ORIGINAL CONTRIBUTION

Biologics and 30-Day Postoperative Complications After Abdominal Operations for Crohn's Disease: Are There Differences in the Safety Profiles?

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BACKGROUND: The evidence regarding the association of preoperative biologic exposure and postoperative outcomes remains controversial for both antitumor necrosis factor agents and vedolizumab and largely unknown for ustekinumab.

OBJECTIVE: The purpose of this study was to determine differences in the rates of 30-day postoperative overall infectious complications and intra-abdominal septic complications among the 3 classes of biologic therapies as compared with no biologic therapy.

DESIGN: This was a retrospective review.

SETTINGS: The study was conducted at an IBD referral center.

PATIENTS: Adult patients with Crohn's disease who received an antitumor necrosis factor, vedolizumab, ustekinumab, or no biologic therapy within 12 weeks of a major abdominal operation between May 20, 2014, and December 31, 2017, were included.

MAIN OUTCOMES MEASURES: Thirty-day overall postoperative infectious complications and intra-abdominal septic complications were measured.

RESULTS: A total of 712 patients with Crohn's disease were included; 272 patients were exposed to an antitumor necrosis factor agents, 127 to vedolizumab, 38 to ustekinumab, and 275 to no biologic therapy within the 12 weeks before an abdominal operation. Patients exposed to a biologic were more likely to be taking a concurrent immunomodulator, but there was no difference in concurrent corticosteroid usage. The particular class of biologic was not independently associated with total overall infectious complications. Vedolizumab was associated with an increased rate of intra-abdominal sepsis on univariate analysis but not on multivariable analysis. Combination immunosuppression was associated with both an increased rate of overall postoperative infectious complications and intra-abdominal sepsis.

LIMITATIONS: The study was limited by its retrospective design and single-center data.

CONCLUSIONS: The overall rate of total infectious complications or intra-abdominal septic complications was not increased based on preoperative exposure to a particular class of biologic. Rates increased with combination immunosuppression of biologic therapy with corticosteroids and previous abdominal resection. See **Video Abstract** at http://links.lww.com/DCR/B24.

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BIOLÓGICOS Y COMPLICACIONES POSTOPERATORIAS DE 30 DÍAS DESPUÉS DE LAS OPERACIONES ABDOMINALES PARA LA ENFERMEDAD DE CROHN: ¿EXISTEN DIFERENCIAS EN LOS PERFILES DE SEGURIDAD?

ANTECEDENTES: La evidencia sobre la asociación de la exposición biológica preoperatoria y los resultados postoperatorios sigue siendo controvertida controversial tanto para los agentes del factor de necrosis tumoral (anti-TNF) como para el vedolizumab, y en gran parte desconocida para el ustekinumab.

OBJETIVO: Determinar las diferencias en las tasas de complicaciones infecciosas generales postoperatorias de 30 días y complicaciones sépticas intraabdominales entre las tres clases de terapias biológicas en comparación con ninguna terapia biológica.

DISEÑO: Revisión retrospectiva.

AMBIENTE: centro de referencia de la enfermedad inflamatoria intestinal.

PACIENTES: Pacientes adultos con enfermedad de Crohn que recibieron un factor de necrosis antitumoral, vedolizumab, ustekinumab o ningún tratamiento biológico dentro de las 12 semanas de una operación abdominal mayor entre el 5/20/2014 y el 12/31/2017.

PRINCIPALES MEDIDAS DE RESULTADOS: Complicaciones infecciosas postoperatorias generales de 30 días, complicaciones sépticas intraabdominales.

RESULTADOS: Se incluyeron setecientos doce pacientes con enfermedad de Crohn; 272 pacientes fueron expuestos a un anti-TNF, 127 a vedolizumab, 38 a ustekinumab y 275 a ninguna terapia biológica dentro de las 12 semanas previas a una operación abdominal. Los pacientes expuestos a un producto biológico tenían más probabilidades de tomar un inmunomodulador concurrente, pero no hubo diferencias en el uso simultáneo de corticosteroides. La clase particular de productos biológicos no se asoció de forma independiente con las complicaciones infecciosas totales. Vedolizumab se asoció con una mayor tasa de sepsis intraabdominal en el análisis univariable, pero no en el análisis multivariable. La inmunosupresión combinada se asoció tanto con una mayor tasa de complicaciones infecciosas postoperatorias generales como con sepsis intraabdominal.

LIMITACIONES: Diseño retrospectivo, datos de centro único.

CONCLUSIONES: La tasa general de complicaciones infecciosas totales o complicaciones sépticas intraabdominales no aumentó en función de la exposición preoperatoria a una clase particular de productos biológicos. Las tasas aumentaron con la combinación de inmunosupresión de la terapia biológica con corticosteroides y resección abdominal previa. Vea el Resumen del Video en http://links.lww.com/DCR/B24.

KEY WORDS: Antitumor necrosis factor; Biologics; Crohn's disease; Postoperative outcomes; Ustekinumab; Veolizumab.

Crohn's disease (CD) is an idiopathic chronic inflammatory disease of the GI tract, which is thought to affect up to 800,000 people in the United States and continues to increase in incidence for unknown reasons.[1] Biologics have become the cornerstone of medical therapy for moderate-to-severe disease. However, their use is limited by primary nonresponse[2–6] and secondary loss of response,[7,8] as well as the risks of serious and/or opportunistic infections.[9] Despite many patients cycling through numerous systemic immunosuppressives, up to 60% will undergo an abdominal operation, and a third will require multiple abdominal operations.[10] Unfortunately, rates of postoperative morbidity reach 30%, and intra-abdominal sepsis after an anastomosis may be seen in up to 10%.[11,12] Because an increasing number of patients with CD are undergoing abdominal operations in the setting of immunosuppression and refractory disease, it is critical to understand how to best mitigate postoperative risk.

Significant investigation has been performed to better understand the association between perioperative immunosuppression and increased postoperative morbidity, especially infectious morbidity. Corticosteroids have been consistently identified as an independent risk factor for increased postoperative infectious complications after surgery in CD.[13–16] In contrast, immunomodulators seem consistently safe.[17,18] However, the association between postoperative complications and perioperative exposure to biologic therapy remains controversial.[11–16,19–43] This is a difficult question to answer given the challenge in isolating the effect of the biologic alone within a heterogeneous group of patients harboring several confounding variables known to increase rates of postoperative complications, including poor nutritional status,[15,23,24] anemia,[11] repeat intestinal surgery,[11,44] concomitant immunosuppressives,[13,16] and need for emergent surgery.[22] Nevertheless, there is significant concern regarding the risk of preoperative exposure to biologic therapy because of the substantial body of data suggesting worsened postoperative outcomes in the setting of anti-TNFs[11–13,16,36–43] and vedolizumab[45–47] – enough that warrants additional investigation in an attempt to optimize patient outcomes.

Anti-TNFs remain the most well-studied biologics with regard to postoperative outcomes.[11–16,19–43] However, there has been a recent surge in interest in the more recently approved anti-integrin (vedolizumab) and anti-interleukin (ustekinumab). A previous study from our institution and a multicenter consortium study suggested an increased risk of postoperative complications in vedolizumab-exposed patients with IBD and CD as compared with patients exposed perioperatively to the anti-TNFs or no biologic therapy.[45–47] A subsequent multicenter consor-

tium investigation of postoperative complications in the setting of preoperative ustekinumab versus anti-TNF exposure found no difference in postoperative outcomes.[48] However, the 3 classes of biologic therapy (anti-TNF, anti-interleukin, and anti-integrin) have never been directly compared with no biologic therapy as a reference standard. We collected data on 712 patients with CD undergoing major abdominal surgery to describe the differences in rates of 30-day postoperative overall postoperative infectious complications and 30-day postoperative intra-abdominal septic complications in patients with CD who were exposed to each class of biologic as compared with no biologic therapy.

PATIENTS AND METHODS

After institutional review board approval, a retrospective chart review of the Mayo Clinic Rochester electronic medical chart system between May 20, 2014, and December 31, 2017, was performed. A list of all patients with CD who underwent a major abdominal operation was obtained as identified by International Classification of Diseases, Ninth Revision (555.x), and International Classification of Diseases, Tenth Revision, codes for CD (50.x) and Current Procedural Terminology codes for major abdominal surgery (44120, 44125, 44130, 44140, 44141, 44143, 44144, 44145, 44146, 44147, 44150, 44151, 44155, 44156, 44157, 44158, 44160, 44180, 44187, 44188, 44202, 44204, 44205, 44206, 44207, 44208, 44210, 44211, 44212, 44227, 44310, 44314, 44316, 44320, 44340, 44345, 44346, 44615, 44620, 44625, 44626, 44640, 44650, 44660, 44661, 44799, 44950, 44790, 45110, 45111, 45112, 45113, 45114, 45119, 45120, 45136, 45395, 45397, 45800, 45805, 45820, 45825, 49000). Study patients included adults (aged ≥18 y) with CD who received an anti-TNF (infliximab, adalimumab, certolizumab pegol), anti-integrin (vedolizumab), or anti-interleukin (ustekinumab) within 12 weeks of a major abdominal operation. The control cohort included patients not exposed to a biologic within 12 weeks of a major abdominal operation. Patients were excluded if they underwent an emergent operation, did not have ≥30 days of follow-up after their operation, or had their operation performed at an outside hospital. Data abstracted included demographic and disease characteristics, including patient sex, age, BMI category (<18.5 underweight, >30 obese, and 18–30 normal weight), smoking status, duration of disease, previous intestinal resection, and predominant disease phenotype at operation. Preoperative serum laboratories within 4 weeks of surgery (leukocyte count, hemoglobin, platelet count, albumin) and within 2 weeks of surgery (C-reactive protein) were abstracted. Medication history including biologic exposure and concomitant corticosteroid and immunomodulator (azathioprine, 6-mercaptopurine, methotrexate) within 4 weeks of surgery was recorded. The operative characteristics abstracted included operation performed (grouped by colectomy with end ileostomy, proctectomy/proctocolectomy/IPAA excision with end ileostomy, loop ileostomy closure, ostomy formation, end ostomy closure with anastomosis, small bowel resection with anastomosis, or ileocectomy), laparoscopic versus open approach, construction of anastomosis, and use of proximal diversion in the setting of an anastomosis. Abstracted data on complications included postoperative infectious nonsurgical complications (urinary tract infection, pneumonia, bacteremia), 30-day surgical infectious complications (superficial surgical site infection (SSI) or intra-abdominal septic complications (combination of deep space abscess or anastomotic leak)), mucocutaneous separation at the stoma of >50% requiring revision, ileus (requiring placement of nasogastric tube), small bowel obstruction (mechanical obstruction requiring a return to the operating room), 30-day unplanned hospital readmission, 30-day unplanned return to the operating room, and 30-day mortality.

The primary end points were the overall infectious complication rate (combination of nonsurgical and surgical infectious complications listed above) and the rate of intra-abdominal sepsis defined as a deep space abscess or anastomotic leak. The secondary end points were rates of 30-day postoperative nonsurgical infectious complications, 30-day surgical infectious complications, 30-day superficial SSI, 30-day readmission, 30-day return to the operating room, and 30-day mortality.

Categorical variables were expressed as number (percentage) and continuous variables expressed as median (interquartile range). Demographic and clinical characteristic variables were compared among the 3 groups of current biologic use with a χ^2 test or Kruskal–Wallis test, as appropriate.

The association of patient risk factors with 30-day outcomes of any infection (n = 132), SSI (n = 67), and the composite outcome of either intra-abdominal abscess or leak (n = 31) was assessed using logistic regression. Results of these models are reported as ORs and 95% CIs. Multiple variable models were also examined with logistic regression using a backward selection method. For the outcome of any infection, all of the variables with a univariate significance of <0.05 were considered in the multiple variable model, as well as for the outcome of SSI. Including patients with an anastomosis, we assessed the outcome of intra-abdominal sepsis, and all variables with a univariate significance of <0.20 were considered in the multiple variable model. An α level of <0.05 was considered for statistical significance. All of the analyses were performed using SAS version 9.4 (SAS Institute, Inc, Cary, NC).

RESULTS

A total of 712 patients with CD were included in the analysis: 272 patients received an anti-TNF, 127 received

vedolizumab, 38 received ustekinumab, and 275 received no biologic therapy within 12 weeks of an abdominal operation between May 20, 2014, and December 31, 2017, at Mayo Clinic (Rochester, MN). Patients on no biologic therapy were older and more likely to have diabetes mellitus. Ustekinumab-exposed patients were more likely to be obese and to have been previously exposed to a greater number of biologics. Patients exposed to any class of biologic were more likely to be taking a concurrent immunomodulator than if not exposed to biologics (≈40.0% vs 15.6%; $p < 0.001$). However, there were no differences in corticosteroid use among the biologic and no-biologic exposed cohorts ($p = 0.43$), with nearly a quarter of patients on corticosteroids at the time of surgery. There were also no differences in hemoglobin, leukocyte count, platelet count, albumin, and C-reactive protein serum laboratory markers between any of the 4 cohorts. Vedolizumab-treated patients were most likely to have perianal disease at the time of their operation ($p < 0.001$; Table 1).

When comparing operative characteristics, patients exposed to vedolizumab had fewer anastomoses constructed than the anti-TNF or no-biologic cohorts ($p < 0.001$). However, in those patients who did have an anastomosis performed, there was no difference in the rate of temporary fecal diversion among the biologic or no-biologic exposed cohorts. The use of laparoscopy was also consistent across all of the patient cohorts. However, the operations performed across cohorts remained different, with vedolizumab patients composing a greater proportion of colectomy with end ileostomy, ustekinumab patients composing a greater proportion of end ostomy closure with anastomosis, and no biologics composing the majority of small bowel resection and ileocecal resection (Table 2).

A total of 132 patients (19%) had a postoperative infectious outcome. Risk factors having a significant ($p < 0.05$) univariate association with a postoperative infectious outcome included obesity, corticosteroid use in the previous 4 weeks, procedure category (proctectomy, proctocolectomy, or IPAA excision), longer disease duration, and combination immunosuppression with corticosteroids and biologic therapy; age, sex, active tobacco use, presence of diabetes mellitus, previous biologic use, immunomodulator within 4 weeks, serum laboratory values, presence of perianal disease Crohn's phenotype, and

Table 1. Demographics and clinical characteristics by current biologic status

Demographics and clinical characteristics	*None (N = 275)*	*Anti-TNF (N = 272)*	*Vedolizumab (N = 127)*	*Ustekinumab (N = 38)*	*p*
Age, median (IQR)	44.0 (32.0–58.0)	37.0 (28.0–52.0)	34.0 (26.0–43.0)	35.5 (31.0–48.0)	<0.001
Women, n (%)	147 (53.5)	151 (55.5)	77 (60.6)	26 (68.4)	0.24
Tobacco use, n (%)	43 (15.6)	52 (19.1)	19 (15.0)	3 (7.9)	0.29
Diabetes mellitus, n (%)	20 (7.3)	4 (1.5)	5 (3.9)	0 (0.0)	0.004
BMI , median (IQR)	24.0 (20.8–28.4)	23.5 (20.6–27.6)	23.4 (19.8–27.0)	26.3 (20.9–32.3)	0.20
BMI category, n (%)					<0.001
Missing	1	3	0	0	
Underweight	36 (13.1)	32 (11.9)	18 (14.2)	4 (10.5)	
Normal weight	183 (66.8)	200 (74.3)	88 (69.3)	17 (44.7)	
Obese	55 (20.1)	37 (13.8)	21 (16.5)	17 (44.7)	
Disease duration, median (IQR)	13.0 (4.0–21.0)	10.0 (4.0–17.0)	11.0 (7.0–17.0)	13.0 (8.0–18.0)	0.10
Previous biologic, n (%)	168 (61.1)	141 (51.8)	124 (97.6)	38 (100.0)	<0.001
No. of previous biologics, n (%)					<0.001
0	107 (38.9)	131 (48.2)	3 (2.4)	0 (0.0)	
1	71 (25.8)	79 (29.0)	27 (21.3)	4 (10.5)	
2	43 (15.6)	56 (20.6)	45 (35.4)	6 (15.8)	
3	32 (11.6)	3 (1.1)	44 (34.6)	18 (47.4)	
4	19 (6.9)	3 (1.1)	8 (6.3)	10 (26.3)	
5	3 (1.1)	0 (0.0)	0 (0.0)	0 (0.0)	
Corticosteroids, n (%)	73 (26.5)	60 (22.1)	37 (29.1)	10 (26.3)	0.43
IMM, n (%)	43 (15.6)	117 (43.0)	57 (44.9)	16 (42.1)	<0.001
Hemoglobin, n	191	197	91	29	
Median, (IQR)	12.3 (10.7–13.5)	12.6 (11.1–13.6)	12.1 (10.9–13.3)	11.9 (11.3–12.7)	0.32
White blood cell count, n	191	197	91	29	
Median (IQR)	7.6 (6.0–10.0)	7.3 (5.4–9.2)	8.0 (6.4–9.7)	7.8 (6.6–9.9)	0.12
Platelets, n	191	197	91	29	
Median (IQR)	303.0 (230–374)	296 (233–377)	286 (248–397)	339 (276–454)	0.12
Albumin, n	109	116	59	18	
Median (IQR)	4.0 (3.6–4.2)	3.9 (3.4–4.2)	3.8 (3.1–4.3)	3.9 (3.6–4.2)	0.76
CRP, n	75	102	51	16	
Median (IQR)	13.1 (3.0–37.9)	6.7 (3.0–31.3)	11.1 (4.2–32.5)	8.4 (3.0–26.3)	0.48
Perianal disease, n (%)	68 (24.7)	63 (23.2)	61 (48.0)	14 (36.8)	<0.001
Previous abdominal resection, n (%)	210 (76.4)	183 (67.3)	99 (78.0)	32 (84.2)	0.02

TNF = tumor necrosis factor; IQR = interquartile range; IMM = immunomodulator; CRP = C-reactive protein.

Table 2. Operative characteristics

Operative characteristics	*None (N = 275)*	*Anti-TNF (N = 272)*	*Ustekinumab (N = 38)*	*Vedolizumab (N = 127)*	*p*
Procedure category, n (%)					<0.001
Loop ileostomy closure	18 (6.5)	26 (9.6)	0 (0.0)	16 (12.6)	
Colectomy with end ileostomy	14 (5.1)	13 (4.8)	5 (13.2)	25 (19.7)	
End ostomy closure with anastomosis	20 (7.3)	9 (3.3)	4 (10.5)	8 (6.3)	
Ostomy formation	50 (18.2)	30 (18.2)	10 (26.3)	32 (25.2)	
Proctectomy, proctocolectomy, pouch excision with end ileostomy	40 (14.5)	28 (10.3)	5 (13.2)	25 (19.7)	
Small bowel resection, ileocecal resection	166 (61.0)	133 (48.4)	14 (36.8)	32 (25.2)	
Phenotype, n (%)					<0.001
No active disease present	49 (17.8)	35 (12.9)	6 (15.8)	20 (15.7)	
Inflammatory	46 (16.7)	40 (14.7)	9 (23.7)	36 (28.3)	
Stricturing	94 (34.2)	125 (46.0)	12 (31.6)	30 (23.6)	
Fistulizing	61 (22.2)	51 (18.8)	7 (18.4)	20 (15.7)	
Perianal	25 (9.1)	21 (7.7)	4 (10.5)	21 (16.5)	
Anastomosis, n (%)	167 (60.7)	197 (72.4)	21 (55.3)	61 (48.0)	<0.001
Proximal diversion if anastomosis, n (%)	16 (9.6)	15 (7.6)	2 (9.5)	6 (9.8)	0.90
Approach, n (%)					0.17
Open	187 (68.0)	160 (58.8)	25 (65.8)	81 (63.8)	
Laparoscopic	88 (32.0)	112 (41.2)	13 (34.2)	46 (36.2)	

Procedure categories are as follows: A, stoma formation; B, anastomosis with or without resection; C, resection without an anastomosis; D, local revisional surgery.
TNF = tumor necrosis factor.

the current biologic exposed to were not associated with overall postoperative infectious complications. In a multivariable model, corticosteroids within 1 month of surgery ($p = 0.001$; OR = 2.01), open approach ($p = 0.021$; OR = 1.70), obesity relative to normal weight ($p = 0.03$; OR = 1.68), underweight relative to normal weight ($p = 0.03$; OR = 1.85), procedure category ($p = 0.029$) with the strongest association for proctectomy, proctocolectomy or IPAA excision ($p = 0.029$; OR = 4.96), and longer disease duration ($p = 0.016$; OR = 1.05 per mo) remained significant predictors of increased postoperative infectious complications.

A total of 67 patients (9%) experienced an SSI. Risk factors significant for a univariate association ($p < 0.05$) with the occurrence of an SSI included increased BMI, number of previous biologics, anti-TNF within 12 weeks of surgery, corticosteroid use within 1 month of surgery, procedure category, disease phenotype, anastomotic construction, open surgical approach, previous intestinal resection, and increased disease duration; age, active tobacco use, presence of diabetes mellitus, immunomodulator within 4 weeks, serum laboratory values, presence of perianal disease Crohn's phenotype, and the use of immunosuppression alone or in combination were not associated with overall postoperative infectious complications. In a multivariable model, corticosteroids within the previous 4 weeks ($p = 0.002$; OR = 2.42), obesity relative to normal weight ($p = 0.007$; OR=2.29), previous intestinal resection ($p = 0.022$; OR = 2.42), procedure category ($p = 0.003$) with the strongest association for proctectomy, proctocolectomy or IPAA excision ($p=0.008$; OR=7.70), and female sex ($p=0.035$; OR=1.85) remained significant predictors of increased postoperative superficial SSI.

Of the 446 patients who had construction of an anastomosis, 31 patients (7%) experienced postoperative intra-abdominal sepsis. Risk factors significant for a univariate association ($p < 0.05$) with the occurrence of an intra-abdominal sepsis included obesity, previous abdominal surgery, corticosteroid use in the previous 4 weeks, vedolizumab exposure within the previous 12 weeks, and combination immunosuppression with corticosteroids and a biologic or corticosteroids/biologic/immunomodulator (Table 3). The rates of intra-abdominal sepsis for categories of current biologic use in the no-biologic, anti-TNF, vedolizumab, and ustekinumab groups were 3.6%, 8.1%, 11.5%, and 9.5%. On multivariable analysis, combination immunosuppression with corticosteroids and a biologic ($p = 0.01$) or corticosteroids/biologic/immunomodulator ($p = 0.005$) remained a significant predictor of increased intra-abdominal septic complications but not any particular biologic alone. Previous abdominal surgery also remained predictive of intra-abdominal sepsis ($p = 0.01$; Table 4).

DISCUSSION

Despite an ever-increasing number of published reports addressing the association of preoperative exposure to biologic therapy and postoperative outcomes, the data remain controversial; some authors report no increased risk of postoperative complications, whereas others report a significantly increased risk.[11–16,19–43] It remains difficult to isolate the effect of biologic therapy as a stand-alone risk

Table 3. Risk factors associated with intra-abdominal sepsis in patients with an anastomosis

Risk factors	*N*	*No. of infections (%)*	*Univariate OR (95% CI)*	*p*	*Overall p*
Age, per 10 y	–	–	0.82 (0.63–1.06)	0.14	
Sex					
Men	202	14 (6.9)	0.99 (0.48–2.07)	0.99	
Women	244	17 (7.0)	1.0 (reference)		
Tobacco					
Yes	77	8 (10.4)	1.74 (0.75–4.06)	0.20	
No	369	23 (6.2)	1.0 (reference)		
Diabetes mellitus					
Yes	17	2 (11.8)	1.84 (0.40–8.43)	0.43	
No	429	29 (6.8)	1.0 (reference)		
BMI, per 1 unit	–	–	0.99 (0.93–1.05)	0.69	
BMI					
Underweight, <18.5	47	6 (12.8)	1.89 (0.73–4.92)	0.19	
Obese, ≥30	75	2 (2.7)	0.35 (0.08–1.53)	0.16	
Normal weight, 18.5–29.9	320	23 (7.2)	1.0 (reference)		0.12
Disease duration, per y	–	–	0.99 (0.96–1.02)	0.50	
Previous biologic use					
Yes	253	19 (7.5)	1.22 (0.58–2.59)	0.60	
No	193	12 (6.2)	1.0 (reference)		
No. of previous biologics, per 1	–	–	1.09 (0.82–1.46)	0.54	
Steroid use within 1 mo of surgery					
Yes	110	13 (11.8)	2.37 (1.12–5.01)	0.02	
No	336	18 (5.4)	1.0 (reference)		
IMM use within 4 wk					
Yes	147	13 (8.8)	1.51 (0.72–3.18)	0.27	
No	299	18 (6.0)	1.0 (reference)		
Hemoglobin within 4 wk					
<10 g/dL	32	2 (6.3)	0.81 (0.18–3.60)	0.78	
Missing	126	7 (5.6)	0.71 (0.30–1.71)	0.45	
≥10 g/dL	288	22 (7.6)	1.0 (reference)		0.74
Platelet count within 4 wk					
>450 × 10^9/L	29	1 (3.4)	0.42 (0.05–3.20)	0.40	
Missing	126	7 (5.6)	0.69 (0.29–1.64)	0.40	
≤450 × 10^9/L	291	23 (7.9)	1.0 (reference)		0.52
Albumin within 4 wk					
<3 g/dL	9	0 (0.0)	1.50 (0.07–31.52)	0.80	
Missing	253	18 (7.1)	1.01 (0.48–2.11)	0.98	
≥3 g/dL	184	13 (7.1)	1.0 (reference)		0.97
CRP within 2 wk					
>8 mg/L	69	5 (7.2)	0.99 (0.29–3.39)	0.99	
Missing	295	20 (6.8)	0.92 (0.36–2.37)	0.86	
≤8 mg/L	82	6 (7.3)	1.0 (reference)		0.98
WBC within 4 wk					
>10.5 × 10^9/L	269	21 (7.8)	1.35 (0.39–4.72)	0.63	
Missing	126	7 (5.6)	0.94 (0.23–3.79)	0.93	
≤10.5 × 10^9/L	51	3 (5.9)	1.0 (reference)		0.68
Perianal disease					
Yes	75	5 (6.7)	0.95 (0.35–2.55)	0.92	
No	371	26 (7.0)	1.0 (reference)		
Phenotype					
Fistulizing	85	5 (5.9)	0.72 (0.26–1.99)	0.52	
Inflammatory	47	5 (10.6)	1.36 (0.48–3.87)	0.56	
Non-CD	84	2 (2.4)	0.28 (0.06–1.23)	0.09	
Perianal fistulizing	6	1 (16.7)	2.29 (0.25–20.67)	0.46	
Stricturing	224	18 (8.0)	1.0 (reference)		0.33

(*Continued*)

Table 3. Continued

Risk factors	*N*	*No. of infections (%)*	*Univariate OR (95% CI)*	*p*	*Overall p*
Diversion					
Yes	39	2 (5.1)	0.70 (0.16–3.07)	0.64	
No	407	29 (7.1)	1.0 (reference)		
Approach					
Laparoscopic	171	13 (7.6)	1.17 (0.56–2.46)	0.67	
Open	275	18 (6.5)	1.0 (reference)		
Disease duration, y	–	–	0.99 (0.94–1.03)	0.60	
Albumin, per g/dL	–	–	0.79 (0.27–2.34)	0.67	
Current biologic					
Anti-TNF	197	16 (8.1)	2.37 (0.91–6.21)	0.08	
Ustekinumab	21	2 (9.5)	2.82 (0.53–15.00)	0.22	
Vedolizumab	61	7 (11.5)	3.48 (1.12–10.80)	0.03	
None	167	6 (3.6)			0.16
Treatment(s)					
Biologic ± IMM	216	15 (6.9)	2.91 (0.83–10.26)	0.10	
Steroid ± IMM	47	3 (6.4)	2.66 (0.52–13.67)	0.24	
Steroid + biologic	43	6 (14.0)	6.32 (1.51–26.54)	0.01	
Biologic + steroid + IMM	20	4 (20.0)	9.75 (2.00–47.60)	0.005	
IMM/none	120	3 (2.5)	1.0 (reference)		0.03
Previous abdominal resection					
Yes	319	16 (5.0)	0.39 (0.19–0.82)	0.01	
No	127	15 (11.8)	1.0 (reference)		

Procedure categories are as follows: A, stoma formation; B, anastomosis with or without resection; C, resection without an anastomosis; D, local revisional surgery.
IMM = immunomodulator; WBC = white blood cells; CD = Crohn's disease; CRP = C-reactive protein; TNF = tumor necrosis factor.

factor in each of these studies given the presence of multiple confounding factors known to increase postoperative complications. Moreover, it is challenging to make conclusive statements because of significant heterogeneity in study design, patient populations, and primary outcomes. Thus, we collected data on all patients with CD undergoing a major abdominal operation since the Food and Drug Administration (FDA) approval of vedolizumab in May 2014 to compare infectious postoperative complications in those patients exposed to each class of biologic versus no biologic therapy. Our goal was to improve the understanding of whether biologics as a whole, any particular class of biologic, or combination immunosuppression increased the risk of postoperative infectious complications or intra-abdominal septic complications. Of the 19% of patients who experienced an infectious complication or 7% who experienced intra-abdominal sepsis, no particular class of biologic independently increased the risk of either outcome. However, combination immunosuppression of a biologic with corticosteroids increased the risk of total infectious complications, and combination immunosuppression of a biologic with steroids or biologic with steroids and immunomodulator therapy increased the risk of intra-abdominal septic complications.

Table 4. Multivariable analysis of risk factors for intra-abdominal sepsis in patients with construction of an anastomosis

Risk factors for multivariable analysis	*OR (95% CI)*	*p*	*Overall p*
Age, per 10 y	0.98 (0.74–1.29)	0.88	
BMI			
Underweight <18.5	1.82 (0.65–5.13)	0.26	
Obese ≥30.0	0.40 (0.09–1.79)	0.23	
Normal weight 18.5–29.9	1.0 (reference)		0.22
Previous abdominal resection			
Yes	0.46 (0.21–0.99)	0.047	
No	1.0 (reference)		
Treatment(s)			
Biologic ± IMM	2.98 (0.83–10.73)	0.09	
Steroid ± IMM	2.47 (0.47–12.90)	0.28	
Steroid + biologic	6.31 (1.46–27.24)	0.01	
Biologic + steroid + immunosuppressive	8.38 (1.64–42.77)	0.01	
IMM/none	1.0 (reference)		0.06

IMM = immunomodulator.

The most widely studied biologic with regard to postoperative outcomes is infliximab, an anti-TNF approved by the FDA in 1998 for the treatment of moderate-to-severe CD. The literature has remained controversial regarding the association of preoperative anti-TNF therapy and postoperative infectious complications, with several papers reporting an increased risk[11–13,16,36–43] and others reporting no increased risk.[14,15,19–35] Serum drug levels at the time of surgery have not helped solve this dilemma, as the literature is again controversial. One retrospective single-center review reported that increased serum anti-TNF levels correlated with increased postoperative complications.[39] However, another multicenter prospective study, which drew serum TNF levels on the day of surgery, did not report such an association.[14] Therefore, it is difficult to definitively state whether anti-TNF therapy is associated with increased postoperative complications, as has

been described for corticosteroids.[13–16] In our cohort, we did not find anti-TNF therapy to be associated with infectious complications, surgical infectious complications, or intra-abdominal sepsis, unless in combination with corticosteroids and immunomodulator therapy.

Because of the systemic effect and increased risk of opportunistic infection with anti-TNF therapy, there was great enthusiasm when the FDA approved vedolizumab in 2014 for the treatment of moderate-to-severe CD because of its gut-specific mechanism theoretically providing an improved safety profile. Despite several clinical trials demonstrating the safety and efficacy of vedolizumab in patients with CD,[49,50] controversial surgical literature has drawn attention to the potential increased risk of postoperative complications in the setting of preoperative vedolizumab exposure, in both single-center and multicenter series.[45–47] Unfortunately, the mechanism of increased postoperative infectious complications remains largely unknown, but a recent study found that vedolizumab reduced the number of M2 macrophages at the site of bowel injury in a mouse model, a crucial cell in wound healing that could have implications in anastomotic healing.[51] In contrast to our previous study of preoperative vedolizumab exposure in patients with CD, which identified vedolizumab to be an independent predictor of postoperative SSI,[46] we herein found that vedolizumab, although associated with an increased rate of intra-abdominal sepsis as compared with the other cohorts (11.5% vs 9.5% in ustekinumab, 8.1% in anti-TNF, and 3.6% in the no-biologic cohort), was not a significant independent predictor of postoperative complications on multivariable analysis. It may be that the use of vedolizumab is likely a surrogate marker for increased disease severity, and we are unable to objectively account for all of the variables associated with an increased disease severity in the vedolizumab-exposed patient. Previously finding vedolizumab to be an independent predictor of postoperative complications may have been related to its use as a second- or third-line biologic, whereas now it is becoming increasingly used as a first-line therapy. Another important consideration is that vedolizumab takes up to 6 months to take effect. Patients who do not respond to vedolizumab are left untreated for a significant duration of time while waiting to assess the efficacy; this additional time without clinical response, and the common addition of corticosteroids to achieve mucosal healing, may result in significant worsening of disease severity, degradation of any physiologic reserve, and thus increased postoperative complications.

Ustekinumab, an anti-interleukin, was recently approved by the FDA in 2016 after the phase 2 and 3 studies demonstrating its efficacy for induction and maintenance of remission in patients with moderate-to-severe CD.[52–54] These large clinical trials also highlighted the safety profile of ustekinumab with a lack of increased adverse events. The only study reporting outcomes on ustekinumab-exposed surgical patients found no increased risk of postoperative complications when compared with anti-TNF–exposed patients.[48] However, despite combining data from 6 IBD referral centers, this report only included 44 ustekinumab-exposed surgical patients, leaving the perioperative safety profile largely unknown. In our series herein, we found a greater rate of infectious complications (26.3% vs 16.5% in the anti-TNF cohort and 17.8% in the no-biologic cohort) and intra-abdominal septic complications (9.5% vs 3.6% in the no-biologic cohort) in patients exposed to ustekinumab, but these differences were not statistically significant. These findings may reflect our inability to power a statistically significant difference because of small sample size or may be a true finding of no increased risk. Until greater patient numbers are available for data analysis, the effect of ustekinumab on postoperative outcomes will remain largely unanswered.

Consistent with previous data, corticosteroid use was independently associated with any postoperative infectious complication and superficial SSI but not intra-abdominal sepsis. Interestingly, each independent biologic class was not associated with any postoperative infectious complication, superficial SSI, or intra-abdominal sepsis, as has been reported previously for both anti-TNF[11–13,16,36–43] and vedolizumab.[46] However, when biologic therapy was combined with corticosteroid and/or immunomodulator, rates of infectious complications, superficial SSI, and intra-abdominal sepsis were significantly increased. Patients exposed to both biologics and corticosteroids reflect a cohort of patients in which biologic therapy is failing and corticosteroids are used to bridge to an alternative therapy or wait for biologic efficacy. Therefore, the findings of combination immunosuppression may not be a reflection of biologic therapy increasing infectious complications but may be a surrogate marker of those patients who have the most severe disease, unresponsive to escalation of medical therapy, and represent the sickest cohort. Again, it remains difficult to discern the independent effect of immunosuppression versus increased disease severity.

There are several limitations to our analysis worth mentioning. First, this is a single-center retrospective review performed at a large IBD referral center, where patients are typically referred after failing multiple immunosuppressive agents and present with severe or uncontrolled disease. Thus, our findings may not be applicable to patient populations treated at other centers. Second, because ustekinumab was just recently approved by the FDA in 2016, there remain a limited number of patients included in the analysis as compared with anti-TNF and vedolizumab, limiting the conclusions drawn regarding the impact of ustekinumab as compared with the other biologics. On a related note, a number of these ustekinumab-treated patients were particularly refractory and had been started on off-label ustekinumab years before FDA ap-

proval. Third, the comparison of intra-abdominal sepsis is limited by the small number of events to power significant differences. Fourth, because we did not stratify patients by time from biologic to an operation, we do not have comparison data between patients exposed at 4, 8, or 12 weeks before a major abdominal operation to better understand whether a washout period is useful. This may have been more important had we identified a particular biologic to be an independent predictor of infectious morbidity. Similarly, the half lives of each biologic are different, ranging from 7 to 10 days with infliximab up to 25 days with vedolizumab. Because all patients exposed within 12 weeks of surgery are included, those exposed to anti-TNFs have a greater number of half lives and may have a better washout period than those patients exposed to vedolizumab. This may account for a lower number of infectious complications in the anti-TNF group versus vedolizumab. An analysis where patients are included based on the number of half lives may better address the question, but we still do not understand receptor saturation or the meaning of serum levels with respect to surgical complications. Lastly, we did not draw serum drug levels on every patient to determine whether increased serum drug levels are associated with increased complications. However, the meaning and impact of serum vedolizumab and ustekinumab levels remain largely unknown.

CONCLUSION

No particular class of biologic therapy has an independent increased risk of postoperative infectious complications. However, combination immunosuppression increases the risk of both overall infectious complications and rates of intra-abdominal sepsis. Whether it is the dual and triple immunosuppression itself or a surrogate of failing disease, being unresponsive to 1, 2, and 3 agents remains difficult to discern. It is likely a combination of both that lead to adverse outcomes in this highly refractory cohort of patients.

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