



Risk of post-operative complications associated with anti-TNF therapy in inflammatory bowel disease

Tauseef Ali, Laura Yun, David T Rubin

Tauseef Ali, University of Oklahoma Health Sciences Center & VA Medical Center. Section of Digestive Diseases and Nutrition, Oklahoma City, OK 73104, United States

Laura Yun, David T Rubin, University of Chicago, Inflammatory Bowel Disease Center, Chicago, IL 60637, United States

Author contributions: Rubin DT and Ali T conceptualized and planned the study; Ali T and Yun L collected and interpreted the data; all authors contributed to drafting the manuscript; Rubin DT reviewed and edited the final draft and all authors approved the final draft.

Correspondence to: Tauseef Ali, MD, Assistant Professor of Medicine, University of Oklahoma Health Sciences Center, WP 1345, 920 SL Young Blvd, Oklahoma City, OK 73104, United States. tauseef-ali@ouhsc.edu

Telephone: +1-405-2715428 Fax: +1-405-2715803

Received: March 30, 2011 Revised: July 14, 2011

Accepted: July 21, 2011

Published online: January 21, 2012

Abstract

There have been increasing concerns regarding the safety of perioperative anti-tumour necrosis factor (anti-TNF) α agents. We performed a literature review to evaluate the post-operative complications associated with perioperative anti-TNF use in patients with inflammatory bowel disease. A comprehensive review was performed with a literature search utilizing Pub Med, Cochrane, OVID and EMBASE databases according to published guidelines. To date, there are only data for infliximab. There are three published studies which have assessed post-operative complications with perioperative infliximab use in patients with Crohn's disease (CD), four studies in ulcerative colitis (UC) patients, and one study on both CD and UC patients. Two out of the three studies in CD patients showed no increased post-operative complications associated with perioperative infliximab. Two out of four studies in UC patients also did not show an increase in post-operative complications, and the combined study with CD and UC patients did not show an increased risk as well. Study

results could not be combined secondary to significant differences in study designs, patient population and definition of their endpoints. There appears to be a risk of post-operative complications associated with TNF therapy in some patients. Based on these data, careful patient selection and prospective data collection should be performed.

© 2012 Baishideng. All rights reserved.

Key words: Crohn's disease; Ulcerative colitis; Colectomy; Post-operative complications

Peer reviewers: Xiao-Fa Qin, MD, PhD, Department of Surgery, UMDNJ-New Jersey Medical School, 185 South Orange Avenue, Newark, NJ 07103, United States; Jürgen Büning, MD, Internal Medicine I, Department of Gastroenterology, University Hospital of Schleswig-Holstein, Ratzeburger Allee 160, D-23538 Lübeck, Germany

Ali T, Yun L, Rubin DT. Risk of post-operative complications associated with anti-TNF therapy in inflammatory bowel disease. *World J Gastroenterol* 2012; 18(3): 197-204 Available from: URL: <http://www.wjgnet.com/1007-9327/full/v18/i3/197.htm> DOI: <http://dx.doi.org/10.3748/wjg.v18.i3.197>

INTRODUCTION

Therapeutic options for the management of inflammatory bowel disease include aminosalicylates, antibiotics, corticosteroids, antimetabolite immunomodulators (e.g., 6-mercaptopurine, azathioprine and methotrexate), and biologic therapies such as anti-tumour necrosis factor (anti-TNF) agents (e.g., infliximab, adalimumab, certolizumab pegol) and natalizumab^[1-3]. The anti-TNF therapies are associated with adverse events including serious infections. In large controlled clinical trials of infliximab (IFX), the percentage of patients with serious infections ranged from 4.0% to 4.6%, and the mortality rate was 0.7% to 1.3%^[4,5]. IFX-related adverse events, including serious

opportunistic infections such as tuberculosis, listeriosis and histoplasmosis, have also been documented in reports of open-label or retrospective trials^[6-9]. However, the TREAT (Crohn's therapy, resource, evaluation, and assessment tool) Registry, a large-scale, ongoing, observational registry designed to examine the safety of Crohn's disease (CD) therapies, found prednisone use (OR: 2.21, 95% CI: 1.46-3.34, $P < 0.001$), narcotic analgesic use (OR: 2.38, 95% CI: 1.56-3.63, $P < 0.001$), and moderate-to-severe disease activity (OR: 2.11, 95% CI: 1.10-4.05, $P = 0.024$) were significantly associated with serious infections. Although the unadjusted analysis showed an increased risk for infection with IFX use, multivariate logistic regression analysis show that IFX was not an independent predictor of serious infections (OR: 0.99, 95% CI: 0.64-1.54)^[10].

Despite optimal medical therapy, about two-thirds of patients with CD and one-third of those with ulcerative colitis (UC) eventually require surgery for disease control^[11]. Factors increasing the risk of post-operative complications include: preoperative sepsis^[12,13] (such as abdominal abscess or systemic infection), impaired nutritional status and intestinal obstruction^[14-17]. Common early post-operative complications include abdominal wound infection, anastomotic leakage, pelvic sepsis and small bowel obstruction. Late complications include: anastomotic leak with pelvic sepsis or fistula, anastomotic stricture and pouchitis, and ileo-anal pouch dysfunction^[18].

While anti-TNF use has been shown to induce and maintain steroid-free disease remission, improve quality of life and decrease the rate of hospitalizations and surgeries^[4,19], concerns have risen regarding the potential harm of these medications. Most recently attention has also been focused on perioperative outcomes for patients who have received anti-TNF therapy and require surgery. The purpose of this review is to analyze the evidence regarding post-operative complications associated with anti-TNF in patients with inflammatory bowel disease.

LITERATURE SEARCH

Separate literature searches were conducted in the Pub Med, Ovid, EMBASE and Cochrane library databases (1950-2010) in accordance with published recommendations^[20,21]. Databases were used to search English language literature using search terms such as "post-operative complications", "post-operative sepsis" and "surgical outcomes" in combination with words such as "anti-TNF therapy", "infliximab", "adalimumab", "certolizumab pegol", "natalizumab", "inflammatory bowel disease", "Crohn's disease" and "ulcerative colitis". Exploded terms were reviewed and included or excluded as per their relevance. A comprehensive review of the reference lists of all selected articles was also performed. Two investigators separately performed the literature search. Studies with patients having a diagnosis of ulcerative colitis, Crohn's disease and indeterminate colitis who had received anti-TNF therapy prior to surgical intervention

were included. The initial search yielded one hundred and eight articles. Studies published as full articles were included in our systematic review. Only studies involving adult patients (18 years and older) and including control groups were included for the review. Odd ratios were calculated by 2×2 tables where the studies failed to include them, with the help of an online calculating system accessed *via* a website (<http://faculty.vassar.edu/lowry/odds2x2.html>).

No randomized prospective trial was identified. After applying the above mentioned selection criteria, only three retrospective studies assessing IFX associated complications in CD were selected for review^[22-24]. Similarly, four retrospective studies involving patients with UC and infliximab were identified^[25-28]. One additional study that included patients with both UC and CD was also included in the review and discussed separately^[29]. A recently published meta-analysis examining the relationship between IFX and short term complications in patients with UC was also reviewed^[30].

AVAILABLE STUDIES IN LITERATURE

Studies with Crohn's disease

No prospective randomized control trial has been published to determine the post-operative complication risks associated with anti-TNF therapy. Three retrospective studies were identified in the literature addressing risk of post-operative complications with IFX^[22-24]. Individual study characters (including study design, use of concomitant medications use and dosing of IFX in relation to surgery) are presented in Table 1. Study endpoints and various complications assessed in each study are presented in Table 2, and the results of the risks of complications are presented in Table 3.

Marchal *et al*^[22] retrospectively studied a cohort of three hundred and thirteen consecutive patients with CD who received infliximab between 1998 and 2002. A trend towards an increased early infection rate was found in IFX pre-treated patients (6 patients *vs* 1 patient $P = 0.10$), but the authors concluded this was probably due to the increased use of corticosteroids and/or immunosuppressive agents in this group^[22]. However, the limited number of patients suggests the possibility of a type II error.

In a study by Colombel *et al*^[23], a group of investigators identified two hundred and seventy patients who underwent abdominal surgery for CD between 1998 and 2001. This retrospective analysis suggested that perioperative use of IFX use was not associated with an increased risk of post-operative complications. A multiple variable model including both steroid and IFX use was also performed and there was no independent association with either septic or total complications. However, these data were not presented in the published manuscript. Odds ratios were calculated from univariate regression analysis and additional multiple regression analysis was not performed secondary to the limited number of patients.

The investigators of the Appau *et al*^[24] study evaluated

Table 1 Crohn's disease study characteristics

Author study center	Study design	Total patients	Study endpoints	Concomitant medication	Case (%)	Control (%)	P value	IFX dosing	Last dose IFX prior to surgery < 12 wk (%)
Marchal ^[22] , 2004, Belgium	Case-control	79 total, 40 cases, 39 controls	Early (10 d) and late (3 mo) complications	5-ASA	30	54	N.S.	Episodic 100%	78
				6MP/AZA	45	26	N.S.		
				Steroids	73	41	< 0.00017		
				Antibiotics	25	28	N.S.		
Colombel ^[23] , 2004, Mayo Clinic, Rochester	Retrospective	270 total, 52 cases	Early (30 d) septic and non-septic complications	5-ASA	-	-	-	Episodic 80%	96
				6MP/AZA	7	-	-		
				Steroids	7	-	-		
				Antibiotics	-	-	-		
Appau ^[24] , 2008, Cleveland Clinic, Cleveland	Case-control	458 total, 329 Non IFX, 60 IFX, 69 pre IFX	30 d post-operative complications	5-ASA	60	58	0.95	-	100
				6MP/AZA	62	15	< 0.001		
				Steroids	65	77	< 0.052		
				Antibiotics	-	-	-		
Kunitake ^[29] , 2008, Massachusetts General Hospital, Boston (combined study)	Case-control	413 total, 101 cases, 312 control	Post-operative complications	5-ASA	-	-	-	-	100
				6MP/AZA	37	6	0.04		
				Steroids	75.30	77	0.79		
				Antibiotics	-	-	-		

IFX: Infliximab; 5-ASA: 5-aminosalicylic acid; AZA: Azathioprine; 6MP: 6-mercaptopurine; N.S.: Not significant.

Table 2 Complications defined in crohn's disease

Study	Study endpoints	Infectious	Non-infectious	Major	Minor
Marchal ^[22]	Early (10 d) and late (3 mo) complications	Catheter sepsis, wound, upper respiratory, Diarrhea, yeast		Sepsis, leak, peritonitis, abscess, wound failure, severe anemia, bulbar ulcer bleeding	Hematoma, fever, delayed transit, mild infection, intestinal obstruction
Colombel ^[23]	Early (30 d) septic and non septic complications	Wound sepsis, leak, abscess, fistula, sepsis, pneumonia, bacteremia, urosepsis	CD recurrence, small bowel obstruction, GI bleeding, thromboembolism		
Appau ^[24]	30 d post-operative complications	Wound infection, sepsis, intra abdominal abscess, 30 d mortality, readmission rate, anastomotic leak and wound complications			
Kunitake ^[29] (combined study)	Post-operative cumulative complications	Infections, hypomotility, thrombotic, cardiac complications, hepato-renal complications, anastomotic leak, bleeding and death			

CD: Crohn's disease; GI: Gastrointestinal.

Table 3 Post-operative risks of complications with Crohn's disease

Authors	Complications	Cases (%)	Controls (%)	Risks of complications, OR (95% CI)
Marchal ^[22]	Early Minor (10 d)	15	13	1.2 (0.3-4.3)
	Late Minor (3 mo)	2.50	5.10	1.1 (0.3-4.0)
	Early Major (10 d)	12.50	7.70	1.7 (0.3-7.7)
	Late Major (3 mo)	17.50	12.80	1.4 (0.4-5.0)
Colombel ^[23]	Septic	17		0.9 (0.4-1.9)
	Non-septic	23		1.0 (0.5-2.0)
Appau ^[24]	30 d readmission	20	9.4 + 2.9	2.3 (1.0-5.3)
	30 d sepsis	20	9.7 + 5.8	2.6 (1.1-6.1)
	30 d intra-abdominal abscess	10	4.3 + 4.3 (Non IFX + pre IFX group)	5.8 (1.7-19.7)
Kunitake ^[29] (combined study)	Post-operative cumulative complications	16.80	15.70	1.1 (0.6-2.0)

IFX: Infliximab; OR: Odd ratio; CI: Confidence interval.

30 d post-operative outcomes for CD patients treated with IFX (60 patients) within 3 mo *vs* infliximab-naïve patients (329 patients) prior to ileocolonic resection from 1998 to 2007. In an effort to reduce selection bias, the IFX group was also compared with pre-IFX patients (69 patients) undergoing ileocolonic surgery before 1998. Using multivariate analysis, the IFX group appeared to have an increased risk of 30 d post-operative readmission, sepsis, and intra-abdominal abscess. IFX patients who had a stoma ($n = 17$) above their anastomosis had a lower incidence of sepsis when compared with those without a stoma. While the sample size for the IFX group was larger than any published data, the sample size of 60 patients is still low; thus, differences in postsurgical outcomes that were found in this study might be further underestimated.

Studies with ulcerative colitis

There have not been any reported differences in the incidence and type of side effects attributed to IFX in patients with CD *vs* UC in general, but one area that has been getting more attention recently is post-operative complications. Four studies evaluating IFX and post-operative complications in UC patients were identified^[25-28]. Individual study characters, including study design, use of concomitant medications and dosing of IFX in relation to surgery, are presented in Table 4. Study endpoints and various complications assessed in each study are presented in Table 5, and the results of the risks of complications are presented in Table 6.

The primary aim of the Selvasekar *et al.*^[25] study was to assess short-term post-operative infectious complications in UC patients who received preoperative IFX and underwent colectomy with ileal pouch anal anastomosis (IPAA) from 2002-2005. The overall post-operative complications in both groups were similar ($P = 0.1$). This was the first published study addressing post-operative complications and preoperative IFX use in UC. However, this was a single center study with a retrospective design and small sample size. This study was primarily before its approval by the Food and Drug Administration (FDA) in September 2005 and thus it represents off-label use, so ideal dosing was not defined and one might speculate that these were more severely ill patients. Therefore, the use of IFX may simply be a surrogate marker for more severe disease and sicker patients.

The Schluender *et al.*^[26] study was conducted to assess the 30-d post-operative medical and surgical complications of medically refractory UC patients who received preoperative IFX and underwent colectomy (subtotal or total proctocolectomy with IPAA) from October 2000-October 2005. There was a difference in concomitant 6-mercaptopurine (6-MP)/6-thioguanine (6-TG) use, with 94% in the IFX group also on 6-MP/6-TG *vs* 44% in the non-infliximab group ($P = 0.03$). However, that there was no significant difference in medical, surgical or infectious complications in patients receiving both IFX and 6-MP compared to patients receiving 6-MP alone was determined. This study was also limited by its single-

center single surgeon retrospective design, and small sample size of seventeen patients who received IFX, and therefore lacks the statistical power to detect significant differences related to the two groups. Potential confounders, such as disease severity, were not assessed. However, the article highlighted the significantly increased risks of complications, including infectious complications, in patients exposed to cyclosporine and IFX which has also been reported in another study in steroid refractory UC^[31].

The primary aim of a case-matched retrospective study by Mor *et al.*^[27] was to evaluate post-operative complications after restorative proctocolectomy in UC patients who received IFX preoperatively from January 2000-December 2006. Overall, the prevalence of early post-operative complications (35% *vs* 15%, $P = 0.027$) was significantly different, and the difference was mostly due to pelvic sepsis (22% *vs* 2%, $P = 0.016$) in the IFX and non-IFX groups, respectively. On further examination of the patients with pelvic sepsis, an ileo-anal pouch anastomotic leak was identified in eight of ten patients treated with IFX. There was no difference in overall late post-operative complications (52% *vs* 37%, $P = 0.23$), but pouchitis was more common (39% *vs* 15%, $P = 0.037$) in IFX *vs* non-IFX groups, respectively. In addition, the rate of three stage procedures was higher in those treated with IFX preoperatively (OR: 2.07, 95% CI: 1.18-3.63) even when adjusting for extent and severity of colitis, as well as steroid and immunomodulators use. The limitations of this study include its retrospective nature and single-center location. Disease severity was assessed in this study, but the retrospective use of hemoglobin and platelet counts are limited markers for severity assessment. Although the study found an increased rate of pouchitis in patients who had received preoperative IFX, risk factors for pouchitis were not controlled, and the diagnosis was not confirmed by endoscopy and histology. In addition, the finding of more frequent three stage procedures in the IFX group must be taken with caution, as the surgeons were not blinded to IFX use and thus may have influenced their decision.

The Ferrante *et al.*^[28] study evaluated the impact of IFX on post-operative infectious complications in UC or indeterminate colitis patients undergoing restorative proctocolectomy between 1998 and 2008. Short-term post-operative pouch-specific surgical and non-surgical site infectious complications were not significantly different in those who received IFX preoperatively. In multivariate analysis, a moderate-to-high dose of corticosteroids was associated with short-term post-operative pouch-specific complications ($P = 0.001$), surgical site complications ($P = 0.002$) and infectious complications overall ($P = 0.003$). This study, like its predecessors, was a single-center retrospective study with only 22 patients who received IFX within 12 wk of surgery and was too underpowered to detect significant differences between the two groups.

Recently, a meta-analysis was performed by Yang *et al.*^[30] examined the relationship between preoperative IFX treatment and short term post-operative complications in patients with UC. A total of 5 studies and 706 patients

Table 4 Ulcerative colitis study characteristics

Author and study center	Study design	Total patients	Study endpoints	Concomitant medication	Case (%)	Control (%)	P value	IFX dosing	Last dose of IFX prior to surgery < 12 wk
Selvasekar ^[25] , 2007, Mayo Clinic, Rochester	Case-control	301 patients, 47 cases, 254 controls	Post-operative pouch specific and infectious complications	5-ASA	100	60	< 0.0001	Scheduled (majority)	49% (< 8 wk)
				6MP/AZA	91	44	< 0.0001		
				Steroids	47	77	< 0.001		
				Steroids + AZA	70	21	< 0.001		
Schluender ^[26] , 2007, Cedars-Sinai LA	Case-control	151 patients, 17 cases, 134 controls	30 d post-operative surgical and medical complications	5-ASA	-	-	-	2 infusions (median)	Majority (8 wk median)
				6MP/AZA	94	44	0.03		
				Steroids	100	100	1		
Mor ^[27] , 2008, Cleveland Clinic	Case-control	92 patients, 46 cases, 46 controls	Early (30 d) and late post-operative complications	5-ASA	-	-	-	3 infusions (median)	Majority (13.5 wk median)
				6MP/AZA	39	28	0.27		
				Steroids	2 (ranked dose score)				
						2.24	0.42		
Ferrante ^[28] , 2009, Belgium	Case-control	141 patients, 22 cases, 119 controls	Early (30 d) post-operative complications	5-ASA				Scheduled 2.5 Infusions (median)	Majority (3.9 wk median)
				6MP/AZA	59	55	0.7		
				Steroids (high dose)	9	25	0.163		
Kunitake ^[29] , 2008, Massachusetts General Hospital, Boston (combined study)	Case-control	413 total, 101 cases, 312 control	Post-operative complications	5-ASA	-	-	-	-	100%
				6MP/AZA	37	26	0.04		
				Steroids	75.30	77	0.79		
				Antibiotics	-	-	-		

IFX: Infliximab; 5-ASA: 5-aminosalicylic acid; AZA: Azathioprine; 6MP: 6-mercaptopurine.

Table 5 Complications defined in ulcerative colitis studies

Study	Study Endpoints	Infectious	Medical	Surgical	Pouch
Selvasekar ^[25]	Post-operative pouch specific and infectious complications	Pouch complications plus; wound infections			Anastomotic leak; pelvic abscess
Schluender ^[26]	30 d post-operative surgical and medical complications	Not defined	Major: pneumonia, DVT, pancreatitis, ARF, CVA; minor: dehydration, thrombophlebitis, pyoderma gangrenosum, urinary retention	Major: SBO, abscess, bleeding, leak; minor: wound infection, ileus, bleeding	
Mor ^[27]	Early (30 d) and late post-operative complications	Early: pelvic sepsis, bleeding, thrombosis, ileus; Late: pouchitis, SBO, stricture			
Ferrante ^[28]	30 d post-operative complications	Surgical infections: pouch complications plus wound infection; non surgical: UTI and respiratory infections			Anastomotic leak; pelvic abscess
Kunitake ^[29] (combined study)	Post-operative cumulative complications	Infections, hypomotility, thrombotic, cardiac complications, hepato-renal complications, anastomotic leak, bleeding and death			

DVT: Deep vein thrombosis; ARF: Acute renal failure; CVA: Cerebrovascular accident; SBO: Small bowel obstruction; UTI: Urinary tract infections.

were included in their meta-analysis. The analysis failed to find a strong association between preoperative treatment of IFX and short term infectious (OR: 2.24, 95% CI: 0.63-7.95) or non-infectious (OR: 0.85, 95% CI: 0.5-1.45) post-operative complications. However, preoperative IFX

use increased short term total post-operative complications (OR: 1.80, 95% CI: 1.12-2.87). These results need to be interpreted with caution. There are significant differences in patient population, characteristics, and study endpoints in the studies included in the meta-analysis. For

Table 6 Post-operative risks of complications with ulcerative colitis

Authors	Complications	Cases (%)	Controls (%)	Risks of complications, OR (95% CI)
Selvasekar ^[25]	Pouch specific	19	7	2.6 (0.9-7.5)
	Infectious	28	10	2.7 (1.1-6.7)
Schluender ^[26]	Medical	6	10	0.6 (0.1-4.8)
	Surgical	30	18	1.9 (0.6-5.9)
	Infectious	18	8	2.4 (0.6-9.6)
Mor ^[27]	Early	35	15	3.5 (1.5-8.3)
	Late	52	37	2.2 (0.9-5.3)
	Sepsis	22	1	13.8 (1.8-105)
Ferrante ^[28]	Pouch specific	0	17	0.9 (0.8-0.9)
	Surgical infections	11	23	0.2 (0.03-1.6)
	Total Infectious	11	28.60	0.3 (0.07-1.4)
Kunitake ^[29] (combined study)	Post-operative cumulative complications	16.80	15.70	1.1 (0.6-2.0)

OR: Odd ratio; CI: Confidence interval.

example, only one study^[29] included patients who received their last dose of IFX within 12 wk prior to surgery and the remaining studies included patients where such characteristics and important distinctions were not accounted for. Even the definitions of infectious and non-infectious complications were different in the various studies^[25-29]. In the presence of such confounders, it is hard to draw any meaningful results from this meta-analysis.

Combined Crohn's disease and ulcerative colitis study

Kunitake *et al.*^[29] retrospectively studied 413 patients (45% with CD, 38% with UC and 17% with IC) who underwent abdominal surgery between 1993 and 2007, evaluating the association of preoperative IFX use with post-operative complications. There were trends for higher rates of post-operative death, anastomotic leak, thrombotic complications, hypomotility, hepatorenal complications, and post-operative bleeding in the IFX group, but this did not reach statistical significance. Given its retrospective design, this study shared the same weaknesses as its predecessors. A sample size of approximately 250 patients in each arm to identify a 5% difference in post-operative outcomes was required. This study, while the largest to date in the literature, could only identify 101 patients who underwent IFX treatment within the 12 wk preceding their abdominal surgery. While no statistical significance was observed between the groups, some of the trends seen in the IFX group, such as the higher death rate, were indeed worrisome, especially as the deaths in both groups were because of failure of multiple organ systems due to intra-abdominal sepsis.

RISK OF POST-OPERATIVE COMPLICATIONS

Surgery plays an integral role in the treatment of inflammatory bowel disease, both to control symptoms and to treat complications. The rate of surgery within 3 years of diagnosis of CD varies from 25 percent to 45 percent. Twenty-five percent to 38 percent of patients require a second surgery by 5 years after the first, and about one

third of patients who need a second surgery eventually require a third^[32]. Indications for surgery include complications such as intra-abdominal abscess, medically intractable fistula, fibrotic stricture with obstructive symptoms, toxic megacolon, hemorrhage, and cancer^[33]. Approximately 25 percent of UC patients ultimately require colectomy for the management of their disease^[34]. Common indications for surgical therapy of UC are medically refractory disease, intractable disease with an impaired quality of life, and unacceptable side effects from medical therapy. Other indications for surgery include uncontrolled hemorrhage, toxic megacolon, perforation, dysplasia or carcinoma, systemic complications, and growth retardation.

Surgery in inflammatory bowel disease (IBD) patients is associated with morbidity and mortality. The common early post-operative complications include abdominal wound infection, anastomotic leakage, pelvic sepsis and small bowel obstruction. Late complications include anastomotic leak with pelvic sepsis or fistula, anastomotic stricture and, with IPAA, pouchitis and pouch dysfunction^[18]. Post-operative infections increase length of hospital stay, cost, mortality and morbidity rates^[35]. In one study, the post-operative infections in colectomy patients resulted in an approximately 2 wk longer hospital stay, with an increase of more than 300 percent in the total direct cost^[36].

Patients receiving immunosuppressant medications, including biologic therapies, are at increased risk of bacterial, fungal and protozoal infections due to multiple effects on the immune system^[7,37,38]. TNF α functions to stimulate angiogenesis and fibroblast proliferation, as well as to increase collagenase and prostaglandin synthesis^[39]. In addition, the TNF α receptor has been shown to be necessary for an effective immune response to mycobacteria in animal models^[7,39,40]. In addition to the above, reports of histoplasmosis, coccidiomycosis, listeriosis, pneumocystosis, and other fungal, bacterial and mycobacterial infections have been observed in patients receiving IFX.

The perioperative management of a patient with IBD requires a multifaceted approach involving both tradi-

tional and disease-specific considerations. As with any surgical candidate, preoperative risk assessment is crucial. Whether to suspend immunomodulating therapy during the perioperative period has been a challenging question. The difficulty lay in striking a balancing between that of maintaining disease control and that of optimizing wound healing, along with minimizing the post-operative risk of infection and other morbidity. As the use of biologic therapy in IBD continues to grow, we are faced with the additional task of providing recommendations for their use as well, and there is little information on which to base any definitive guidelines^[41].

There have been several studies now published evaluating IFX use and perioperative complications. However, as described above, they suffer from similar weaknesses such as their retrospective design, small sample size (most studies included only 40-60 patients receiving IFX), dissimilar study populations (different IBD phenotypes, surgical procedures, and time periods on infliximab), single referral center populations, and use of the medication prior to FDA approval and thus generating selection bias with more ill patients receiving IFX and non-standardized usage of IFX. Potential confounders are generally not well addressed, especially severity and duration of disease, malnutrition, comorbidities, race and type of surgical procedure. Studies evaluating effect of IFX in CD are not adjusted for disease severity. Disease severity determined retrospectively is often inaccurate and surrogate covariates may be inadequate substitutions for validated methods of assessing disease activity. However it is interesting to note that in the studies of UC, those that were adjusted for disease activity showed a relationship between IFX and complications, while the converse was true for those studies that did not. Inappropriate use of anti-TNF therapy among some patients may also confound existing studies owing to their retrospective nature. Studies of the pharmacokinetics of IFX in IBD suggest that the elimination half-life is between 7 and 18.5 d^[42,43]. By 12 wk (84 d, or 4.5 half-lives), most IBD patients should have undetectable levels of IFX. A window of 12 wk used by several of these studies may not reflect outcomes associated with the presence of drug at the time of surgery. Ideally, the duration between last infusion and surgery should be included as a continuous variable, but it is difficult to do this in retrospective analyses. Referral practice patterns also may account for the heterogeneous findings of these studies, as these may differ substantially in various regions of the world. Using anti-TNF therapy late in the course of disease in patients less likely to benefit from it (e.g., fixed stricture in CD) may introduce risk without clear benefit. Also, continuing to use anti-TNF therapy after it is clear that it has failed may send a higher risk patient to the operating room. These factors are difficult to measure and could be better addressed in a prospective, randomized study.

CONCLUSION

To date, all of the studies of anti-TNF therapy are of

infliximab and are mixed in their reports of the risk of post-operative complications associated with it. The studies are limited by small numbers of patients, disparate comparison groups, different definitions of measured outcomes and varying timeframes of drug exposure and follow-up. Larger controlled studies, with well-defined standardized criteria, are needed to clarify this issue. In the meantime, physicians must be aware of these potential risks so that prudent decisions about patient selection and timing of interventions can be made.

REFERENCES

- 1 **Hanauer SB.** Inflammatory bowel disease. *N Engl J Med* 1996; **334**: 841-848
- 2 **Podolsky DK.** Inflammatory bowel disease. *N Engl J Med* 2002; **347**: 417-429
- 3 **Rutgeerts P,** Van Assche G, Vermeire S. Optimizing anti-TNF treatment in inflammatory bowel disease. *Gastroenterology* 2004; **126**: 1593-1610
- 4 **Hanauer SB,** Feagan BG, Lichtenstein GR, Mayer LE, Schreiber S, Colombel JF, Rachmilewitz D, Wolf DC, Olson A, Bao W, Rutgeerts P. Maintenance infliximab for Crohn's disease: the ACCENT I randomised trial. *Lancet* 2002; **359**: 1541-1549
- 5 **Sands BE,** Anderson FH, Bernstein CN, Chey WY, Feagan BG, Fedorak RN, Kamm MA, Korzenik JR, Lashner BA, Onken JE, Rachmilewitz D, Rutgeerts P, Wild G, Wolf DC, Marsters PA, Travers SB, Blank MA, van Deventer SJ. Infliximab maintenance therapy for fistulizing Crohn's disease. *N Engl J Med* 2004; **350**: 876-885
- 6 **Cohen RD,** Tsang JF, Hanauer SB. Infliximab in Crohn's disease: first anniversary clinical experience. *Am J Gastroenterol* 2000; **95**: 3469-3477
- 7 **Colombel JF,** Loftus EV, Tremaine WJ, Egan LJ, Harmsen WS, Schleck CD, Zinsmeister AR, Sandborn WJ. The safety profile of infliximab in patients with Crohn's disease: the Mayo clinic experience in 500 patients. *Gastroenterology* 2004; **126**: 19-31
- 8 **Farrell RJ,** Shah SA, Lodhavia PJ, Alsahli M, Falchuk KR, Michetti P, Peppercorn MA. Clinical experience with infliximab therapy in 100 patients with Crohn's disease. *Am J Gastroenterol* 2000; **95**: 3490-3497
- 9 **Ricart E,** Panaccione R, Loftus EV, Tremaine WJ, Sandborn WJ. Infliximab for Crohn's disease in clinical practice at the Mayo Clinic: the first 100 patients. *Am J Gastroenterol* 2001; **96**: 722-729
- 10 **Lichtenstein GR,** Feagan BG, Cohen RD, Salzberg BA, Diamond RH, Chen DM, Pritchard ML, Sandborn WJ. Serious infections and mortality in association with therapies for Crohn's disease: TREAT registry. *Clin Gastroenterol Hepatol* 2006; **4**: 621-630
- 11 **Andres PG,** Friedman LS. Epidemiology and the natural course of inflammatory bowel disease. *Gastroenterol Clin North Am* 1999; **28**: 255-281, vii
- 12 **Greenhalgh DG,** Gamelli RL. Is impaired wound healing caused by infection or nutritional depletion? *Surgery* 1987; **102**: 306-312
- 13 **Hesp FL,** Hendriks T, Lubbers EJ, de Boer HH. Wound healing in the intestinal wall. Effects of infection on experimental ileal and colonic anastomoses. *Dis Colon Rectum* 1984; **27**: 462-467
- 14 **Jönsson K,** Jiborn H, Zederfeldt B. Healing of anastomoses after obstruction of small intestine. *Surg Gynecol Obstet* 1988; **167**: 324-330
- 15 **Cooper JC,** Jones D, Williams NS. Outcome of colectomy and ileorectal anastomosis in Crohn's disease. *Ann R Coll Surg Engl* 1986; **68**: 279-282

- 16 **Heimann TM**, Greenstein AJ, Mechanic L, Aufses AH. Early complications following surgical treatment for Crohn's disease. *Ann Surg* 1985; **201**: 494-498
- 17 **Young S**, Smith IS, O'Connor J, Bell JR, Gillespie G. Results of surgery for Crohn's disease in the Glasgow region, 1961-70. *Br J Surg* 1975; **62**: 528-534
- 18 **Scott-Conner CE**. Current surgical management of inflammatory bowel disease. *South Med J* 1994; **87**: 1232-1241
- 19 **Feagan BG**, Yan S, Bala M, Bao W, Lichtenstein GR. The effects of infliximab maintenance therapy on health-related quality of life. *Am J Gastroenterol* 2003; **98**: 2232-2238
- 20 **Haynes RB**, Wilczynski N, McKibbin KA, Walker CJ, Sinclair JC. Developing optimal search strategies for detecting clinically sound studies in MEDLINE. *J Am Med Inform Assoc* 1994; **1**: 447-458
- 21 **Hunt DL**, McKibbin KA. Locating and appraising systematic reviews. *Ann Intern Med* 1997; **126**: 532-538
- 22 **Marchal L**, D'Haens G, Van Assche G, Vermeire S, Noman M, Ferrante M, Hiele M, Bueno De Mesquita M, D'Hoore A, Penninckx F, Rutgeerts P. The risk of post-operative complications associated with infliximab therapy for Crohn's disease: a controlled cohort study. *Aliment Pharmacol Ther* 2004; **19**: 749-754
- 23 **Colombel JF**, Loftus EV, Tremaine WJ, Pemberton JH, Wolff BG, Young-Fadok T, Harmsen WS, Schleck CD, Sandborn WJ. Early postoperative complications are not increased in patients with Crohn's disease treated perioperatively with infliximab or immunosuppressive therapy. *Am J Gastroenterol* 2004; **99**: 878-883
- 24 **Appau KA**, Fazio VW, Shen B, Church JM, Lashner B, Remzi F, Brzezinski A, Strong SA, Hammel J, Kiran RP. Use of infliximab within 3 months of ileocolonic resection is associated with adverse postoperative outcomes in Crohn's patients. *J Gastrointest Surg* 2008; **12**: 1738-1744
- 25 **Selvasekar CR**, Cima RR, Larson DW, Dozois EJ, Harrington JR, Harmsen WS, Loftus EV, Sandborn WJ, Wolff BG, Pemberton JH. Effect of infliximab on short-term complications in patients undergoing operation for chronic ulcerative colitis. *J Am Coll Surg* 2007; **204**: 956-962; discussion 962-963
- 26 **Schluender SJ**, Ippoliti A, Dubinsky M, Vasilias EA, Papadakis KA, Mei L, Targan SR, Fleshner PR. Does infliximab influence surgical morbidity of ileal pouch-anal anastomosis in patients with ulcerative colitis? *Dis Colon Rectum* 2007; **50**: 1747-1753
- 27 **Mor IJ**, Vogel JD, da Luz Moreira A, Shen B, Hammel J, Remzi FH. Infliximab in ulcerative colitis is associated with an increased risk of postoperative complications after restorative proctocolectomy. *Dis Colon Rectum* 2008; **51**: 1202-1207; discussion 1202-1207
- 28 **Ferrante M**, D'Hoore A, Vermeire S, Declerck S, Noman M, Van Assche G, Hoffman I, Rutgeerts P, Penninckx F. Corticosteroids but not infliximab increase short-term postoperative infectious complications in patients with ulcerative colitis. *Inflamm Bowel Dis* 2009; **15**: 1062-1070
- 29 **Kunitake H**, Hodin R, Shellito PC, Sands BE, Korzenik J, Bordeianou L. Perioperative treatment with infliximab in patients with Crohn's disease and ulcerative colitis is not associated with an increased rate of postoperative complications. *J Gastrointest Surg* 2008; **12**: 1730-1736; discussion 1730-1736
- 30 **Yang Z**, Wu Q, Wu K, Fan D. Meta-analysis: pre-operative infliximab treatment and short-term post-operative complications in patients with ulcerative colitis. *Aliment Pharmacol Ther* 2010; **31**: 486-492
- 31 **Maser EA**, Deconda D, Lichtiger S, Ullman T, Present DH, Kornbluth A. Cyclosporine and infliximab as rescue therapy for each other in patients with steroid-refractory ulcerative colitis. *Clin Gastroenterol Hepatol* 2008; **6**: 1112-1116
- 32 **Whelan G**, Farmer RG, Fazio VW, Goormastic M. Recurrence after surgery in Crohn's disease. Relationship to location of disease (clinical pattern) and surgical indication. *Gastroenterology* 1985; **88**: 1826-1833
- 33 **Hurst RD**, Molinari M, Chung TP, Rubin M, Michelassi F. Prospective study of the features, indications, and surgical treatment in 513 consecutive patients affected by Crohn's disease. *Surgery* 1997; **122**: 661-667; discussion 661-667
- 34 **Metcalfe AM**. Elective and emergent operative management of ulcerative colitis. *Surg Clin North Am* 2007; **87**: 633-641
- 35 **Green JW**, Wenzel RP. Postoperative wound infection: a controlled study of the increased duration of hospital stay and direct cost of hospitalization. *Ann Surg* 1977; **185**: 264-268
- 36 **Rios J**, Murillo C, Carrasco G, Humet C. [Increase in costs attributable to surgical infection after appendectomy and colectomy]. *Gac Sanit* 2003; **17**: 218-225
- 37 **Present DH**, Meltzer SJ, Krumholz MP, Wolke A, Korelitz BI. 6-Mercaptopurine in the management of inflammatory bowel disease: short- and long-term toxicity. *Ann Intern Med* 1989; **111**: 641-649
- 38 **Lamers CB**, Griffioen G, van Hogezaand RA, Veenendaal RA. Azathioprine: an update on clinical efficacy and safety in inflammatory bowel disease. *Scand J Gastroenterol Suppl* 1999; **230**: 111-115
- 39 **Busti AJ**, Hooper JS, Amaya CJ, Kazi S. Effects of perioperative antiinflammatory and immunomodulating therapy on surgical wound healing. *Pharmacotherapy* 2005; **25**: 1566-1591
- 40 **Keane J**, Gershon S, Wise RP, Mirabile-Levens E, Kasznica J, Schwieterman WD, Siegel JN, Braun MM. Tuberculosis associated with infliximab, a tumor necrosis factor alpha-neutralizing agent. *N Engl J Med* 2001; **345**: 1098-1104
- 41 **Rosandich PA**, Kelley JT, Conn DL. Perioperative management of patients with rheumatoid arthritis in the era of biologic response modifiers. *Curr Opin Rheumatol* 2004; **16**: 192-198
- 42 **Klotz U**, Teml A, Schwab M. Clinical pharmacokinetics and use of infliximab. *Clin Pharmacokinet* 2007; **46**: 645-660
- 43 **Ternant D**, Aubourg A, Magdelaine-Beuzelin C, Degenne D, Watier H, Picon L, Paintaud G. Infliximab pharmacokinetics in inflammatory bowel disease patients. *Ther Drug Monit* 2008; **30**: 523-529

S- Editor Tian L L- Editor Rutherford A E- Editor Xiong L