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Use of Infliximab within 3 Months of Ileocolonic Resection is Associated with Adverse Postoperative Outcomes in Crohn's Patients

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Abstract
Background Few studies have evaluated preoperative infliximab use and postoperative outcomes in Crohn's patients. Our aim was to evaluate 30-day postoperative outcomes for Crohn's patients treated with infliximab within 3 months prior to ileocolonic resection.
Methods The study is a retrospective evaluation of data for patients undergoing ileocolonic resection after 1998 from a prospective Crohn's disease database. Patient characteristics and 30-day complications were compared for patients treated with infliximab within 3 months before surgery and an infliximab naïve group. The infliximab group was also compared with non-infliximab patients undergoing ileocolonic surgery before 1998.
Results Sixty of 389 Crohn's patients undergoing ileocolonic resection received infliximab. The infliximab and non-infliximab groups had similar characteristics, preoperative risk factors, and surgical procedure. However, steroid use was higher ($p<0.05$) in the non-infliximab group while concurrent immunosuppressive use was higher ($p<0.001$) in the infliximab group. Multivariate analysis showed infliximab use to be associated with 30-day postoperative readmission ($p=0.045$), sepsis ($p=0.027$), and intraabdominal abscess ($p=0.005$). The presence of diverting stoma ($n=17$) in the infliximab group was associated with lower risk of sepsis (0% vs. 27.9%, $p=0.013$). Similar results were noted when the infliximab group was compared to the pre-infliximab patients.
Conclusions Infliximab use within 3 months before surgery is associated with increased postoperative sepsis, abscess, and readmissions in Crohn's patients. Diverting stoma may protect against these complications.

Keywords Infliximab · Crohn's disease · Ileocolonic resection · Postoperative complications · Abscess · Sepsis · Anastomotic leak · Readmissions

Introduction

Various strategies have been adopted in an effort to treat exacerbations, maintain remission, and prevent or postpone surgery in Crohn's disease (CD) patients. Before 1998, this consisted of 5-ASA compounds,[1,2] steroids,[3,4] and immunosuppressants.[3–5] Failure of medical treatment, toxicity of medication, or steroid dependence prompted surgical intervention,[3–5] although surgery is associated with multiple advantages including relief of symptoms, improvement in quality of life, and withdrawal of potentially toxic medication.[6,7] Potential disadvantages of surgery also exist,[6–9] which have spurred the ongoing search for agents that could avoid surgery and maintain remission.

The demonstration of significant clinical response of CD patients to infliximab (IFX)[10,11] has changed clinical practice since 1998 with its use in patients unresponsive to other medications. IFX use has been shown to improve quality of life, maintain disease remission, facilitate discontinuation of

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steroids and immunosuppressive drugs, and avoid surgery.[12,13] Concerns regarding the potential harm of the medication in terms of septic perioperative outcomes for patients on IFX requiring surgery remain. Some studies report that IFX is associated with significant adverse outcomes such as severe infections, sepsis, abscess, cancer, infusion reactions, neurological complications, and death.[14,15] There is a paucity of data on perioperative outcomes for CD patients on IFX undergoing surgery. Two previous studies[22,23] reported outcomes in a small heterogeneous group of patients on the medication at variable time intervals before and after surgery. Since the complexity of surgery in CD patients may be variable and may, in itself, influence outcomes, we evaluated 30-day perioperative outcomes for CD patients who received IFX at any time within 3 months prior to undergoing ileocolonic resection. We hypothesized that by using a larger sample size and standardizing the timing of medication use and surgical procedure, any difference in postoperative outcomes for CD patients treated with IFX and an IFX naive group could be better determined. The aim of this study was to investigate outcomes for contemporary and historical cohorts of CD patients who underwent ileocolonic resection to see if use of IFX 3 months before ileocolonic resection may be associated with increased adverse postsurgical outcomes.

Methods

Patients

All patients undergoing surgery in the department of colorectal surgery at the Cleveland Clinic are currently accrued into an institution review board approved Crohn's disease database. Patient-related data pertaining to demographics, smoking history, ASA class, and indication of surgery; disease-related factors such as severity of disease, perioperative type, and dose of medication; and operative data such as type and extent of procedure performed and postoperative complications are prospectively maintained. From this database, data of all contemporary and historical cohort patients undergoing ileocolonic resection before and after 1998 were identified. One hundred and thirty-three patients who underwent ileocolonic resection from 1998 to 2007 had taken IFX. Of these, 24 had been administered IFX more than 3 months before surgery, 49 at some point after surgery, and 60 within 3 months before undergoing ileocolonic resection (IFX group). None of the patients who had taken IFX within 3 months of ileocolonic resection were treated with other types of antitumor necrosis factor. Medication use was verified with the pharmacy department at the Cleveland Clinic Foundation. Charts were reviewed, and all patients who took IFX contacted over the telephone to confirm the last dose of IFX infusion before ileocolonic resection. When patients could not recall the last date of their IFX infusion, the facilities where they received the medication were contacted for this information.

The 60 IFX patients were compared with 329 contemporary cohort patients undergoing ileocolonic resection who had never received IFX (non-IFX group). Differences between groups in relation to 30-day complications were evaluated. Since IFX has been used sometimes successfully for some patients in whom surgery was otherwise felt to be inevitable, patients treated with IFX may be expected to be sicker than those not on IFX. Thus, any potential adverse effects detected in the IFX patients undergoing surgery may be related to the fact that they are sicker rather than due to IFX. We, hence, chose to include a comparative group of patients in the pre-IFX era who underwent surgery since such patients may be expected to more accurately represent a comparative group with similar patients characteristics as might be expected if IFX were unavailable and, hence, not used. This group of 69 patients, who constituted a historical cohort (pre-IFX group), had undergone ileocolonic resection before IFX was approved in 1998.

Inclusion and Exclusion Criteria

Patients who had their first ileocolonic resection performed at outside institutions were excluded. Other exclusions included those with ulcerative colitis, indeterminate colitis, and other underlying immunodeficiency unrelated to their CD; when the last dose of IFX was longer than 3 months before surgery; if patients never took IFX until after surgery; and if they had perianal CD. Patients with a prior stoma for other reasons before their first ileocolonic resection for CD were also excluded. All patients included had ileocolonic CD confirmed endoscopically and/or radiographically.

Diagnostic Criteria

Demographics, comorbidity, and other patient characteristics were reviewed (Table 1). Diagnosis of CD was made clinically, endoscopically, and, where appropriate, radiographically. Failure of medical therapy was the most common indication for surgery—this consisted of persistent symptoms despite being on appropriate therapy for an appropriate length of time.

Surgical Procedure

The surgical procedure involved resecting part of the distal ileum and part of the proximal colon for ileocolonic CD and then anastomosing the ileum to the proximal colon to create an ileocolonic anastomosis. Loop stomas involved

Table 1 Patient Characteristics

	Non-IFX group (998–2007) n=329		IFX group (1998–2007) N=60	Pre-IFX group (1991 to 1997) N=69	p-Value
Gender (F)	178 (54.1%)		31 (51.7%)	33 (47.8%)	0.73[a] 0.66[b]
Age	36.84±14.37		35.83±11.90	37.96±12.49	0.92[a] 0.38[b]
Comorbidity	DM	5 (1.5%)	0 (0%)	0 (0%)	0.99[a]
	Cardiac	4 (1.2%)	3 (5.0%)	0 (0%)	0.8[a] 0.1[b]
	Renal	0%	0%	1 (1.4%)	0.99[b]
	HTN	18 (5.5%)	6 (10.0%)	9 (13.0%)	0.24[a] 0.59[b]
	Lung	5 (1.5%)	2 (3.3%)	2 (2.9%)	0.30[a] 0.99[b]
ASA Class	2	2	2		
Never smoked	141 (49.5%)	26 (48.1%)	33 (50.8%)	0.80* 0.78†	
Smoked	143 (50.2%)	28 (51.9%)	32 (49.2%)	0.80* 0.78†	

[a] p: Non-IFX vs. IFX
[b] p: Pre-IFX vs. IFX

the creation of a diverting stoma above the ileocolonic anastomosis with intention to close the stoma in the near future.

Definition of Variables

Intraabdominal sepsis was defined as the presence of abdominal complaints, fever, elevated white blood cell count, with a finding on imaging studies of an intra-abdominal fluid collection with or without anastomotic leak. Anastomotic leak was defined as patients with similar clinical presentations as those with intraabdominal sepsis which were found to have intraabdominal fluid collection and a true anastomotic leak that resulted in a surgical management of the leak. Patients with intraabdominal abscess clinically presented similarly and were found to have intraabdominal abscess that resulted in surgical or computed tomography-guided drainage of the abscess. Patients receiving 5-ASA derivatives, steroids, and immunosuppressives within 3 months of ileocolonic resection were considered to be on this therapy.

Outcome Measurement

Outcomes evaluated included 30-day mortality, wound infection, wound complications, anastomotic leak, sepsis, intraabdominal abscess, and readmissions rate.

Statistical Analysis

Fisher's exact test and Kaplan–Meier estimation with log rank tests were performed to assess differences in proportions between groups. Multivariable Cox models were used to assess the association between IFX use and each of 30-day outcomes (readmission, sepsis, and intra-abdominal abscess), adjusting for age, gender, comorbidities, penetrating abscess before surgery, diverting stoma, disease phenotypes, narcotics use, 6-mercaptopurine, azathioprine, and methotrexate. Odds ratios of the outcome with 95% confidence intervals were estimated for each variable in a multivariable model using R version 2.3.1 statistical program.

Results

Sixty of 389 CD patients undergoing ileocolonic resection received IXF (non-IFX—329). IFX and non-IFX groups had comparable patient characteristics (Table 1), disease behavior (Table 2), and operative procedure performed (Table 3). Table 4 gives the comparison of the perioperative medications used in the group.

Differences in Medication Use

As noted in Table 4, immunosuppressive use was higher in the IFX group (61.7%) compared with the non-IFX group (16.7%; p=0.001). However, steroid use was higher in the non-IFX group (76.9%) than the IFX group (65.0%; p= 0.05). When the IFX was compared with the pre-IFX group, immunosuppressive use was again higher in the IFX group (61.7%) compared with the pre-IFX 7.2% (p=0.001), while steroid use was higher in the pre-IFX group (80%; p=0.06). The 5-ASA use was similar between the groups.

Intraoperative and Postoperative Outcomes in IFX and non-IFX

Intraoperative complications, intraoperative, and postoperative transfusion use was similar between the groups.

Table 2 Disease Characteristics

	Non-IFX group (1998–2007) n=329	IFX group n=60	Pre-IFX group (1991 to 1997) n=69	p-Value
Nonstricturing/nonpenetrating Crohns	115 (48.7%)	16 (43.2%)	22 (44.9%)	0.68[a] 0.17[b]
Stricturing Crohns	66 (28.0%)	10 (27.0%)	20 (40.8%)	0.68[a] 0.17[b]
Penetrating Crohns	55 (23.3%)	11 (29.7%)	7 (14.3%)	0.68[a] 0.17[b]
Fibrostenosing Crohns	214 (65.0%)	36 (60.0%)	44 (63.8%)	0.45[a] 0.66[b]
Inflammatory	8 (2.4%)	0 (0%)	0 (0%)	0.61[a]
Abscess before or at surgery	144 (43.8%)	23 (38.3%)	22 (31.9%)	0.43[a] 0.44[b]

[a] p: Non-IFX vs. IFX
[b] p: Pre-IFX vs. IFX

Postoperative ileus, cardiopulmonary, neurological, and renal complications were also similar. Outcomes that were different on univariate analysis are as in Table 5. Although the non-IFX group had increased use of preoperative steroids, adverse postsurgical outcomes appeared to be lower in this group when compared with the IFX group. Using Cox multivariate analysis to adjust for differences in medication use, age, gender, comorbidity, disease phenotypes, and the presence of an abscess before or at surgery, the IFX group still appeared to have an increased risk of 30-day postoperative readmission (OR—2.33 [1.02–5.33], p=0.045, Table 6), sepsis(OR—2.62 [1.12–6.13], p=0.027, Table 7), and intraabdominal abscess (OR—5.78 [1.69–19.7], p=0.005, Table 8).

Presence of Diverting Stoma and Differences in Postoperative Adverse Outcome

IFX patients who had stoma (n=17) above their anastomosis had a lower incidence of sepsis when compared with those without a stoma (sepsis 0% vs. 27.9%, p=0.013). A slightly decreased rate of postoperative sepsis was also noted in the non-IFX group who had a stoma above their anastomosis (10.4% vs. 6.8%) though this was not statistically significant (p=0.40).

Comparison of Postoperative Outcomes between IFX and Pre-IFX Groups

When comparing the IFX group to the non-IFX group before 1998 (pre-IFX era), despite similar preoperative and perioperative factors, the IFX group still appeared to have higher postoperative sepsis (20 vs. 5.8%, p=0.021), anastomotic leak (10% vs. 1.4%, p=0.049), and readmission rate (20% vs. 2.9%, p=0.007). Because there were only five patients who had diverting stoma in the pre-IFX group, statistical analysis could not be performed to determine whether or not a stoma above anastomosis made any difference in adverse outcomes among this group.

Timing of IFX Use

Evaluation of postoperative outcomes for a subset of patients who received IFX within 2 months of surgery did not reveal any difference when compared with those who

Table 3 Characteristics at Operation

	Non-IFX group (1 998–2007) n=329	IFX group n=60	Pre-IFX group (1991 to 1997) n=69	p-Value
Laparoscopic-assisted	95 (28.9%)	18 (30.0%)	13 (18.8%)	0.91[a] 0.35[b]
Open	228 (69.3%)	41 (68.3%)	54 (78.3%)	0.91[a] 0.35[b]
Diverting stoma	60	17	5	
hand sewn	50 (20.9%)	8 (18.6%)	3 (6.2%)	0.69[a] 0.08[b]
Stapled	183 (76.6%)	35 (81.4%)	45 (93.8%)	0.69 0.08[b]

[a] p: Non-IFX VS. IFX
[b] p: Pre-IFX VS. IFX

Table 4 Medication Use before Surgery

	Non-IFX group (1998–2007) n=329	IFX group n=60	Pre-IFX group (1991 to 1997) n=69	p-Value
5-ASA-	196 (59.6%)	36 (60.0%)	35 (50.7%)	0.95[a] 0.29[b]
6MP/AZA/MTX	55 (16.7%)	37 (61.7%)	5 (7.2%)	<0.001[a] <0.001[b]
IFX	0 (0%)	60 (100%)	0 (0%)	<0.001[a] <0.001[b]
Steroids	253 (76.9%)	39 (65.0%)	55 (79.7%)	<0.052[a] 0.06[b]

[a] p: No IFX vs. IFX
[b] p: Pre-IFX vs. IFX

received the medication within 3 months of ileocolonic resection.

Discussion

The decision as to when to proceed with surgery or to persist with medical treatment in patients with CD is often difficult.[16] The need for surgery in patients who develop complications of the disease whilst on medical treatment is self-evident. Traditional strategies revolved around progressing to surgery when medical treatment with 5-ASA derivatives, steroids, and immunosuppression failed.[1,2] The availability of IFX in 1998 has been associated with its use and a decreased need for surgery[10,11] in addition to the long term side effects of IFX,[17] whether its use in patients undergoing surgery leads to adverse outcomes needs further investigation.

A study from the Mayo Clinic reported significant adverse outcomes associated with the use of IFX in ulcerative colitis (UC) patients undergoing ileal pouch-anal anastomosis (IPAA) procedures.[18] We found similar results in UC patients on IFX after IPAA.[19] The few studies investigating postsurgical outcomes in CD patients treated with IFX have not revealed any significant adverse outcomes in the IFX-treated and IFX-naïve groups[20,21]. These studies, however, included mixed groups of patients undergoing various procedures who received IFX at various periods before and after surgery. Colombel et al.[20] reported post operative outcomes for 52 CD patients treated with IFX who underwent abdominal operations. Patients who underwent a variety of procedures and some who received IFX 8 weeks before and 4 weeks after surgery were included. Marchal et al.[21] evaluated outcomes in 40 CD patients who received treatment with IFX within 12 weeks before surgery. This study was limited by small sample size, lack of standardi-

Table 5 Post Operative Outcomes

	Complication	Non IFX group (1998–2007) n=329 (%)	IFX group n=60 (%)	Pre-IFX group (1991 to 1997) n=69 (%)	Odd's ratio (95%CI)	p-Value
30-Day complications	Urinary complications	0	1.7	0.0		0.15[a] 0.47[b]
	Wound dehiscence	0.30	0.0	1.4		1.0[a] 1.0[b]
	30-Day mortality	0	1.7	0.0		1.0[a] 1.0[b]
30-Day complications	Readmission rate	9.4	20.0	2.9	2.40(1.15,5)* 8.37(1.79,39.15)†	0.019[a] 0.007[b]
	Sepsis	9.7	20.0	5.8	2.32(1.12, 4.82)* 4.06(1.23,13.37)†	0.024[a] 0.021[b]
	Intraabdominal abscess	4.3	10.0	4.3	2.50(0.92, 6.79)* 2.44(0.58,10.23)†	0.10[a] 0.30[b]
	Anastomotic leak	4.3	10.0	1.4		0.09[a] 0.049[b]
	Reoperation	3.0	8.3	0.0	2.9(0.95,8.81)*	0.06[a] 0.02[b]

[a] p: No IFX vs. IFX
[b] p: Pre-IFX vs. IFX

zation of surgical procedures, and the potential confounding effect of multiple operations.

Since patients with CD may have varying complexity of surgery, we chose to standardize the surgical procedure performed. Only patients undergoing ileocolonic resection with anastomosis (ICRA) were selected. In particular, those requiring additional procedures such as stricturoplasty, small bowel, or colonic resections were excluded. Since patients who underwent previous surgery may need more complex surgery, we excluded patients who had previously undergone surgery prior to ICRA. Although the half life of IFX is 10 days,[22] a previous study suggested that the use of IFX within 2 months prior to surgery may influence outcomes.[18] Since it is not clearly known whether the effect of IFX persists for a longer period, we chose to look at outcomes for CD patients treated with IFX within 3 months before surgery. We found that the use of IFX within 3 months before ileocolonic resection in CD patients appears to be associated with adverse outcomes such as 30-day postoperative intraabdominal sepsis, intraabdominal abscess, anastomotic leak, and readmission. Considering the function of TNF-alpha as a potent inflammatory mediator, one would expect that if this compound is blocked, there could be a potential risk for increased infection as shown in multiple studies.[23,24] Therefore, our finding of an increased incidence of sepsis and abscess after surgery is not surprising. It is also conceivable that the immunosuppressive effects of IFX may last well beyond the time when IFX is cleared from the body. A subgroup analysis of our data showed that there was no difference in the rate of complications for patients receiving IFX 2 and 3 months prior to ileocolonic resection.

In this study, we also found that having a stoma above an anastomosis appears to be associated with less postoperative infectious adverse outcomes. The presence of a defunctioning stoma has previously been demonstrated to reduce septic complications from anastomotic leak in other studies.[25] For those who did not have stoma above their anastomosis, perhaps some of these patients could not mount inflammation strong enough to control the infection due to blunted TNF alpha effect by IFX,[26–28] and ultimately, some of these patients proceeded to develop intraabdominal abscess, sepsis, and anastomosis leak.

Our study has some limitations. Firstly, the study is a retrospective review of data of a historical cohort. Subsequently, the results obtained may be overestimated or underestimated. Secondly, while our sample size for the IFX group is larger than published data, the sample size of 60 patients is still low; thus, differences in postsurgical outcomes that we found in this study might be further underestimated. Patients who were administered IFX more than 3 months before surgery and those who took IFX after surgery were also excluded; thus, the effect of IFX in these subsets of patients could not be ascertained. Furthermore, there was not enough sample size for the pre-IFX group to see if having stoma made a difference in postoperative outcome among this group.

In conclusion, use of IFX 3 months before ileocolonic resection appears to be associated with an increased risk of 30-day postoperative intraabdominal abscess, sepsis, anastomotic leak, and readmission rate. However, presence of stoma above the anastomosis appears to be associated with a decrease in these risks. A prospective study investigating IFX use 3 months before ileocolonic resection and anastomosis (with and without stoma) and postoperative outcome may help provide further crucial data in CD patients undergoing surgical procedures.

Table 7 Multivariable Logistic Regression Model Results for 30-day Sepsis

Variable	Odds ratio(95% CI)	*p*-Value
IFX	2.62 (1.12–6.13)	0.027
6MP/AZA/MTX	1.40 (0.66–2.98)	0.38
Steroids	1.10 (0.50–2.42)	0.81
Comorbidity	0.37 (0.08–1.67)	0.20
Penetrating abscess	1.71 (0.89–3.30)	0.11
Diverting stoma	0.28 (0.09–0.83)	0.021

Parameter estimate and odds ratio relative to a 5-year difference.

Table 6 Multivariable Logistic Regression Model Results for 30-day Readmission

Variable	Odds ratio(95% CI)	*p*-Value
IFX	2.33 (1.02–5.33)	0.045
6MP/AZA/MTX	1.14 (0.53–2.46)	0.74
Steroids	0.95 (0.45–2.03)	0.90
Comorbidity	0.98 (0.32–3.01)	0.97
Penetrating abscess	1.22 (0.63–2.35)	0.55
Diverting stoma	0.82 (0.35–1.92)	0.66

Parameter estimate and odds ratio relative to a 5-year difference.

Table 8 Multivariable Logistic Regression Model Results for 30-day Intraabdominal Abscess

Variable	Odds ratio(95% CI)	*p*-Value
IFX	5.78 (1.69–19.7)	0.005
6MP/AZA/MTX	0.41 (0.11–1.52)	0.18
Steroids	2.94 (0.63–13.6)	0.17
Comorbidity	0.30 (0.03–2.73)	0.29
Penetrating abscess	1.40 (0.55–3.57)	0.48
Diverting stoma	0.16 (0.02–1.25)	0.08

Parameter estimate and odds ratio relative to a 5-year difference.

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