# ADVANCES IN IBD

Current Developments in the Treatment of Inflammatory Bowel Disease

Section Editor: Stephen B. Hanauer, MD

## The Impact of Biologic Therapy on Outcomes of Inflammatory Bowel Disease Surgery

Edward V. Loftus Jr, MD
Professor of Medicine
Division of Gastroenterology and Hepatology
Mayo Clinic
Rochester, Minnesota

**G&H** Has the rate of inflammatory bowel disease surgery changed since biologic agents were introduced?

**EL** The surgical rate has decreased with the advent of biologic agents. According to the results of Olmsted County studies, the cumulative risks for surgery (defined as bowel resection, and not perianal surgery, for Crohn's disease, and as colectomy for ulcerative colitis) 30 years from diagnosis were approximately 60% for Crohn's disease and approximately 30% for ulcerative colitis. Several population-based inflammatory bowel disease (IBD) cohorts (eg, from Denmark, Wales, Olmsted County, South Limburg) have seen declines in surgical rates over time, and this trend has been confirmed in a meta-analysis published in *Gastroenterology* in 2013. However, this is only indirect evidence that biologic agents have played a role in the decrease in surgery over time because many of the patients in these cohorts were not treated with biologic agents.

A decrease in IBD surgery can also be seen in secondary analyses in several of the clinical trials of anti–tumor necrosis factor (TNF) agents. A reduction in the need for surgery was seen with infliximab (Remicade, Janssen) in the ACCENT 1 and ACT trials, as well as with adalimumab (Humira, AbbVie) in the CHARM trial. In a meta-analysis published in *Alimentary Pharmacology & Therapeutics* in 2017, the pooled risk reduction with anti-TNF agents was 77% for Crohn's disease surgery and 33% for colectomy in ulcerative colitis.

**G&H** What has research found regarding the use of biologic therapy and surgical outcomes such as postoperative complications?

**EL** Many studies over the past 10 to 15 years have looked at this issue. At times, surgical colleagues have had the anecdotal impression that some patients on biologic agents experienced more postoperative complications, such as wound infections, anastomotic leaks, or abscesses. However, these impressions could have been confounded by a factor such as overall disease severity or another medication (eg, high-dose corticosteroids). It is challenging to tease out what exactly is driving a complication. For example, studies in the surgical literature have shown that patients on corticosteroids, especially on high doses, are more likely to have complications. On the other hand, the underlying disease could be causing these complications.

Researchers have tried to perform multivariate analyses to adjust for all of the possible factors, but the findings have been conflicting. There are as many studies suggesting that the cause of postoperative complications is the biologic agent as there are studies suggesting that it is not the biologic agent but the underlying disease severity or concomitant medications. Ulcerative colitis studies seem to suggest that it may be possible that, following J-pouch surgery, patients who were recently on a biologic agent may be at an increased risk of pouch complications, such as anastomotic leaks, abscesses, or pelvic sepsis. The results of a study that my colleagues and I conducted, published in the *Journal of the American College of Surgeons* in 2007,

suggested that perioperative use of infliximab was associated with increased infectious complications after J-pouch surgery, even after controlling for factors such as disease activity and concomitant medications. However, even the various meta-analyses of this topic have slightly differing conclusions with respect to whether complications are significantly associated with biologic use. There has also been debate as to whether wound infections might be associated with recent use of vedolizumab (Entyvio, Takeda), an anti-integrin biologic agent. Most of the meta-analyses of the Crohn's disease studies suggest that preoperative biologic use is significantly associated with infectious but not anastomotic complications, with odds ratios for infectious complications ranging from 1.15 to 1.93 in a review published in *Gastroenterology Report* this year. The mixed findings of meta-analyses and systematic reviews highlight the difficulty of retrospective examination when multiple factors could be involved.

Results from the PUCCINI registry, which will be presented at this year's Digestive Disease Week meeting, will provide further insight on this issue. Patients who were planning to go for surgery were prospectively enrolled at various Crohn's & Colitis Foundation Clinical Research Alliance sites to capture any confounding variables, and then were followed in a systematic manner looking for specific complications. The complete results have not yet been released, but it is my understanding that they showed that biologic agents were not associated with increased postoperative outcomes.

Irrespective of the effect on postoperative complications, it is important to stress that biologic agents provide a benefit, at least in reducing the overall surgical rate.

### G&H What is the ideal interval between the last biologic dose and surgery?

**EL** This question comes up for both intestinal and nonintestinal surgery. If a patient is on infliximab every 8 weeks, the surgeon might try to time the procedure toward the end of the cycle but not quite at the very end. I often recommend performing surgery at week 6 so that drug levels are likely low. However, there is concern that holding protein-based biologic agents—which are all immunogenic molecules, even the ones that claim to be fully human—for too long and then restarting them after a prolonged interval might increase the likelihood that the patient will develop drug antibodies. Sometimes I recommend performing the surgery toward the end of the cycle and holding the dose of infliximab until the patient is 3 or 4 weeks out from surgery, and there have not been any complications. Timing is more challenging with adalimumab because this drug is typically given every other week. However, like with infliximab, the adalimumab dose is usually held for a brief period of time and then the surgery is performed.

If an ulcerative colitis patient has high disease severity or has recently received biologic therapy, one surgical option is to perform a 3-stage J-pouch surgery instead of a 2-stage surgery. In this scenario, the surgeon performs a protective diverting ileostomy (leaving the rectum in place), at a later date removes the rectum and forms the J-pouch, and then waits at least 2 to 3 months to perform the takedown. Studies in the surgical literature have shown that staged procedures are associated with better outcomes and fewer complications. At my institution, rather than avoiding surgery because the patient is on a certain therapy, 3-stage J-pouch surgery is often used instead of 2-stage surgery (or if the surgery is a Crohn's resection and there is high disease activity, the surgeon might perform a diverting loop ileostomy to allow the ileocolonic anastomosis to heal). Therefore, it is important to make sure that the surgeon knows whether a patient is currently (or was recently) on biologic therapy.

### G&H How soon should biologic therapy be restarted after the surgery?

**EL** If all is going well and the surgeon is not concerned about wound infections or other complications, I generally have patients restart biologic therapy approximately 4 weeks after the surgery.

### G&H Does the patient's biologic level seem to affect surgical outcomes?

**EL** The data are conflicting. A few studies have suggested that the higher the level, the more it matters, but other studies have said the opposite. As previously mentioned, these studies are difficult to conduct and are performed retrospectively. That is the beauty of PUCCINI—this registry is, instead, capturing data prospectively and then systematically tracking all of the patients for complications, which makes for building a more robust study. In real life, if a patient has a complication but goes to another hospital for treatment, that information would not necessarily be available for the purposes of a retrospective study.

### G&H Do certain biologic agents seem to have a greater impact on surgical outcomes?

**EL** Initially, it was thought that perioperative use of vedolizumab might increase surgical complications. My colleagues and I conducted a study on this issue and published our findings in the *Journal of Crohn's and Colitis* in 2017. There was concern that we had seen an increased number of superficial surgical site infections in patients

on vedolizumab. However, this was difficult to determine because we were assessing patients who were treated with vedolizumab right after it was approved, and there had been a 6-year lag between the time the previous biologic agent had been approved for Crohn's disease and vedolizumab's approval. Thus, there was pent-up demand for this new agent, and there were many sick patients who were holding off on surgery waiting for the new drug. Some patients received vedolizumab, did not get better, and then underwent surgery, making it difficult to tease out disease severity.

More recently, most of the systematic reviews and meta-analyses on this issue have been suggesting that vedolizumab does not have a signal for increased perioperative complications. It is my understanding that PUCCINI had the same finding when tracking patients on vedolizumab.

### **G&H** Are any of the effects on surgical outcomes greater in certain patient subgroups?

**EL** The sicker the patient, the higher the rate of postoperative complications. One of the ways to track this is with the patient's albumin level. Often, a patient with hypoalbuminemia will cause concern. In such a case, the surgeon is more likely to perform a staged operation or may hold off on surgery for a week or two, possibly giving the patient total parenteral nutrition to improve his or her nutrition before going to the operating room.

### **G&H** Is it known why biologic therapy might affect surgical outcomes?

**EL** The answer is still not well understood. There is speculation that biologic agents could be impacting the ability of cells to lay down collagen or form scar tissue.

### **G&H** Are there any ways to optimize surgical outcomes in patients on biologic therapy?

**EL** Most of the recommendations that surgeons make in general to IBD patients can apply to those on biologic therapy. For example, studies have shown that active cigarette smoking significantly impacts outcomes such as wound infections, so if a patient is smoking, he or she needs to stop for at least a week or two before the surgery. Studies have also shown that the warmer the ambient temperature in the operating room, the better the outcomes in terms of wound infections.

*Dr Loftus has consulted for and received research support from AbbVie, Janssen, UCB, and Takeda.*

## Suggested Reading


Feagan BG, Panaccione R, Sandborn WJ, et al. Effects of adalimumab therapy on incidence of hospitalization and surgery in Crohn's disease: results from the CHARM study. *Gastroenterology*. 2008;135(5):1493-1499.

Frolkis AD, Dykeman J, Negron ME, et al. Risk of surgery for inflammatory bowel diseases has decreased over time: a systematic review and meta-analysis of population-based studies. *Gastroenterology*. 2013;145(5):986-1006.

Lightner AL, Raffals LE, Mathis KL, et al. Postoperative outcomes in vedolizumab-treated patients undergoing abdominal operations for inflammatory bowel disease. *J Crohns Colitis*. 2017;11(2):185-190.

Mao EJ, Hazlewood GS, Kaplan GG, Peyrin-Biroulet L, Ananthakrishnan AN. Systematic review with meta-analysis: comparative efficacy of immunosuppressants and biologics for reducing hospitalization and surgery in Crohn's disease and ulcerative colitis. *Aliment Pharmacol Ther*. 2017;45(1):3-13.

Nasir BS, Dozois EJ, Cima RR, et al. Perioperative anti-tumor necrosis factor therapy does not increase the rate of early postoperative complications in Crohn's disease. *J Gastrointest Surg*. 2010;14(12):1859-1865; discussion 1865-1866.

Selvasekar CR, Cima RR, Larson DW, et al. Effect of infliximab on short-term complications in patients undergoing operation for chronic ulcerative colitis. *J Am Coll Surg*. 2007;204(5):956-962; discussion 962-963.

Wong DJ, Roth EM, Feuerstein JD, Poylin VY. Surgery in the age of biologics. *Gastroenterol Rep (Oxf)*. 2019;7(2):77-90.