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Surgery for Crohn's disease in the era of biologicals: A reduced need or delayed verdict?

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Abstract

Crohn's disease (CD) is a chronic inflammatory bowel disease that can affect the entire gastrointestinal tract. Ultimately, up to 70% of all patients will need surgery, despite optimized medical therapy. Moreover, about half of the patients will need redo-surgery because of disease recurrence. The introduction of anti-tumor necrosis factor (TNF) drugs (Infliximab in 1998) revolutionized the treatment of CD. Different randomized trials assessed the efficacy of anti-TNF treatment not only to induce, but also to maintain, steroid-free remission. Furthermore, these agents can rapidly lead to mucosal healing. This aspect is important, as it is a major predictor for long-term disease control. Subgroup analyses of responding patients seemed to suggest a reduction in the need for surgery at median-term follow up (1-3 years). However if one looks at population surveys, one does not observe any decline in the need for surgery since the introduction of Infliximab in 1998. The short follow-up term and the exclusion of patients with imminent surgical need in the randomized trials could bias the results. Only 60% of patients respond to induction of anti-TNF therapy, moreover, some patients will actually develop resistance to biologicals.

Many patients are diagnosed when stenosing disease has already occurred, obviating the need for biological therapy. In a further attempt to change the actual course of the disease, top down strategies have been progressively implemented. Whether this will indeed obviate surgery for a substantial group of patients remains unclear. For the time being, surgery will still play a pivotal role in the treatment of CD.

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INTRODUCTION

Crohn's disease (CD) is a chronic inflammatory disorder which can affect the complete gastrointestinal tract. Only a minority of patients (10%-15%) will experience a prolonged relapse-free interval after initial diagnosis; most patients develop a mild chronic disease pattern^[1]. This relapsing inflammation results in progressive bowel occlusion and/or fistula and abscess formation. A large majority of patients (70%-80%) will require surgical treatment within a time frame of 10 years^[2,3]. The type of surgery is dictated by the anatomic location and/or the related complication(s). Depending on the localization of the disease, CD tends to have a different clinical

phenotype. Indeed, ileocolonic and small bowel involvement is more prone to develop occlusive disease than colonic affection^[2,4]. Thus, small bowel or ileocolic distribution will increase the rate of surgery compared to Crohn's colitis. Intractable inflammation is a rather seldom indication for surgery. Penetrating anal disease often leads to surgery in order to control sepsis and drain fistulas. Unfortunately, surgery in CD is not curative and the majority of patients will have early endoscopic relapse, despite clinical remission^[5]. Over time, symptomatic recurrence demands medical treatment, and up to 40% of patients will eventually need secondary surgery^[2]. This explains the tendency to avoid 'too early' surgery. If surgery is needed, the focus should be on bowel sparing and minimally invasive surgical techniques.

Progressive understanding of the pathogenesis of CD resulted in significant changes and improvements in its medical treatment. The use of immunomodulators (such as azathioprine and methotrexate) has not decreased the need for surgery, nor has it decreased hospitalization rates either^[2,6]. The introduction of anti-tumor necrosis factor (TNF) treatment in 1998 revolutionized the treatment paradigms. TNF antagonists proved to induce a rapid clinical remission in about 60% of the cases^[7,8]. In randomized controlled trials, anti-TNF therapy seemed to maintain remission in contrast to steroid regimens^[9-12]. Moreover, mucosal healing has even been obtained in a subset of patients, which could support a sustained clinical remission^[13-15]. Therefore, one could expect that, in the long run, fewer patients would need to undergo major abdominal surgery. This paper reflects on some aspects of the impact of anti-TNF treatment on the rates of surgery in CD patients.

NEED FOR SURGERY IN THE MARGIN OF LARGE RANDOMIZED TRIALS

Several randomized controlled trials have analyzed the maintenance of clinical remission in CD comparing patients who received anti-TNF agents or placebo^[9-12]. Besides an initial response rate of about 60%, a majority of patients will show sustained remission with anti-TNF therapy. Steroid discontinuation was also significantly better in the treatment groups. Moreover, an endoscopic substudy of a Crohn's disease clinical study evaluating infliximab in a new long-term treatment regimen demonstrated that about 50% of patients with a clinical response will also have mucosal healing^[14]. Considering that control of inflammation and induction of mucosal healing is predictive for long-term disease activity and bowel preservation, one could expect an effect of anti-TNF treatment on the rate of surgery^[13]. Feagan *et al*^[16] evaluated the influence of maintenance adalimumab therapy on the rate of hospital admissions and surgery in a post-hoc analysis of the Crohn's Trial of the Fully Human Antibody Adalimumab for Remission Maintenance trial. The authors came to the conclusion that adalimumab maintenance therapy significantly reduced hospitaliza-

tions and surgery for CD amongst the enrolled patients. Mucosal healing seems a promising surrogate marker of deep and prolonged clinical remission. This alteration in disease course should lead to a reduced need for surgery. More predictors are needed, not only to select those patients who will develop an aggressive and complicated disease pattern to enable early installment of immunosuppressive therapy, but also to select patients for "early" surgery to obtain a prolonged clinical remission.

One year after primary surgery, as many as 72% of the patients had already developed endoscopic recurrence, mainly at the anastomosis. Clinical manifestations of the disease are, however, often absent in this early postoperative stage^[17]. About one half of patients will need redo-surgery over a 20-year period^[2]. Although a high recurrence-rate is observed after surgery, there is no consensus about the postoperative therapy regimen. Considering the high amount of endoscopic recurrences, one could wonder if prophylactic medical therapy after surgery can play a role. Studies have been conducted to find the best prophylactic regimen. Aminosalicylates regimens seem to have modest effects on the postoperative recurrence rate. It is therefore not recommended to use them in a postoperative setting^[18,19]. Nitromidazole and ornidazole have demonstrated a significant drop in recurrence, but at the expense of important side effects, making these therapies not longer suitable for prophylactic use. Budenoside has no long term effect, but is indicated to suppress acute relapse. Azathioprine and 6-Mercaptopurine have already been used in randomized controlled trials to assess the effect on rate of recurrence after surgery. Because there was a high drop-out rate during the follow-up period, no convincing results have been found in these series^[20,21]. The advent of anti-TNF agents and their demonstrated effect on mucosal healing in the preoperative setting has given hope to care providers that relapses can be avoided when administered postoperatively. Regarding this important clinical question, two randomized controlled trials have been published so far. Twenty-four patients were randomized after ileocaecal resection to receive infliximab or a placebo for one year^[22]. The endoscopic and histologic recurrence rate after one year was significantly lower in the infliximab group. There was no significant difference in clinical recurrence rate, though more patients showed relapse after one year in the placebo group. Another study randomized 26 postoperative patients with proven endoscopic recurrence six months after receiving mesalamine in three different groups: one received infliximab, another azathioprine and the last group continued mesalamine^[23]. Control of endoscopic inflammation was improved in the infliximab group compared to the azathioprine and mesalamine group, demonstrating the clear suppressive effect of infliximab. In these two small trials, the positive impact of infliximab in avoiding postoperative recurrence has been demonstrated. These conclusions have to be interpreted with the greatest caution considering the small sample sizes and the short follow-up periods. No conclusion can be made about the usefulness of infliximab to

prevent recurrences. Large prospective randomized trials with a long follow-up have to be designed to assess the benefit of anti-TNF agents on postoperative recurrence. Moreover, one could wonder if it is reasonable to give prophylactic treatment after resection, considering the high costs and the number of patients who will be treated that would not develop recurrence. It is more likely to stratify the risk factors of every patient to assess the need of postoperative medical treatment. One of the most powerful methods for assessing patients is performing a colonoscopy six to twelve mo after resection. Rutgeerts *et al*^[51] demonstrated the predictive value of endoscopic recurrence. Indeed, patients with severe endoscopic recurrence within one year after surgery are at greater risk of developing clinical recurrence.

Approximately one third of all CD patients will develop perianal disease, including skin tags, ulcers, low and high fistulas, rectovaginal fistulas, perianal abscesses, anorectal strictures and cancer^[24]. Complex perianal fistulas are challenging to treat and can lead to destruction of the anal sphincters with intractable incontinence as a result. Twenty-five percent of patients with anal CD will eventually need a proctectomy^[25]. The classical medication used for CD, like antibiotics and immunomodulators, have not demonstrated any beneficial effect in the treatment of fistulizing CD^[26-28]. In contrast, infliximab maintenance therapy seems to reach superior durable and complete fistula closure, even in patients not responding to other medical treatments^[29,30]. This seems to have an impact on the surgery rate and hospital stay^[31]. There is, however, some concern about treatment with infliximab inducing healing of the external opening and suppressing the inflammatory reaction around the fistula tract without eradicating the tract^[32]. Magnetic resonance imaging of patients in clinical remission after infliximab treatment still showed inflammation and subsisting fistula tracts. Some are concerned about the possibility of fistula recurrence after withdrawal of treatment. More extensive investigation will be needed to test this hypothesis.

NEED FOR A WIDE SURGERY POPULATION (THE REAL WORLD)

In view of the aforementioned randomized controlled trials, it may be possible to change the course of the disease in patients treated with biologicals, perhaps leading to a decreasing need for resectional surgery. Other large population based series, however, are less convincing. Lazarev *et al*^[33] showed that, despite the increasing use of infliximab, the rate of small bowel resection has remained unchanged over the years in a large referral centre in Pittsburgh. Moreover, the relative frequency of stricturing and penetrating disease did not change over time. Bewtra *et al*^[34] analyzed hospitalization and surgery trends for inflammatory bowel disease from 1990 to 2003. They observed a steady rate in the number of surgical interventions for CD with a significant increase in hospitalization rate, despite the introduction of inflix-

imab in 1998. Jones *et al*^[35] concluded in their series that surgery for penetrating small bowel disease increased with 60% from 1993 to 2004 despite the increasing use of infliximab.

In contrast, two population-based series reported a significant decrease in hospitalization and surgery rate^[36,37]. In a series from Wales, stoma formation and the long-term need for steroids are likely to have been influenced by the use of infliximab, but only 16% of patients had been prescribed anti-TNF agents in this series. Moreover, 614 consecutive patients responding to induction therapy with infliximab were observed to evaluate the long term clinical benefit of this anti-TNF agent^[38]. Two thirds of these patients seemed to have a sustained benefit of this therapy regimen. There seemed to be a decreased rate of surgery for patients responding to medication. Loss of response was inadvertently associated with an increased risk of surgery. This study demonstrated that infliximab could have an impact on disease course in responding patients. However, this group was not compared to patients not receiving anti-TNF agents. More recently it has been shown that the use of infliximab, and to a lesser extent of azathioprine, seems to be associated with a decreased risk of surgery^[39]. Interestingly, in this retrospective cohort study including 296 patients with CD between 2000 and 2008, the median follow-up was 57 mo, which was much longer than in the randomized controlled trials.

DISCUSSION

The introduction of anti-TNF agents significantly changed clinical practice and treatment algorithms. Optimized medical treatment should not only achieve symptomatic relief and clinical remission, but also aim to reduce the need for hospitalization and surgery. The use of these agents evolved over time and is mainly based on evidence from different large clinical trials on the efficacy for induction and maintenance treatment. The achievement of mucosal healing in a subgroup of patients raised the expectation that anti-TNF treatment could lead to a decrease in disease-related complications and the ultimate need for surgery. Biological therapies have shown to alter the natural history of psoriatic arthritis and ankylosing spondylitis^[40]. Indeed, anti-TNF therapy has been shown to reduce the need for surgery in different randomized clinical trials. Medium follow-ups of those trials have been rather limited, and the question remains whether the natural history of CD can be changed. Population-wide studies during the anti-TNF era have not yet demonstrated a decrease in the need for hospitalization and surgery. Different reasons can explain this discrepancy: firstly, the selection criterion for the randomized trials excluded patients with an imminent need for surgery and therefore contains a selection bias. Secondly, not all patients respond to anti-TNF therapy and the presence of a stricture and/or penetrating disease at the time of diagnosis is highly predictive for the need of surgery and

conservative treatment failure. Thirdly, most experience has been gained with the use of infliximab. The immunogenicity of the drug will lead to a substantial loss of response over time^[41,42]. Finally, a genuine resistance (irrespective to immunogenicity) to anti-TNF drugs has been observed. This will lead to a drop-out of 10% of patients per year. Results of recent top-down strategies clearly demonstrate the beneficial effect of early "aggressive" treatment of luminal inflammation^[43]. The medium-term benefits with regard to clinical remission and the need for surgery seem to indicate that a disease modification can indeed be obtained in a subset of patients. This concept therefore needs to be further explored and implemented into clinical practice.

The face of surgery has also evolved over time. Today, most patients can benefit from a minimally invasive approach (laparoscopy and single site laparoscopy). Furthermore, isoperistaltic stricturoplasty has demonstrated its safety and long-term efficacy in the treatment of long strictures of the small bowel and reduces the ultimate risk for intestinal failure^[44]. The implementation of enhanced recovery protocols further expedites patient rehabilitation after surgery. These aspects open a more attractive alternative to protracted medical treatment. Surgical-recurrence free survival at 5 years after primary ileocaecal resection is as high as 91% (own unpublished data). However early endoscopic and symptomatic disease recurrence hampers the enthusiasm for an early surgical approach. In patients with anorectal CD, surgery remains an essential, and often first, step in the treatment algorithm. Anal examination under anesthesia and drainage of perianal abscess precedes maintenance medical treatment. This combined approach is essential to safeguard anorectal function in the maximum number of patients, and to avoid definitive proctocolectomy and stoma formation.

The introduction of anti-TNF agents in the 1990s changed treatment algorithms in CD and has the potential to alter the natural history of the disease. Randomized data show a significant decrease in the development of complications and the need for surgery. Sustained mucosal healing seems a good predictor for fewer complications and surgery in the long-term. No reduction in the need for surgery has been documented in population-based surveys. This discrepancy is multifactorial. Further evolution and implementation of top-down treatment strategies should eventually lead to a genuine reduction in the need for surgery. For the time being, surgery still plays a pivotal role in a large subset of patients in order to obtain long-term disease remission and improvement of patient quality of life. However, the evolving concept of disease modification will certainly alter the role and need for surgery in the future. Optimal treatment of CD remains a joint effort of dedicated physicians and surgeons.

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