Targeting Mucosal Healing in Crohn's Disease

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Abstract: The goal of medical treatment for Crohn's disease includes improving patients' quality of life while reducing the need for hospitalization and surgery. The current medical armamentarium includes 5-aminosalicylates, corticosteroids, immunomodulators, and biologic agents. In the past, response to treatment was measured by clinical improvement in symptoms; however, with the advent of disease-modifying medications, mucosal healing has emerged as an increasingly important goal of therapy. Mucosal healing, or endoscopic remission, is associated with increased rates of clinical remission, fewer hospitalizations, and fewer abdominal surgeries. Both the immunomodulator and biologic classes of medications are effective at inducing mucosal healing. Despite several limitations, mucosal healing has become a desirable and valid measure of disease activity.

Keywords
Crohn's disease, mucosal healing, endoscopic remission, deep remission, biologic agents, immunomodulators

The medical therapies currently available for treating Crohn's disease (CD) can improve patients' quality of life, achieve and maintain disease remission, and decrease the need for hospitalizations and surgeries. The current pharmaceutical armamentarium for treating CD includes 5-aminosalicylates (5-ASAs), corticosteroids, immunomodulators (6-mercaptopurine, azathioprine, and methotrexate), and biologic agents (infliximab [Remicade, Centocor], adalimumab [Humira, Abbott], certolizumab pegol [Cimzia, UCB], and natalizumab [Tysabri, Elan/Biogen Idec]).[1] Unfortunately, despite the potency of these treatments, many CD patients do not respond or only partially respond to these drugs and continue to experience ongoing symptoms and documented inflammation. The characterization of a response to medication has evolved over time; in the past, response was based primarily on clinical symptoms. In fact, various scoring systems—such as the Crohn's Disease Activity Index (CDAI) and the Harvey-Bradshaw Index—have been developed to better categorize disease activity. Clinical symptoms, however, do not always correlate with endoscopic or radiographic findings of disease activity. Currently,

disease activity can be assessed using various parameters, including clinical, endoscopic, histologic, laboratory, radiographic, and fecal marker findings. Clinicians often use a combination of these markers to determine disease severity and appropriate therapy. In clinical trials, severe endoscopic findings have been shown to predict aggressive disease and the need for surgery.[2] As such, some investigators have proposed that mucosal healing (MH) should be used as the therapeutic endpoint in research trials, as well as in clinical practice, to optimize long-term outcomes. This paper focuses on the importance of MH in CD by discussing the long-term effects of MH, the limitations of using MH in clinical practice, and the ability of current CD therapies to achieve MH.

Outcomes of Mucosal Healing

CD is an inflammatory disorder of the gastrointestinal tract that is characterized by radiologic, endoscopic, and histologic changes. Typical findings on capsule endoscopy and ileocolonoscopy include erythema, edema, nodularity, aphthous ulcers, and ulceration. The degree of friability and spontaneous bleeding, as well as the depth and size of ulcerations, correlates with clinical severity.[3] The value of using endoscopic findings to predict the course of CD was first noted by Rutgeerts and associates over 2 decades ago.[4,5] In these seminal studies, the severity of endoscopic inflammation in the neoterminal ileum 1 year after ileocolonic resection predicted the likelihood of subsequent clinical recurrence.[4,5] Further evidence regarding the importance of MH emerged from a prospective cohort study conducted in Norway that assessed the predictive value of MH in inflammatory bowel disease (IBD). In this study of 740 patients with ulcerative colitis (UC) and CD, which was performed before the advent of biologic therapies, the investigators noted that MH was associated with improved clinical outcomes during long-term follow-up.[6] MH, which is also referred to as "endoscopic remission," has increased in value as an outcome measure in CD clinical trials. Several long-term benefits of MH have been identified, including decreased need for surgery and hospitalization, lower steroid use, lower CDAI scores, decreased risk of colorectal cancer, and higher remission rates. More recently, the terms "stable remission" and "deep remission" have been coined to encompass MH plus a measure of clinical and/or laboratory improvement.[7]

With the advent of biologic therapy for CD, MH has become an achievable and important outcome that may predict subsequent disease course. In a study published by Allez and colleagues in 2002, the severity of endoscopic lesions at colonoscopy was a risk factor for penetrating disease and future colectomy.[2] The probability of colectomy was 31% at 1 year, 42% at 3 years, and 62% at 8 years among patients with severe endoscopic lesions. In the absence of severe endoscopic lesions, the corresponding rates of colectomy dropped to 6%, 8%, and 18% at 1, 3, and 8 years, respectively ($P<.0001$).[2] In a 2009 study of the long-term outcomes of CD patients treated with infliximab, patients who achieved complete or partial MH at follow-up endoscopy had lower rates of major abdominal surgeries (14.1%) compared to patients who did not exhibit MH (38.4%; $P<.0001$); major abdominal surgery was defined as any intestinal resection, stricturoplasty, or fecal diversion.[8] In the Norwegian cohort of 141 CD patients who underwent endoscopic re-evaluation at 1 and 5 years after initial diagnosis, 11% of patients who achieved MH after 1 year underwent surgical resection by 5 years, whereas 20% of patients who failed to achieve MH at 1 year required surgery by 5 years ($P=.10$).[6] Although this finding was not statistically significant at 5 years, when the follow-up period for this cohort was extended to 10 years, the risk of surgery was reduced by 60% among patients who achieved MH compared to patients who did not achieve MH (hazard ratio, 0.42; 95% confidence interval [CI], 0.20–0.89).[9] These studies highlight the relationship between endoscopic appearance and subsequent risk of major abdominal surgery.

The impact of MH on other long-term outcomes—such as hospitalization, steroid use, and CDAI scores—has also been studied. In addition to lower colectomy rates, patients treated with infliximab who achieved MH had lower hospitalization rates. After a median follow-up period of 68.7 months, 42.2% of patients with MH needed hospitalization compared to 59.3% of patients without MH ($P=.0018$).[8] This trend was also noted in a subgroup of the ACCENT 1 study population, but it did not reach statistical significance. Endoscopic response was noted at 10 and 54 weeks after induction with infliximab, and a trend toward lower rates of CD-related hospitalizations was observed in patients who achieved MH.[10] In an endoscopic study conducted by Baert and coworkers of a CD patient cohort randomized to conventional management versus combined azathioprine and infliximab, higher rates of steroid-free remission were noted among patients with endoscopic remission.[11,12] In this study, 49 patients underwent ileocolonoscopy 2 years after initiation of treatment. Forty-six of these 49 patients were then followed for an additional 2 years. The investigators reported that complete MH at Year 2 predicted steroid-free remission 3 and 4 years after the onset of treatment. Among patients with MH, 70.8% achieved sustained steroid-free remission, whereas only 27.3% of patients with persistent lesions achieved the same type of remission (odds ratio, 4.352; 95% CI, 1.10–17.22; $P=.036$).[12] In this small cohort, there was no difference between

the groups in terms of the number of surgeries or major hospitalizations.

In the study conducted by Baert and associates, CDAI scores did not correlate with MH.[12] However, further evidence supporting the association between MH and clinical remission emerged from the ACCENT 1 study. In this study, patients were randomized to receive either episodic or scheduled infliximab. In both groups, patients with MH at Week 54 had a longer time until clinical relapse when followed for a median of 20 weeks after their last infliximab infusion.[13] Preliminary data from the EXTEND trial, which evaluated the efficacy of adalimumab in moderate-to-severe CD, demonstrated that early MH is associated with improved quality of life after 1 year and improved CDAI scores.[14] In the MUSIC study, patients with moderate-to-severe CD received open-label certolizumab pegol and were followed for 54 weeks. Among the intent-to-treat population with an available endoscopic assessment at Week 10, the overall IBD Questionnaire remission rate was 69.7% in patients with MH compared with 33.3% in patients not achieving MH. Similar results were observed with endoscopic assessment at Week 54.[15]

A relationship between clinical remission and MH was seen in a study that examined the effect of azathioprine versus budesonide on MH in 77 patients with steroid-dependent CD. In this study, significantly more patients in the azathioprine group achieved MH. After 18 months, 76% of patients in the azathioprine group had reached clinical remission compared to only 36% in the budesonide group (P=.03).[16] In a study conducted by Schnitzler and colleagues on the effects of MH on long-term outcomes in CD, 64.8% of patients who achieved MH were in clinical remission at the end of 5 years, whereas only 39.5% of patients who did not achieve MH attained clinical remission (P=.0004).[8] These studies indicate that clinical relapse may be reduced when endoscopic remission is attained, and they demonstrate the importance of MH as an outcome in clinical practice as well as in clinical trials.

The severity of endoscopic and histologic inflammation is an established risk factor for developing colorectal cancer in patients with UC. A case-control study of 68 patients with UC found that the degree of histologic inflammation was positively correlated with an increased risk of neoplasia.[17] Similarly, a cohort study of 418 patients with UC found a positive association between the degree of microscopic inflammation and advanced neoplasia.[18,19] Although these studies did not include CD patients, they provide indirect evidence to support the theory that achieving MH may reduce the risk of colorectal cancer in CD. However, additional studies examining patients with CD are needed to provide further evidence.

Limitations of Mucosal Healing

It is generally accepted that MH is valuable for predicting and managing CD; however, there are limitations to the endoscopic assessment of MH. The exact definition of MH in CD is unclear, as MH may represent complete absence of any characteristic endoscopic lesions or marked improvement in the severity of previously noted lesions. In addition, no guidelines have been developed to determine the optimal timing for follow-up endoscopy to identify MH. Furthermore, there is considerable heterogeneity among endpoints in the literature. Several endoscopic disease activity indices have been developed in an effort to describe and codify endoscopic appearance. The Crohn's Disease Endoscopic Index of Severity (CDEIS) is a prospectively developed, reproducible, validated scoring system considered to be the gold standard for classifying the appearance of gut mucosa.[20] However, the CDEIS has multiple variables, making it difficult to use and impractical for clinical practice.[10,21] The Simple Endoscopic Score for Crohn's Disease (SES-CD) is a validated score that correlates with the CDEIS but is simpler to use. Four variables—the size of ulcers, the amount of ulcerated mucosa, the amount of affected mucosa, and the presence of narrowing—are assessed in 5 segments of the bowel.[22] The easy-to-use Rutgeerts score was developed to assess the severity of disease recurrence 1 year after ileal resection. A score of 0 or 1 predicts a low risk of clinical recurrence, whereas a score of 3 or 4 is a validated predictor of clinical relapse.[4,5] However, this system is only valid for predicting postoperative recurrence, not therapeutic response. Importantly, each of these scoring systems is limited by interobserver variability. In 2002, a consensus panel identified the CDEIS and the Rutgeerts score as gold standards for evaluating MH in patients with CD.[21]

In addition to the difficulty of defining MH, endoscopic evaluation is time-consuming and costly, and it subjects patients to a small but real risk of adverse events. Less invasive methods for determining the degree of inflammation include laboratory tests, imaging, and stool studies. The 2 most common laboratory values for assessing disease activity in CD are the erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) level. Both ESR and CRP level are useful for predicting the risk of short-term relapse and are valuable for managing CD. However, ESR and CRP level can be highly variable and inaccurate, which limits their use in long-term management.[23] Stool calprotectin and lactoferrin levels correlate

with SES-CD scores and histologic activity for ileocolonic and colonic CD.[24] In a study conducted by Rimola and coworkers, magnetic resonance (MR) findings, such as wall thickness, edema, contrast enhancement, and ulcers, correlated with endoscopic disease severity (as measured by the CDEIS) and were validated in a subsequent study conducted by the same group.[25,26] In a study comparing MR enterography (MRE), computed tomography enterography (CTE), and ileocolonoscopy findings, CTE and MRE were equally accurate for assessing disease activity.[27] It is unclear whether MH, transmural healing, or histologic remission is responsible for better clinical outcomes, and the relationship among all 3 measures has not yet been elucidated.

Another limitation of using MH as the gold standard outcome is the observation that MH and clinical improvement may not correspond. The possible disconnect among MH, clinical improvement, serologic improvement, and radiographic improvement has been noted and has led to the development of various composite endpoints that include clinical improvement and/or normalization of serum markers of inflammation. Terms such as "stable remission" and "deep remission" have been used to define these composite endpoints; however, their definitions have not yet been validated. A position paper discussing endpoints for CD clinical trials that was published by the International Organization for the Study of Inflammatory Bowel Diseases proposed that meaningful clinical remission include withdrawal of steroids; the paper also accepted MH as a desirable outcome. However, the authors noted the need for determining and validating consensus definitions of remission.[28]

Many patients with IBD exhibit persistent symptoms, such as abdominal pain, bloating, and diarrhea, in the absence of mucosal or serologic inflammation. A study conducted by Keohane and associates attempted to discern the presence of occult inflammation among IBD patients in clinical remission—defined as a CDAI score of no more than 150 points, a serum CRP level of less than 10 mg/L, and no use of steroids for 6 months—who fulfilled Rome II criteria for irritable bowel syndrome (IBS).[29] Stool calprotectin levels were significantly higher in CD patients who met the criteria for IBS than in patients without IBS-type symptoms (414.7±80.3 vs 174.9±49.1 mg/kg; P=.0087).[29] Although this study did not assess mucosal disease, it highlighted the role of ongoing inflammation, even in patients who achieve apparent remission. Once remission is established, alternative explanations for persistent symptoms—such as celiac disease, small intestinal bacterial overgrowth, pancreatic insufficiency, pelvic floor dyssynergia, bile acid malabsorption, and IBS—must then be excluded.[30]

Mucosal Healing and Crohn's Disease Treatments

5-Aminosalicylates

Clinical trial data confirm that treatment with 5-ASAs can result in clinical remission and MH in mild-to-moderate UC.[31-37] Although 5-ASA agents are often used to treat mild-to-moderate CD, there are no published data on the ability of 5-ASAs to achieve MH in CD.

Corticosteroids

Although corticosteroids are frequently used to ameliorate disease flares, data indicate that these agents are unlikely to achieve MH in CD. Two studies conducted by the GETAID group demonstrated poor correlation between clinical improvement and endoscopic remission following treatment with oral prednisolone.[38,39] After 7 weeks of corticosteroid therapy in 142 patients, only 38 of the 131 (29%) patients in clinical remission demonstrated some degree of MH.[39] A study conducted by Hellers and colleagues investigated the efficacy of budesonide versus placebo for preventing postoperative endoscopic recurrence of CD.[40] After 1 year of treatment, there was no benefit in terms of the prevention of endoscopic recurrence among patients who received budesonide.[40] These studies provide further support for using corticosteroids only for short-term treatment, as they cannot significantly modify disease course.

Immunomodulators

The immunomodulators 6-mercaptopurine, azathioprine, and methotrexate are well-established treatments for achieving and maintaining clinical remission in patients with CD. Several studies have evaluated the ability of these medications to attain MH in CD.

A small number of clinical trials suggest that methotrexate can achieve MH in CD. A case series reported that 62.5% (5/8) of patients with steroid-dependent CD attained complete or partial MH after a median of 15 months of methotrexate therapy.[41] A recent study conducted by Laharie and coworkers reported on MH rates with methotrexate, azathioprine, or infliximab therapy.[42] In this study, only 11% (2/18) of CD patients on methotrexate achieved complete MH. However, when using the less stringent CDEIS criteria, more than half of the patients on methotrexate achieved some degree of MH. The MH rates in the azathioprine and infliximab groups surpassed the rate of MH achieved in the methotrexate group.[42]

Studies evaluating the effect of thiopurines on MH are more substantive. Sandborn and associates published 1 of the first studies on azathioprine and MH in

1995.[43] In this study, 6 patients with severe ileocolonic CD received 36 hours of intravenous azathioprine followed by daily oral dosing. After 16 weeks, 50% of these patients achieved MH.[43] A subsequent study conducted by D'Haens and coworkers reported a complete MH rate of 40% among postoperative patients with severe recurrent ileitis of the neoterminal ileum with 6 months of azathioprine therapy.[44] A similar MH rate (45%) was seen in another study conducted by D'Haens and colleagues; in this study, a cohort of patients with refractory CD was treated with azathioprine after withdrawal of corticosteroids.[45] Azathioprine's efficacy for preventing postoperative endoscopic recurrence was further investigated in a study that randomized CD patients after curative ileocecal resection to metronidazole for 3 months and either azathioprine or placebo for 12 months. Significant endoscopic recurrence, as measured by the Rutgeerts score, was noted in 43.7% of the azathioprine group and 69.0% of the placebo group.[46] A prospective, randomized, controlled trial conducted by Mantzaris and associates in patients with steroid-dependent CD demonstrated the efficacy of azathioprine for attainting MH.[16] In this study, 38 patients were randomized to azathioprine and 39 patients were randomized to budesonide for 1 year. At the end of the study, 58% (22/38) of patients who received azathioprine achieved MH, as measured by CDEIS score, compared to 15% (6/39) of the group receiving budesonide (P<.0001).[16] When MH was evaluated as a secondary endpoint in the SONIC trial, only 16.5% (18/109) of patients on azathioprine alone achieved MH after 26 weeks.[47] Overall, despite this lower-than-expected rate, these studies support the use of thiopurines for achieving MH in patients with CD.

Biologic Agents

The development of biologic agents for the treatment of CD sparked interest in MH and the potential for altering disease course. An endoscopic substudy of 99 patients in the ACCENT 1 trial, which evaluated the efficacy of infliximab in refractory CD, revealed MH in 29% (13/45) of patients 10 weeks after induction therapy. The rate of MH rose to 44% (16/36) after 54 weeks of maintenance infliximab compared to 18% (4/22) among patients who received episodic infliximab.[48,49] The SONIC study reported on MH rates after 26 weeks of treatment. Among patients who received infliximab monotherapy, 30.1% (28/93) achieved MH, compared to 43.9% (47/107) of patients who received infliximab plus azathioprine (P=.06). MH rates in the SONIC study paralleled clinical remission rates.[47] Several other studies have provided evidence supporting the ability of infliximab to induce and maintain MH.[10,11,48,50-54]

Data on infliximab—the first and most extensively studied anti–tumor necrosis factor (TNF) agent—and MH are abundant; in addition, data showing the ability of adalimumab and certolizumab pegol to achieve MH have been presented. In fact, the absence of mucosal ulcerations was used as the primary endpoint of the EXTEND trial. This placebo-controlled trial compared MH in 2 groups of patients with colonic CD. Both treatment groups received induction therapy with adalimumab followed by maintenance treatment with either adalimumab or placebo. After 12 and 52 weeks, 27.4% and 24.2%, respectively, of patients undergoing scheduled maintenance therapy achieved MH compared to 13.1% and 0.0%, respectively, of patients receiving placebo.[55] A post-hoc analysis of data from the EXTEND study that was presented in abstract form revealed improved MH rates at Week 12 among patients with a shorter disease duration (<5 years).[56] The MUSIC trial investigated the use of certolizumab pegol among patients with severe endoscopic disease, as measured by CDEIS score. Patients received induction and maintenance therapy with certolizumab pegol; the primary endpoint was a change in baseline CDEIS score, and 1 of the secondary endpoints was endoscopic remission (CDEIS <7). At Week 10, the mean reduction in CDEIS score was 6.5 points. At Week 54, complete endoscopic response was observed in 33% of patients, and endoscopic remission was observed in 15% of patients.[57]

The concept of deep remission—defined as MH with clinical remission (CDAI <150)—has been introduced as a desirable outcome that may identify individuals who are candidates for withdrawal of biologic agents.[7] The STORI trial, which was presented in abstract form, hypothesized that some patients in stable remission may be candidates for withdrawal of biologic agents. In this study, patients who had been receiving scheduled infliximab plus an immunosuppressive medication for at least 1 year and who were in steroid-free remission for more than 6 months were prospectively followed after withdrawal of infliximab. Active tobacco use, previous steroid treatment, lower hemoglobin levels, higher CDAI and CDEIS scores, and higher CRP and fecal calprotectin levels were associated with a higher risk of relapse.[58] Additional studies are needed to determine the significance of deep remission and its role in the management of CD patients.

Natalizumab, a humanized monoclonal antibody to α-4 integrin, has been shown to achieve clinical response, as measured by CDAI score.[59,60] When 53 patients were evaluated in a substudy from the ENACT-1 trial, 22% of patients with mucosal ulcerations at study entry showed complete MH after 10 weeks, compared to 8% of the placebo group.[59,61]

Summary

The goal of CD therapy remains centered on achieving a good quality of life, fewer hospitalizations, and fewer surgeries. Traditionally, remission has been defined as an improvement in subjective clinical symptoms; however, recent clinical trials have provided compelling data to suggest that MH—whether assessed via endoscopic, radiologic, serum, or fecal marker findings alone or in combination—is critical for achieving both clinical remission and improved long-term outcomes. Among the treatments currently available for CD, both immunomodulators and biologic agents have the ability to induce and maintain MH.

Despite several limitations, MH has emerged as a desirable and valid measure of disease activity, particularly in the subgroup of patients with extensive CD and severe endoscopic lesions. However, if a patient is in clinical remission but has persistent endoscopic lesions, the next step in management is unclear. There are no prospective studies showing that escalation of therapy or switching to an alternative agent is associated with better outcomes in asymptomatic patients with ongoing endoscopic inflammation. Further research is required to investigate these outcomes. In the meantime, endoscopic evaluation is appropriate in CD patients who experience continued symptoms, have severe initial lesions, and/or are on long-term therapy. Additional studies are also needed to determine whether patients who have MH and are in prolonged clinical remission are candidates for withdrawal of immunosuppressive or anti-TNF therapy.

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