ADVANCES IN IBD

Current Developments in the Treatment of Inflammatory Bowel Disease

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Current Approach to Postoperative Crohn's Disease

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G&H How common are endoscopic recurrence and clinical recurrence of Crohn's disease following surgery?

MR The simple answer is that both are common. Endoscopic recurrence refers to the appearance of ulcerations or inflammation representing Crohn's disease on colonoscopy, usually within the first year after surgical treatment. Historically, in patients with Crohn's disease who have been treated with surgery and have not started a postoperative medication, endoscopic recurrence has been reported in up to 90%, which is quite high. Clinical recurrence, on the other hand, involves the return of symptoms that represent active Crohn's disease, and often a complication such as stenosis or penetrating disease. Usually within the first year of surgical treatment of Crohn's disease, clinical recurrence can be quite low. Patients typically do not feel the endoscopic recurrence that occurs within the first year. Many patients are clinically silent until they start to develop more tissue damage, deeper ulcerations, or scarring. Historically, the clinical recurrence rate has been approximately 50% by 5 years after Crohn's disease surgery.

G&H What are the most significant risk factors for postoperative recurrence of Crohn's disease?

MR Clinicians usually talk about high risk for recurrence or low risk for recurrence of Crohn's disease after surgery. Generally, risk is based upon certain features or factors that are associated with Crohn's disease. For example, a high risk for recurrence after surgery is a history of at least 1 resection for Crohn's disease. The highest-risk patients may be on their second, third, fourth, or more surgeries and have already shown recurrence after their first surgery. Another high-risk factor is penetrating disease such as a fistula or abscess. Patients who are cigarette smokers also have a high risk for recurrence, and younger patients with Crohn's disease are thought to have higher risk as well.

On the other hand, patients who have a lower risk of recurrence, or who may not have an aggressive course of Crohn's disease after surgery, are those who had their first surgery for Crohn's disease after having the disease for more than 10 years and required surgery for a stricture that involved a short length of ileum (eg, 10-15 cm). This does not mean that such patients are cured of their Crohn's disease; however, the likelihood of aggressive disease occurring shortly after their surgery is quite low.

G&H What is the current role of prophylactic therapy for postoperative recurrence of Crohn's disease?

MR Quite a few medical therapies have been evaluated for the prevention of postoperative recurrence; however, only several have shown benefit after surgery in terms of preventing postoperative recurrence. One is the antibiotic metronidazole, which speaks to the potential for the gut microbiome playing a role in postoperative recurrence. Early studies have shown that starting an antibiotic such as metronidazole at 1 to 2 g per day shortly after surgery can prevent Crohn's disease recurrence. However, metronidazole can be difficult for patients to take, as it often

causes side effects, even at lower doses (250 mg orally 3 times per day). In addition, patients need to stay on this antibiotic to prevent recurrence. Studies have found that taking metronidazole immediately after surgery for several months prevents early Crohn's disease recurrence. However, once the antibiotic is stopped, the likelihood of recurrence increases. Thus, although it might work in the short term, it is not a very good long-term solution.

The other treatments that have been most evaluated and studied, and I have been involved in several of these studies investigating the prevention of postoperative recurrence, have been biologic agents. The biologic agent that has been best studied is the anti–tumor necrosis factor (TNF) agent infliximab. Randomized, placebo-controlled studies, including the pivotal PREVENT study, have shown that infliximab significantly decreases endoscopic recurrence of Crohn's disease following surgery, although the drug does not cure it. I am often asked for the rate of endoscopic recurrence on infliximab after surgery and quote a 20% chance of recurrence. This is based upon several studies showing this low endoscopic rate of recurrence. Adalimumab, another anti-TNF agent, has also shown benefit in this area, although prospective studies are lacking.

> True postoperative prophylactic therapy should be started within 4 weeks of surgery; if therapy is started later (eg, 3-6 months after surgery), Crohn's disease has usually already returned endoscopically.

In addition, the REPREVIO study, which was presented at this year's meeting of the European Crohn's and Colitis Organisation, found that vedolizumab (Entyvio, Takeda) may show benefit and efficacy in preventing postoperative recurrence of Crohn's disease. This study was smaller than the PREVENT study and had a shorter time point assessment; however, it did show a similar low endoscopic recurrence rate. At this point, I think there are 2 good biologic options for the prevention of postoperative Crohn's disease recurrence, anti-TNF agents and vedolizumab.

G&H What is the optimal time to initiate prophylactic treatment following Crohn's disease surgery?

MR For true prevention of postoperative recurrence, the best time to initiate treatment with a biologic agent such as infliximab is within 4 weeks of surgery. Generally in my practice, by the second week after surgery, I discuss with the surgeon whether the patient is doing well. If there has been no postoperative complication or infection, I think that the ideal time to start treatment is usually within 2 to 4 weeks of surgery (the earlier, the better). However, I also want to wait a little after surgery to make sure that the patient has recovered and does not have a complication. There was a misconception in the past that starting a biologic agent within a month of surgery could be harmful, but a number of studies have now shown that this is safe and that providers should not wait for a recurrence. True postoperative prophylactic therapy should be started within 4 weeks of surgery; if therapy is started later (eg, 3-6 months after surgery), Crohn's disease has usually already returned endoscopically. Now, we are not talking about preventive treatment but about active treatment of Crohn's disease.

G&H Should any other measures be taken to help prevent postoperative recurrence of Crohn's disease?

MR The one environmental factor that is modifiable is cigarette smoking. Obviously, this does not apply to all patients, but for those who do smoke cigarettes, it is imperative not only for their general health, but for prevention of postoperative Crohn's disease that they quit smoking. Cigarette smoking has been linked to high rates of recurrence, and smoking cessation likely decreases these rates.

There have been many studies looking at whether postoperative recurrence can be prevented by altering diet, but conclusive data remain to be seen. Nevertheless, I encourage patients to have a healthy diet and avoid ultra-processed or high-sugar foods. I believe that for all Crohn's disease patients, a lower-carbohydrate, healthy diet, such as the Mediterranean diet, is prudent.

G&H How should patients be monitored if their risk of postoperative recurrence is low or if it is high?

MR Monitoring for postoperative recurrence of Crohn's disease is generally the same regardless of risk factors. Fecal calprotectin, the stool test for calprotectin, can be a good noninvasive measure of postoperative recurrence. Studies have shown that a fecal calprotectin level greater

than 150 µg/mg is associated with a higher likelihood that Crohn's disease has already returned or is active. I typically measure a patient's 3-month postoperative fecal calprotectin level. If it is less than 150 µg/mg, I recommend that the patient undergo a colonoscopy by 6 to 12 months after surgery. If a patient has a low fecal calprotectin level independent of risk factors and is taking a drug such as infliximab, my tendency now is to wait an entire year before having the patient undergo a colonoscopy. However, if the patient is not receiving any prophylactic treatment for postoperative recurrence after surgery, a colonoscopy is recommended at 6 months. If the fecal calprotectin level is over 150 µg/mg, I will recommend a colonoscopy shortly after that measurement.

One of the take-home messages is that clinicians should have a monitoring strategy in place within the first year of surgery, unlike in the past …

G&H Does small bowel ultrasound have a role for monitoring these patients?

MR There are data showing that small bowel ultrasound may be uniquely useful in evaluating postoperative recurrence. It is a noninvasive test that can be performed at the patient's bedside in the clinic. It is possible that in the future small bowel ultrasound may be used along with fecal calprotectin for monitoring postoperative recurrence of Crohn's disease in the first year. However, practically speaking, outside of centers in Europe and Canada, and perhaps a few centers in the United States, small bowel ultrasound is not widely used; many US gastroenterologists are not yet familiar with it or do not have access to it. This may change in the future, but currently in the United States, the majority of clinicians still use fecal calprotectin as a measurement for postoperative recurrence and use colonoscopy over small bowel ultrasound.

G&H What is the clinical significance of the presence of i2 disease on colonoscopy?

MR The Rutgeerts score for postoperative recurrence of Crohn's disease is based upon a 5-point score. A score of i3 or i4 represents more severe inflammation at the anastomosis or within 10 cm, whereas a score of i0 or i1 represents no or very minimal inflammation. At both ends, this score is a good predictor of progression to clinical and surgical recurrence, with low scores meaning that another surgery is less likely and high scores meaning that another surgery is more likely. i2 sits right in the middle of the scores. Based upon the Rutgeerts score, i2 historically represented more than 5 aphthous ulcerations. However, we are now realizing that some patients develop inflammation only at the anastomosis. Therefore, i2 is now being broken into i2A (with A standing for anastomosis) in which ulcerations are only at the anastomosis, and i2B in which there are ulcerations at the anastomosis that extend into the ileum. i2B leans more toward i3 and i4 (ie, more aggressive recurrence) and is treated as significant recurrence, whereas i2A is lumped more with i1, which is less likely to be aggressive recurrence. Treatment may not be changed if a patient has only i2A disease, but close monitoring should follow.

I would like to emphasize the importance of monitoring patients because clinicians cannot rely on symptoms alone; as discussed previously, many of these patients feel fine but show signs of recurrence via fecal calprotectin, small bowel ultrasound, or colonoscopy. One of the take-home messages is that clinicians should have a monitoring strategy in place within the first year of surgery, unlike in the past when we would wait for a recurrence over the years; by then, it would be too late and the patient would need to undergo another surgery. We are now much better at monitoring for early Crohn's disease recurrence after surgery, which is probably why we are seeing fewer repeat surgeries.

G&H How do Crohn's disease presentation and treatment typically compare pre- and postsurgery?

MR Generally speaking, regardless of whether patients had inflammatory, stricturing, or penetrating Crohn's disease before surgery, if the disease recurs in the small bowel, where they had it before, it typically does so in the same fashion. In other words, if the patient had a stricturing or penetrating phenotype prior to surgery, it is common for the same phenotype to recur after surgery. However, patients are now being monitored after surgery for postoperative recurrence, so inflammation is being picked up earlier, before it progresses to the same complicating factor that required surgery in the first place, such as a stricture or fistula.

When Crohn's disease recurs, treatment is similar to what would be done in any patient who has not undergone surgery—that is, there is an entire host of drugs that

clinicians can use to treat active Crohn's disease. I use the same drugs that would be used for active Crohn's disease, regardless of whether the patient had surgery. The only caveat is that when Crohn's disease aggressively recurs in a patient who was receiving medical therapy prior to surgery, the patient might be switched to a treatment with a different mechanism of action following surgery.

G&H What studies are currently underway?

MR There are several studies looking at the timing of starting therapy after surgery. However, I think the studies that have the greatest interest are those looking at the microbiome and whether particular bacteria may be linked to Crohn's disease and thus postoperative prevention of Crohn's disease in the intestine. The hope is, as mentioned previously, that some microbiome-altering approach (eg, antibiotics or other agents) may prevent postoperative recurrence. Perhaps someday we will find that altering a patient's diet by itself or altering the microbiome may be a way to prevent Crohn's disease.

Disclosures

Dr Regueiro has served on the advisory board and as a consultant for AbbVie, Janssen, UCB, Takeda, Pfizer, BMS, Organon, Amgen, Genentech, Gilead, Salix, Prometheus, Lilly, Celgene, TARGET Pharma Solutions, Trellis, and Boehringer Ingelheim Pharmaceuticals, Inc.

Suggested Reading

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