A Review of the Impact of Biologics on Surgical Complications in Crohn's Disease

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Abstract: Anti–tumor necrosis factor therapy has revolutionized the treatment of Crohn's disease. Despite the increased use in the past decade and a half, a majority of patients with Crohn's disease with ultimately require operative management of their disease. No clear consensus has been made in the literature regarding the surgical outcomes in patients who have been exposed to anti–tumor necrosis factor therapy. This review highlights the most recent and relevant literature regarding the safety and effects of anti–tumor necrosis factor use in the perioperative period.

Crohn's disease (CD) is a chronic inflammatory condition that can affect any part of the gastrointestinal tract thought to arise from immune response dysregulation to intestinal microflora in a genetically susceptible host.[1] The treatment of CD in the past 2 decades has been revolutionized with the identification of tumor necrosis factor alpha (TNF-α) as an important mediator in the amplification and perpetuation of the chronic inflammatory response.[2] In 1998, infliximab, a humanized chimeric monoclonal antibody that binds to TNF-α causing apoptosis of macrophages and activated T-lymphocytes, became the first biologic anti–TNF-α agent approved for CD.[3] Two other monoclonal antibody-based TNF-α inhibitors (anti-TNF) have since been approved by the United States Food and Drug Administration for the treatment of moderate-to-severe CD: adalimumab and certolizumab pegol.[4–9] Anti-TNF agents have shown efficacy in inducing and maintaining remission in CD.[10,11] Despite the increased use of anti-TNF therapies, nearly one-third of patients with CD will require major abdominal resection within 5 years after diagnosis, and two-thirds of all patients with CD will ultimately require operative management at least once during the course of their disease.[12–17]

Surgery is most commonly indicated for medically refractory disease, medication side effects, and complications of disease, including hemorrhage, perforation, obstruction, and fistula formation.[18–21] The use of anti-TNF agents in CD is markedly increasing with 60% of patients with CD receiving anti-TNF treatment before their first abdominal surgery and almost one-third of patients receiving anti-TNF treatment in the 6 months before abdominal resection.[22] The stress of surgery results in an overall reduction in cell-mediated immunity leading to concerns regarding the impact of anti-TNF agents on surgical outcome.

Anti-TNF therapy has been associated with several adverse events including an increased incidence of overall and opportunistic infections, as well as lymphoma.[23–25] In addition, TNF-α promotes angiogenesis and collagen production, whereas inhibition is thought to inhibit wound healing in postoperative patients.[26] Furthermore, murine models have shown that the addition of TNF-α promotes wound healing, whereas inhibition of TNF-α decreases wound strength.[27] Although corticosteroids have been clearly shown to be a significant risk factor for postoperative infections and immunosuppressives seem safe, the perioperative risk of infection associated with anti-TNF agents in CD remains controversial because of limited heterogeneous data from small retrospective studies.[25,28,29] No clear consensus has been made as to whether exposure to anti-TNF therapy is associated with increased risk of postoperative complications. In this review, we will highlight the most recent and relevant literature regarding the safety and effects of anti-TNF use in the perioperative period.

Single Institutional Studies on Postoperative Outcomes in Patients with CD Treated with Anti-TNF Agents

Single-center studies of postoperative outcomes for patients with CD on anti-TNF therapy have been plagued by retrospectively reviewing small heterogeneous groups of patients on anti-TNF agents at variable intervals before and after surgery.[30,31] Existing studies have used different definitions for anti-TNF agent exposure. The most commonly accepted definition for anti-TNF exposure has been use within 12 weeks before surgery. This definition is based on the pharmacokinetics of intravenously dosed infliximab (5 mg/kg). The half-life of infliximab is

TABLE 1. Common Studied Adverse Events Based on Infectious Versus Noninfectious Complications

Infectious Complication	Noninfectious Complication
Wound infection or dehiscence	Small bowel obstruction
Anastomotic leak	Ileus
Abscess	Bleeding or hematoma or anemia
Sepsis	Thromboembolus (DVT or PE)
Fistula	
Pulmonary infection or pneumonia	
Urinary tract infection	

DVT, deep vein thrombosis; PE, pulmonary embolism.

approximately 10 days, and by week 12, drug levels are no longer detectable.[30,32,33] Postoperative adverse events have generally been classified into infectious and noninfectious complications typically within 30 days of surgery (Table 1).

In 2004, Colombel et al reported the outcome of 270 patients with CD after bowel resection and 52 patients

experienced septic complications (Table 2). They found that there was no association between the use of moderate-to-high dose steroids, immunomodulators, or infliximab with greater complication rates.[34] Marchal et al also found no association between infliximab and postoperative complications in their case–control study of 31 patients with CD treated within 12 weeks of surgery. However, the study did find a trend toward increased rate of infectious complications in the infliximab-treated group. The authors speculated this could be secondary to more exposure to glucocorticoids and/or immunosuppression in this group.[35] In 2008, Kunitake et al compared 413 consecutive patients with inflammatory bowel disease (IBD), including CD, ulcerative colitis, and indeterminate colitis undergoing abdominal surgery who received (N = 101) and did not receive infliximab within 12 weeks of surgery. Although patients receiving infliximab were more likely to be concurrently treated with 6-mercaptopurine and have CD, there was no difference in corticosteroid use. Again, no significant differences were found in postoperative infectious and noninfectious complications and mortality. The only statistical significant difference from this study was that the mean length of hospital stay was slightly longer in the infliximab-treated versus infliximab-naive group (12.2 versus 10.2 d, $P < 0.0001$).[36]

TABLE 2. Single Institutional Studies on Postoperative Outcomes in Patients with CD Treated with Anti-TNF Agents

Author	Inclusion Period	Non–anti-TNF Group (%)	Anti-TNF Group (%)	Overall complication Rate (Non-therapy Versus Therapy) (P)	Infectious complication Rate (Non-therapy Versus Therapy) (P)
Colombel et al[34]	1998–2001	218 (81)	52 (19)	23% versus 23% (NS)	20% versus 17% (NS)
Marchal et al[35]	1998–2002	57 (72)	22 (28)	8% versus 12% P = NS	3% versus 15% P = 0.03
Kunitake et al[36]	1993–2007	131 (70)	57 (30)	16% versus 17% [a]P = 1.00	10% versus 6% [a]P = 1.00
Appau et al[37]	1998–2007	329 (85)	60 (15)	10% versus 22% [b]P = not reported	10% versus 20% [b]P = not reported
Nasir et al[38]	2005–2009	251 (68)	119 (32)	30% versus 28% P = 0.63	3% versus 2% P = 0.44
Myrelid et al[39]	2005–2011	187 (63)	111 (37)	29% versus 34% P = 0.40	14% versus 16% P = 0.59
Krane et al[40]	2004–2011	181 (74)	63 (26)	24% versus 25% [c]P = 0.93	11% versus 12% [c]P = 0.92
Nørgård et al[41]	2000–2010	2079 (91)	214 (9)	Overall rate not reported[d]	Infectious rate not reported[d]
Waterman et al[42]	2000–2010	94 (58)	69 (42)	Overall rate not reported[e]	Infectious rate not reported[e]
Syed et al[43]	2004–2011	175 (54)	150 (46)	27% versus 31% P = 0.52	36% versus 0.25% P = 0.05

[a]Cumulative complication rates included patients with UC, indeterminate colitis, and CD. There was no complication rate reported for patients with CD; however, based on logistic regression analysis performed, preoperative diagnosis of CD or UC was not a predictor of postoperative complications.
[b]Comprehensive P values were not reported for overall postoperative and infectious postoperative complications. However, multivariate analysis revealed anti-TNF therapy to have an increased risk for 30-day postoperative readmission (OR—2.33 [1.02–5.33], P = 0.045), sepsis (OR—2.62 [1.12–6.13], P = 0.027), and intra-abdominal abscess (OR—5.78 [1.69–19.7], P = 0.005).
[c]Cumulative complication rates included patients with UC and CD. Subgroup analyses confirmed similar rates of overall and infectious complications regardless if the patient had UC or CD.
[d]No cumulative overall and infectious complication rates were determined; however, this study showed no statistically significant increased relative risks of death, reoperation, anastomotic leakage 30 or 60 days postoperatively, or abscess drainage 30 or 60 days postoperatively.
[e]No cumulative overall and infectious complication rates were determined, however, within the subcategories of each individual complication, P values were determined to not be statistically significant.
NS, nonsignificant; UC, ulcerative colitis.

Contrary to this data, Appau et al evaluated 30-day postoperative outcomes for patients with CD and recommended fecal diversion of patients on anti-TNF therapy who were undergoing terminal ileal resection secondary to increased risk of anastomotic complications. To reduce selection bias, the study by Appau et al compared postoperative outcomes of infliximab-exposed (n = 60), infliximab-naive (n = 329), and historical controls (n = 69) before the advent of infliximab. Although multivariate analysis revealed infliximab use to be associated with 30-day postoperative readmission (odds ratio [OR]: 2.33; 95% confidence interval [CI], 1.02–5.33), sepsis (OR 2.62; 95% CI, 1.12–6.13), and intra-abdominal abscess (OR 5.78; 95% CI, 1.59–19.7), the presence of a diverting ostomy was significantly associated with a lower risk of sepsis (OR 0.28; 95% CI, 0.09–0.83).[37]

More recent studies have noted minimal association between preoperative anti-TNF therapies with increased postoperative complications. Nasir et al expanded inclusion criteria to include all potential procedures that would result in anastomosis formation in patients with CD. Of the 370 patients identified, 119 patients (32%) were exposed to anti-TNF agents perioperatively (defined as within 8 wk preoperatively or 4 wk postoperatively). Although the exposed and unexposed groups were similar in most characteristics, the group exposed to perioperative anti-TNF therapy was found to have more severe disease. Half the patients in the anti-TNF–exposed group were categorized with severe fulminant disease as compared with only 18% in the nonexposed group (*P* < 0.001). There was no significant association between anti-TNF therapy and increased overall postoperative complications, nor was there any association with intra-abdominal infectious complications. Moreover, univariate analysis revealed age and the presence of penetrating disease as the only predictors of intra-abdominal infectious complications.[39]

Myrelid et al studied 298 patients undergoing at least 1 intestinal anastomosis. Anti-TNF–exposed patients were considered to be those who received anti-TNF therapy within 2 months of surgery (N = 111 patients) and unexposed patients were those who received anti-TNF therapy more than 2 months before surgery or at least 6 weeks postoperatively (N = 187 patients). The groups were similar in disease behavior and outcomes including frequency of overall postoperative complications, anastomotic and nonanastomotic infectious complications. Factors found to be significantly associated with anastomotic complications were extensive adhesiolysis and proximal small bowel disease rather than the use of anti-TNF therapy.[39]

In a more recent study, Krane et al examined the outcome of postoperative patients with IBD exposed to anti-TNF agents undergoing laparoscopic resection. From 2004 to 2011, 518 patients were identified and included, of which 142 patients (38%) were treated with preoperative anti-TNF therapy within 12 weeks of surgery. The exposed group was significantly more likely to be concurrently treated with corticosteroids and immunomodulators, suggesting more refractory disease. Although there was no increased rate of conversion to laparotomy and no increased risk of overall, anastomotic, infectious, and thrombotic

complications associated with preoperative anti-TNF therapy, there was a trend toward increased infectious complications associated with patients with CD exposed to anti-TNF therapy in the subgroup analysis. Regardless, the authors concluded that anti-TNF therapy in patients refractory to conventional therapy did not seem to negatively impact their short-term postsurgical outcomes.[43]

One large population-based study including a nationwide Danish cohort consisted of 2293 patients who underwent surgery for CD. Two-hundred fourteen patients (9.3%) were treated with anti-TNF therapy within 12 weeks of surgery. To counter the potential impact of disease, a subgroup of the unexposed cohort who were exposed to corticosteroids or immunomodulators within the 12 weeks before surgery was selected. This study showed no increased relative risks of death, reoperation, or abscess drainage 30 or 60 days postoperatively in the anti-TNF–exposed versus both groups of unexposed patients. There was an insignificant trend toward greater relative risk of anastomotic leak in the anti-TNF–exposed group. Further subanalysis showed that there was no increase in relative risk of complications with anti-TNF therapy when it was given less than 14 days before surgery.[41]

Waterman et al specifically examined rates of postoperative infectious complications at variable anti-TNF exposure time points leading up to IBD surgery. The cohort included 195 patients with IBD who were exposed to anti-TNF therapy, and they found no increased rate of postoperative infectious complications, anastomotic complications, or overall complications when exposure was within 14 days, 15 to 30 days, or 31 to 180 days before surgery compared with matched controls based on major operative procedure, IBD subtype, exposure to preoperative corticosteroids, and patient age at the time of operation.[42] Interestingly, the study by Waterman et al is the only published study to have looked at preoperative anti-TNF levels as a marker for postoperative complications in a small subset of their cohort study. The association between serum infliximab levels and postoperative complications was evaluated in 19 patients. Ten patients had detectable serum levels of infliximab, and 9 patients had undetectable serum levels. These groups were matched in terms of age, gender, and concurrent corticosteroid therapy. There was no difference in overall infectious complication rates between the 2 groups. Ultimately, both Nørgård and Waterman's studies did not support the clinical practice of delaying surgery for patients with CD who received anti-TNF therapy within 8 to 12 weeks of abdominal surgery.[41,42]

In the largest single-center study of anti-TNF–treated patients with CD, Syed et al demonstrated an increased rate of infectious postoperative and surgical site complications when patients were exposed to anti-TNF therapy within 8 weeks of abdominal surgery. Nearly half of patients (150 of 325) who underwent abdominal surgery for CD were exposed to anti-TNF from July 2004 to May 2011. Complications studied by the authors are listed in Table 1. There were no differences seen in preoperative systemic corticosteroid, immunomodulator, and narcotic exposure, preoperative nutritional status (defined by body mass index and albumin),

presence of active infection, or age-adjusted preoperative morbidity score.[44] Although there was no difference in frequency of individual postoperative complications between the anti-TNF–exposed and unexposed group, multivariate analysis showed that preoperative anti-TNF was an independent predictor of overall infectious (OR 2.43; 95% CI, 1.18–5.03) and surgical site (OR 1.96; 95% CI, 1.02–3.77) complications.[43]

The authors noted that although other studies have found that the use of anti-TNF therapy has been associated with increased disease severity, this study found that both cohorts were similar in this respect. With this result suggesting an association between anti-TNF therapy and surgical postoperative complications, this study stands alone with Appau et al years earlier,[37] with results contrary to the majority of recent single-institution studies.

Systematic Reviews and Meta-analysis of These Studies in the Literature

Although the majority of single-institution studies do not support a relationship between the use of anti-TNF and postoperative complications, results of pooled data have been suggestive of an increased risk in infectious postoperative complications (Table 3). This data must be regarded in a circumspect manner, however, before drawing definitive conclusions.

Billioud et al pooled 7 studies for a total analysis of 1699 patients with CD. Only 2 included studies found that preoperative anti-TNF increased the risk of infectious postoperative complications.[37,43] Among analyzed patients, a total of 484 patients received preoperative anti-TNF therapy. The pooled data revealed that the prevalence of infectious postoperative complications in patients with CD was increased with an OR of 1.45. This risk is comparable with that associated with systemic corticosteroids.[48] However, it is important to note that this study only accounted for 23% of all patients with CD included in the calculation of risk for infectious postoperative complication in their meta-analysis.[45]

Kopylov et al demonstrated a similar statistically significant increased risk of infectious complications and a non-significant trend toward increased rate of noninfectious and overall complications (Table 3). In their subanalysis of infectious complications, they found these infectious complications to be unrelated to surgical complications such as anastomotic leak or intra-abdominal abscess. The authors suggest that the increased rate of infections are secondary to remote systemic infections such as respiratory or urinary infections, and/or sepsis, which is consistent with the systemic immunosuppression by anti-TNF agents.[47]

Narula et al pooled studies of postoperative outcomes in patients with both CD and ulcerative colitis and found similar modest statistically significant increases in infectious and non-infectious complications in those treated with anti-TNF agents. Sensitivity analyses were performed limiting studies to those with only CD and found a statistically significant increase in infectious (OR 1.93; 95% CI, 1.28–2.89) and total complications (OR 2.19; 95% CI, 1.69–2.84), with a trend toward an increase in noninfectious complications (OR 1.73; 95% CI, 0.94–3.17). When analysis was limited to patients with ulcerative colitis, the pooled OR was no longer significant for infectious, noninfectious, or total complications. The authors also noted that in 7 of the 15 pooled studies, patients demonstrated a higher concurrent use of immunomodulators or corticosteroids in the anti-TNF agent treatment group, suggesting more severe disease in these patients.[46]

DISCUSSION

Before the advent of anti-TNF agents in the treatment of CD, Yamamoto et al determined that preoperative low albumin serum level, preoperative corticosteroid use, and intra-abdominal abscess or fistula at the time of laparotomy significantly increased the risk of postoperative infectious complications. The risk of septic complications in a patient with 3 of these risk factors was 29% and in a patient with all 4 of these risk factors was 50%. Diversion was therefore recommended with 3 or more risk factors.[49,50]

An algorithm such as this, however, has not been successfully developed to incorporate the impact of anti-TNF agents as the data are so mixed. Although many single-institution retrospective cohort studies reveal no association between exposure to anti-TNF agents and an increased risk of postoperative

TABLE 3. Characteristics of the Meta-analyses Reviewed in the Literature

| Study (Author, yr)	Type of Complication	No. Studies Included	Study Population	Total complication Rate (%)	Non–anti-TNF Group Complication Rate (%)	Anti-TNF Group Complication Rate (%)	OR (CI)
Billioud, et al[45]	Overall	6	1316	281/1316 (21)	196/980 (20)	85/336 (25)	1.31 (0.96–1.77)
	Infectious	7	1699	268/1699 (16)	169/1215 (14)	99/484 (21)	1.45 (1.03–2.05)
Kopylov, et al[46]	Overall	6	1316	426/1316 (32)	284/980 (30)	142/336 (42)	1.72 (0.93–3.19)
	Infectious	6	1159	243/1159 (21)	165/872 (19)	78/287 (27)	1.50 (1.08–2.08)
	Noninfectious	4	834	99/834 (11)	60/634 (9)	39/200 (20)	1.26 (0.65–2.42)
Narula, et al[48]	Infectious	15	3244	542/3244 (17)	328/2257 (15)	214/987 (22)	1.56 (1.09–2.24)
	Noninfectious	11	2496	543/2496 (22)	316/1683 (9)	227/813 (28)	1.57 (1.14–2.17)
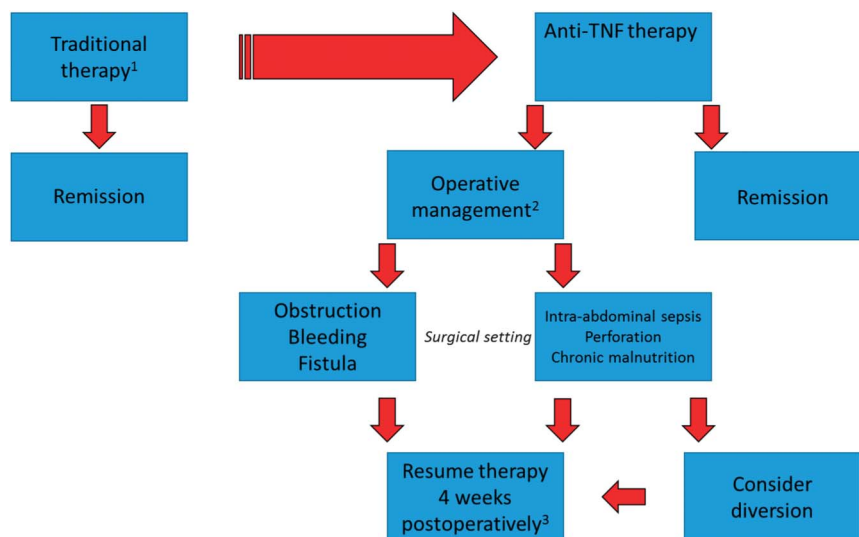
FIGURE 1. The current treatment algorithm at our institution. [1]Traditional therapy, including corticosteroids, 6-mercaptopurine, and azathioprine. [2]Elective repair is scheduled 4 weeks after the last anti-TNF infusion dose to optimize therapy. In the setting of urgent or emergent surgery, this timing may not always be able to be attained. [3]If no contraindications to resuming anti-TNF therapy (Table 1), the therapy is resumed 4 weeks postoperatively.

complications in CD, pooled data do advocate a modest increase in the risk of infectious postoperative complications.

The majority of the studies to date have been retrospective studies with small cohort sizes. Meta-analyses have attempted to increase the power of these studies to better determine the impact of perioperative anti-TNF agents on the postoperative outcomes of patients with CD but have lost some of the specificity required to draw definitive conclusions. Several limitations include variable inclusion criteria, the type and technique of surgical interventions, and heterogeneous definitions of complications and the timing in which they were assessed. As many of these studies were observational studies, it was difficult to control for confounding factors, such as disease severity, indication and timing of surgery, the nutritional status of the patient, and the training of the surgeon, which are all known to affect postoperative outcomes.[50,51] Moreover, increases in the rate of complications may have been a reflection of differences in morbidity secondary to disease severity and a higher likelihood of concurrent use of immunomodulators or corticosteroids rather than a direct effect from anti-TNF therapy. These confounding factors and selection biases may become cumulative in meta-analyses with the pooling of multiple studies.

In the setting of nonemergent surgery, the consideration of whether anti-TNF therapy is a modifiable risk factor is important to determine to weigh the risk of increased postoperative complications versus the potential impact of anti-TNF interruption on subsequent immunogenicity, decreased drug levels, and potential for disease flares.

Our Take

At our institution, as maintenance anti-TNF therapy is administered in 8-week intervals, we recommend scheduling

elective abdominal surgery 4 weeks after the last infusion dose so as to resume therapy 4 weeks postoperatively, provided there are no contraindications such as listed in Table 1. Unfortunately, many patients who are receiving anti-TNF therapy ultimately require emergent or urgent surgery, rendering this ideal 4-week window irrelevant. In this case, a decision of whether or not to divert the patient is made on a case by case episode, based more on the overall nutritional status of the patient and the intraoperative surgical findings, rather than a simple question regarding the status of immunologic therapy (Fig. 1).

CONCLUSIONS

Although many of the earlier studies have presented conflicting data regarding the association between anti-TNF therapy and increased infectious postoperative complications in CD, the pooled data from the more recent meta-analyses suggest that exposure could be associated with a modest, but significant, increased risk. In summary, there is currently no absolute recommendation in the administration and cessation of anti-TNF therapy. These studies confirm the need for large, prospective randomized placebo-controlled clinical trials to elucidate the definitive risks and benefits of continuing anti-TNF agents in the perioperative period for clinical practice equipoise in this patient population.

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