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Optimizing post-operative Crohn's disease treatment

Eugeni Domènech, Míriam Mañosa, Triana Lobatón, Eduard Cabré

Hospital Universitari Germans Trias i Pujol and Centro de Investigaciones Biomédicas en Red de Enfermedades Hepáticas y Digestivas, Spain

Abstract

Despite the availability of biological drugs and the widespread and earlier use of immunosuppressants, intestinal resection remains necessary in almost half of the patients with Crohn's disease. The development of new mucosal lesions in previously unaffected intestinal segments (a phenomenon known as post-operative recurrence, POR) occur within the first year in up to 80% if no preventive measure is started soon after resectional surgery, leading to clinical manifestations (clinical recurrence) and even needing new intestinal resection (surgical recurrence) in some patients. That is the reason why endoscopic monitoring has been recommended within 6 to 12 months after surgery. Active smoking is the only indisputable risk factor for early POR development. Among several evaluated drugs, only thiopurine and anti-tumor necrosis factor therapy seem to be effective and feasible in the long-term both for preventing or even treating recurrent lesions, at least in a proportion of patients. However, to date, it is not clear which patients should start with one or another drug right after surgery. It is also not well established how and how often POR should be assessed in patients with a normal ileocolonoscopy within the first 12 months.

Keywords Crohn's disease, recurrence, thiopurines, anti-TNF, ileocolonoscopy, calprotectin

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Introduction

Crohn's disease (CD) is a chronic relapsing and remitting inflammatory condition of the intestine. Most patients present a pure inflammatory pattern at disease onset, but up to 80% of them will either present chronic inflammatory activity despite medical therapy, or develop intraabdominal penetrating complications or intestinal stenosis within the first ten years after CD diagnosis leading to intestinal resection in most of these cases [1-3]. In fact, large hospital- and population-based cohorts recently reported a surgical rate as high as 50-60%, 10 years after diagnosis [4,5].

It is still controversial whether the most powerful currently available drugs are able to modify the natural history of CD and, thus, reduce the need for surgery. In a classical retrospective study, Cosnes *et al* showed that the increasing use of thiopurines during the eighties and nineties was not associated with a reduction in the rate of intestinal resection. The authors suggested that this was probably due to a late introduction of such drugs [6]. In a similar study, our group assessed the impact of the availability of infliximab on the natural history of CD [7]. Once again, we did not find differences in terms of surgical requirements between two inception cohorts before and after infliximab availability, suggesting that, when used in a step-up strategy, anti-tumor necrosis factor (anti-TNF) therapies do not decrease the need of intestinal resections. A trend towards an earlier and more intensive therapeutic approach has emerged in the last years. However, none of the randomized control trials (RCTs) performed to assess the impact of the early introduction of thiopurines [8-10] on the natural course of CD have been able to demonstrate a reduction in the need of intestinal resections, even when associated with an induction schedule with anti-TNF [11]. It is noteworthy that all these studies were not powered enough and had a too short follow up to address surgical outcomes. In a recently published population-based CD cohort from Cardiff, Ramadas *et al* showed that surgical rates had been progressively reduced in the last 3 decades. Moreover, they showed that, at the beginning of the 21st century, most patients who underwent surgery for CD did so within the first two years from disease diagnosis. This suggested that surgery is only inevitable among those patients with complicated disease patterns (stenosis, penetrating

IBD Unit, Gastroenterology Department, Hospital Universitari Germans Trias i Pujol and Centro de Investigaciones Biomédicas en Red de Enfermedades Hepáticas y Digestivas, Spain

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Correspondence to: Dr. Eugeni Domènech, Hospital Germans Trias i Pujol, Carretera del Canyet s/n, Servei d'Aparell Digestiu, 5ª planta, edifici general, 08916 Badalona, Catalonia, Spain, Tel.: +34 93 497 8909, Fax: +34 93 497 8951, e-mail: eugenidomenech@gmail.com

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behavior) at disease onset or early in its course [12], and that the earlier use of immunosuppressants and/or biological agents do impact in the long-term.

Anyway, as shown in many population-based studies, 20-40% of CD patients will present intestinal stenosis or penetrating abdominal complications at disease onset [12-14]; at least this proportion of patients are unlikely to avoid surgery in their lives with currently available drugs and treatment strategies.

Natural history of post-operative CD

Although intestinal resection remains a cornerstone in the management of CD, surgery is not curative and new intestinal lesions develop in previously non-affected intestinal segments (mainly the neoterminal ileum), a phenomenon known as post-operative recurrence (POR). POR may be defined in different ways; the most frequently used are: endoscopic POR (development of mucosal lesions seen at ileocolonoscopy); clinical POR (development of clinical symptoms related to the development of intestinal CD lesions); and surgical POR (need for a second intestinal resection due to POR). Rutgeerts *et al*, in a classical study, clearly showed that morphological (endoscopic) lesions precede symptoms, and re-intervention is often the last event in the natural history of post-operative CD [15]. Some years later, in a landmark article, the same group designed an endoscopic score that correlated the severity of endoscopic lesions in the neoterminal ileum with the risk of clinical and surgical POR [16]. The so-called "Rutgeerts' endoscopic score" is still the gold standard for assessing POR and is routinely used as a surrogate marker of clinical POR in all RCTs and also in clinical practice.

POR is almost constant in the absence of preventive treatment. In the setting of RCTs assessing the efficacy of several drugs for POR prevention, up to 50-90% of patients in the placebo arms recurred within two years after surgery [17-19]. Moreover, POR occurs early after surgery. In an elegant study, D'Haens *et al* demonstrated that microscopic inflammation occurred only a few days after the infusion of the intestinal content downstream a protective ileostomy [20]. Afterwards, several RCTs showed that macroscopic lesions (endoscopic POR) occur in 30-60% of patients as soon as 12 weeks after surgery [18,21-23]. Under this perspective, it seems reasonable to prevent POR early after surgery and in almost all patients.

Risk factors of POR

As mentioned before, most patients' lesions recur after surgery; there is, however, a small proportion of operated CD patients who will remain free of recurrence and thus will not need preventive measures. Many studies and meta-analyses aimed to identify risk factors for POR. Several clinical and epidemiological factors (gender, age of CD diagnosis, time from CD diagnosis to surgery, stenosing or penetrating disease pattern), surgical-related factors (type of anastomosis, length of the resected intestinal segment, blood transfusions, postoperative complications), histological features (presence of granulomata, myenteric plexitis, involvement of resected margins), or even serologic markers (such as anti-*Saccharomyces cerevisiae*) or genetic polymorphisms (i.e., NOD2) have been contradictorily correlated with POR. All these factors were recently addressed in an accurate systematic review [24]. Several factors may account for such controversial results. First, the retrospective design of most of the studies dealing with risk factors for POR often leads to missed relevant information. Second, in a majority of these studies clinical or surgical POR (instead of endoscopic) were the main outcomes, inducing bias in many possible ways. There is no widely accepted definition of clinical POR; in this sense, clinical symptoms or a change in medical treatment should not be accepted for the definition of clinical POR in the absence of morphological POR (endoscopic, radiological). This might be the reason why most of the above mentioned risk factors have not been confirmed in the setting of prospective RCTs or in studies were endoscopic POR was the main outcome. Time of follow up should also be always taken into account. For instance, it is widely known that patients with stenosing behavior may need repeated resections in their lifetime, but with longer intervals as compared with those patients requiring re-interventions for penetrating disease. In studies where the follow up is not long enough, penetrating but not stenosing behavior may wrongly appear as a risk factor for surgical recurrence. Finally, patients with endoscopic or clinical POR may have changed or started medical therapies, a factor that is often disregarded in this kind of study.

By contrast, active smoking has been repeatedly correlated with an increased risk of POR [25,26]. Four recent studies (three of them prospective, two reported only in abstract form) that included a large number of patients have not only confirmed this relationship but also found active smoking to be an independent risk of endoscopic POR [27-30]. Thus, quitting tobacco should be emphatically advised in patients undergoing intestinal resection; conversely, patients who continue smoking after surgery are at high risk of POR and active preventive measures and/or close monitoring are warranted.

In addition, there are some clinical scenarios that are commonly considered as high-risk for POR although they are not established risk factors themselves. For instance, patients undergoing a second or third intestinal resection are usually considered as a high-risk population; however, this is related to the risk of developing short bowel syndrome if POR develops, rather than to the risk of POR itself. The same applies for patients operated on at disease onset or after a short duration of disease.

Prevention of POR

The first and the only universally accepted preventive measure for POR is giving up smoking. As mentioned before, active smoking is the only confirmed independent and reversible risk factor. Unfortunately, smoking cessation is missed too often in prevention algorithms and reviews. Two

recent studies reported smoking cessation rates of 30-40% at one year among smokers who attempted to give up smoking after only a careful warning to patients about the deleterious role of tobacco in CD [31,32]. Dedicating time and effort to smoking cessation should be a priority, particularly in this clinical setting.

Since POR is almost constant after intestinal resection, many drugs have been evaluated for medical prophylaxis in RCTs. Probiotics, interleukin-10, and corticosteroids have not proven to be effective. Some others (such as fish oil or enteral nutrition) suggested some efficacy in small trials [24]. To date, only four compounds can be considered for POR prevention: 5-aminosalicylates (5-ASA), imidazolic antibiotics (metronidazole or ornidazole), thiopurines (azathioprine or mercaptopurine), and anti-TNF agents.

5-ASA compounds are the most frequently tested drugs for POR prevention, as compared to placebo or even to other drugs. The great heterogeneity among RCTs raised the publication of several meta-analyses; four of them agreeing that 5-ASA are only of marginal benefit [33-36]. In fact, their results point at no efficacy to prevent endoscopic but clinical POR, suggesting that 5-ASA might only delay the development of symptoms. Despite this, and probably due to their good safety profile and tolerability, 5-ASA have been repeatedly considered for patients at "low" risk for POR in several reviews [24,37,38]. Imidazolic antibiotics have been evaluated in two RCTs from the same group, reporting efficacy in preventing both endoscopic and clinical POR in the short-term [39,40]. However, the rate of discontinuation because of side effects (up to 20%) and, most importantly, the risk of serious and irreversible long-term adverse effects are major drawbacks for their use. Trials evaluating the role of thiopurines show excessive heterogeneity, with relevant differences between trials regarding dosing, timing for endoscopic evaluation and study populations. Nevertheless, three different meta-analyses concluded that these drugs are efficient in preventing both endoscopic and clinical POR [35,36,41]. Finally, anti-TNF agents are the latest group of drugs that have been included in the medical armamentarium to prevent POR. Although only two small RCTs evaluating infliximab and adalimumab for the prevention of endoscopic and clinical POR are available [42,43], their results raised great expectations in this clinical setting. Surprisingly, despite the fact that no direct comparison to thiopurines has been reported yet, some authors consider anti-TNFs as the drug of choice for patients at high risk for POR [44,45]. Fortunately, at least four RCTs comparing different anti-TNFs (2 with adalimumab, 1 certolizumab and 1 infliximab) to placebo, thiopurines or mesalazine are already ongoing [46].

To pose an algorithm for POR prevention is not easy. First, patients' stratification in "high" or "low" risk becomes quite a fairy tale. In real life, almost half of these patients are active smokers at the time of surgery, but we cannot guess who will make up this 30-40% of patients that (hopefully) will become long-term quitters, and POR prevention should start soon after surgery. Beyond active smoking, no one knows whether risk should be considered as "high" in patients presenting with only one or more of the proposed risk situations. Under the premises that: 1) POR is almost constant in the majority of patients; 2) 5-ASA is of marginal benefit; 3) imidazolic antibiotics are efficient in the short-term; 4) thiopurines are the most effective drugs to prevent POR to date; and 5) anti-TNF drugs are expensive and unrestricted use for POR prevention is not evidence-based, our proposed algorithm is shown in Fig. 1. All patients should be strongly advised to avoid smoking and, if possible, active cessation programmes should be available. We firmly believe that prevention with thiopurines should be started in all patients unless there is intolerance or contraindications for them, with the exception of those patients operated on for pure and short intestinal stenosis. Two RCTs evaluated the role of metronidazole for the first three months after surgery in addition to azathioprine. In the first, this combination therapy resulted in a higher efficacy as compared to metronidazole alone [47]. In the second, although the study was not powered enough, a marked trend towards a higher efficacy was found for combination therapy as compared to azathioprine alone [48]. Thus, the addition of an initial 3-month course of metronidazole may be a cost-effective strategy. In this algorithm, anti-TNF treatment should be limited to those patients in whom thiopurines previously failed to prevent POR or those who are intolerant to these drugs.

Who, how, and when in monitoring POR

Clinical monitoring should be the easiest way to assess the development of POR (clinical POR). However, ileocecal resection (particularly in case of extensive ileal resection) may be associated with the development of abdominal symptoms such as diarrhea or abdominal cramps secondary to bacterial overgrowth, bile salt malabsorption, or short bowel syndrome, and these might be misinterpreted as disease recurrence. Moreover, no clinical activity index has been validated for patients with previous ileocolonic resection, and the value of the changes in Crohn's disease activity or Harvey-Bradshaw indices in this clinical setting is still to be established. As mentioned above, the severity of mucosal lesions correlate with the likelihood to develop clinical POR, allowing the use of the Rutgeerts' endoscopic score as a surrogate marker of clinical recurrence. This index scores recurrent ileal lesions as i0 (no lesions); i1 (less than 5 aphthous lesions); i2 (more than 5 aphthous lesions with normal mucosa between the lesions, or skip areas of larger lesions or lesions confined to <1 cm from the ileocolonic anastomosis); i3 (diffuse aphthous ileitis with diffusely inflamed mucosa); and i4 (diffuse inflammation with larger ulcers, nodules, and/or narrowing) [16].

Rutgeerts' score is widely used both in the setting of RCTs and in clinical practice, but it has some limitations. The cut-off to define endoscopic POR is usually i2, but a careful reading of the Rutgeerts' study shows that, while the clinical outcome was markedly worse in patients with i3 or i4, patients with i2 had a less predictable outcome. The relevance of those mucosal lesions confined to the anastomosis (scored as i2 in the Rutgeerts' index) is under debate, and some authors claimed that they could be related to staples and/or ischemia [49]. Our group,

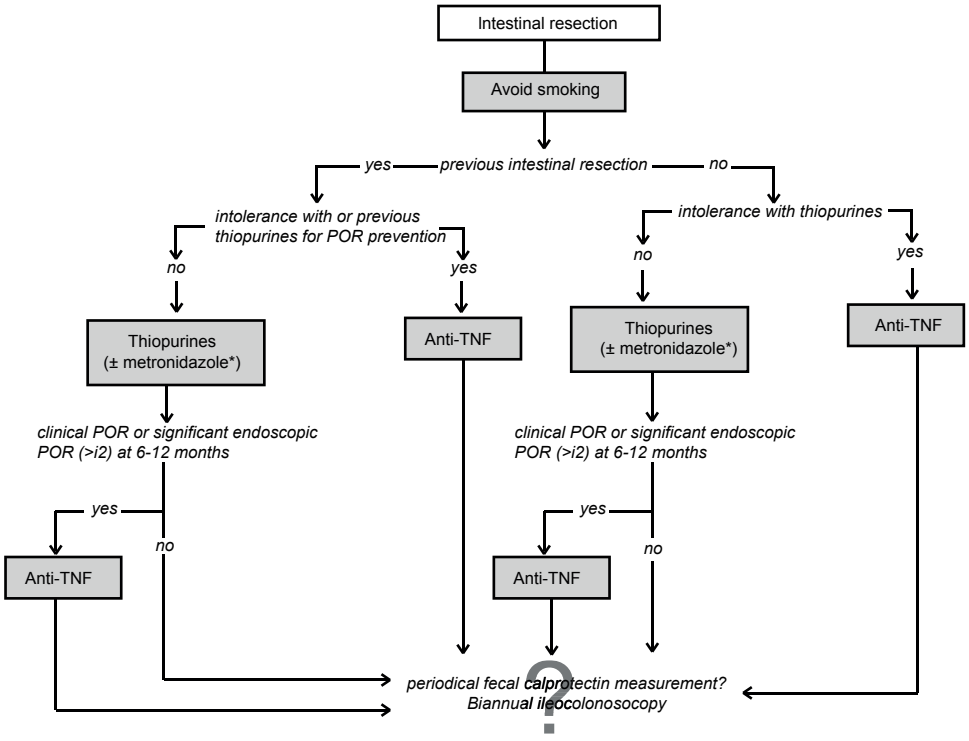

Figure 1 A rational preventive, therapeutic, and monitoring strategy for post-operative Crohn's disease
*15-20 mg/kg/day for the first 3 months after surgery
POR, post-operative recurrence; i2, Rutgeerts' endoscopic score of 2

in a prospective study, found that these localized lesions have a low probability to progress to more severe endoscopic lesions or to clinical POR in the mid-term [50]; for this reason we proposed to differentiate them as i2a. This debate prompted the emerging concept of "significant" or "severe" endoscopic POR (score i3 or i4) that has been increasingly used in recent years. Finally, although POR usually occurs at the neoterminal ileum after ileocecal resection, some patients may develop mucosal lesions in the colon. The Rutgeerts' score does not cover this possibility and a modified version including recurrent lesions in the colon has been proposed by some authors [51].

Despite the advantages of POR assessment by means of ileocolonoscopy, this is an invasive test and neoterminal ileum is not always accessible due to surgical anastomotic configurations. Thus, alternative non-invasive imaging techniques should be useful in certain settings. Wireless capsule endoscopy (WCE) is more comfortable and better tolerated by patients than colonoscopy, it does not need sedation, and it is less influenced by technical limitations (impossibility to access the neoterminal ileum). WCE demonstrated a similar efficacy to ileocolonoscopy to detect mucosal lesions in the neoterminal ileum [52-54]. However, WCE detect mucosal lesions in upper segments of the gastrointestinal tract whose significance is uncertain; whereas some authors argue that they must be considered as disease recurrence, the lack of a careful assessment of the upper gastrointestinal tract prior to surgery makes it impossible to know whether they were already present before surgery. Furthermore, WCE interpretation is associated to a moderate interobserver variability [55]. Small bowel magnetic resonance (MR) imaging is also a non-invasive technique that allows visualization of the entire intestine. It has been compared to ileocolonoscopy with good correlation to the Rutgeerts' score [55-57]; in addition to the scarce data available, MR enterography has the disadvantage of underestimating superficial mucosal lesions seen at ileocolonoscopy or WCE. Abdominal ultrasonography is also non-invasive, well-tolerated, and it is cheaper than the other techniques. The administration of polyethylene glycol as an anechoic luminal contrast (small intestine contrast ultrasonography, SICUS) to overcome the presence of gas in the intestinal loops overcomes these limitations and allows a good assessment of wall thickness. Several studies comparing SICUS to ileocolonoscopy in assessing POR suggest a good correlation with the Rutgeerts' endoscopic score [58-60]. However, it has to be kept in mind that abdominal ultrasonography is operator-dependent and always requires an experienced sonographist. Despite the fact that good correlation has been reported for all these imaging techniques with ileocolonoscopy, there is no validated index of POR for any of them.

Fecal markers seem to be the most realistic alternative to ileocolonoscopy in the forthcoming years. Fecal calprotectin has been demonstrated to correlate with intestinal lesions better than clinical indices or C-reactive protein and it is increasingly used in clinical practice. In the setting of POR, calprotectin showed good correlation with the Rutgeerts' score in three large series (two of them still in abstract form), and levels below 100 mg/kg showed good specificity of lack of mucosal lesions [61-63].

Bearing all this information in mind, there is agreement in that all CD patients undergoing intestinal resection with ileocolic anastomosis should be monitored with ileocolonoscopy 6-12 months after surgery, regardless of risk factors or treatment received. It is still to be evaluated whether faecal calprotectin could be used as screening tool for the first or subsequent endoscopic assessments. For patients who refuse ileocolonoscopy or those in whom neoterminal ileum is not accessible, MR enterography seems to be the best alternative although SICUS might be even better in experienced hands. There is no widely accepted consensus on how–often those patients should be monitored for POR assessment. Recent data from our own group showed that in patients on thiopurines who have no evidence of endoscopic POR at the first endoscopic assessment there is a steady increase of endoscopic POR over time, suggesting that even in the absence of mucosal lesions within the first year these patients should be repeatedly monitored [64]. It remains to be established whether imaging techniques should be periodically repeated in all patients or if they should be only considered in case of repeated high levels of fecal calprotectin.

Since the study of Rutgeerts *et al* suggesting that POR did not develop in patients with terminal or diverting ileostomy [65], no assessment and prophylaxis for POR is generally advised in this subset of patients. However, two recent series reported clinical POR in up to 30% 10 years after surgery [66,67]. In this perspective, it seems reasonable that morphological assessment (ileoscopy through ileostomy, MR enterography, CT enterography) should be performed anyway, but perhaps at longer intervals. Even less data is available for patients with Crohn's colitis undergoing subtotal colectomy with ileo-rectal anastomosis. From a logical point of view, it is the authors' perception that these patients should follow the same monitoring strategy as those with ileocolic anastomosis after ileocecal resection, although preventive therapy might be limited to those with previous rectal involvement.

Treatment of POR

Whether patients are on preventive medical therapy or not, early endoscopic monitoring is advised in order to consider treatment escalation in case of early POR. As previously commented, 30-90% of patients will develop endoscopic POR at 6-12 months in the absence of preventive therapy. Even if thiopurines are started soon after surgery, up to 50% of patients may show ER within the first year following surgery [47,48], and it has been shown that this percentage may increase over time [50]. Therefore, it is reasonable to escalate treatment if endoscopic POR develops in order to avoid clinical POR or, at least, surgical POR.

Some studies have shown that, in untreated patients with subclinical endoscopic POR, thiopurines and anti-TNF agents can avoid CR and even improve or reverse mucosal lesions. D'Haens *et al* reported the reversion of what they called "severe recurrent ileitis" into mucosal healing in 4 of 6 patients treated with corticosteroids and azathioprine [68]. Reinisch *et al* provided the results of the first RCT comparing the efficacy of azathioprine versus mesalazine to prevent clinical POR in patients with asymptomatic POR [69], showing that almost two thirds of patients treated with azathioprine and around one third of those treated with mesalazine improved mucosal lesions (P=0.023). More recently, Regueiro reported the long-term follow up of his RCT [42] in which patients treated with placebo were treated open-label with infliximab, showing that infliximab is also efficient in preventing clinical POR and reverting mucosal lesions in patients with asymptomatic POR [70].

Few data are available on treatment of patients who develop POR while on medical prevention. Yamamoto *et al* reported the efficacy of infliximab and azathioprine for 6 months in 16 patients with endoscopic POR despite mesalazine preventive therapy [71]. Infliximab achieved endoscopic improvement in 75%, as compared to 38% with azathioprine, with complete mucosal healing in 38% and 13%, respectively. Conversely, our own research failed to show any benefit of adding mesalazine in patients with endoscopic POR (i2 or i3) while on azathioprine [72].

Concluding remarks

Intestinal resection is still needed in more than half of our CD patients. POR is almost the rule in most CD patients undergoing ileocecal resection with ileocolic anastomosis; thus, most patients should start efficient preventive measures (give up smoking and, in a vast majority, thiopurine therapy). Despite preventive measures, all patients must be endoscopically monitored within the first year after surgery. Treatment escalation is advised in the setting of advanced mucosal lesions. However, there are still many issues to be evaluated in the near future such as risk factors for endoscopic POR and treatment stratification, subsequent monitoring beyond the first year from surgery, or the management of mild-to-moderate mucosal lesions.

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