Cronh’s disease: to cut or not to cut?

An historical perspective

In the history of Crohn’s Disease (CD) three different periods may be recognized: the period of surgical therapy, the period of surgical and medical therapy and the period of biological therapy.

The period of surgical therapy

Although the earliest description of CD likely belongs to G.B. Morgagni in his treatise “The seats and causes of diseases” (1761), the landmark article that identified CD was written by B. Crohn, L. Ginzburg and G. Oppenheimer and published in 1932 in the Journal of the American Medical Association (JAMA). The paper followed the oral presentation entitled “Terminal ileitis” by Crohn at the annual congress of the American Medical Association (New Orleans, 1932).

The presentation concerned 14 patients who showed segmentary inflammation of the terminal ileum. As 13 out of the 14 patients were treated successfully with surgery, the condition was considered to be a surgical disease. The eponym of CD was ascribed to Crohn by way of a fascinating set of circumstances. Out of the Authors Crohn was gastroenterologist, Ginzburg and Oppenheimer were pathologists. All worked at the Mount Sinai Hospital in New York City. An interesting question therefore is why the first report of a surgical disease did not include a surgeon. In fact all the patients were operated by A.A. Berg, senior surgeon at Mount Sinai. However Berg refused to present the oral communication at the congress and preferred to go looking for the widespread antique dealers in New Orleans. As at that time the Journal policy was to order the Authors alphabetically by last name, if Berg had presented the oral communication, today Crohn’s disease would be probably named Berg’s disease.

After the first publication of CD many other cases of the disease were recognized over the US and Europe and CD was found to occur throughout the GI tract. However, CD became very popular only in 1956 when US President Eisenhower required an emergent operation for bowel obstruction due to CD. CD than shifted from a medical curiosity to a well-known disease.

Surgery (ileal resection or ileo-colonic by-pass) was the treatment of choice. In 1960 the British surgeon H.E. Lockart-Mummery firstly recognized the CD of the colon and made the distinction between Ulcerative Colitis and CD of the colon.

From 1932 to 1970 CD was regarded as a most exclusively surgical disease.

The period of surgical and medical therapy (1970-1997)

In the Seventies it became evident the high incidence of post-operative recurrence after curative resection for CD (up to 75% at 1 year). The trend of treatment therefore did change dramatically as the surgeons became reluctant to operate CD patients. The medical treatment (antibiotics, corticosteroids, budesonide, immunosuppressors, mesalazine) then became the first line therapy. Surgery was mainly reserved to complications (obstruction, perforation, abscesses, fistulas) and the role of surgeon shifted from central to marginal.

In this period the prevention of post-operative recurrence was considered as one of the most important issue in the management of CD. Endoscopy had proved to be the best method to detect post-operative recurrence. It was also demonstrated that the post-operative clinical course of CD could be predicted by the severity of endoscopic lesions during the first year after resection.

A number of drugs (antibiotics, mesalazine, corticosteroids, 6-MP, azathioprine, metotrexate, tacrolimus) were studied by randomized clinical trials (RCTs) with the aim of preventing post-operative recurrence. However available data including meta-analysis do not show a robust protective effect for any medical therapy.

The period of biological therapies (1997-present)

In 1977 SR Targan et al. published in the NEJM the first clinical trial on the effectiveness of mono-clonal chimeric antibody anti TNF-α (infliximab) for CD. This landmark article opened a completely new era in the treatment of IBD and numerous other biologic agents blocking various mechanisms of the inflammatory process were studied. To date, three additional drugs are available: adalimumab, a fully human monoclonal
anti-TNF antibody, vedolizumab a monoclonal antibody that inhibits chemotaxis from the blood to intestinal wall by selectively blocking the α4β7 integrin and ustekinumab, a fully human IgG1κ monoclonal antibody that inhibits the p40 subunit shared by the proinflammatory cytokines. These agents for the first time showed that mucosal lesions of CD may completely heal after treatment. Therefore the end points of the clinical trials completely changed. Historically patients were treated based on the reduction of clinical symptoms (CDAI). Today we understand that symptoms poorly correlate with the underlying intestinal inflammation. Other more objective disease activity parameters (CRP, faecal calprotectin, reduction of intestinal lesions) have been therefore introduced. “Mucosal Healing” is now the preferred primary endpoint in ongoing trials. The combination of symptoms remission and endoscopic remission is called “deep remission”. However it must be taken into consideration that fibro-stenotic lesions are irreversible and no treatment strategies are available. 

Individualizing therapy to optimize treatment is possible by stratifying patients at low and high risk. Patients with age > 30 years, limited anatomic involvement, no peri-anal disease, stricturing or fistula and no previous surgery were considered at low risk. Patients with age < 30 years, extensive anatomic involvement, peri-anal disease, stricturing/fistula and previous surgery were considered at high risk.

The emergency of biological therapy in the treatment of CD has led to a clinical debate about so called “step-up” versus “top down” strategy. Step up refers to the classic therapeutic approach, namely progressive intensification of treatment as disease severity increase. Treatment starts with corticosteroids/budesonide, moving to immunosuppressors (6-MP, AZT, MXT) and eventually to biologics when the response is poor. Top-down refers to the early introduction of biological agents and eventually go down to immunosuppressors when the response is positive.

However, although the existing guidelines recommend to follow the stratification of patients risk to select the best treatment strategy, most of the gastroenterologists use in any case anti TNF-α as first-line treatment and switch to other biologics when anti TNF-α fails. However it should be taken into consideration that epidemiological studies have shown that over 50% of CD patients have a mild disease over time and will never require aggressive therapies. The indiscriminate use of top-down strategy would therefore represent an over treatment for most of CD patients. Toxicity and high cost of biologics are also drawbacks for their indiscriminate use.

With the spreading of biological therapies, surgery has become obsolete. However it is common experience that medical therapy (biological included) is poorly effective in “stricturing” or “penetrating” CD and that these patients still undergo surgery in 60-70% of the cases within 10 years of diagnosis. Results of recent trials with anti TNF-α showed that mucosal healing in CD was associated with a higher clinical response, reduced hospitalization rates and need for surgery. However, recent data from population-based cohorts studies showed that the rate of surgery within 5 years of diagnosis was of the same order in pre- and post- anti TNF-α era. Surgery therefore should not be dismissed as the end of the road after all medical options have failed, but should be considered a significant component of the entire management strategy of CD. The early surgery in the presence of obstruction, abscess-fistula or lesions limited to a short ileal segment maintains a primary role.

Very good results have been also reported by mini-invasive laparoscopic surgery. It appears that the advent of biological agents has deeply changed the clinical practice and the therapeutic algorithms in CD. The possibility of inducing mucosal healing hold out much hope of changing the natural history of CD as it occurred in rheumatoid arthritis, psoriasis arthritis and ankylosing spondylitis. However, it is not yet demonstrated that biological therapies can influence the long-term natural history of CD. Despite the great therapeutic advances in CD no drug prevents, nor reverses established strictures.

In the last few years, however, a new era seems to arise. In fact, a recent study (POCER) demonstrated that a combination of surgery and biological therapies, could improve the outcomes of these patients, by early treatment the post-operative recurrence with anti-TNF drugs. Perhaps a new battle begun and we look forward for long-term results.

To conclude, though the advent of the biological therapies has deeply changed the conventional therapy of CD, this fascinating story is not over yet and the best management still results from the tight collaboration of the gastroenterologist and surgeon expert in IBD.

We ultimately need to have cost utility analyses to help us select the most appropriate medical or surgical therapies both for the patients and the society.

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