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**Inflammatory bowel disease surgery in the biologic era**

Ferrari L *et al*. IBD surgery in biologic era

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**Abstract**

Anti-tumour necrosis factor (TNF)-α therapy has revolutionized inflammatory bowel disease (IBD) treatment. Infliximab (IFX) and adalimumab (ADA) either as monotherapy or in combination with an immunomodulator are able to induce clinical and biological remission in patients with moderate and severe Crohn’s disease (CD) and ulcerative colitis (UC). These new therapies have led to a shift in the goals of IBD management from just controlling clinical symptoms to preventing disease progression. However, despite these advances in medical therapy, surgery is still required in 30%-40% of patients with CD and 20%-30% of patients with UC at some point during their lifetime. While biologics certainly play a major role in the medical treatment of IBD, there is concern about the effects of these anti-TNF-α agents on postoperative complications and morbidity. The purpose of this article is to review the role of surgery in the treatment of IBD in the age of biologics and the impact of these medications on per-operative outcomes. In this manuscript we review the relationship between biologic agents and surgery in the treatment of IBD. We also discuss in detail the periopetative risks and complications.

**Key words:** Inflammatory bowel disease; Crohn’s disease; Ulcerative colitis; Infliximab; Anti-tumour necrosis factor alpha agents

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**Core tip:** We review the relationship between biologic agents and surgery in the treatment of inflammatory bowel disease. We also discuss in detail perioperative risks and complications in this setting.

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**INTRODUCTION**

Anti-tumour necrosis factor (TNF)-α therapy has revolutionized inflammatory bowel disease (IBD) treatment. Infliximab (IFX) and adalimumab (ADA) either as monotherapy or in combination with an immunomodulator are able to induce clinical and biological remission in patients with moderate and severe Crohn’s disease (CD)[1-6] and ulcerative colitis (UC)[7,8]. These new therapies have led to a shift in the goals of IBD management from just controlling clinical symptoms to preventing disease progression.

The concept of composite or deep remission based on clinical and biological remission and mucosal healing has recently emerged. The ability to achieve composite remission seems to be correlated with better long-term outcomes, improved quality of life, and fewer surgical operations[6].

However, despite these advances in medical therapy, surgery is still required in 30%-40% of patients with CD and 20%-30% of patients with UC at some point during their lifetime[9,10]. In CD patients, the risk for surgery seems to be related to stenosing phenotype, perianal disease, smoking, younger age at diagnosis, and delay in biologic therapy[11]. Surgery in patients with CD is not curative but is necessary when medical therapy is unable to achieve symptomatic control. For patients with UC, surgery is curative and indicated for failure of medical management, acute complication including fulminant colitis, perforation, severe bleeding and toxic megacolon, and chronic conditions such as development of dysplasia or malignancy.

While biologics certainly play a major role in the medical treatment of IBD, there is concern about the effects of these anti-TNF-α agents on postoperative complications and morbidity. The purpose of this article is to review the role of surgery in the treatment of IBD in the age of anti-TNF-α agents and the impact of these medications on peri-operative outcomes.

**CROHN’S DISEASE**

***Luminal disease***

Medical treatment for luminal CD focuses on the achievement of composite remission, which is best obtained thorough initiation of combination therapy with anti-TNFα agents (IFX or ADA) and immunomodulators within 18-24 mo of diagnosis in patients with moderate to severe CD. Composite remission is correlated with fewer-hospitalization and CD-related surgeries and better quality of life. In the ACCENT I trial[2] scheduled IFX was associated with a two-fold lower rate of surgery at 54 wk compared with on demand treatment (3% *vs* 7.5% respectively, *P* = 0.01). In the CHARM trial[5] the rate of surgery at one year was 9 times lower in the group treated with ADA than in the placebo group (0.6% *vs* 3.8% respectively, *P* = 0.001).

However, despite improvements in medical management at least 30%-40% of patients with CD require surgery at some point during their lifetime[9,10]. Schnitzler *et al*[12] found that of 614 patients treated with IFX, 24% had required major abdominal surgery at a median follow-up of 4.6 years. Peyrin-Biroulet *et al*[13] followed 296 patients diagnosed with CD and reported that 26% underwent at least one major abdominal surgical procedure at a median follow-up of 57 mo. In addition, among patients treated with ADA as a second line therapy after IFX failure, the rate of surgical intervention was 18% at 130 wk[14]. Given the continued role of surgery and the increasing use of biologic therapy in the management of CD, it is imperative to understand how these treatments influence each other.

***Postoperative complications***

Studies on the effect of biologic agents on postoperative complications have yielded conflicting results[15-29]. Appau *et al*[15] analyzed 389 patients who underwent ileocolonic resection for CD, 60 patients had been treated with IFX within 3 mo of surgery and 329 patients had not. The IFX group appeared to have a higher rate of postoperative sepsis (20% *vs* 5.8%, *P* = 0.021), anastomotic leak (10% *vs* 1.4%, *P* = 0.049) and hospital readmission (20% *vs* 2.9%, *P* = 0.007).

On the contrary, a recent multicenter trial including 6 tertiary referral centers[21] encompassing 298 patients with CD treated with IFX or ADA showed no differences in major or minor complications between patients who received biologics within 2 mo of surgery compared to patients who received biologics more than 2 mo before surgery. The rate of anastomotic leak was similar between the two groups, 7.2% in the biologic group and 8% in the non-biologic group (*P* = 0.976), and they concluded that the use of anti-TNFα agents within 2 mo of surgery for CD with intestinal anastomosis did not increase the risk of anastomotic, infectious, or other complications. Canedo *et al*[17] studied 225 CD patients who underwent surgery and divided them into 3 categories based on exposure to IBD medications within 90 d of surgery: infliximab (IFX), other drugs including steroids and/or immunosuppressive agents (OD), and no drugs (ND). Ileocolonic resection was the most common procedure followed by total colectomy and proctectomy. Laparoscopy was performed in 47.7%, 45.9% and 29.3% of patients in the IFX, OD and ND groups respectively (*P* = 0.04). There was no statistically significant difference in the incidence of intra-operative complications or length of hospital stay in the three groups. In addition rates of postoperative pneumonia (*P* = 0.14), wound infection (*P* = 0.35) and abscess (*P* = 0.34) were similar between the three groups. Anastomotic leak was reported in 5.7%, 6.66% and 2.43% of patients respectively for the IFX, OD and ND groups (*P* = 0.39).

Kasparek *et al*[22] recently analyzed their experience in 96 patients with CD of which 48 patients had received IFX within 3 mo of a Crohn’s related abdominal surgery, with a median of 60 d (range 1-90 d) between the last infliximab dose and surgery and compared them to a control group who had undergone abdominal surgery for CD without prior IFX treatment. They evaluated minor complications, including wound infections, urinary tract infections and paralytic ileus, and major complications such as anastomotic leak, intra-abdominal abscess, postoperative hemorrhage, small bowel enterocutaneous fistula, and death. There was a trend toward a greater rate of anastomotic leaks and intra-abdominal abscesses in the control group (13% *vs* 4% *P* = 0.27), but it did not reach statistical significance. Analysis of the interval between the last administered dose of infliximab and surgery demonstrated no difference in complication rates. They recommended scheduling elective surgery halfway between infusions, 4 wk after infliximab infusion assuming an 8-wk interval for maintenance therapy, and re-initiating IFX 4 wk post-operatively in the absence of complications.

We recently published our experience[29] of 518 IBD patients, 143 treated with IFX within 12 wk of surgery (IFX group) and affected by CD (63), UC (71) and indeterminate colitis (8), and 376 not treated with biologics (NIFX group). Total abdominal colectomy followed by proctocolectomy and ileocolonic resection was the most frequent operations performed and all procedures were done laparoscopically. Operative time and blood loss were similar between the 2 groups (*P* = 0.50 and *P* = 0.34 respectively). In addition the incidence of infectious complications (12% *vs* 11.2%, *P* = 0.92), anastomotic leak (5.2% *vs* 2.9% *P* = 0.69), and thrombotic complications (3.5% *vs* 5.6% *P* = 0.46) was not statistically different between the IFX and NIFX groups. Subgroup analysis confirmed similar rates of overall, thromboembolic, anastomotic, and infections complications regardless of whether the patients had CD or UC.

With the emerging trend toward initiating biologic therapy early in the course of disease and a resultant increase in the proportion of patients on these agents pre-operatively, there has been increased debate regarding not only whether anti-TNFα therapy needs to be discontinued prior to elective surgery but if so what the minimum interval should be between the last dose of the biologic agent and the surgery. Depending on individual metabolism, the half-life of IFX is 7-18 d[28] and serum antibodies disappear at 3 mo.

In a series of 195 patients with IBD Waterman *et al*[19] compared postoperative complications and infections between patients exposed to biologics (IFX or ADA) within 14 d, 15-31 d, and 31-180 d before surgery. Most of these patients receive concomitant thiopurine (double therapy) or thiopurine and corticosteroids (triple therapy). They found that biologic therapy alone was not associated with an increased rate of 30-d postoperative infectious complications, hospital stay, readmission, reoperation or anastomotic leak. However, combination therapy with thiopurine and biologics increased rates of postoperative complications including UTI, wound infection, bacteremia and the need for postoperative antibiotics. In addition, a shorter interval between the last dose of anti-TNFα therapy and surgery did not increase postoperative complications. They concluded that it is not necessary to delay surgery until anti-TNFα washout has been achieved. Several other recent trials have been demonstrated no correlation between overall postoperative infections or anastomotic leaks and the interval (ranging from 1-12 wk) between last IFX administration and surgery[17,21,22,29].

***Postoperative recurrence***

Several factors are related to recurrence: smoking, the NOD2/CARD15 gene mutation, young age at diagnosis, short duration of disease prior to an operation and multiple sites of disease[11,30-34]. Rate of recurrence may also to be influenced also by surgical technique[30,34] including the type of anastomosis, resection margin and the decision to perform a stricturoplasty *vs* a resection[35]. The role of biologic therapy in reducing the incidence of surgical recurrence is yet unknown but we can infer the impact that anti-TNFα agents may have based on mucosal healing. Early observational studies have demonstrated reduced rates in endoscopic and clinical recurrence in patients post-operatively treated with IFX[36], Regueiro *et al*[37] demonstrated in a placebo-controlled randomized trial that endoscopic recurrence was significantly lower in the IFX group compared to controls at 1 year (9.1% *vs* 84.6%, *P* = 0.0006) but the sample size was too small to detect differences in clinical recurrence. Yoshida et38 al also conducted a randomized control trial comparing IFX to placebo and found the clinical remission rate with IFX was 100% *vs* 68% in the placebo group (*P* < 0.03) at one year[38].

Recently Savarino *et al*[39] published the results of a prospective randomized study in which 51 patients with CD who had undergone an ileocolonic resection were assigned to receive ADA at a dose of 160/80/40 mg every two weeks, azathioprine (AZA) at 2 mg/kg per day, or mesalamine at 3 g/d starting 2 wk after surgery. Patients were followed for 2 years. The rate of endoscopic recurrence was lower in the ADA group (6.3%) compared with both the AZA (64.7%; OR = 0.036; 95%CI: 0.004-0.347) and mesalamine groups (83.3%; OR = 0.013; 95%CI: 0.001-0.143). In addition patients in ADA arm had a lower rate of clinical recurrence (12.5%) compared with the AZA (64.7%; OR = 0.078; 95%CI: 0.013-0.464) and mesalamine groups (50%; OR = 0.143; 95%CI: 0.025-0.819).

The role of infliximab in preventing relapse of Crohn’s disease after surgical resection is currently being evaluated in the multicentric randomized prevent trial[40,41]. In this study, patients are post-operative assigned to receive either IFX or placebo. Patients in both groups are treated according to their treatment arm at week 0 and then every 8 wk through week 200. However if a patient initially randomized to the placebo group relapses, IFX therapy may be initiated. Data collection for this trial has been completed and the results are being awaited.

***Perianal disease***

Perianal Crohn’s disease (PCD) is considered an aggressive and disabling phenotype, which manifests in about 40% of patients diagnosed with CD. Quality of life is often compromised due to anal pain, discharge and fecal incontinence[41]. Before the introduction of biologics, 40% of patients with PCD underwent proctectomy. Recently anti-TNF-α agents have been demonstrated to induce and maintain perianal fistula closure in two randomized control trials[42,43].

Perianal fistulas may be classified as simple if a single, low, transphincteric tract without abscess, stenosis or inflammation is present, or complex if there is more than one tract, granulomatous inflammation, presence of an abscess or it is rectovaginal[44]. The majority of Crohn’s patients experience complex fistulas during their disease course.

Treatment of perianal fistula requires a multidisciplinary approach between surgery, gastroenterology, and radiology. Initial management begins with assessment of the extent and complexity of disease[45]. Endoscopy evaluates the presence of proctitis, which is predictive of a non-healing fistula tract. Rectal examination under anesthesia (EUA) helps identify and classify fistulas and enables control of the infection through drainage of the abscess and insertion of a seton. MRI is considered the gold standard for imaging of PCD with higher specificity compared to transrectal ultrasound. It enables evaluation of the abscess volume and maximum fistula length and can be used to restage and assess response to treatment[46].

Once the extent and nature of the PCD is characterized combination treatment consisting of surgical and medical therapy (TNFα with or without immunomodulator) results in improved rates of fistula healing compared with surgery or medical therapy alone[46-50]. Depending on the study, the endpoint may be fistula healing, usually defined as absence of fistula or drainage by medical examination, or clinical improvement, defined as reduction of symptoms or drainage.

Initially, the role of surgery is to control sepsis and define the anatomy of the fistula track after which definitive treatment can be planned. Surgical options for the treatment of perirectal abscesses or fistulas in patients with CD favor conservative approaches including incision and drainage and placement of non-cutting setons. Non-cutting setons preserve the integrity of the anal sphincter, drain fistula tracts and limit abscess formation and recurrences[45]. More aggressive procedures including fistulotomy or advancement flap may be appropriate in certain circumstances but are generally avoided because they are associated with increased morbidity and risk of fecal incontinence.

According to recent literature the most effective approach for PCD consists of seton placement prior to starting medical treatment with anti-TNFα agents or anti-TNFαagents plus thiopurine[50-53]. El-Gazzaz *et al*[50] showed complete healing in 36.6% of patients treated with biologic agents plus surgery *vs* 26.5% for patients treated with surgery alone with a median follow-up of over 3 years but this was not statistically significant (*P* = 0.1). Bouguen *et al*[51] reported a study of 156 patients with PCD treated with IFX. Sixty-two percent of patients also underwent seton placement and 56% were on concomitant immunomodulators. At a median follow-up of 57 mo, 46% of total patients and 69% of patients treated with IFX and seton placement for a median of 8 mo had sustained complete fistula closure. Haenning *et al*[52] reported data on 81 IBD patients with perianal fistula, 62 (80.5%) underwent drainage with loose seton plus IFX therapy and 73 (90%) received treatment with immunomodulators (either Azathioprine or Methotrexate) in addition to anti-TNFα. At a median follow-up of 64 mo fistula closure was achieved in 75% of patients.

The need and timing of seton removal and the appropriate duration of anti-TNF therapy remain debated topics[53]. Bouguen *et al*[51] found improved outcomes when the seton was removed within 34 wk of starting biologic therapy. Haenning *et al*[52] hypothesize that the optimal time for seton removal should be determined by the surgeon based on clinical characteristics and recommend that it be left in situ between 2 and 8.5 mo. Most series evaluate the status of the fistula by clinical examination, however there is increasing data that MRI may be the more accurate instrument to guide decisions regarding timing of seton removal. MRI often shows residual inflammation and disease activity even when the external tract is closed, which is the basis for recurrence[45,46]. In terms of how long biologic therapy should be maintained, no consensus can be found in literature but there is a suggestion that long-term anti-TNFα therapy is associated with better long-term results.

**ULCERATIVE COLITIS**

Anti-TNFα agents are approved to treat moderate to severe ulcerative colitis (UC) as second line treatment in patients refractory to corticosteroids and immunomodulators[54-56]. Infliximab was approved for UC refractory to standard medications in 2006[7], adalimumab was approved in 2012[57,58] and recently, golimumab received approval in Europe and the United States[59,60].

A recent meta-analysis[8] demonstrated that anti-TNFα therapy is more effective than placebo in reducing UC-related hospitalizations. The study analyzed results of IFX[54], ADA[55,56] and golimumab[7,57] trials and found that IFX and ADA achieve long-term mucosal healing at 52-54 wk in 35.6% of patients compare to 16.8% in the placebo group. In addition IFX and ADA were able to reduce UC-related hospitalizations[61-64] and IFX alone was superior to placebo in reducing the need for colectomy.

***Postoperative complications***

Unlike CD, in UC a proctocolectomy is curative and removes the risk of developing colorectal cancer. In the era of conservative management, the timing of surgery *vs* medical therapy with biologics or other medications is challenging[65]. A colectomy for UC may be done as an emergent/urgent or elective procedure depending on the clinical scenario. An emergent/urgent colectomy is indicated for significant hemorrhage, perforation, megacolon, and severe colitis refractory to medical management. Elective colectomies may be performed in patients with UC that experience chronic symptoms refractory to medical therapy, those who can’t tolerate the adverse effects of medication[66] and patients with high-grade dysplasia, multifocal low-grade dysplasia or cancer[53]. There is increasing evidence that in current practice the threshold for surgery is too high and that it is important to consider surgery an alternative therapy rather than a failure of medical therapy[65,67,68]. Roberts *et al*[67] compared 3 year mortality for patients who had urgent or elective surgery *vs* medical management in over 28,000 patients hospitalized with UC. The elective colectomy group had the lowest mortality rate (3.7%), while the medical management and urgent colectomy groups had similar mortality rates (13.6% and 13.2% respectively, *P* = 0.001).

In terms of the postoperative effects of anti-TNF therapy on surgery in UC patients, studies of infliximab have shown differing results[20,29,69-76]. The Cleveland Clinic group reported that patients undergoing restorative proctocolectomy with ileoanal pouch anastomosis (IPAA) who were treated pre-operatively with IFX had a 3.54 times greater risk of developing early complications (*P* = 0.004), with the rate of sepsis increased by 13.8 fold (*P* = 0.011), even though the majority of cases were done in 3 stages[72]. However, Gainsbury *et al*[69] demonstrated that preoperative IFX use was not associated with an increased risk of short-term postoperative complications after IPAA performed in 2 or 3 stages. They evaluated 81 patients, 29 treated with IFX within 12 wk of surgery and 52 not exposed to IFX. Overall short-term postoperative complications were similar between the IFX and non-IFX groups (44.8% *vs* 44.2%, *P* = 0.960). Infections complications, defined as pelvic/intra-abdominal abscess or wound infection, were similar between the IFX and non-IFX groups (17.2% *vs* 26.9%, *P* = 0.32). In multivariate analysis the risk of wound infection while correlated with a higher BMI (ORT 0.88, CI 0.78-0.9, *P* = 0.049) was not related with biologic treatment. Similar results were found by Ferrante *et al*[70] who analyzed 119 patients undergoing restorative proctocolectomy with IPAA in 1 or 2 stages with 22 of the patients having received IFX 12 wk before surgery. Short-term post-operative complications were not significantly different between the two groups. The two predictors of short-term postoperative complications were use of moderate to high dose corticosteroids (> 20 mg of methylprednisolone for > 2 mo) and absence of a diverting ileostomy.

A recent meta-analysis[73] of 5 studies including 132 patients on IFX who underwent a restorative proctocolectomy with IPAA in either 2 or 3 stages demonstrated an increase in total postoperative complications (OR 1.80, 95% CI 1.12 - 2.87), but not short-term infectious complications (OR 2.24, 95% CI 0.63 - 7.95) or non-infectious complications (OR 0.85, 95% CI 0.50 to 1.45) in the IFX group.

In our experience[29], we found no correlations between exposure to IFX within 12 wk of surgery and the rate of postoperative adverse events in 237 UC patients (71 in the IFX group and 166 in non-IFX group). The majority of patients in our study underwent a three stage restorative proctocolectomy with IPAA with only 15 (10.6%) patients in the IFX group and 37(9.8%) patients in the NIFX group undergoing a two stage procedure (*P* = 0.94).

Higher levels of infliximab are associated with increased rates of remission and improved endoscopic outcomes but there is concern that it may be correlated with postoperative complications as well. Waterman *et al*[19] analyzed 108 IBD patients who underwent a colectomy (94/108 for UC), 51 patients had received biologics before surgery and 57 patients had not and they found that preoperative biological therapy was not associated with increased rates of infectious complications or poor wound healing. Preoperative serum levels of IFX were measured within 2 mo of surgery using a microplate ELISA with a cut-off value of 1.4 μg/mL for detectable levels and the association between serum infliximab levels and short-term complications was assessed in 19 patients with UC. Of those 19 patients, 10 had detectable levels of IFX and 9 were undetectable. As expected, the group with detectable levels had a shorter time interval between the last dose of IFX and surgery (median 18 d *vs* 34 d, *P* = 0.03) and while the rate of wound infection trended higher in the detectable group, this was not statistically significant (3/10 *vs* 0/9 respectively, *P* = 0.21); there was no difference in the rates of any other complications. A limitation of the study is that the sample size was quite small and data from larger populations is needed to draw more definitive conclusions.

In a recent study published by Lau *et al*[25] anti-TNFα levels were measured in 217 IBD patients treated with biologic therapy prior to surgery. An anti-TNFα value of ≥ 0.98 μg/mL was considered a detectable level even though a cutoff of ≥ 3μg/mL is usually used for clinical efficacy. Patients were stratified into: low (0.98-3 μg/mL), medium (≥ 3 μg/mL ≤ 8 μg/mL), and high (≥ 8 μg/mL) level groups. Ninety-four of the 217 patients were diagnosed with UC of which 42 patients had a three stage and 52 had a two stage restorative proctocolectomy with IPAA. The infectious complication rate between the undetectable and detectable serum anti-TNFα drug level groups was not significantly different (9% *vs* 12%, *P* = 0.78). The rates of overall postoperative morbidity (40% *vs* 47%, *P* = 0.59) and hospital readmission (19% *vs* 24%, *P* = 0.67) also did not differ. They concluded that even detectable levels of anti-TNFα agents were not associated with adverse outcomes postoperatively.

**CONCLUSION**

Anti-TNFα therapy for the treatment of IBD has improved long-term outcomes including symptom management, mucosal healing, and endoscopic recurrence and is being used earlier in the course of the disease and with increased frequency. However, surgery continues to be an important part of the management of both UC and CD. While the data is mixed, increasing evidence is emerging that surgery can safely be performed while patients are undergoing biologic therapy. More data is needed on the impact that anti-TNFα agents will have on the rates of surgical recurrence in CD.

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