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Does infliximab increase complications after surgery for inflammatory bowel disease?

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Abstract

Conflicting data exist regarding the association between pre-operative monoclonal anti-tumor necrosis factor-alpha antibody therapy with infliximab for Crohn disease and chronic ulcerative colitis, and the occurrence of post-operative complications. This report reviews the current literature that supports and refutes this association.

Introduction and context

Gastroenterologists and surgeons who specialize in the treatment of Crohn disease (CD) and chronic ulcerative colitis (CUC) have become increasingly aware of the implications of different forms of medical therapy on surgical outcomes. This is especially important in the era of 'top-down' and multi-agent therapy for inflammatory bowel disease (IBD) [1, 2]. Although relatively little literature exists regarding the relationship between pre-operative corticosteroid use and post-operative complications, several authors have found that increasingly higher doses of such immunosuppressive medications may result in an increased rate of post-operative septic complications [3, 4]. Similarly, there is increasing concern that combination immunomodulatory therapy with multiple agents may also be associated with an increase in post-operative infectious complications [5, 6]. Given reports of the association of monoclonal anti-tumor necrosis factor-alpha (anti-TNF-α) antibody therapy with pulmonary infections, this concern has specifically been focused on infliximab (IFX), which until recently has been the only FDA-approved biologic agent for IBD [7-11].

A recent meta-analysis of the association between immunomodulatory therapy and post-operative complications after surgery for IBD, which included studies of azathioprine, cyclosporine A, and three studies of IFX, found that the available evidence did not support this association [12]. Since then, several studies have been published suggesting that IFX is indeed associated with an increased risk of post-operative complications [12]. Thus, the potential association between IFX and surgical complications is controversial; studies both support and refute this potential relationship [5,13–19]. This *F1000 Medicine Report* will review the major findings of these studies.

Recent advances

Crohn disease

In a study of 270 patients by Colombel *et al.* [14], 52 patients experienced intra-abdominal septic complications (IASCs) after bowel resection for CD. Analysis did not reveal any increased risk in the IFX-treated subgroup, the moderate-to-high-dose corticosteroid subgroup, or the immunomodulator subgroup. Likewise, a matched case-control study from Belgium of 31 CD patients also concluded that pre-operative IFX use did not result in a significantly increased rate of post-operative complications, or increased hospital length of stay, as compared to a control group of IFX-naïve patients [15]. That study did note, however, a trend towards increased early post-operative infections in the IFX group. More recently, a study of 413 IBD patients (156 with CD), of which 101 had received IFX within 12 weeks of surgery, also did not find any relationship between pre-operative IFX therapy

and post-operative complications [18]. That study, similar to others, was relatively limited by the absolute number of complications.

In contrast, a more recent study from Appau *et al.* [17] found an association between pre-operative IFX therapy for CD and post-operative complications. They concluded that IFX therapy within 3 months of surgery was associated with an increased rate of IASCs, and of hospital re-admissions. They also found that patients who received a diverting stoma had a lower risk of IASCs, thus prompting the observation that a diverting stoma may be prudent when surgeons are faced with CD patients who have recently received IFX. In light of this study, the risks associated with stoma reversal surgery must be weighted against the potential increase in complications associated with IFX for CD.

Chronic ulcerative colitis

In a study of 151 patients with CUC, 17 (10%) of whom failed IFX therapy and went to surgery and 134 of whom were IFX-naïve, no association between IFX and complications was observed [5]. However, the authors observed that IFX patients who had concurrent cyclosporine A treatment were at increased risk for overall and infectious complications.

In a larger study by Selvasekar *et al.* [16] in which 47 CUC patients received pre-operative [ileal pouch-anal anastomosis (IPAA)] IFX therapy and 254 did not, those who received IFX were more likely to have anastomotic leak, and after multivariate adjustment for both disease severity and other medication use, IFX remained independently associated with an increased risk of ileal pouch-related and infectious complications [16]. Finally, a recent study of 85 patients with CUC who received IFX pre-operatively also found that patients who receive pre-operative IFX were at increased risk of post-operative septic complications as well as late complications [19]. Importantly, the authors also noted that patients who received IFX were more likely to have undergone a 3-stage IPAA, likely due to surgeon reluctance to perform an anastomosis in the setting of pre-operative IFX administration.

Common limitations

Many of these retrospective studies suffer from common limitations. First is lack of adjustment for disease severity (Table 1). Disease severity determined retrospectively is

Table 1. Summary of literature of the association of IFX with post-operative complications

Article	Institution	Year	IBD	IFX subjects/Total subjects	IFX window	Specifically adjusted for disease severity	IFX increased complications?	Comments
Colombel [14]	Mayo Clinic, Rochester	2004	CD	52/270 (19%)	8 weeks before to 4 weeks after surgery	No	No	Multivariate adjustment for steroid use showed no increase in complications for IFX or combination immunosuppressive therapy patients. Trend towards increased complications with pre-operative steroids
Marchal [15]	University Hospital, Gasthuisberg	2004	CD	31/313 (10%)	12 weeks	No	No	Univariate analysis showed no increase in post-operative length of stay or complications, but trend towards increased early post-operative complications
Appau [17]	Cleveland Clinic, Ohio	2008	CD	60/389 (15%)	3 months	No	Yes	Multivariate adjustment (6 covariates) showed increase in post-operative sepsis, abscess, and readmissions. Stoma use decreased rate of sepsis
Schluender [5]	Cedars Sinai	2007	CUC	17/151 (11%)	1–12 months	No	No	Univariate analysis showed no increase unless combined with cyclosporine A. Study likely underpowered
Selvasekar [16]	Mayo Clinic, Rochester	2007	CUC	47/301 (16%)	6 months	Yes	Yes	Multivariate adjustment (4 covariates) showed increased pouch-related and infectious complications
Mor [19]	Cleveland Clinic, Ohio	2008	CUC	85/523 (16%)	4–37 weeks	Yes	Yes	Multivariate adjustment (5 covariates) showed increased risk for both 2-stage and 3-stage IPAA
Kunitake [18]	Mass General	2008	Both	101/413 (24%)	12 weeks	No	No	Multivariate adjustment (3 covariates) showed IFX patients had a longer hospital stay. No difference seen between CD and CUC patients

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 CUC, those that adjusted for disease activity showed a relationship between IFX and complications, while the converse was true for those studies that did not. Another major limitation of several of these studies is the relatively long pre-operative IFX window, often 12 weeks or more (Table 1). Recent studies of the pharmacokinetics of IFX in IBD suggest that the elimination half-life is between 7 and 18.5 days [20, 21]. By 12 weeks (84 days, or 4.5 half-lives), most IBD patients should have undetectable levels of IFX. A window of 12 weeks used by several of the studies published to date may theoretically produce negative results regarding the occurrence of post-operative outcomes if a significant proportion of patients had an interval this long between IFX administration and surgery. Ideally, the duration between last infusion and surgery should be included as a continuous variable, but outpatient infusion often makes these data unavailable retrospectively.

Referral practice patterns may too account in part for the heterogenous findings of these studies, as these may differ substantially in various regions of the world, as demonstrated by at least a 10% variation in the proportion of surgical IBD patients who received IFX. Thus, as is usually true of most retrospective studies, results from a single institution may not be broadly generalizable; the institutions themselves may be considered as a potential confounding factor when comparing results of different studies to each other.

In one of the largest studies of the association of IFX and serious infections and mortality, the TREAT Registry study of 6290 patients found that after adjustment for corticosteroid use and disease severity, IFX was not independently associated with increased risk, although both corticosteroids and disease severity were associated with those adverse outcomes [22]. Although this study did not include surgical endpoints, the implications are nonetheless important, especially given the lack of large-scale surgical data.

Implications for clinical practice

Whether pre-operative IFX use is associated with post-operative complications after surgery for IBD remains controversial; current evidence favors this association after surgery for CUC but does not favor an increased risk after surgery for CD. The potentially practice-changing implications of this debate are occurring now; increasingly some surgeons are waiting until anti-TNF-α agents are washed out before operating or, if that is not possible, performing resections for CD with temporary diverting stomas or advising 3- rather than 2-staged IPAA.

Larger studies and/or formal meta-analysis of the relationship between IFX and post-operative complications after surgery for IBD are needed before definitive treatment recommendations can be made. The decision of whether or not to perform staged surgery for IBD patients on IFX needs to be made on an individual basis, based on the clinical context and other known risk factors, such as hypoalbuminemia and high-dose corticosteroid treatment.

Abbreviations

CD, Crohn disease; CUC, chronic ulcerative colitis; IASC, intra-abdominal septic complication; IBD, inflammatory bowel disease; IFX, infliximab; IPAA, ileal pouch anal anastomosis; TNF, tumor necrosis factor.

Competing interests

The authors declare that they have no competing interests.

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