Perioperative Management of Biologic and Immunosuppressive Medications in Patients With Crohn's Disease

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CASE SUMMARY: A 23-year-old man with a 7-year history of Crohn's disease presents with a 20-cm segment of terminal ileal inflammation with an associated 12-cm stricture. The patient describes obstructive-like symptoms and a recent 20-pound weight loss. He has previously lost response to both infliximab and adalimumab, and has not had an improvement in his symptoms despite 8 months of vedolizumab. He was placed on 20 mg of corticosteroids last month because of ongoing symptoms. There is now a joint discussion with gastroenterology and the patient regarding the initiation of ustekinumab versus proceeding with a laparoscopic ileocecal resection.

CLINICAL QUESTIONS

- Do corticosteroid-treated patients have an increased risk of postoperative complications?
- Do biologic-treated patients have an increased risk of postoperative complications?
- Should elective surgery be delayed in the setting of immunosuppression?

BACKGROUND

Before the advent of biologic therapy, when corticosteroids were the cornerstone of medical management for Crohn's disease (CD), treatment algorithms were simple. Patients were treated with increasing levels of immunosuppression in parallel with disease progression. Once patients did not improve on corticosteroids and/or immunomodulator (IMM) therapy, surgery was the next step. Today, the availability of biologics has resulted in a major paradigm shift in the management of moderate to severe CD. Simple algorithms have been largely supplanted by an aggressive approach with combination biologic and IMM therapy at the time of diagnosis, in an effort to alter the trajectory of the disease, otherwise known as the "top-down approach." This is especially true in patients with severe disease, patients most likely to need operative intervention.

The most widely studied and prescribed biologics are the anti-tumor necrosis factor alpha (TNFα) agents (infliximab, adalimumab, and certolizumab pegol). However, their efficacy is limited by primary nonresponse in a third of patients, secondary loss of response in another third, and increased risk of serious opportunistic infections. Currently, if a patient has a loss of response to an anti-TNFα therapy, antibody and drug levels are obtained, and dose escalation may be attempted to induce responsiveness. Otherwise, an alternative anti-TNFα agent, or a biologic with an entirely different mechanism such as vedolizumab (anti-α4β7 integrin) or ustekinumab (anti-interleukin-12 and -23) can be initiated.

There was great enthusiasm following the Food and Drug Administration's approval of vedolizumab because of its gut selectivity and, therefore, the theoretically improved safety profile.[1] Unfortunately, vedolizumab may take up to 28 weeks to demonstrate clinical improvement in the maintenance phase.[1] Therefore, nonresponding patients may be left largely untreated during this period, becoming increasingly deconditioned and malnourished while waiting to see if vedolizumab is effective. Ustekinumab, on the other hand, offers a more immediate response, but did not achieve the same clinical response rates when compared with placebo as the anti-TNFα agents in initial large phase III trials.

Despite the increasing number of biologics and use of a top-down approach, 60% to 80% of patients with CD will require an abdominal operation in their lifetime,

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and over half will undergo multiple resections. As biologics become more widespread, not only are more patients exposed at the time of surgical consultation, but many patients have been experiencing medically refractory disease while trialing 1, 2, or 3 different agents. Thus, patients are increasingly malnourished, anemic, and experiencing complicated disease by the time surgery is considered.

PRESENTATION AND DIAGNOSIS

The 23-year-old patient above presents to your office malnourished because of ongoing obstructive symptoms. Magnetic resonance enterography shows a 20-cm segment of terminal ileal disease. Colonoscopy confirms these findings, and the endoscopist is unable to traverse the narrowed segment of terminal ileum. The gastroenterologist has a discussion with the patient that, despite 8 months of vedolizumab therapy, the patient is not improving. Therefore, he can 1) increase the dosing interval of vedolizumab, 2) switch to ustekinumab, or 3) undergo an ileocecal resection. After a multidisciplinary discussion, the plan is to proceed to the operating room for a laparoscopic ileocecal resection. To minimize postoperative risk, questions are raised regarding the perioperative management of the patient's corticosteroids and vedolizumab.

TREATMENT

At the time of surgery, 30% to 40% of patients with moderate to severe CD are steroid dependent. Several studies have consistently reported significantly increased rates of postoperative complications, including superficial surgical site infections, deep space infections, and anastomotic leaks in the setting of corticosteroids.[2] Unfortunately, many patients are unable to wean off steroids before surgery because of severe symptoms, or may have recently tapered their dose. Both scenarios raise questions about the intraoperative "stress-dose" and subsequent postoperative steroid taper. Interestingly, the widespread use of a "stress-dose" dates back to the 1950s following the publication of 2 postoperative fatalities presumably related to adrenal crises in corticosteroid-dependent patients who had not received perioperative corticosteroid supplementation. However, recent literature actually shows no advantage to stress-dose corticosteroids, causing us to rethink this dogma and shift our practice toward a modified, lower dose regimen of "stress-dose" steroids.[3] Therefore, we now use a treatment algorithm for intraoperative and postoperative corticosteroid administration based on data from recent retrospective and prospective trials (see *Algorithm and Treatment Algorithms*, top).

Immunomodulators (6-mercaptopurine, methotrexate, azathioprine) have been widely used as glucocorticoid-sparing agents for the maintenance of remission, or in conjunction with biologic therapy to increase rates of remission and decrease antibody formation to biologic therapy. Fortunately, evidence from both large retrospective reviews and systematic reviews suggests that the perioperative use of IMM does not adversely affect postoperative outcomes.[4] Because the elimination half-life of mercaptopurine and azathioprine is approximately an hour, and neither are associated with an increased risk of postoperative complications, patients can safely hold IMM on the day of surgery and resume them on postoperative day 1.

Unlike the consistent findings with corticosteroids and IMM, the data regarding postoperative outcomes in the setting of biologic therapy remain controversial. Several large single-center studies and systematic reviews have found an increased risk of infectious complications with the use of anti-TNFα preoperatively,[5] whereas others have not.[6] This conflict may be driven, in part, by the variability in time from the most recent dose of anti-TNFα, variability in drug levels at the time of surgery, or simply a reflection of disease severity rather than the biologic agent itself. Regardless, given that large systematic reviews of anti-TNFα in CD patients reported increased rates of overall infectious complications,[7] and anastomotic complications,[8] it may be important to consider the following treatment algorithm for an anti-TNFα-treated patient undergoing an ileocecal resection: a) in a CD patient with inflammatory disease who has been on maintenance biologic therapy every 8 weeks, recommend discontinuing the biologic 4 weeks before surgery and resume 4 weeks after surgery, keeping the patient on the same dosing interval; b) in a patient with stricturing CD who has been on biologic therapy without improvement, discontinue the biologic when surgery is decided upon, and ideally wait 4 weeks before operating; c) in urgent or emergent situations, there is no need to delay the operation because the potential increased risk of infectious complications does not outweigh the risk of delaying surgery; and d) the decision to divert an anastomosis intraoperatively should take into account the overall health (eg, serum albumin, >10% loss in ideal body weight) and total immunosuppression (eg, corticosteroids in conjunction with a biologic) of the patient rather than the isolated factor of whether or not the patient is on anti-TNFα therapy.

Similarly, the literature regarding postoperative outcomes in the setting of vedolizumab also remains controversial. We found a significantly increased rate of postoperative infectious complications in our own series combing all patients with IBD[9] and CD in isolation,[10] but other centers have not found the same increased risk with vedolizumab.[11] This may be related to the increased severity of disease in our referral center, or may be that our comparison cohort, the anti-TNFα-treated patients, had lower rates of infections than other centers, making

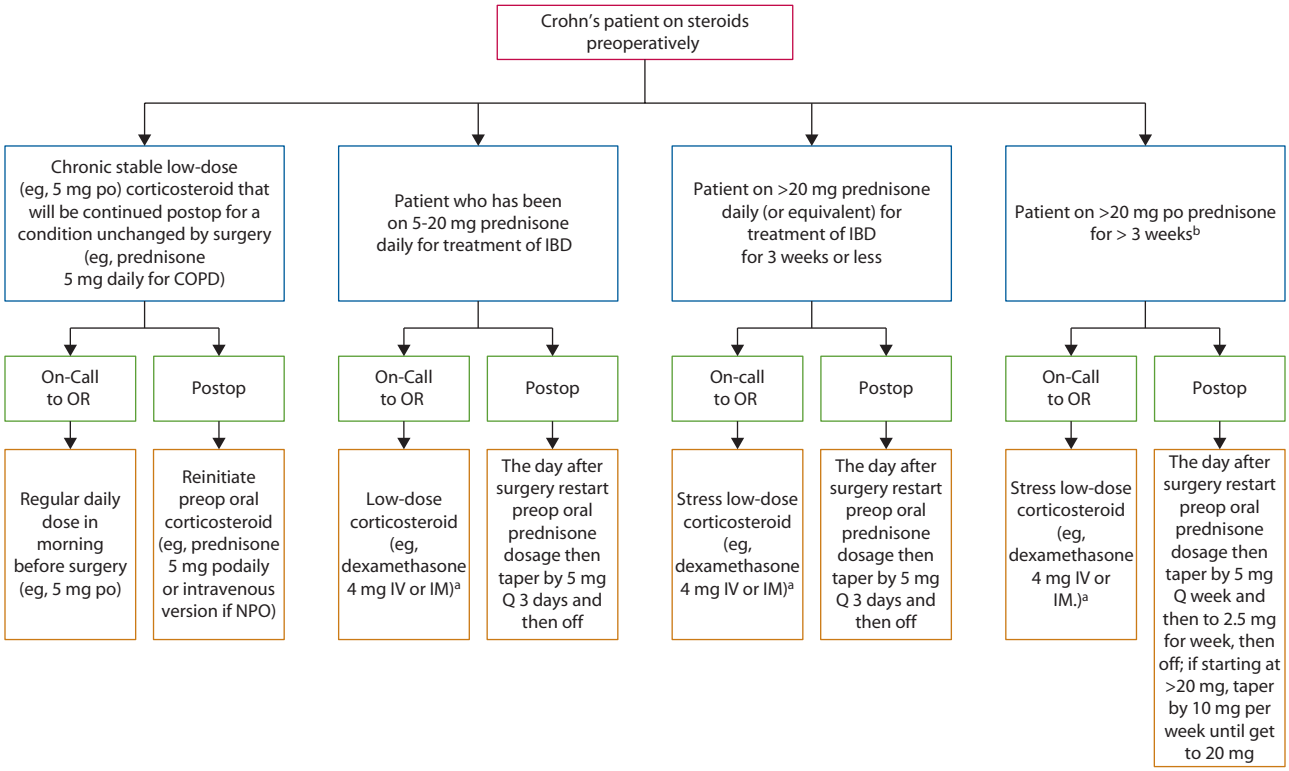
the delta between vedolizumab-treated patients and non-vedolizumab-treated patients greater. Given the outcomes we have reported in our series, it is reasonable to use the following treatment algorithm for vedolizumab-treated CD patients undergoing an ileocecal resection: a) in an elective case, delay the surgery at least 1 half-life (25 days), and up to 2 half-lives if possible; b) consider diversion in the setting of an anastomosis, especially if the patient is on concurrent corticosteroids, has an albumin <3, and/or uses tobacco; c) if emergent, counsel the patient appropriately that he or she may be at higher risk of an infectious complication and consider leaving the skin incision open to heal by secondary intention in this setting.

We recently reported our results in a multicenter retrospective review comparing postoperative infectious complications in ustekinumab-treated patients with anti-TNFα-treated patients and found no difference in the 2 groups.[12] We therefore concluded that ustekinumab was safe in the perioperative period. Thus, the same treatment algorithm as anti-TNFα-treated patients can be used until more data regarding outcomes in the setting of ustekinumab is available (see *Evaluation and Treatment Algorithms*, bottom).

CONCLUSIONS

As we enter an era marked by an expanding repertoire of biologic therapies and escalating disease severity at the time of surgery, standardization of perioperative medical management in CD is desperately needed. Future research will hopefully lead to evidence-based guidelines for the perioperative administration of immunosuppressive drugs to optimize postoperative outcomes.

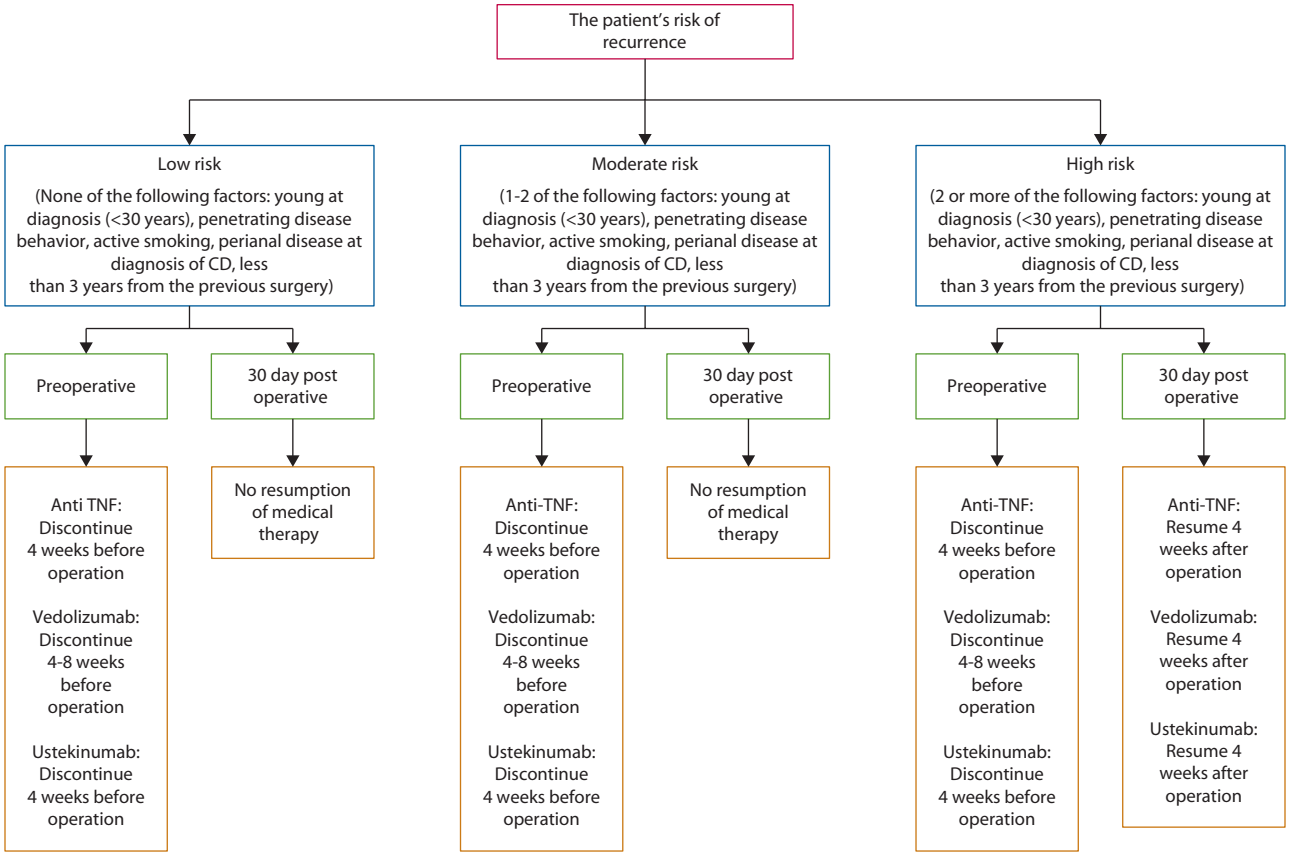
EVALUATION AND TREATMENT ALGORITHMS



[a]Or equivalent

[b]Patients who received more than 20 mg/day of prednisone or its physiologic equivalent via IM, IV, oral, per rectum, or topical routes for more than 3 weeks within 6 months before to surgery,

COPD = chronic obstructive pulmonary disease; NPO = nothing by mouth; OR = operating room; po = orally; TNFα = tumor necrosis factor alpha.



Expert Commentary on Perioperative Management of Biologic and Immunosuppressive Medications in Crohn's Disease

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Perioperative drug management of the patient with IBD is of critical interest to colorectal surgeons for at least 2 reasons. Despite the drastic improvement in medical therapy for IBD, the need for surgical intervention remains high. In addition, because IBD drugs act against various molecular players in the host immune system, there is also a rightful concern about the effects of these drugs on wound healing and infectious complications in patients undergoing surgery.

What is the evidence driving the management principles succinctly summarized by Dr Lightner in this issue of the Journal? In regard to steroids, the practice of administering high-dose perioperative intravenous steroids largely stems from just 2 case reports in the 1950s of cardiovascular collapse and death after surgery in corticosteroid-treated patients who were taken off of their preoperative steroid dose during the perioperative period. There is now level I evidence demonstrating the safety of low-dose corticosteroids. On a practical level, surgeons should order prednisone or intravenous hydrocortisone (if the patient is nil per os) at the same dose the patient was taking coming into surgery. Surgeons should also advise the anesthesiologist that there is no need for stress dose steroid dosing on induction. Perioperative use of immunomodulators appears safe, albeit solely based on retrospective data. I usually have patients stop their 6-mercaptopurine or methotrexate dose on the day before surgery.

About 20 years ago, the editor of *The Lancet* rocked the surgical world by suggesting that surgical research was dreadful, calling it a "comic opera performance." Although the quality of surgical research has improved