks prior to major abdominal surgery. Ustekinumab-exposed patients were younger, less likely to have diabetes mellitus or active tobacco exposure, were more often obese, and more often taking a concurrent immunomodulator. Ustekinumab remained an independent predictor of intra-abdominal sepsis on multivariable logistic regression. Immunomodulator exposure was associated with significantly increased rates of sSSI and overall complication rates.

Conclusions: Ustekinumab is associated with increased rates of 90-day postoperative intra-abdominal sepsis following a major abdominal operation for CD.

Key Words: Crohn's disease, postoperative outcomes, ustekinumab

INTRODUCTION

The anti-TNF class of biologics have largely replaced corticosteroids as the cornerstone of medical management for moderate to severe Crohn's disease (CD). As one-third of patients are primary nonresponders,[1–4] and another one-third lose response,[5,6] research and development has created alternative biologics and, more recently, small molecule inhibitors with varying mechanisms of action [e.g., anti-integrins, anti-interleukins, and Janus kinase (JAK) inhibitors] for the treatment of inflammatory bowel disease, including CD. Despite this ever-growing armamentarium of approved biologic therapies to treat moderate to severe CD, up to 60% of CD patients still require a major abdominal operation in their lifetime for medically refractory disease.[7–9] While increasing the number of options available for medical control of CD is largely positive, the downside is that refractory CD patients are now arriving to the operating room having cycled through many biologic medications, with or without concomitant immunomodulators to prevent secondary loss of response,[5,6] and/or corticosteroids to attempt to achieve better symptom control while growing increasingly malnourished and anemic. As the patient profile changes, the operation becomes a higher risk. Thus, we continue to seek modifiable risk factors to mitigate any potential postoperative morbidity.

A large body of literature has attempted to better isolate, and understand, the effect of immunosuppressive therapy on adverse postoperative outcomes in order to answer the important practical question of whether immunosuppression should be held prior to surgical intervention for perioperative optimization. Unfortunately, the literature has remained largely controversial for both anti-TNF therapy and vedolizumab, with some studies reporting an increase in postoperative infectious complications and others reporting no difference in postoperative outcomes following biologic exposure. To date,

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ustekinumab remains largely unstudied given its relatively short duration since approval by the Food and Drug Administration (FDA). One study, in which 6 centers combined their data to investigate postoperative outcomes in the setting of ustekinumab exposure, reported no increase in adverse complications as compared to anti-TNF therapy.[10]

Postoperative infectious complications increase patient morbidity, length of hospital stay, and overall costs.[11,12] Therefore, with each new approved immunosuppressive therapy, it becomes important to understand its effect on postoperative outcomes, as each pharmaceutical is a potential modifiable risk factor for postoperative outcomes. We sought to determine the difference in 90-day postoperative overall and infectious complication rates among CD patients exposed to ustekinumab within 12 weeks of an abdominal operation and compared to no biologic therapy to address the impact of ustekinumab on adverse postoperative outcomes.

MATERIALS AND METHODS

Following institutional review board approval, a retrospective chart review was performed on adult CD patients undergoing abdominal surgery at Mayo Clinic, Rochester, Minnesota, between January 1, 2017 and December 31, 2018. A list of all CD patients who underwent a major abdominal operation during the study was obtained. Study patients included adults (aged 18 to 70 years) with CD exposed to ustekinumab within 12 weeks prior to a major abdominal operation. The control group was all CD patients who underwent a major abdominal operation during the same study interval without exposure to biologic therapy in the 12 weeks prior to a major abdominal operation. The preoperative period of 12 weeks was chosen based on previous reports investigating the association of adverse postoperative outcomes following anti-TNF exposure.[13,14] Patients were excluded if they did not have 90 days of follow-up after their operation or if their index operation was performed at an outside hospital.

Data collected included patient demographics [sex, age, body mass index (BMI), cigarette smoking history, presence of perianal disease, duration of disease, prior biologic exposure], preoperative serum laboratory values within 2 weeks of surgery (hemoglobin, leukocyte count, platelet count, albumin, C-reactive protein), concurrent immunosuppressive therapy within 4 weeks of surgery [corticosteroids, immunomodulators (6-mercaptopurine, azathioprine, methotrexate)], operative variables (primary anastomosis, use of diversion in setting of anastomosis, open versus laparoscopic approach, and procedure category (defined as A: stoma creation; B: anastomosis with or without resection (e.g., ileocecal resection, segmental resection, colostomy closure); C: resection without anastomosis (e.g., colectomy, proctectomy, proctocolectomy); D: local revision (e.g., ileostomy revision, parastomal hernia repair), and 90-day postoperative infectious complications and mortality. Complications included superficial surgical site infection (sSSI), intra-abdominal sepsis (defined as a combined endpoint of intra-abdominal abscess and anastomotic leak), and overall infectious complication (sSSI, intra-abdominal sepsis, urinary tract infection, pneumonia, and sepsis). The primary endpoint was the 90-day rate of postoperative intra-abdominal sepsis. Secondary outcomes included the rates of 90-day sSSI, overall infectious complications, unplanned hospital readmission, return to the operating room, and mortality.

Statistical Analysis

Chi-squared tests were used to compare patients in the ustekinumab cohort versus the patients in the no current biologic group for categorical demographics and surgical variables that were not outcomes. Kruskal-Wallis test was used to compare patient groups for continuous variables. Logistic regression was used to examine the odds of intra-abdominal sepsis for demographic and surgical variables of interest with the primary variable of interest being exposure to ustekinumab within 12 weeks of an abdominal operation. Variables included in the multiple variable logistic regression were chosen using clinical judgment and included current biologic, corticosteroid use, cigarette smoking, immunomodulatory therapy, gender, BMI, age, and duration of disease. The alpha-level was set at $P < 0.05$ for statistical significance.

RESULTS

A total of 334 adult CD patients were included in the analysis: 57 patients were exposed to ustekinumab and 277 were not exposed to a biologic therapy within 12 weeks of an abdominal operation between January 1, 2017 and December 31, 2018 at Mayo Clinic, Rochester MN. Of all patients included, 54.2% were female, median age was 43 years (range, 18 to 92 years), and the median BMI was 24.1 kg/m^2 (range, 12.6–53.8 kg/m^2) (Table 1). Nearly one-third of patients had active perianal disease at the time of their operation, 13.5% were actively smoking, and 6.0% had diabetes mellitus. The median duration of disease was 13 years (range, 0 to 69 years). Patients in the ustekinumab group were older, less likely to smoke, and less likely to have diabetes compared to patients in the no current biologic group.

All ustekinumab-exposed patients had been on a prior biologic as compared to 61.4% of the no biologic cohort ($P < 0.0001$); the median number of prior biologics was 4 in the ustekinumab group compared to 1 in the no biologic group ($P < 0.0001$) (Table 2). A greater proportion of ustekinumab-treated patients were receiving immunomodulator therapy at the time of an abdominal operation (35.1% versus 15.9%; $P = 0.0008$); there was no difference in corticosteroid exposure (35.1% versus 26.4%; $P = 0.1803$). Within 14 days of surgery, the median hemoglobin was 12.2 g/dL (7.9–16.3 g/dL), leukocyte count was 7.6 × 10^9/L (1.8–23.7), platelet count was 307 × 10^9/L (58–1045 × 10^9/L), median serum albumin was 4.0 g/dL (range, 1.7–5.0), and a median C-reactive protein of 13.7

TABLE 1. Demographics

	All Patients (n = 334)	UST (n = 57)	No Biologic (n = 277)	*P*
Age (years), median (range)	42.5 (17.7–70)	34.8 (17.7–67)	44 (18.9–70)	**0.0008**
Gender (female) (%)	181 (54.2)	32 (56.1)	149 (53.8)	0.7457
BMI (kg/m^2), median (range)	42.1 (12.6–54)	24.4 (13.3–46)	24 (12.6–53.8)	0.3369
Tobacco (%)	45 (13.5)	2 (3.5)	43 (15.5)	**0.0155**
Diabetes (%)	20 (6)	0	20 (7.2)	**0.0364**
Perianal disease (%)	90 (26.9)	21 (36.8)	69 (24.9)	0.0644
Duration of disease (years)				
Median (range)	13 (0–59)	12.5 (2–35)	13 (0–59)	0.9727

Baseline demographics of patients with ustekinumab (UST) exposure (n = 57) and patients without exposure to biologics within 12 weeks of surgery. Bold characters indicate significant values ($P < 0.05$).

TABLE 2. Previous Biologics and Laboratory Values

	All patients (n = 334)	UST (n = 57)	No biologic (n = 277)	*P*
Previous biologic exposure (%)	227 (68)	57 (100)	170 (61.4)	**<0.0001**
IFX (%)	190 (56.9)	51 (89.5)	139 (50.2)	**<0.0001**
ADA (%)	162 (48.5)	50 (87.7)	112 (40.4)	**<0.0001**
CZP (%)	70 (21)	25 (43.9)	45 (16.2)	**<0.0001**
VED (%)	73 (21.9)	31 (54.4)	42 (15.2)	**<0.0001**
UST (%)	70 (21)	57 (100)	13 (4.7)	**<0.0001**
Number of prior biologics				
Median (range)	1 (0–5)	4 (1–5)	1 (0–5)	**<0.0001**
Preoperative IMM (%)	64 (19.2)	20 (35.1)	44 (15.9)	**0.0008**
Preoperative steroids (%)	93 (27.8)	20 (35.1)	73 (26.4)	0.1803
Preoperative hemoglobin (g/dL)	12.2 (7.9–16.3)	12 (9.5–15.4)	12.3 (7.9–16.3)	0.1689
Preoperative leukocyte count (×10^9/L)	7.6 (1.8–23.7)	8 (3.4–23.5)	7.6 (1.8–23.7)	0.5816
Preoperative platelet count (×10^9/L)	308 (58–1045)	341 (184–737)	303 (58–1045)	**0.0042**
Preoperative albumin (g/L)	4 (1.7–5)	3.9 (2.7–4.5)	4 (1.7–5)	0.6016
Preoperative CRP (mg/L)	13.7 (3–151)	19.6 (3–54.4)	13.1 (3–151)	0.4410

Previous Crohn's-disease specific treatments and laboratory values in patients with ustekinumab (UST) exposure (n = 57) and patients without exposure to biologics within 12 weeks of surgery. Bold characters indicate significant values ($P < 0.05$).
IFX, infliximab; ADA, adalimumab; CZP, certolizumab pegol; VED, vedolizumab, UST, ustekinumab; IMM, immunomodulator; CRP, C-Reactive Protein. Laboratory values expressed as median (range).

(range, 3.0–150.5); ustekinumab-exposed patients had higher median platelets than non-biologic exposed (341 × 10^9/L versus 302 × 10^9/L; $P = 0.004$). (Table 2).

A greater proportion of patients without biologic exposure underwent primary anastomosis at the time of the abdominal operation compared to those in the ustekinumab group (60.9% versus 43.9%; $P = 0.0194$), but an equivalent number of patients were diverted (9.5% versus 8.0%; $P = 0.8069$) (Table 3). A greater proportion of non-biologic exposed patients had their surgery performed laparoscopically (68.2% versus 50.9%; $P = 0.0122$). There were an equivalent number of operations performed in each procedure category from each group (Table 3).

There were 42 patients (13%) identified within the patient cohort who experienced an sSSI after abdominal surgery; 13% of patients in the no biologic cohort and 12% in the ustekinumab cohort. Risk factors that were significantly associated with sSSI on univariate analysis included exposure to imunnomodulators preoperatively [OR, 2.42; 95% confidence interval (CI), 1.19–4.92; $P = 0.01$] (Table 4). Stated another way, a patient currently exposed to immunomodulators had a more than twofold increased probability of having an sSSI than a patient not exposed to any immunomodulators. Using multivariable logistic regression, the only significant predictor of sSSI was exposure to immunomodulators preoperatively (OR, 2.60; 95% CI, 1.25–5.40; $P = 0.11$) when also including current biologic, steroid use, and gender (Table 4). Preoperative exposure to ustekinumab was not significantly associated with sSSI on either univariate or multivariable analysis.

TABLE 3. Operative Characteristics

	All Patients (n = 334)	UST (n = 57)	No Biologic (n = 277)	*P*
Procedure group				0.1787
A (%)	35 (10.5)	6 (10.5)	29 (10.5)	
B (%)	204 (61.1)	36 (63.2)	168 (60.6)	
C (%)	74 (22.2)	15 (26.3)	59 (21.3)	
D (%)	21 (6.3)	0	21 (7.6)	
Anastomosis (%)	193 (57.8)	25 (43.9)	168 (60.6)	**0.0194**
Diversion (%)	18/193 (9.3)	2/25 (8)	16/152 (9.5)	0.8069
Laparoscopy (%)	116 (34.7)	28 (49.1)	88 (31.8)	**0.0122**

Operative characteristics of patients with ustekinumab (UST) exposure (n = 57) and patients without exposure to biologics within 12 weeks of surgery. Procedure groups: A: stoma creation; B: anastomosis with or without resection (e.g., ileocecal resection, segmental resection, colostomy closure); C: resection without anastomosis (e.g., colectomy, proctectomy, proctocolectomy); D: local revision (e.g., ileostomy revision, parastomal hernia repair). Bold characters indicate significant values ($P < 0.05$).

TABLE 4. Univariate and Multivariable Risk Factors for Superficial Surgical Site Infection

		Univariate Results		Multivariable Results	
	Event/Total	Odds Ratio (95% CI)	*P*	Odds Ratio (95% CI)	*P*
Overall	42/334				
Current biologic			0.9418[a]		0.5404[a]
None	35/277	Reference		Reference	
UST	7/57	0.97 (0.41–2.30)		0.75 (0.31–1.86)	
Gender			0.0859[a]		0.0659[a]
Female	28/181	Reference		Reference	
Male	14/153	0.55 (0.28–1.09)		0.52 (0.26–1.04)	
BMI			0.7836[a]		
Normal (18–30 kg/m^2)	29/225	Reference			
Obese (>30 kg/m^2)	10/75	1.04 (0.48–2.25)			
Underweight (<18 kg/m^2)	3/34	0.65 (0.19–2.28)			
Preoperative steroids			0.6311[a]		0.4640[a]
No	29/241	Reference		Reference	
Yes	13/93	1.19 (0.59–2.40)		1.31 (0.64–2.69)	
Preoperative immunomodulator			**0.0147[a]**		**0.0107[a]**
No	28/270	Reference		Reference	
Yes	14/64	**2.42 (1.19–4.92)**		**2.60 (1.25–5.40)**	
Tobacco			0.4260[a]		
No	38/289	Reference			
Yes	4/45	0.64 (0.22–1.90)			
Age in years	42/334	1.01 (0.99–1.03)	0.2361[a]		
Number of prior biologics	42/334	1.16 (0.95–1.42)	0.1388[a]		
Duration of disease in years	42/333	1.04 (1.01–1.06)	0.0013[a]		

Univariate and multivariable risk factors for superficial surgical site infection. Bold characters indicate significant values ($P < 0.05$).
[a]Type 3 Wald *P*-value.
UST, ustekinumab.

There were 22 patients (7%) identified within the cohort who experienced intra-abdominal sepsis post-operatively; 5% of the patients in the no biologic cohort and 14% in the ustekinumab cohort. Risk factors significantly associated with intra-abdominal sepsis included exposure to ustekinumab (OR, 3.07; 95% CI, 1.22–7.70; $P = 0.02$), immunomodulators (OR, 2.61; 95% CI, 1.05–6.53; $P = 0.04$), and male sex (OR, 2.70; 95% CI, 1.07–6.81; $P = 0.04$) (Table 5). Using multivariable logistic regression, ustekinumab

TABLE 5. Univariate and Multivariable Risk Factors for Intra-Abdominal Sepsis

		Univariate Results		Multivariable Results	
	Event/Total	**Odds Ratio (95% CI)**	***P***	**Odds Ratio (95% CI)**	***P***
Overall	22/334				
Current biologic			**0.0170**[a]		**0.0230**[a]
None	14/277	Reference		Reference	
UST	8/57	**3.07 (1.22–7.70)**		**2.93 (1.16–7.40)**	
Gender			**0.0351**[a]		
Female	7/181	Reference			
Male	15/153	**2.70 (1.07–6.81)**			
BMI			0.9849[a]		
Normal (18–30 kg/m^2)	15/225	Reference			
Obese (>30 kg/m^2)	5/75	1.00 (0.35–2.85)			
Underweight (<18 kg/m^2)	2/34	0.88 (0.19–4.01)			
Preoperative steroids			0.1629[a]		0.2234[a]
No	13/241	Reference		Reference	
Yes	9/93	1.88 (0.77–4.56)		1.75 (0.71–4.28)	
Preoperative immunomodulator			**0.0398**[a]		
No	14/270	Reference			
Yes	8/64	**2.61 (1.05–6.53)**			
Tobacco			0.1961[a]		
No	17/289	Reference			
Yes	5/45	2.00 (0.70–5.72)			
Age in years	22/334	0.98 (0.95–1.00)	0.1025[a]		
Number of prior biologics	22/334	1.16 (0.89–1.51)	0.2703[a]		
Duration of disease in years	22/333	1.00 (0.96–1.03)	0.8881[a]		

Univariate and multivariable risk factors for intra-abdominal sepsis. Bold characters indicate significant values ($P < 0.05$).
[a]Type 3 Wald *P*-value.
UST, ustekinumab.

remained significantly associated with intra-abdominal sepsis (OR, 2.93; 95% CI, 1.16–7.40; $P = 0.02$) (Table 5).

There were 81 patients (24%) identified within the cohort who experienced any infectious complication post-operatively; 22% in the no biologic cohort and 35% in the ustekinumab cohort. Risk factors significantly associated with any infectious complication included exposure to ustekinumab (OR, 1.91; 95% CI, 1.04–3.54; $P = 0.04$), immunomodulators (OR, 2.05; 95% CI, 1.14–3.69; $P = 0.02$), number of prior biologics (OR, 1.22; 95% CI, 1.05–1.43; $P = 0.01$), and duration of disease (OR per year, 1.02; 95% CI, 1.00–1.04; $P = 0.04$) (Table 6). Using multivariable logistic regression, exposure to immunomodulators (OR, 2.01; 95% CI, 1.08–3.76; $P = 0.03$) and duration of disease (OR per year, 1.02; 95% CI, 1.00–1.05; $P = 0.03$) remained significantly associated with any infectious complication when also including current biologic use, corticosteroid use, smoking, gender, BMI, and age (Table 6).

Of the 70 patients with unplanned hospital readmission within 90 days of surgery, ustekinumab and corticosteroid exposure were significantly associated with readmission on both univariate and multivariable analysis (Supplementary Table I). Of the 35 patients who had a return to the operating room within 90 days of their index operation, corticosteroid and immunomodulator exposure were both significantly associated with return to the operating room on both univariate and multivariable analysis (Supplementary Table II).

DISCUSSION

The risk of postoperative infectious complications following major abdominal surgery for CD in the setting of anti-TNF therapy[13–43] and vedolizumab remains controversial,[44–47] largely due to study heterogeneity and many confounding factors known to increase postoperative complications. Ustekinumab, the most recent biologic approved for moderately to severely active CD by the FDA in September of 2016, remains largely unstudied to date except 2 multi-center studies reporting no differences in postoperative complications between ustekinumab and anti-TNF exposed patients.[10,48] We herein collected data over a 24-month period at a large tertiary center on all CD patients exposed to ustekinumab in the 12 weeks prior to major abdominal operation as compared to those not exposed to biologic therapy in order to better determine any association of ustekinumab on

TABLE 6. Univariate and Multivariable Risk Factors for Any Infectious Complication

		Univariate Results		Multivariable Results	
	Event/Total	Odds Ratio (95% CI)	*P*	Odds Ratio (95% CI)	*P*
Overall	81/334				
Current biologic			**0.0381**[a]		0.2089[a]
None	61/277	Reference		Reference	
UST	20/57	**1.91 (1.04–3.54)**		1.54 (0.78–3.03)	
Gender			**0.0390**[a]		0.0519[a]
Female	52/181	Reference		Reference	
Male	29/153	**0.58 (0.35–0.97)**		0.58 (0.34–1.00)	
BMI			0.7835[a]		0.8108[a]
Normal (18–30 kg/m^2)	52/225	Reference		Reference	
Obese (>30 kg/m^2)	20/75	1.21 (0.67–2.20)		1.09 (0.57–2.06)	
Underweight (<18 kg/m^2)	9/34	1.20 (0.53–2.73)		1.32 (0.56–3.12)	
Preoperative steroids			0.1222[a]		0.0927[a]
No	53/241	Reference		Reference	
Yes	28/93	1.53 (0.89–2.62)		1.63 (0.92–2.89)	
Preoperative immunomodulator			**0.0166**[a]		**0.0284**[a]
No	58/270	Reference		Reference	
Yes	23/64	**2.05 (1.14–3.69)**		**2.01 (1.08–3.76)**	
Tobacco			0.2797[a]		0.6589[a]
No	73/289	Reference		Reference	
Yes	8/45	0.64 (0.29–1.44)		0.83 (0.36–1.92)	
Age in years	81/334	1.00 (0.98–1.01)	0.9519[a]	1.00 (0.98–1.01)	0.6244[a]
Number of prior biologics	81/334	**1.22 (1.05–1.43)**	**0.0115**[a]		
Duration of disease in years	80/333	**1.02 (1.00–1.04)**	**0.0427**[a]	**1.02 (1.00–1.05)**	**0.0339**[a]

Univariate and multivariable risk factors for any infectious complication. Bold characters indicate significant values ($P < 0.05$).
[a]Type 3 Wald *P*-value.
UST, ustekinumab.

adverse postoperative outcomes. We found ustekinumab to be an independent risk factor for 90-day intra-abdominal sepsis, but not associated with 90-day sSSI, overall infectious complications, readmission, reoperation, or mortality.

Immunosuppressive therapy plays a pivotal role in the treatment of luminal CD in order to achieve mucosal healing. Prior to the advent of biologics, corticosteroids were the cornerstone of medical management. However, corticosteroids are limited by their side effect profile including Cushingoid appearance, early cataracts,[49] bone loss, psychiatric disturbances, and severe infections.[50] Similarly, corticosteroids have been consistently associated with an increased risk for 30-day postoperative infectious complications.[51] Biologics, on the other hand, have remained controversial with regard to their independent effect on postoperative infectious complications. Some single-center reviews and meta-analyses have reported no increase in complications following exposure to anti-TNF therapy[20,22–24,28,52] or vedolizumab[46,47] whereas others have reported a significant increase in postoperative complications.[32,33,36,37,41,42,53–55] The most recent data, a multicenter prospective study of nearly 1000 patients, found no association of anti-TNF drug levels or exposure within 12 weeks of surgery was significantly associated with postoperative complications.[56] Our previous multicenter report of 44 patients exposed to ustekinumab suggested it was safe in the perioperative period as compared to anti-TNF medications[10]; similarly, in a series of 20 patients, there was no increased risk of infectious complications among the ustekinumab treated patients.[48] We herein found slightly different results in a larger series of ustekinumab patients. Ustekinumab was associated with a significantly increased rate of intra-abdominal sepsis, even after accounting for corticosteroid exposure, with an odds ratio of 2.93. While the total number of events remains low at 8 of 57 ustekinumab-exposed patients (14%) compared to 14 of 277 non-biologic treated patients (5%), and we were unable to account for nutritional status and overall severity of disease, it is worth considering that ustekinumab-exposed patients may be at increased risk, whether related to ustekinumab itself or because the patient population represents a "sicker" cohort with exposure to a greater number of biologics and increased rates of obesity.[57] Either way, it is an important consideration when making intra-operative decisions for bowel diversion in the setting of multiple risk factors.

The overall rates of sSSI and overall infectious complications were 13% and 24%, respectively, similar to previous reports in the literature following major abdominal operations for CD. Interestingly, on multivariable analysis, exposure to immunomodulators was associated with increased rates of sSSI and total overall complications in this Crohn's cohort. While some authors have found an increased rate of complications following exposure to immunomodulators,[58,59] the vast majority of published data has not found this association,[15,60–62] even on systematic review.[63] Rather than immunomodulators, corticosteroids have been the class of immunosuppression consistently associated with an increased rate of complications.[51] Given that we accounted for corticosteroid use and biologic use, it suggests that the impact of immunomodulators was not a reflection of concurrent immunosuppression but rather an independent association. It is unclear as to why 35% of ustekinumab treated patients were on concurrent immunomodulator therapy when large clinical trials have found much lower rates of antibody formation in the setting of ustekinumab as compared to anti-TNF therapy (2.3% versus 40%–50%).[64] Regardless, future research will be needed to validate the finding that immunomodulators are associated with postoperative sSSI and complications, especially as this has not been previously reported on a consistent basis.

There are several limitations to this study. First, this is a single-center retrospective review performed at a large inflammatory bowel disease referral center. Thus, our patient population may not accurately reflect CD patients treated outside inflammatory bowel disease centers, as many patients are referred after failing most available medical options. Second, since ustekinumab was only recently approved by the FDA in September of 2016, we still have relatively small numbers of patients exposed to ustekinumab as compared to anti-TNF therapy, which has been approved since 1998. Future studies, preferably in a prospective and multi-center fashion, will be important to confirm any association of ustekinumab and adverse postoperative outcomes because these results may change as ustekinumab is utilized as a first-line agent, or as there is more experience and a greater number of patients. For example, in our initial retrospective review of vedolizumab, we found an independent association of vedolizumab and postoperative infectious complications.[55] However, future studies, including those from our own institution, did not find have the same results; vedolizumab was not independently associated with increased risk of postoperative overall or infectious complications. The same situation may occur with ustekinumab—early findings show an increased risk of complications, whereas subsequent data does not corroborate these findings. Third, serum drug levels were not measured in this study. Increased anti-TNF serum drug levels have been previously shown to be associated with postoperative complications in CD cohorts,[38] but this remains unstudied for ustekinumab. Lastly, and perhaps most importantly, it remains difficult to isolate the effect of ustekinumab from overall disease severity and general well-being of the patient in the perioperative period. We attempt to account for as many objective confounders as possible, but disease state and overall health remain difficult to objectively assess.

In conclusion, ustekinumab was not associated with an increased rate of overall postoperative infectious complications or sSSIs in adult CD patients undergoing a major abdominal operation, but was significantly associated with an increased risk of intra-abdominal sepsis and readmission rates. Given the small number of patients included in this retrospective series, further multicenter prospective evaluation will be useful for further investigation of the effect of ustekinumab on postoperative morbidity.

SUPPLEMENTARY DATA

Supplementary data are available at *Crohn's & Colitis 360* online.

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