Healing the mucosa in Crohn’s disease: does it matter?

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ABSTRACT Clinical remission has been the therapeutic goal of Crohn’s disease treatment for many years. While it has helped to ameliorate the symptoms, this treatment strategy has not brought about significant changes in the need for abdominal surgery in the natural history of Crohn’s disease. The advent of biological agents (biologics) has shown that it is possible to induce and maintain mucosal healing in a significant proportion of treated patients. Data is also emerging to show that this has translated to fewer instances of hospitalisation and surgery for these patients. This is a paradigm shift in the therapeutic goal of Crohn’s disease treatment.

Keywords: Crohn’s disease, drug therapy, mucosal healing

INTRODUCTION

Crohn’s disease (CD) is a chronic inflammatory disease of the gastrointestinal (GI) tract. Patients with CD present with a host of symptoms, including diarrhoea, haematochezia, abdominal pain, weight loss and fever. The last few decades have seen a gradual increase in the number of drugs available for use in the treatment of CD. From a time when only sulfasalazine, steroids and antibiotics were used, we now have immunomodulators such as thiopurines and methotrexate, as well as biological agents. While these newer drugs are effective for inducing clinical remission in CD, data have recently emerged to show that they are also effective in reducing complications, and consequently, the need for surgery in CD patients.

INTESTINAL ULCERS AND INFLAMMATION IN CROHN’S DISEASE

Chronic intestinal inflammation causes GI ulcers in CD. This is a transmural inflammation.1,2 The intact GI mucosa is a vital part of the mucosal barrier that separates the luminal microbiota from the mucosal immune system. In the intestines, components of the mucosal barrier include the intact epithelial cell layer, tight junctions, and antimicrobial peptides such as defensins, which are produced by the intestinal mucosa. Defects in different components of this barrier have been found in patients with inflammatory bowel disease (IBD). For example, it has been suggested that altered defensin production plays an important role in the pathogenesis of IBD.2,3 Similarly, defects in proteins that make up the tight junctions, such as the occludins and claudins, have also been described in patients with IBD. These defects are believed to cause breaks in the mucosal barrier, which permit the passage of microorganisms into the mucosa and submucosa. There, the microorganisms meet and activate the mucosal immune system, causing chronic intestinal inflammation.

An altered mucosal immune response has also been shown in animal models and IBD patients.1,2 A relative deficiency of immune suppressor cells (e.g., regulatory T cells) have been found in IBD patients.4 Differences in the way antigen-presenting cells and effector T cells respond to bacterial stimuli have also been shown in IBD patients, compared to normal controls.5,6 One way by which this is mediated is through differences in the way the pattern recognition receptor NOD2/CARD15 recognises microorganisms in IBD patients versus healthy controls.5 The NOD2/CARD15 gene is the first IBD gene to be discovered.

THERAPEUTIC ENDPOINTS FOR CROHN’S DISEASE

The target of gastroenterologists in treating patients has not changed for many years.6 Although endoscopic, histological and radiological proof is required before a diagnosis of IBD can be made, gastroenterologists often treat CD patients only to relieve symptoms and achieve biochemical remission. The aim is not to achieve complete healing of the ulcers. This, however, is not unique to routine clinical practice. For instance, clinical trials examining the efficacy of novel therapies make use of disease activity indices, such as the Crohn’s disease activity index (CDAI), which measure clinical symptoms and not endoscopic disease activity.

Until the advent of infliximab in the 1990s, it was not uncommon to find significant ulcers in CD patients in clinical and biochemical remission after a course of steroids. Trials of biological agents since the 1990s have taught us that a proportion of patients in clinical and biochemical remission, as defined by CDAI, also achieve complete healing of mucosal ulcers.7 The impressive images of ulcer healing in patients who had received only one dose of infliximab demonstrated that contrary to what was often seen in CD patients with steroid-induced remission, it was possible for a significant proportion of patients to achieve ulcer healing.

MUCOSAL HEALING AND ENDOSCOPIC SCORING INDICES

Complete mucosal healing can be simplistically defined as the complete absence of ulcers and inflammation. However, since

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this is difficult to achieve even in patients on biological agents, it would be useful to define partial mucosal healing. Endoscopic activity indices would enable one to grade different degrees of mucosal healing – from complete healing to absence of mucosal healing. A number of endoscopic scoring indices for CD have been devised and used in different drug trials. The Crohn’s disease endoscopic index of severity (CDEIS) calculates the percentage of involvement of different ileocolonic segments. It is complex to use, requires training and experience for estimating the extent of ulcerated or diseased mucosal surfaces, as well as experience in distinguishing deep from superficial ulceration. While some studies have demonstrated good correlation between CDEIS (which measures mucosal activity) and CDAI (which measures clinical symptoms), others have shown poor correlation between the two indices. As the complexity of CDEIS limits its usefulness in clinical practice, its use is largely restricted to a clinical trial setting. The Simple Endoscopic Score for Crohn’s Disease (SES-CD) includes four variables – ulcer size, extent of ulcerated surface, extent of affected surface, and stenosis – in five segments of the bowel. SES-CD correlates well with CDEIS. Although it is now possible to describe mucosal lesions in a consistent manner using either CDEIS or SES-CD, there is still no commonly agreed cutoff value in either scoring system for defining endoscopic response to treatment, endoscopic remission or mucosal healing.

Of all the CD endoscopic indices, the Rutgeerts score is the only postoperative endoscopic grading system that has been used to describe the severity of endoscopic recurrence at the ileocolic anastomosis and preanastomotic ileum post resection. Scoring is based on the presence of ulcers, ileitis, nodularity and strictures. Grading ranges from i0 to i4. Although the reproducibility of the Rutgeerts scale has not been prospectively validated, the severity of endoscopic lesions at one-year post operation has been demonstrated to be predictive of clinical recurrence. Postoperative recurrence was initially defined as Rutgeerts score i1, but most clinical trials have used i2 as the cutoff to define endoscopic recurrence. In a recent study, the preexisting Rutgeerts endoscopic score was modified to incorporate a scoring system of colonic lesions after surgery.

**CLINICAL SIGNIFICANCE OF MUCOSAL HEALING**

When contemplating the use of mucosal healing as a therapeutic goal, it is important for both the clinician and patient to consider whether the presence of ulcers can predict future disease activity and future need for hospitalisation or major abdominal surgery, as well as whether mucosal healing will modify the natural history of IBD. This is especially important in patients who have already undergone their first abdominal surgery.

Allez et al have shown that the presence of deep ulcerations in CD patients was a risk factor for penetrating complications and surgery. Among patients with severe endoscopic lesions in their cohort, the probability of colectomy was 31%, 42%, and 62% at one, three and eight years, respectively, whereas in the absence of severe endoscopic lesions, the probability of colectomy was 6%, 8% and 18% at the same time points. A study of postoperative patients revealed that CDAI could discriminate between those with and without endoscopic recurrence in only 65% of cases, suggesting that CDAI alone was inadequate for the detection of postoperative recurrence of CD. These findings were supported by a small, randomised controlled study by Regueiro et al, which found poor correlation between postoperative endoscopic recurrence and clinical symptoms, CDAI and C-reactive protein.

**ALTERING THE NATURAL HISTORY OF IBD**

CD is characterised by a relapsing and remitting disease course. Medical therapy is required by the majority of patients in order to maintain remission, coupled with intermittent induction therapy to manage flares. Just over 80% of Singaporean patients present with inflammatory, non-stricturing, non-penetrating disease. In the long term, inflammation results in stricturing and penetrating disease in 50% of all CD patients. About 50% of patients with either penetrating or stricturing disease require major abdominal surgery within six months of developing the disease. Even after the first abdominal surgery, CD often recurs either at or proximal to the anastomosis. Up to 70% of patients require reoperation within ten years. Risk factors for surgery include smoking, young age at diagnosis, perianal disease and the need for steroids at initial diagnosis. Such a disease course is obviously disabling and has significant morbidity. It would, therefore, be important for both the patient and society to delay or interrupt the natural history of CD.

Although evidence for this is still sparse, directly targeting tissue damage with treatments that induce and maintain mucosal healing in the early stage of disease may reduce complications and alter or halt the progression of disease. As endoscopic assessment provides objective evidence of mucosal healing or damage, endoscopic outcomes are being increasingly used as efficacy endpoints in clinical trials. In the short term, mucosal healing has been associated with reductions in CDAI and reduced steroid use. In the longer term, mucosal healing has been shown to be associated with durable remission, lower complication rates and reduced need for surgery and hospitalisation. Although mucosal healing is associated with improved outcomes, there is currently insufficient evidence to corroborate that treatment escalation to induce mucosal healing results in improved outcomes.

**DRUGS AND MUCOSAL HEALING**

Not all drugs are equally effective in inducing and maintaining mucosal healing in CD. We present below a description of the common drugs used and their efficacies in the treatment of CD.

**Steroids**

Corticosteroids are effective suppressors of inflammation and can induce clinical remission. 60% of patients have a complete clinical response to steroids, while 30% have partial response and
10%, no response. Only 10% of patients will have complete or partial mucosal healing at the end of their course of steroids, and only 30% of patients will have a prolonged clinical response to the initial course of steroids at one year. It is clear from multiple clinical trials that corticosteroids – both prednisolone and budesonide – are of no benefit in maintaining clinical remission or preventing new flares, and they do not alter the natural history of the disease. They are also not useful for the maintenance of mucosal healing.

**Thiopurines**

Thiopurines (azathioprine and 6-mercaptopurine) have been shown to induce clinical and endoscopic remission. Among CD patients who achieved clinical remission in D’Haens et al’s study, 70% of those with colonic disease and 54% with ileal disease had complete mucosal healing. Another study, which consisted of 53 Japanese patients, reported a complete clinical response in 23% of the patients, with 42% showing clinical improvement. Colonoscopy done before and after azathioprine treatment for the Japanese cohort showed complete mucosal healing in 56%, partial mucosal healing in 19% and no healing in 25% of the patients.

**Methotrexate**

Methotrexate is often used as the second immunomodulator when patients stop thiopurines because of treatment failure or adverse effects. In CD, methotrexate has been shown to induce and maintain clinical remission in placebo-controlled randomised trials. An early study has shown that 36% of CD patients achieve mucosal healing. Laharie et al, who compared mucosal healing induced by methotrexate, azathioprine and infliximab in a single-centre study, found that mucosal healing was achieved in 11%, 50% and 60% of patients, respectively.

**Biologics**

Biologics, also known as biological agents, have been the most potent agents in inducing clinical and endoscopic remission in CD patients. Van Dullemen et al reported dramatic endoscopic improvement in patients given just a single dose of infliximab. Subsequent trials with infliximab, adalimumab and certolizumab have demonstrated the efficacy of anti-tumour necrosis factor (TNF) agents in inducing mucosal healing in CD patients. The ACCENT I (A Crohn’s Disease Clinical Trial Evaluating Infliximab in a New Long-term Treatment Regimen) endoscopic substudy showed that over 40% of patients who received infliximab regularly had complete mucosal healing compared with 18% of patients who did not. In the SONIC (Study of Biologic and Immunomodulator Naive Patients in Crohn’s Disease) trial, 30% of patients on infliximab monotherapy achieved mucosal healing compared with 44% of patients on combined azathioprine and infliximab therapy. The EXTEND (Extend the Safety and Efficacy of Adalimumab Through Endoscopic Healing) placebo-controlled trial evaluated the impact of adalimumab on mucosal healing in patients with active ileocolonic CD. Patients received open-label adalimumab 160 mg, then 80 mg induction therapy at Weeks 0 and 2, and were then randomised at Week 4 to maintenance therapy with fortnightly adalimumab 40 mg or placebo. Mucosal healing at Week 12 was seen in 27% of the treatment group compared to 13% in the placebo group. At Week 52, mucosal healing was demonstrated in 24% and 0% of patients in the treatment and placebo arms, respectively.

The MUSIC (endoscopic MucoSal Improvement in patients with active CD treated with certolizumab pegol) trial studied mucosal healing in patients treated with certolizumab pegol. Patients on subcutaneous certolizumab pegol showed improvement in the endoscopic appearance of mucosal ulcers at both Weeks 10 and 54. However, complete mucosal healing was only seen in a small percentage of patients – 4% and 8% at Week 10 and Week 54, respectively.

**NONINVASIVE METHODS OF ASSESSING MUCOSAL DISEASE ACTIVITY**

In the vast majority of clinical trials, mucosal healing was assessed using colonoscopy with ileoscopy. However, endoscopy is expensive and associated with the risk of perforation. It is also difficult to justify to an asymptomatic patient the need for regular ileocolonoscopy. If the attainment of complete mucosal healing is to play a greater role in the evaluation of therapeutic response to drugs, there will be a need for noninvasive surrogate markers to quantify asymptomatic mucosal disease activity, so as to allow serial monitoring. Regular monitoring with endoscopy or noninvasive surrogate markers can then identify patients with active mucosal disease so that appropriate treatment escalation can be instituted.

**Stool calprotectin**

Calprotectin, a marker of inflammation, is produced by intestinal epithelial cells and leukocytes. It is a heterodimer made up of S100A8 and S100A9. Elevated levels of stool calprotectin have been found in IBD patients, and this has been shown to correlate with endoscopic disease activity measured using CDEIS and SES-CD. Stool calprotectin levels have also been found to decrease with anti-TNF therapy-induced endoscopic mucosal improvement. The reduction in stool calprotectin with anti-TNF therapy is found to correlate with endoscopic mucosal healing as measured by CDEIS. The levels seldom normalise to that seen in normal controls, suggesting ongoing subclinical inflammatory activity even in the absence of mucosal lesions. The value of stool calprotectin in predicting future clinical activity has been studied. In the STORI (infliximab diSConTinuation in CrOhn’s disease patients in stable Remission on combined therapy with Immunosuppressors) study, stool calprotectin levels were higher in patients who relapsed than in patients who had sustained remission. A normal stool calprotectin level had a high negative predictive value for a flare of disease activity, for up to three months. Predictive accuracy diminishes beyond three months.
In the post-surgical setting, it has been suggested that a stool calprotectin value of more than 200 mg/L is predictive of early mucosal disease recurrence.\(^\text{44}\)

**Noninvasive cross-sectional imaging**

Computed tomographic enterography and magnetic resonance enterography (MRE) have been used in the initial assessment of disease extent and activity in patients with CD, and as tools to follow up on disease activity after the initiation of therapy.\(^\text{44}\) While both modalities have been found to be useful, MR imaging has an advantage in that it does not expose the patient to ionising radiation, and can therefore be used repeatedly to follow up on the resolution of disease activity. Rimola et al have described an MR activity index for CD activity that correlates well with CDEIS, and this index has been validated.\(^\text{45-47}\) In the postoperative setting, MRE has 100% sensitivity and 89% specificity in detecting postoperative recurrence, and current evidence suggests that it may be as good as endoscopy.\(^\text{48}\)

Stool calprotectin and MRE are useful noninvasive tests that can be performed on patients who cannot or will not undergo regular endoscopy to monitor for mucosal healing. It is conceivable that algorithms will be established where a CD patient is monitored for endoscopy to monitor for mucosal healing. It is conceivable that patients who cannot or will not undergo regular intervals to monitor for mucosal healing, the procedure to follow up on the resolution of disease activity. Rimola et al have described an MR activity index for CD activity that correlates well with CDEIS, and this index has been validated.\(^\text{45-47}\) In the postoperative setting, MRE has 100% sensitivity and 89% specificity in detecting postoperative recurrence, and current evidence suggests that it may be as good as endoscopy.\(^\text{48}\)

**CONCLUSION**

The goal of treatment strategies for CD has traditionally been clinical remission and resolution of symptoms. The advent of more efficacious treatment modalities means that in addition to symptom resolution, it is now possible to aim for healing of intestinal ulcers. Randomised trials have demonstrated that immunomodulators and biological agents can induce and maintain clinical remission and mucosal healing. Mucosal healing is associated with several benefits, including steroid-free remission, improved quality of life, reduced hospitalisation and decreased need for surgery. Mucosal healing is still largely assessed using endoscopy, an invasive procedure. However, there is current evidence that certain noninvasive tests correlate well with mucosal disease activity. The results of tests such as stool calprotectin and MRE have been shown to correlate with endoscopic activity, although these noninvasive tests are not widely available.

Several questions about mucosal healing remain unanswered. While it would be ideal to examine patients with endoscopy at regular intervals to monitor for mucosal healing, the procedure is expensive and associated with a risk of adverse events. It is still unknown when and how often endoscopy should take place after the initiation of a new therapy or post-surgery. Whether the escalation of therapy in asymptomatic patients with evidence of ongoing mucosal inflammation would be of any benefit is yet to be ascertained. It is also unknown if treatment de-escalation would be possible in patients who have demonstrated both clinical remission and complete mucosal healing. The coming years should see the completion of clinical trials that may unravel some of these questions, which will help physicians decide on the most appropriate treatment strategies for patients with CD.

**REFERENCES**