Do Anti-TNF Therapies Increase the Risk of Postoperative Complications in Inflammatory Bowel Diseases?

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Despite the increasing use of biologics in the treatment of Inflammatory Bowel Diseases (IBD), an important proportion of patients still require surgery. Nearly one third of Crohn’s Disease (CD) patients still require a major abdominal surgery in the five years following disease diagnosis [1]. In UC, between 10% and 36% of patients need a colectomy [2]. To what extent immunomodulators could affect postoperative outcomes should therefore be of particular interest for the clinician. It has been shown that immunosuppressant treatment such as azathioprine would not increase the rate of postoperative complication in IBD [3]. In the contrary, it appears that systemic steroids significantly affect postoperative outcomes with an increased risk of 41% of all postoperative complications and of 68% of postoperative infectious complications [4]. Up to 60% of CD patients received an anti-TNF before first abdominal surgery and a recent study showed that between Ulcerative Colitis (UC) diagnosis and colectomy, 30% of patients received at least one anti-TNF agent [5,6]. It remains controversial, if a large number of studies already investigated postoperative complication rate in anti-TNF treated patients, whether exposure to anti-TNF agents is associated with worth surgical outcomes.

In CD, most of studies failed to identify a negative impact of biologics on early postoperative outcomes (usually defined as 30 days postoperative complications) [7-12]. The first study on this topic has shown a protective effect of immunomodulators even if these results have not been further reproduced [13]. Importantly, the study which has shown an increased rate of postoperative complications is also the largest one. Among 389 patients, infliximab exposure in the previous three months before surgery was associated with an increased risk of sepsis, intra-abdominal abscess and readmission [14]. Similarly, in a smaller case-control study (79 patients), Marchal et al. [15] identified a trend towards an increased early infection rate in infliximab pre-treated patients (6 versus 1 patients) [15]. In a recent meta-analysis, 8 studies including a total of 1641 patients were reviewed. Anti-TNF were associated with a slightly increased risk of postoperative infectious complication (Odds ratio (OR)=1.50), especially nonlocal (OR=2.07), even if the rate of total complications was not increased [16].

Conflicting results also exist regarding anti-TNF treated patients undergoing surgery for UC. In a retrospective study, the charts of 301 patients were reviewed for short-term complications after ileal pouch Anal Anastomosis (IPAA) for patients with chronic UC, including 49 patients who were preoperatively treated with infliximab. The authors failed to identify an increased risk of overall complication but they revealed infliximab as the only factor independently associated with infectious complications [17]. In a case-control study, Mor et al. [18] have shown that the odds of sepsis, early complication and late complication were respectively 14, 2 and 4 times greater for infliximab treated patients following restorative proctocolectomy [18]. In addition, UC patients who received both infliximab and cyclosporine A preoperatively presented significantly more postoperative complications compared to the cyclosporine A only-treated group (80% versus 29%). In this study, it is interesting to note that infliximab treated patients did not experience more complication compared to infliximab non-treated patients, suggesting a synergic effect of anti-TNF and cyclosporine A [19]. A similar synergistic effect between thiopurines and infliximab could also exist. Waterman et al. [20] reviewed the postoperative outcomes of 195 IBD patients exposed to anti-TNF, matched with 278 controls. They did not find any difference between the two groups but a concomitant therapy with biologics and thiopurines was associated with more urinary tract infections and wound infections [20]. Regarding surgical procedures, Eshuis et al. [21] suggested that a two-stage proctocolectomy with IPAA should be performed in anti-TNF patients. The authors have shown that infliximab-treated patients had more anastomotic leakage and non-infectious complications among 31 one-stage procedures whereas no difference was observed in the 39 two-stage procedures [21]. The largest study including UC patients used a nationwide Danish cohort of patients which permit to identify 1226 patients having their first surgery for the period of January 2003 to December 2010. Among the 199 UC patients exposed to infliximab in the 12 weeks before surgery, there was no increase rate of reoperation or postoperative anastomotic leakage [22]. This safety profile of anti-TNF agents in UC patients have been confirmed in a recent meta-analysis including 13 studies and involving 2933 patients. There was no significant association between infliximab therapy preoperatively and total, infectious and non-infectious postoperative complications [23].

In conclusion, anti-TNF therapies appear to be quite safe in IBD patients at risk for surgery. In UC, the last meta-analysis failed to identify an increased rate of complication in patients expose to infliximab before surgery and the increased risk of infectious postoperative complication is modest in CD. However, no definitive recommendations could be drawn. Most of the studies are retrospective or case-control studies and thus do not allow the control of important confounding factors such as concomitant immunosuppressants or steroids. In addition, few data are provided for other biologics than infliximab. Finally, preoperative anti-TNF duration varies through studies and the influence of the time between the last anti-TNF injection and the surgery is not known. Waterman et al. [20] tried to answer this question by analyzing postoperative outcomes regarding last preoperative biologic administration or infliximab levels. An operation performed less than 14 days after infliximab administration or a detectable infliximab level were not responsible of more postoperative complications [20]. Further prospective data able to control confounding factors and various pharmacokinetic conditions are therefore keenly needed. Awaiting the publication of clear recommendations, clinicians should consider delaying surgery after anti-TNF treatment discontinuation.
when possible, especially in CD patients. In UC patients a two-stage IPAA instead of a one-stage procedure should be discussed in anti-TNF treated patients requiring a proctocolectomy.

References