EDITORIAL

Is an Ounce of Prevention Worth a Pound of Cure: Postoperative Recurrence of Crohn's Disease?

See "Infliximab reduces endoscopic, but not clinical, recurrence of Crohn's disease after ileocolonic resection," by Regueiro M, Feagan BG, Zou B, et al, on page 000.

In Crohn's disease (CD), even complete resection of the affected intestine usually leads to recurrence of the disease starting at the anastomosis, or proximal to it.[1,2] Patients at high risk of recurrence include those with penetrating or perforating disease, those with multiple surgeries in the past and those who smoke before surgery or after surgery,[3,4] although these and other risk factors are poorly validated against all endpoints. Recurrent CD provides an opportunity to follow the evolution of the disease almost from its inception, with histologic disease preceding endoscopic ulceration, which precedes clinical symptoms and may ultimately lead to complications and further surgery (Figure 1). Intestinal content flow through the anastomotic continuity is necessary for recurrence, suggesting a role for intestinal microbiota, nutritional antigens, or other components of the intestinal contents.[5] Initial immunohistopathologic features of recurrence may manifest very early after resection and anastomosis within days, but endoscopic recurrence followed by clinical recurrence occurs at variable interval after surgery.[1,6,7] The grade of colonoscopic lesions at 1 year after resection defined by the Rutgeerts score is the best predictor of postoperative clinical disease course.[1]

After ileocolonic resection for CD, patients demonstrate endoscopic recurrence of ulceration, in 73%-95% at 1 year and 83%-100% at 3 years based on older series.[8] A more recent publication suggested lower endoscopic recurrence rates of 38% within 2 years after surgery in untreated patients followed at academic centers in The Netherlands.[9]

Reported clinical recurrence rates are significantly lower, reaching 20%-37% at 1 year and 34%-86% at 3 years.[8] A recent small prospective study reported clinical recurrence rate of 40% at 5 years after resection.[10] The variability of this clinical recurrence rate is in part owing to variable clinical endpoints used and the population of patient cohorts studied, including duration of disease, number of previous surgeries, smoking, disease phenotype, and medication history. The largest intervention studies reported a 1- to 1.5-year clinical recurrence rate of 25%,[11] 23%,[12] and 31%.[13] Second surgery rates in CD after initial surgery has been recently reported in a meta-analysis.[14]

Patients with more severe colonoscopic recurrence have earlier clinical recurrence and a more severe disease course, including repeat surgery, whereas patients with no or mild colonoscopic recurrence tend to do well over a 3-year follow-up period.[2,6,7] For the purpose of endoscopic severity scoring, the Rutgeerts score has been best established to predict disease course with the tiered endoscopic severity score reflecting well the aggressiveness of disease evolution, although small intestinal ultrasound examination, magnetic resonance imaging, wireless capsule endoscopy, and fecal calprotectin also demonstrate peri-anastomotic recurrence and predict recurrence of CD symptoms. Conventional therapies such as 5-aminosalicyclic acid, probiotics and corticosteroids are either ineffective or, at best, only modestly effective in preventing clinical recurrence, and their efficacy have led to limited adoption in clinical practice.[8] However, studies with thiopurines with or without nitroimidazole antibiotics have been positive in clinical trials to preventing endoscopic and/or clinical recurrence,[15-18] although their benefit to risk ratio and tolerability are contentious. For thiopurines, a meta-analysis of trials reported numbers needed to treat for prevention of endoscopic recurrence as 7, and for prevention of clinical recurrence as 13, with more patients suffering from adverse events leading to drug discontinuation in the thiopurine arms than in the placebo arms.[18]

The first randomized controlled trial with a tumor necrosis factor inhibitor (TNFi) was small with only 24 patients randomized after ileocolonic resection to 5 mg/kg infliximab started within 4 weeks of resection or placebo.[19] Only 1 of 11 patients on infliximab had endoscopic recurrence after 1 year compared with 11 of 13 patients who demonstrated endoscopic recurrence on placebo. Continued therapy and long-term follow-up of this study for ≥5 years showed striking long-term benefit of infliximab in reducing anastomotic recurrence demonstrated at follow-up colonoscopies (22.2% vs 93.7 in infliximab versus no infliximab groups) and surgery with a low incidence of adverse effects and no increase in postoperative complications.[20] An important finding from this study published as a separate manuscript was the poor correlation between the CD Activity Index and Rutgeerts endoscopic recurrence score,[21] reinforcing the generally poor correlation between clinical disease activity scores and endoscopic scores in CD, particularly in the postoperative phase. This makes designing a postoperative intervention study with clinical recurrence as outcome measure difficult unless the follow-up in long enough (Figure 1).

The PREVENT study, published in this issue of *Gastroenterology*, was conducted to find a definitive answer to the role of TNFi in preventing postoperative recurrence.[22] In this study, 297 patients were randomized to infliximab or placebo within 45 days of surgical resection. The primary outcome of the PREVENT trial was a composite of clinical recurrence defined as a CD Activity Index of >200 and a ≥70-point increase above baseline and endoscopic

EDI 5.4.0 DTD ■ YGAST60445_proof ■ 30 April 2016 ■ 4:47 pm ■ ce

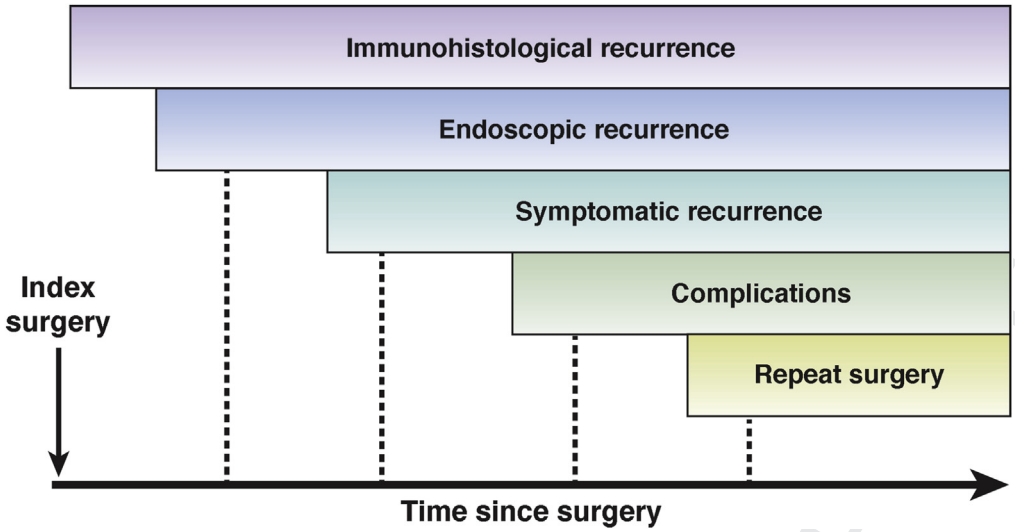

Figure 1. Sequential evolution of immunohistologic changes, endoscopic anastomotic ulcerations, clinical symptoms, and complications such as stricture, perforation, abscess, and further surgery after initial intestinal resection and anastomosis and no preventive therapy. The choice of the follow-up period to study an endpoint will affect the timing of the efficacy endpoint of an intervention after initial surgery. The pace of evolution varies depending on patient characteristics and other yet undefined factors. A 76-week outcome readout may be appropriate for endoscopic recurrence, but not necessarily clinical recurrence.

recurrence with Rutgeerts score of ≥i2 as determined by a central reader or development of a new or re-draining fistula or abscess before or at week 76. This composite endpoint has not been validated previously and its operating characteristics in the context of clinical trials are uncertain. Endoscopic recurrence before or at week 76 was a major secondary endpoint. Initiation of antibiotics or corticosteroids was prohibited and continuation of immunosuppressive drugs or 5-aminosalicylates, but not initiation, was allowed. Randomization was stratified by the number of risk factors (1 or >1) and by use of immunosuppressive drugs. Power calculations were done based on the small Regueiro et al study[19] consisting of 24 patients, which may not be representative of a much larger study. The earlier study had quite a dramatic effect size and this study considerably influenced the design and conduct of the PREVENT trial. Small underpowered studies, however, tend to exaggerate effect size and have uncertain reproducibility. This small randomized study may also have exaggerated the recurrence rate in the placebo arm and effect size for power calculation of the PREVENT study and resulted in an underpowered study.

The PREVENT study used every 8 week dosing without any induction loading on the assumption that no active disease was present at initiation; however, immunohistologic recurrence may have occurred within days of surgery and treatment was initiated as late as 45 days after resection. One may wonder if this window may have jeopardized the outcome of the trial. The lack of induction dosing was also driven by the fact that patients on infliximab before surgery may be prone to infusion reaction at second induction dosing after a variable treatment holiday. Patients who had received infliximab previously could participate in the trial provided they had not failed the drug previously or had not had complications of immunogenicity. Therefore, this study did not examine the use of infliximab continuously through surgery without a break in therapy or use induction loading after the gap in therapy or new initiation; this may also have compromised optimum dosing. In case of clinical recurrence, the dose of infliximab could be increased, but not in the case of endoscopic recurrence; scientifically, assay of therapeutic drug level and appropriate dose adjustment after endoscopic recurrence might have been optimal. Combination therapy with immunosuppressive drugs could also have optimized infliximab therapy and the lack of an opportunity to escalate therapy on detection of significant ulceration at colonoscopy is an unusual aspect of this study (see the POCER study mentioned below). The study was planned for 208 weeks maximum, but was terminated prematurely at week 104 because the primary efficacy endpoint was not met. However, this termination unfortunately minimized the assessment period over which complications may have developed requiring hospitalization and surgery.

The primary efficacy endpoint of clinical recurrence before or at week 76 was 12.9% and 20% in the infliximab and placebo groups, respectively ($P = .097$). However, the clinical recurrence rate of 50% at 1.5 years that was used as an assumption by the PREVENT study authors seems to be generally higher than supported by the literature. Time to clinical recurrence was also not significantly different between the infliximab and placebo arms.

Endoscopic recurrence at or before week 76 as defined by centrally read Rutgeerts score of ≥2 as well as fistula or abscess recurrence or development of treatment failure, was observed in 30.6% in the infliximab group and 60% in the placebo group. This is an impressive difference in treatment effect but this itself is an unvalidated composite