LEADING ARTICLE

Mucosal healing in inflammatory bowel disease: impossible ideal or therapeutic target?

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The main goal of treatment for Crohn's disease and ulcerative colitis has always been the induction and maintenance of symptomatic improvement or at best remission. It has been shown by many studies that the long-term outcome of these diseases is not influenced by standard treatments and that the need for surgery is not decreasing in this population over the years. There is recent evidence that with immunosuppression and treatment with infliximab long-term healing of the bowel can be achieved and that this affects the outcome of both Crohn's disease and ulcerative colitis. We propose that future studies should focus on healing and disease course as primary outcome measures.

Chronic idiopathic inflammatory bowel diseases (IBDs) including Crohn's disease, ulcerative colitis and indeterminate colitis are characterised by the presence in the gut of extensive areas of ulceration. These ulcerations are the origin of fistulas, of translocation of microbes and can lead to toxic megacolon, to perforation and bleeding. These complications are the main indications for resection of the diseased bowel. Surgery, however, does not stop the progression of the disease. It seems, therefore, logical that effective treatment of IBD should imply thoroughly and, if possible, complete healing of bowel ulcerations in parallel with clinical remission. Yet, until recently the focus of our treatment was on improvement of signs and symptoms of the disease without aiming at mucosal restitution. In most drug studies, especially in Crohn's disease, mucosal healing was not included as an end point although this is clearly the most important outcome variable. The main reason why mucosal healing was rather neglected as a goal for treatment in Crohn's disease was the fact that most treatments in IBD are not disease modifying, and that we did not have medicines that were able to heal the bowel mucosa. Glucocorticosteroids even at high doses and prolonged administration induce endoscopic remission of colonic Crohn's disease in no more than 29% of patients who achieve clinical remission with this treatment.[1] Steroids are also not able to improve the severity of ileal lesions.[2] The inability of steroids to heal the bowel, although they effectively down regulate inflammation, may be due to their deleterious effects on tissue restitution in segments of bowel with deep ulcers. By contrast, long lasting remission maintained with immunomodulators may be associated with thorough bowel healing. This was shown with azathioprine for the colon[3 4] as well as for the ileum.[5] Kozarek *et al*[6] also reported healing of the bowel with methotrexate. However, only about 40% of patients maintain steroid induced remission while on azathioprine.[7] Great interest was raised recently by the finding that the biological agent, infliximab, an immunoglobulin G1 monoclonal antibody against tumour necrosis factor, not only rapidly improves symptoms in patients with refractory luminal Crohn's disease, but also induces important healing of ileocolonic lesions by week 4 after intravenous administration.[8] For the first time, a close relationship was found between clinical improvement and improvement of endoscopically viewed bowel ulcerations. All segments of the ileo colon healed equally well. In the Accent I endoscopy substudy[9] induction with infliximab 5 mg/kg at weeks 0, 2 and 6 resulted in complete bowel healing (disappearance of all ulcers) in 29% of the patients by 10 weeks versus 3% in patients who received only one infusion at baseline. Systematic maintenance with infliximab 5 mg/kg or 10 mg/kg every 8 weeks resulted in complete bowel healing at 1 year in 44% of the patients treated with systematic maintenance treatment with infliximab every 8 weeks in comparison with 7% in patients treated episodically (on flare) with 5 mg/kg.

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The key question of course is whether healing of the mucosa of the bowel improves the outcome of the disease. There are only limited data available, but in the Accent I study patients who had persistent healing of the mucosa with maintenance treatment with infliximab needed considerably fewer hospitalisations, surgeries and intensive care unit stays.[9]

Crohn's disease is not associated with perforating complications or fibrostenosis from the onset. The great majority (if not all) of patients start with having pure inflammatory lesions. With continued or relapsing inflammatory activity of the disease, the rate of complications increases and eventually nearly all patients will have either stricture formation or fistulisation.[10] Therefore, the concept has grown that we should treat Crohn's disease more aggressively from the onset to improve the outcome of the disease. This aggressive approach

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should involve the use of therapeutic strategies that heal and maintain healing of the bowel mucosa. The validity of this approach still has to be shown. Indeed, it seems that the more widespread use of azathioprine or 6 mercaptopurine has not led to less surgeries in Crohn's disease, although this drug is able to maintain remission over time and heal the bowel mucosa to some extent.[11] We need evidence from prospective studies to show that indeed early potent suppression of inflammation leading to mucosal healing changes the outcome of the disease. The goal of the Benelux step-up/top-down trial,[12] which awaits full publication, was to prove that early induction with disease modifying treatment changes the outcome of the disease. Although the study was not powered for detecting differences in outcomes like hospitalisations and surgeries, this study certainly shows that treatment of early Crohn's disease is possible without the use of glucocorticosteroids.

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The mucosa of the colon in ulcerative colitis is more prone to healing than in Crohn's disease. Treatment with 5-aminosalicylic acid used rectally or orally may heal the mucosa in patients who respond to this treatment. Steroids also induce important mucosal healing in ulcerative colitis probably because ulceration is limited to the mucosa and down regulation of inflammation suffices to heal the mucosa. Steroids, however, do not maintain remission or healing in ulcerative colitis similarly to Crohn's disease. There are no data on healing of the mucosa with azathioprine or methotrexate in ulcerative colitis, but again the data with infliximab are impressive. This drug heals the mucosa of the colon in up to 60% by 8 weeks and maintains this healing in 50% by week 30 and 46% by week 54.[13] Mucosal healing at 8 weeks in the active ulcerative colitis trials predicted long-term remission during maintenance with infliximab. Efficacious mucosal healing in the long-term in ulcerative colitis might prevent proximal extension of the disease, toxic colitis and dysplasia or cancer but this remains to be proved.

Unfortunately treatments that heal the mucosa do not cure Crohn's disease or ulcerative colitis. When one stops treatment, the disease will recur almost inevitably. Healing of the bowel mucosa is not a predictor of better maintenance of remission after discontinuation of the drug. This has been shown for steroids and for azathioprine.[1 4] Healing of the mucosa will at best be associated with a modest prolongation of the symptom free interval in comparison with the non-healed bowel, but eventually the disease will resume its course. Strikingly in patients who achieved mucosal healing with biological treatment, endoscopy on relapse showed exactly the same pattern and location of the disease as before mucosal healing. This strongly suggests that the ''basic disease mechanism in the mucosa'' does not disappear with healing of the ulcers and that the intraluminal trigger ends up damaging the mucosa again in a ''predisposed manner''.

These insights have great impact on the way drug studies need to be designed. At present we are confronted with an increasing number of studies with various biological drugs and small molecules looking at less relevant end points like clinical response defined as a 70 point improvement of the Crohn's Disease Activity Index score for Crohn's disease and changes in clinical indices for ulcerative colitis. Some studies in Crohn's disease include up to >900 patients[14] and even then yield small differences between patients treated with drugs and placebo. The noise in these studies is so large that it is hardly possible to pick up the true signal. Using the hard end point of mucosal healing the numbers of patients needed to show really significant clinical benefit will decrease by probably 75%. An ileocolonoscopy at baseline will already exclude those patients who have no ulcerations and, unless they have proximal intestinal disease, have other causes for their symptoms. Total disappearance of all mucosal ulcerations is certainly a relevant end point for a therapeutic trial, but may be difficult to achieve. For the assessment of more subtle changes in endoscopic activity, we need to rely on endoscopic indices of activity. The Crohn's Disease Endoscopic Index of Severity has been developed as an index to detect changes in mucosal activity of Crohn's disease.[15] This validated index is useful but is difficult to use. A simplified index the Simple Endoscopic Score for Crohn's Disease has been developed and validated,[16] but for the existing indices of endoscopic disease activity no validated cut offs for disease improvement or disease remission have been defined. More work on this is needed. Moreover, one needs to determine the optimal time point for assessment of endoscopic healing. Certain drugs may be more efficacious in inducing healing, whereas other drugs might be efficacious mainly for maintenance.

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In conclusion, we believe that it is time to change our goals for the treatment of Crohn's disease and ulcerative colitis as well as the end points for trials. The future starts now, and we should raise the bar for our treatment goals as listed below.

- Induction and maintenance of remission without steroids
- Complete healing of the intestinal and colonic mucosa
- Avoidance of complications and surgeries
- Avoidance of cancer
- Avoidance of mortality.

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EDITOR'S QUIZ: GI SNAPSHOT

Robert Spiller, *Editor*

GI haemorrhage and an incomplete colonoscopy

Clinical presentation

A 74-year-old woman without any underlying disease was admitted to our institution due to intermittent right low abdominal pain for the past 2 weeks and an episode of tarry stool. The patient reported having had no recent usage of non-steroidal anti-inflammatory drugs. Blood biochemistry results, including liver, renal function and electrolytes, were all within normal limits. Complete blood cell counts and coagulation profiles were also within normal limits. An upper gastrointestinal endoscopy disclosed only superficial gastritis. Thus, a colonoscopy was performed to locate the bleeder.

During colonoscopy, a purplish mass with a light yellowish head obstructing the lumen was disclosed in the ascending colon (fig 1). An abdominal CT scan was performed to evaluate the nature of the tumour (fig 2).

Question

What is the colonoscopic diagnosis and differential diagnosis?

See page 496 for answer.

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Informed consent was obtained from the patient for publication of this material.

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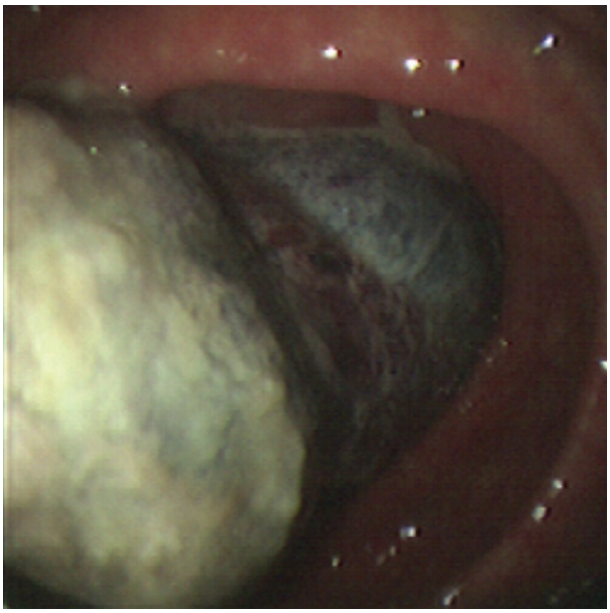

Figure 1 Colonoscopy disclosed a purplish mass in the ascending colon.

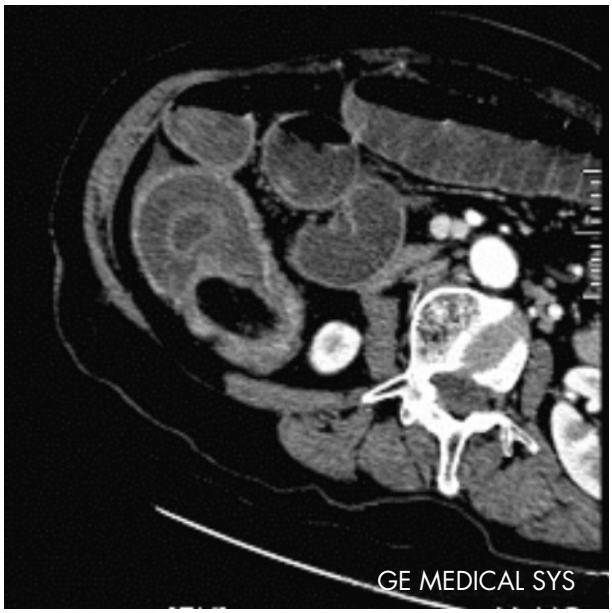

Figure 2 Abdominal CT of the ascending colon.