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Should biologic agents be stopped before surgery for inflammatory bowel disease?

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Despite the widespread use of anti-TNF agents for inflammatory bowel disease (IBD), the need for surgical intervention remains high. As a result, many IBD patients undergoing surgery have recently been exposed to biologic agents. There is considerable controversy regarding the potential adverse effects of biologic agents on surgical outcomes in IBD patients undergoing major colorectal surgery with studies showing conflicting results. There appears to be discordance in the systemic bioavailability of anti-TNF-α in patients with Crohn's disease (CD) versus ulcerative colitis, with greater systemic absorption in CD. In patients with CD, preoperative serum anti-TNF-α levels may help guide timing of surgery as patients with elevated serum anti-TNF-α levels appear to be at higher risk for complications. In patients with ulcerative colitis there is likely no need for stopping biologic agents before surgery as there is poor systemic bioavailability of the drug in a majority of patients.

Biologic agents have revolutionized the management of Crohn's disease (CD) and ulcerative colitis (UC). These agents are genetically engineered therapeutics specifically targeted against various host immune molecules, including TNF, interleukins and adhesions molecules. Unlike corticosteroids, which are nondiscriminant and suppress many host immune processes, the biologic agents act selectively, thereby minimizing the scope of adverse events. Despite the significant improvement in medical therapies for inflammatory bowel disease (IBD) as well as their widespread use, the need for surgical intervention remains high [1,2]. Consequently, many IBD patients attending the operating room have recently been exposed to biologic agents.

Despite the more limited scope for adverse events when compared with corticosteroids, medical therapy with biologic agents is not without consequence. Among its many actions, TNF is implicated in regulating cells central to wound healing and protection against infection [3]. Animal models have demonstrated that TNF blockade is associated with significant alterations in wound healing [4]. Patients receiving anti-TNF therapy also have an increased risk of opportunistic infections with various bacterial and mycotic infections [5]. These findings have raised concerns about the effects of biologic agents on wound healing and infectious complications on patients undergoing major abdominal surgery for CD or UC.

There is considerable controversy regarding the potential adverse effects of biologic agents on surgical outcomes with studies showing conflicting results [6–14]. These inconsistent findings may be attributed to a number of factors including retrospective study design; single institution experiences; variable duration of anti-TNF-α therapies and time periods between the last biologic dose and surgery; difficulty in controlling for disease severity; variable inclusion of CD, UC and inflammatory bowel disease-unclassified in the study cohorts; and overlapping treatment with other

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immunosuppressive medications, especially corticosteroids. The largest series published to date by Waterman *et al.* [14] is a case-control study on 473 IBD patients; 195 patients had preoperative exposure to biologics and were matched to 278 controls. The authors found no significant difference in overall complications in patients exposed to biologic agents and those not exposed. However, combination therapy with biologic agents and thiopurines was associated with an increased frequency of urinary tract infections and wound infections. Operations performed <14 days from the last biologic dose had similar rates of infections and other complications when compared with those performed within 15–30 days or 31–180 days.

Several meta-analyses have attempted to clarify the effect of biologics on postoperative outcomes [15–18]. Most recently, a meta-analysis examined the impact of preoperative immunosuppressive agents on postoperative outcomes in CD [15]. The analysis of 14 studies and over 5000 patients reported the effect of preoperative anti-TNF agents on postoperative outcomes. Most studies used a period of 3 months preoperatively as the cutoff for including patients in the anti-TNF group. Since the majority of studies were nonrandomized, the risk of confounding bias for each study was graded low, medium or high based on matching and similarity of baseline characteristics between study groups. The meta-analysis found no significant difference in total postoperative complications between the anti-TNF and no-anti-TNF groups. However, when only low and medium risk of confounding studies were included, there was a trend toward higher postoperative complications in the anti-TNF group (relative risk [RR]: 1.35; 95% CI: 1.00–1.83). In addition, including all studies, there was a significantly higher incidence of infectious complications in the anti-TNF group (RR: 1.29; 95% CI: 1.07–1.55) and the observed effect was higher when only low and medium risk of confounding studies were included (RR: 1.52; 95% CI: 1.22–1.89). In contrast, a meta-analysis evaluating preoperative anti-TNF-α use in UC patients found no correlation with postoperative morbidity [18].

Despite some standardization of anti-TNF dosing, there is wide variation in drug pharmacokinetics and therefore in observed serum anti-TNF levels. Recent data have suggested that this variation may, in part, explain some of the differences in clinical response observed in IBD patients. It is likely, therefore, that while the duration from the last anti-TNF dose to surgery may have no implication on surgical morbidity [14], perioperative anti-TNF levels may be predictive of adverse postoperative outcomes in IBD patients. A recent study at our institution [19] evaluated the effect of serum anti-TNF drug levels on surgical morbidity in IBD patients undergoing major abdominal surgery. The study cohort included 217 UC and CD patients undergoing major abdominal surgery identified from a prospectively maintained IBD registry. Drug levels were measured from stored frozen serum samples and postoperative complications were retrospectively reviewed. Interestingly, 53% of patients with a history of anti-TNF therapy did not have a detectable drug level at the time of surgery. Detectable anti-TNF levels were significantly more common in CD versus UC patients (odds ratio [OR]: 3.1; 95% CI: 1.6–5.9; p = 0.0005) and patients simultaneously treated with steroids (OR: 2.8; 95% CI: 1.5–5.1; p = 0.001). There was an increased rate of overall complications (36 vs 29%), medical complications (18 vs 9%) and infectious complications (19 vs 11%) in the detectable versus undetectable serum anti-TNF-α drug level groups, but these differences did not reach statistical significance. Subgroup analysis of UC patients with detectable (n = 17) and undetectable (n = 77) serum anti-TNF-α levels revealed no significant difference in overall postoperative morbidity; medical, surgical and infectious complications; or readmissions within 30 days between the two study groups. In the CD cohort, there was a trend toward a higher rate of overall postoperative morbidity (64 vs 25%), infectious complications (44 vs 14%) and readmission within 30 days (32 vs 4%) in the detectable serum anti-TNF drug level group. Using a clinical cutoff serum anti-TNF-α level of 3 μg/ml, both overall postoperative morbidity (34 vs 17%; OR 2.5; 95% CI 1.07–5.85; p = 0.03) and infectious complications (23 vs 9%; OR: 3.0, 95% CI: 1.08–8.43; p = 0.03) were significantly higher in the ≥3 μg/ml group. When adjusting for confounders such as steroid and immunomodulation use in CD patients, the association of ≥3 μg/ml serum anti-TNF-α drug levels remained significant for overall postoperative morbidity and infectious complications.

The poor correlation between preoperative anti-TNF therapy use and detectable levels in the study from our institution suggest that merely using a history of treatment with biologic agents is not rigorous enough to predict postoperative morbidity. In addition, the high proportion of UC patients compared with CD patients in the undetectable serum anti-TNF group suggests that factors specific to UC may be particularly pertinent in this setting [20]. This effect may be largely dependent on the severity of disease as a large volume of inflamed mucosal surface more commonly seen in UC than CD may lead to increased drug clearance [21,22]. An interesting future study would be to investigate serum anti-TNF levels in patients with Crohn's colitis compared with UC.

The lack of correlation between surgical morbidity and serum anti-TNF levels in UC has been examined in only one other retrospective case-control study by Waterman *et al.* discussed earlier [14] who performed a subgroup analysis of 19 UC patients with preoperative serum infliximab levels. Complication rates between detectable (n = 10) and undetectable (n = 9) infliximab level subgroups were not significantly different. Measurement of anti-TNF drug levels in UC patients may, therefore, have no role in the prognostication of postoperative morbidity. More importantly, despite recommendations by some surgeons [10,13] that all UC patients exposed to anti-TNF therapy in the preoperative period should undergo three-stage rather than two-stage ileal pouch-anal anastomosis (IPAA), the more recent studies and meta-analysis [12,18,23] have found no association between two- or three-stage IPAA in patients treated with preoperative biologic agents and

postoperative complications. The lack of effect of serum anti-TNF drug levels on patients undergoing two-stage IPAA suggests that a universal policy of using a three-stage IPAA in anti-TNF-α exposed patients may be unnecessary.

In contrast to the observations in UC, the data suggest that serum anti-TNF drug levels are relevant to postoperative morbidity in CD patients. This is supported by the recent meta-analysis suggesting increased overall postoperative complications and infectious complications in CD patients exposed to preoperative anti-TNF [15]. In addition, higher serum anti-TNF drug levels appear to be associated with higher overall and infectious complications in CD patients. Several factors may be responsible for the differences in postoperative morbidity noted in UC and CD patients exposed to preoperative biologic agents. These include differences in surgical procedures, differences in metabolism of biologic agents and differences in additional risk factors for adverse outcomes in CD versus UC patients such as multiple intraabdominal fistulae, multiple bowel anastomoses, past surgeries and urgent indications for surgery.

To answer the question of whether biologic agents should be stopped before surgery for IBD, one must ask whether the patient has UC or CD, evaluate the urgency of the need for surgery and evaluate preoperative anti-TNF levels if available. In patients with UC, there is likely no role in stopping biologic agents before surgery as there is poor systemic bioavailability of the drug in the majority of patients. In addition, in patients in whom detectable serum anti-TNF levels are found, there does not appear to be a correlation with surgical morbidity. Also, in patients undergoing IPAA, a universal policy of advocating three-stage procedures is likely unfounded. In patients with CD, however, preoperative anti-TNF levels should be considered, and decision regarding stopping treatment before surgery should be made based on the patient's clinical condition and level of anti-TNF with close collaboration between physicians and surgeons. Patients with undetectable levels of anti-TNF can likely go on to surgery with little risk of adverse consequences related to treatment with anti-TNF, whereas those with higher anti-TNF-α levels (>3 μg/ml) have a higher risk for overall postoperative morbidity and infectious complications. In such patients, the decision to wait for the drug serum washout period may be wise in patients undergoing more elective surgery for CD.

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