In the last few years mucosal healing has emerged as an important therapeutic goal for patients with inflammatory bowel disease. Growing evidence suggests that mucosal healing can improve patient outcomes and, potentially, can alter the natural course of the disease. However, several questions remain to be answered: a validated definition of mucosal healing is lacking, the effect size of different drugs is difficult to assess because of different definitions, different study design, and different timing of endoscopic evaluation and, finally, the evidence that mucosal healing has a high positive predictive value for long-term good clinical outcome is still limited. For these reasons, it is still uncertain how mucosal healing should be used in everyday clinical practice. Future studies are needed to answer the most important question if mucosal healing should be systematically assessed in all patients and if treatment strategies should be targeted to achieve complete mucosal healing.

INTRODUCTION

The management of inflammatory bowel disease (IBD) has traditionally been aimed at improving symptoms and little attention has been focused on healing of mucosal lesions. Nevertheless, mucosal healing (MH) has been always considered important in ulcerative colitis (UC), but not in Crohn’s disease (CD). In fact, since the 1960s, clinical studies suggested that the long-term outcome in UC patients after a steroid course was more favorable in patients who achieved both clinical and endoscopic remission compared to those who achieved only clinical remission. Up to the late 1990s, other observational studies reported the lack of a similar correlation in patients with CD. In particular, these studies described the absence of a clear impact of the mucosal lesions healing on relapse rates in CD patients with steroid-induced clinical remission. These observations led clinicians to limit their CD treatment focus to symptomatic improvement and remission, therefore abandoning the idea that MH could affect the natural course of the disease.

The attitude of clinicians towards MH changed drastically when anti-TNFα drugs entered the IBD clinical practice. For the first time, in fact, it was thought possible to achieve a rapid and possibly sustained healing of mucosal lesions also in CD. Since then, the
interest on MH, in both UC and CD, grew so much that, nowadays, there is a trend towards considering MH a relevant end-point in clinical trials and a desirable goal in clinical practice and some authors have suggested that future studies should focus on MH as primary outcome measure.⁴

Over the last years, accumulating evidence suggest that MH is prognostically relevant. In a Norwegian population-based cohort, MH was found to have a significant impact on the long-term outcome of both CD and UC.⁵ Observational studies and subgroup analyses of randomized controlled trials in CD indicate that MH is associated with lower relapse rates, higher corticosteroid-free remission rates, reduced hospitalizations and reduced need of surgery at least in the medium term.⁶-⁸ Moreover, achieving MH may reduce the risk of relapse after infliximab (IFX) therapy is stopped.⁹ Also in UC MH has been associated with a more favorable outcome such as reduced risk of relapse, fewer hospitalizations and lower colectomy rates.¹⁰-¹³ Moreover, the persistence of mucosal inflammation, even in the absence of symptoms, has recently been associated to an increased risk of colorectal cancer in UC; therefore, to address medical treatments beyond clinical remission, could lead to possible reduction of incidence of cancer.¹⁴

Although compelling arguments suggests that MH may be associated with improved disease outcome, the most important question for clinical practice is if we should systematically assess MH in all patients and target our treatment strategies to achieve not only clinical remission but also complete healing of endoscopic lesions. Several questions may arise from this issue: How should MH be defined? What is the impact of current treatments in healing mucosal lesions in CD and UC? What is the real impact of MH on the clinical course of IBD? In other words, is MH a valid surrogate end-point of disease outcome?¹⁵

**Definition of Mucosal Healing**

There is a wide range of possible endoscopic lesions in IBD but, to date, there is no standardized definition of MH.

In CD, MH has be defined in a simple and pragmatic manner as “absence of ulcerations at follow-up endoscopy in patients who had ulcerations at baseline”.⁶ This definition may be simple for clinical practice but it is too rigid and does not consider patients with substantial endoscopic improvement but with persistence of some mucosal lesions. Endoscopic scores, such as the Crohn’s Disease Endoscopic Index of Severity (CDEIS) or the Simple Endoscopic Score for Crohn’s Disease (SES-CD) are generally restricted to clinical trials. They are complex to calculate, require training and expertise and are not suitable for routine clinical practice.¹⁶ Moreover these scores were initially conceived, as continuous-variable systems and no agreement on cut-off values to define MH exist. In fact, in various studies, different cut-off values for the CDEIS and SES-CD have been used for defining MH.¹⁶

For UC, there are several endoscopic scores. All are quite similar, but none of them has ever been properly validated.¹⁷ One of the most used is the Mayo Endoscopic Score that combines 5 variables (erythema, vascular pattern, friability, bleeding, erosions, and ulcerations) in a 4-point scale, as follows: 0=normal or inactive disease; 1=mild disease (erythema, decreased vascular pattern, mild friability); 2=moderate disease (marked erythema, absent vascular pattern, friability, erosions); 3=severe disease (spontaneous bleeding, ulcerations).¹⁸ The International Organization of Inflammatory Bowel Disease (IOIBD) has proposed a definition of MH in UC as “absence of friability, blood, erosions, ulcers in all visualized segments”.¹⁷ This definition corresponds to a Mayo score comprised between 0 and 1 and is simple to use in clinical practice.

A precise definition of MH would be of critical importance. In order to be useful in clinical terms, any definition should carry a prognostic value, in particular, it is discussed whether the definition of MH should be reserved solely for those cases of complete healing of mucosal lesions or whether, less strictly, MH could be defined as a clear improvement of mucosal lesions but without complete mucosal *restitutio ad integrum*. In a retrospective study on a large cohort of CD patients treated with IFX, no difference in the long-term need of major abdominal surgery was observed in patients that achieved complete MH (absence of ulcerations) or partial MH (clear improvement of mucosal lesions but still with ulcerations).⁶ Similarly in UC, a sub-study of the ACT 1 and ACT 2 trials showed that early MH with IFX was associated with a reduced risk of colectomy within 1 year, but the colectomy-free survival was similar in patients who achieved complete MH (Mayo Score = 0) or partial MH (Mayo Score ≤ 1).¹² Taken together, these observations suggest that a distinction between complete and partial MH may not be relevant in clinical terms but further studies are needed.
Current Treatments for IBD and Mucosal Healing

Several drugs currently used in the management of IBD are capable of inducing MH in different clinical settings of disease location and severity. However the effect size of different treatments and the duration of the effect (short-term or sustained MH) are difficult to assess because of different definitions, different study designs, and different timing of endoscopic evaluation.19

Aminosalicylates are the first line treatment for mild to moderate UC. Their efficacy in inducing and maintaining clinical remission has been demonstrated in several randomized controlled trials.20, 21 Several data prove the capacity of both oral and topical aminosalicylates in inducing also MH in mild to moderately active UC. In several studies using different oral 5-ASA doses and formulations, and considering different definitions of MH at different time points, the percentage of patients achieving endoscopic remission ranged from 25% to 70%.19 In a recent meta-analysis involving 3,977 patients treated with oral 5-ASA and 2,513 patients treated with rectal 5-ASA, the overall rate of MH, according to different definitions, was 36.9% in patients receiving oral 5-ASA and 50.3% in patients receiving rectal 5-ASA.22 Optimising oral dose and combining oral and topical aminosalicylates may result in an increased rate of endoscopic remission in the short-term, up to 75%-80% or approximately 30% when MH is defined as completely normal mucosa (Mayo score = 0).10, 23-24

Corticosteroids are the gold standard for the treatment of active moderate to severe IBD. Despite their excellent capacity to induce rapid symptomatic improvement and clinical remission in the short-term, it has been known for a long time that these drugs have a little impact on mucosal lesions. Historical trials showed that approximately one third of patients with CD and UC with corticosteroid-induced remission achieve also endoscopic remission1-25 and similar rates of clinical and endoscopic remission have been recently reported in a prospective study on 157 UC patients receiving their first steroid course.11

Immunomodulators azathioprine (AZA) and 6-Mercaptopurine (6MP) are usually considered effective in inducing MH in CD, even though it is well known that these drugs take a long time to achieve their potential benefits. However, evidence for AZA-induced MH in CD is very limited, deriving from few small studies performed in different clinical settings in which rates of MH, defined with different criteria, range from 36% to 70% within 12-42 months of continuative treatment.26-28 Recently, the SONIC study investigated the effect of a combination of AZA plus IFX vs. AZA or IFX monotherapy in moderate to severe CD patients, immunosuppressive or biologic naïve. The primary outcome was steroid-free remission at week 26 and MH was a secondary end-point evaluated in a subgroup of 309 patients who were assessed endoscopically at baseline and after 6 months of therapy. MH was achieved in only 16.5% of patients receiving AZA monotherapy.29 As far as UC is concerned, data are very limited. In a small prospective study in patients with steroid dependent UC, 55% of patients receiving AZA achieved clinical and endoscopic remission within 6 months.30 Taken together these data suggest that AZA and 6MP may induce MH in a variable proportion of patients with CD and UC but the slow action of these drugs is the major limitation.

In the last 15 years, the advent of anti-TNFα agents has raised treatment expectations beyond symptomatic remission. In fact, the first observations suggested that, compared to conventional therapies, anti-TNFα agents were very effective in inducing and, possibly, in maintaining MH.3 Nevertheless, MH in anti-TNFα treated patients has not been systematically studied and data are available from subgroup analysis of RCTs and observational cohort studies.

In CD, subgroup analyses of RCTs suggest that scheduled IFX every 8 weeks can induce MH in approximately 30% of patients in the short-term, 50% in the long-term, and sustained MH (short and long-term) in approximately 30% of patients.8, 29 Real life experiences report similar data.6 Scheduled adalimumab (ADA) maintenance (40 mg every other week) can induce and maintain complete MH in approximately 25% of patients.31

In UC, scheduled IFX every 8 weeks can induce and maintain MH in approximately 30% to 50% of patients according to the definition of MH (Mayo score = 0 vs. Mayo score ≤ 1).13, 32 Studies with ADA in UC report a short-term MH in approximately 40% of patients and one year MH in approximately 25% of patients.33, 34 Real life experiences with ADA in UC report partial MH (Mayo score ≤ 1) in approximately 50% of responders and complete MH (Mayo score = 0) in approximately 25% of patients after a median of 11 months.35

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Is MH a Valid Surrogate End-Point of Disease Outcome?

Although evidence suggests that MH may improve disease outcome in terms of sustained remission and reduced complications, hospitalization and surgery, it is a surrogate end-point of disease course and an important point for discussion is to establish if MH is a valid surrogate end-point of disease outcome. A surrogate end-point is an outcome measure that per se has not a direct clinical importance but reflects a clinically relevant outcome. The greatest potential for the validity of a surrogate end-point is when the surrogate is in the only causal pathway of the disease process and the therapeutic effect on the true outcome is mediated through its effect on the surrogate. It is difficult to find this ideal setting in a complex and multifactorial disease such IBD and, therefore, surrogate end-points could yield misleading conclusions.

Apart from the difficulties establishing the validity of MH as a surrogate end-point of disease outcome, there are other debated issues; first of all whether histology should be included in the evaluation of MH. Although theoretically appealing, the prognostic relevance of histological healing has not been extensively evaluated but some data suggest that histological healing is relevant in UC as microscopic inflammation, even without gross endoscopic lesions, is predictive of disease relapse in patients who are in clinical and endoscopic remission. Moreover, some studies indicate that ongoing microscopic inflammation is an independent risk factor of colorectal cancer in long-standing UC. Although the effect of different drugs on microscopic inflammation in UC has not been extensively studied, histological healing may be, theoretically, the ultimate therapeutic goal in UC. Conversely, in CD, comes the issue of the appropriateness of MH as a relevant end-point in the treatment of a disease that is typically transmural. A lesson about the inadequateness of superficial healing in a transmural condition, we learnt from fistulizing CD, where it has clearly emerged how the closure of fistulas’ external orifices can be achieved despite the persistence of the fistulous tracks. For this reason, the concept of MH in CD is evolving towards a more complex model of intestinal healing with the elaboration of an instrument, the so-called Lemann score, which should enable an assessment of the cumulative structural bowel damage. The score includes not only endoscopy but also cross-sectional imaging techniques and, in the near future, it could be used in clinical trials and observational studies to measure the progression of bowel damage over time and to assess the effects of treatment on the progression of bowel damage.

Take Home Messages

1. In the last years the therapeutic goals of IBD have changed from mere control of symptoms towards long-term strategies aimed at affecting the natural course of the disease and MH is an emerging end-point in this setting.

2. Although accumulating evidence suggests that MH is associated with improved disease outcome, it remains a weak surrogate end-point of disease course and further studies are needed to prospectively assess the impact of MH on long-term clinical outcomes.

3. There is currently no standardized definition of MH and further studies are needed to develop and validate a definition of MH that carries a clear prognostic value.

4. It is still uncertain how MH should be used in clinical practice. Although corticosteroids-free remission remains the first therapeutic goal in IBD, appropriate use and optimization of conventional and biological strategies may results in short and sustained MH in a variable proportion of patients.

5. The most important question for clinical practice is if we should systematically assess MH and target our treatment strategies to achieve MH in all IBD patients.

6. MH is likely not ready to be the primary therapeutic end-point in clinical practice, but it should be considered in decision-making. If the optimal management of a patient in clinical remission but with persistent endoscopic lesions is unclear (there are no prospective studies showing that escalation of therapy or switching to an alternative agent is associated with better outcomes in this setting), assessment of MH may be useful to select patients in sustained clinical remission in whom withdrawal of immunosuppressive or biologic therapy could be considered minimizing the risk of relapse.
Mucosal Healing as an Emerging Therapeutic End-Point in IBD

References