Inflammatory bowel diseases (IBDs), encompassing ulcerative colitis (UC) and Crohn’s disease (CD) are chronic, progressive and relapsing pathologic conditions caused by a dysregulation of the immune system. IBDs are characterised by inflammation and ulceration of the intestinal mucosa. The main symptoms, such as abdominal pain, altered bowel functions and rectal bleeding, significantly alter a patient’s quality of life (QOL). In the absence of any aetiological therapy, clinical improvement is the main treatment goal. Clinical improvement is typically associated with a gradual reduction in the severity of intestinal lesions; however, it is common for symptoms to recur. Mucosal healing (MH) offers a potential end point for IBDs treatment but until recently the aim of UC and CD treatment was to improve symptoms and prevent relapse episodes with no consideration of mucosal restitution. Improved disease prognosis is possible through the achievement of both clinical (resolution of symptoms) and endoscopic (healing of intestinal mucosa) remission, which represents the best case scenario for patients with IBDs, therefore efforts should be maximised to achieve these endpoints.

MH in the rectum has been reported in UC patients following topical treatment with 5-aminosalicylic acid (5-ASA); however, this observation was used as a diagnostic tool rather than a therapeutic goal. MH has also been reported in a small proportion of CD patients achieving clinical remission following corticosteroid treatment. Healing of endoscopic lesions was first reported in patients treated with methotrexate, azathioprine and infliximab. Existing data showed that persistent MH, following treatment with infliximab, in patients with CD resulted in the need for fewer hospitalisations, surgeries and intensive care unit stays.

The recent availability of biological therapies has provided an invaluable addition to the therapeutic options available for IBDs. In particular, biological therapies offer the possibility of attaining rapid endoscopic remission in some patients. It should be noted that rapid endoscopic remission is not necessary to improve clinical conditions, as most patients never experience the complete disappearance of endoscopic lesions, even if treatment greatly ameliorates their symptoms and therefore, improves their QOL. Whether MH is an attainable goal in IBDs patients, or whether it is simply a sign of improved patient response to an acute treatment is yet to be determined.

When considering MH in the treatment of IBDs an important point for discussion is the definition of MH and the relationship between MH and IBDs symptoms. Unfortunately, most published studies use different definitions of MH for UC and CD such as the Mayo Endoscopic Score, Crohn’s Disease Endoscopic Index of...
Severity (CDEIS) classification or the Baron classification. These varying definitions can generate a degree of confusion, particularly when interpreting data.

MH can be considered appropriate for UC which is a disease of the mucosa, whereas the term intestinal healing should be more correct for CD which is a transmural disease. A complete assessment of intestinal healing in CD can be obtained only by using both endoscopy and cross-sectional imaging modalities (MR, CT, US). Another crucial point is the timing of endoscopic evaluation which was different (range 4–52 weeks) in the studies evaluating the MH.

A key concept in the treatment of IBDs, CD in particular, is that symptoms correlate poorly with objective measures of intestinal inflammation. There have been many studies investigating the relationships between clinical symptoms and IBDs intestinal lesions, but currently there are no prospective data exploring the potential of MH as a primary end point in clinical trials. Despite the lack of scientific evidence that MH may change the natural course of IBDs, the issue of MH is widely debated and it is increasingly being recommended as a relevant clinical goal.

This review focuses on the existing knowledge about MH and assesses the current role of MH in IBDs treatment. As UC is a disease of the mucosa, and CD is a parietal disease, this review separately considers the clinical meaning of MH in both UC and CD.

Ulcerative colitis

In previous years, MH was considered to be an uncommon occurrence in UC. Steroids were typically unable to heal the mucosa and maintain remission. However, treatment with sulfasalazine or 5-ASA, used orally or rectally, was known to heal the mucosa in some patients. As a consequence of this, maintenance treatment is typically continued "indefinitely" in most UC patients receiving salicylate therapy.

It is well known that even when endoscopic examination reveals a "healed" mucosa, histological evidence of past disease often remains. This typically manifests through various histological characteristics including a thinned lamina propria (microscopically evident), glandular disarray with shortening, loss of glandular parallelism and branching of crypts as well as Paneth cell hyperplasia and thickening of the muscularis mucosae. Complete restoration of the mucosal architecture may occur in cases of acute UC when there is a short duration of disease with prompt response to medical therapy.

Previously, it was thought that the severity of mucosal lesions and the depth of ulcers in severe UC were correlated with a requirement for surgery. Recently, the severity of endoscopic mucosal lesions has been used to predict the course of UC disease and to select appropriate medical treatment. In addition, findings from one study showed that macroscopically normal looking colonoscopy lowered the 5-year cancer risk in UC patients to the same as that of the general population.

Currently there is no consensus on the definition of MH as many different scores have been proposed to measure endoscopic lesions in UC. Variation in literature regarding the definition of MH makes the comparison of results problematic. In particular, most studies include some friability of the mucosa among criteria of MH, while by definition MH should be associated with the absence of mucosal friability, as is stated in the International Organisation for the Study of Inflammatory bowel Disease (IOIBD) classification.

In clinical trials, the efficacy of UC therapies is typically assessed by clinical and laboratory data and it is common for clinical remission to occur despite the persistence of endoscopic lesions. However, in the last few years endoscopic improvement or (mucosal) healing has been introduced as one of the goals of UC treatment. In the Active Ulcerative Colitis Trials 1 and 2 (ACT1 and ACT2) patients with refractory moderate-to-severe UC received intravenous infliximab or placebo. MH was observed at week 8 in 61% of patients treated with infliximab (10 mg) compared with 37% in the placebo group (p<0.001). Similarly, at week 54 MH was observed in 44% patients receiving infliximab (10 mg) compared with 20% receiving placebo (p<0.001). However, in this study the primary end point was the clinical response and not MH. Notably, the percentage of patients achieving MH has been reported to be similar with immune suppressants and biologics (53–62% and 30–71% respectively).

Studies have also shown the ability of mesalazine, to induce MH in approximately one-third of UC patients. In more recent studies, MH rates between 32 and 77% have been reported in UC patients receiving mesalazine with Multi Matrix System (MMX) technology therapy. The only prospective trial using MH as a primary end point has been conducted by Ardizzone et al. In this hospital-based, inception cohort study, patients with newly diagnosed UC were treated with corticosteroids and monitored over 5 years. Patients with complete responses, based on the Baron classification, had a lower need for hospitalisation, immunosuppresion therapy and colectomy surgery compared with patients with partial responses. The authors concluded that lack of MH following corticosteroid therapy was associated with a more aggressive disease course.

The suggestion by Ardizzone et al., that endoscopic MH should be a primary objective of therapy, has been questioned in an editorial article by DT Rubin. In particular, Rubin questions the frequency of MH in women and the low overall colectomy rate observed by Ardizzone et al. Rubin hypothesised that patients included in the Ardizzone study may have been affected by less severe UC compared with UC patients in other studies. Therefore, results from this study may not sufficiently support the adoption of MH as a primary end point of UC treatment.

It is interesting to note that in a recent randomised-controlled trial assessing the efficacy and safety of adalimumab in inducing clinical remission in anti-tumour necrosis factor (anti-TNF) naive patients with moderate-to-severely active UC (comparable to ACT 1), MH was not considered as an efficacy endpoint.

In spite of scarce existing scientific evidence, physicians continue to be encouraged by the prospect of MH and are actively intensifying and maintaining treatment regimens with biological agents in UC patients until sustained MH is achieved. This approach has led to increases in pharmaceutical expense, therapy-related side-effects as well as potentially dangerous delays in recommending surgery. However, the achievement of MH may have some relevant clinical implications with regard to potential risk reduction of colorectal cancer and choosing when to withdraw therapy in UC patients.
Crohn’s disease

In patients with CD, which is a transmural disease, MH should be considered only as an aspect of the overall treatment goal. In fact, current treatment options, including biological agents, may relieve inflammatory symptoms but do not improve fibrostenotic obstruction. Under microscopic examination it is common to find endoscopically healed mucosa over symptomatic intestinal stenotic segments.

In clinical trials, the efficacy of CD therapies is usually assessed by clinical activity (a decrease in the Crohn’s Disease Activity Index [CDAI]) and inflammatory activity (a decrease in C-Reactive Protein). It has been demonstrated by the Groupe d’Etudes Therapeutiques des Affections Inflammatoires Digestives (GETAID) that endoscopic pattern severity, as assessed by CDEIS, is poorly correlated with clinical or biological activity. Interestingly, the severity of mucosal lesions has been found to be associated with a higher risk of complications and surgery, but whether complete or partial MH is required to modify the disease course remains to be further investigated.

It is well known that steroid-induced clinical remission is not associated with MH in most CD patients and that endoscopic remission induced by steroids does not correlate with relapse risk after steroid withdrawal. In addition, it is known that long-standing clinical remission may be associated with severe endoscopically active lesions or even the presence of a mass. These observations have led us to the question of whether MH is applicable in clinical practice.

Some studies have proposed MH to be an important predictor of clinical outcomes. In the ACCENT I trial, CD patients were randomised to episodic versus scheduled infliximab infusions. Complete MH was observed in 31% of patients in the scheduled group compared with none in the episodic group (p = 0.010). A relationship between clinical recurrence, as assessed by CDAI and MH could not be demonstrated.

In the Study of Biologic and Immunomodulator Naive Patients in Crohn’s Disease (SONIC) trial patients with active CD were randomised to receive infliximab, azathioprine or combination therapy. At week 26, MH occurred in 30% (infliximab), 17% (azathioprine) and 44% (combination) of CD patients. The primary efficacy end point in this trial was the rate of corticosteroid-free clinical remission, while MH was considered only as a secondary efficacy end point.

The overall percentage of CD achieved MH with anti TNF antibodies (12%–73%) was found the same order as that reported with immune suppressants (35%–73%). In prospective comparative study in CD, the rate of MH achieved by Azathioprine was not statistically different from that obtained with Infliximab.

Most recently, members of the 2nd Scientific Workshop of the European Crohn’s and Colitis Organisation (ECCO) stated that MH in patients with CD was associated with a higher clinical response, lower relapse and hospitalisation rates and a reduced need for surgery. However, recent data from population-based cohorts show that before the era of anti-TNFα, the rate of surgery ranged from 27% to 61% within 5 years of diagnosis, while during the era of anti-TNFα, the rate of surgery ranged from 25% to 33%. Therefore, the need for surgery still remains high in the era of biologics and has not shown a significant decrease. Considering that biologics are claimed to induce MH in a high percentage of cases, a substantial reduction in the rate of surgery would be expected. Hence, surgery should not be dismissed as the end of the road after all medical options have failed, but should be considered a valid component of the overall disease management strategy.

Final considerations

In the last few years, the association between MH and better outcomes has largely been reported in both UC and CD. MH is currently recommended as an end point to assess the efficacy of treatment. However, it should be noted that MH needs to be maintained with continued treatment and that disease recurrence is almost inevitable if treatment ceases.

Overall, evidence showing that MH significantly improves the clinical course of IBDs is still lacking. In addition, several questions remain to be answered. Firstly, there are no prospective trials that assess MH as a primary end point. Secondly, there are no prospective trials comparing MH to disease outcome measures (CDAI, Truelove and Witts Severity index, Powell–Tuck index). Therefore, the time has not yet come to treat IBD with the primary aim of achieving MH. An interesting lesson for consideration comes from the Helicobacter pylori (HP) story. Prior to the discovery of HP, Proton Pump Inhibitors were able to heal peptic ulcers, although mucosal ulcerations inexorably recurred upon cessation of treatment. It was only after the discovery of HP and its subsequent eradication by antibiotics that the recurrence of ulcers was definitively abolished.

In conclusion, until we can better understand the relationships between MH and clinical disease symptoms, as well as the relationships between immune dysregulation and mucosal lesions, we must continue to treat IBD patients with the aim of obtaining stable clinical remission. MH should be considered as a desirable secondary goal in clinical practice which may eventually be used to select which patients are best suited to cessation of therapy. In the meantime we should continue to look towards healing the sick, rather than the wound, and maintain good relationships with the surgeon.

Conflict of Interest

Authors declare no conflict of interest.

References

3. Moser G. How often do patients with IBD have symptom recurrence? Inflamm Bowel Dis 2008; 14:547.
13. Mary JY, Modigliani R. Development and validation of an endo-
16. Allez M, Lemann M. Role of endoscopy in predicting the disease 
17. Rutter MD, Saunders BP, Wilkinson KH, Rumbles S, Schofield G, 
D'Haens G, Sandborn WJ, Hommes DW, van Dullemen HM, van Deventer SJ, Hommes DW, Bijl HA, 
27. Sandborn WJ, Kamm MA, Lichtenstein GR, Lyne A, Butler T, 
29. Rubin DT. We once were blind and now we see: is it time to 
31. Ochsenkuhn T, D'Haens G. Current misunderstandings in the 
2011;60:1294–9.
36. Allez M, Lernard-Jones JE. Role of endoscopy in predicting the disease 
37. Rutter MD, Saunders BP, Wilkinson KH, Rumbles S, Schofield G, 
38. Laharie D, Reffet A, Bellennée G, Chabrun E, Subtil C, Razaire S, 
2011;33:714–21.
