Mucosal Healing in Inflammatory Bowel Disease—A True Paradigm of Success?

Maneesh Dave, MBBS, MPH, and Edward V. Loftus, Jr., MD

Dr. Dave is a Fellow and Instructor of Medicine and Dr. Loftus is a Professor of Medicine in the Division of Gastroenterology and Hepatology at Mayo Clinic in Rochester, Minnesota.

Address correspondence to:
Dr. Edward V. Loftus, Jr.
Division of Gastroenterology and Hepatology
Mayo Clinic
200 First Street SW
Rochester, MN 55905;
Tel: 507-266-0873;
Fax: 507-284-0538;
E-mail: loftus.edward@mayo.edu

Abstract: Mucosal healing is gaining more acceptance as a measure of disease activity in Crohn's disease and ulcerative colitis, and it is also gaining acceptance as an endpoint in clinical trials. Recent publications have correlated achievement of mucosal healing with good outcomes. Currently, there is no validated definition of what constitutes mucosal healing in inflammatory bowel disease. In clinical trials of ulcerative colitis, mucosal healing has been achieved with 5-aminosalicylates, corticosteroids, azathioprine, and infliximab. For Crohn's disease, mucosal healing has been achieved with corticosteroids, infliximab, and adalimumab, and mucosal healing has been maintained with infliximab. Achievement of long-term mucosal healing has been associated with a decreased risk of colectomy and colorectal cancer in ulcerative colitis patients, a decreased need for corticosteroid treatment in Crohn's disease patients, and a trend toward a decreased need for hospitalization in Crohn's disease patients. Unfortunately, assessment of mucosal healing requires regular use of endoscopy, which is associated with increased costs, patient discomfort, and side effects. Biomarkers such as fecal calprotectin, fecal lactoferrin, serum C-reactive protein, and fecal S100A12 have been shown to correlate with disease activity in ulcerative colitis and Crohn's disease; in the future, these biomarkers might be used as surrogate markers for mucosal healing. Newer clinical trials are incorporating mucosal healing as an endpoint for evaluation of efficacy. However, before mucosal healing will be sufficient to guide therapy, clinicians need a standard definition of mucosal healing and a consistently used, prospectively validated scale with good interobserver agreement.

Inflammatory bowel disease (IBD), which includes both Crohn's disease and ulcerative colitis (UC), is a chronic idiopathic inflammatory disorder affecting the gastrointestinal tract. Current evidence suggests that IBD results from an inappropriate inflammatory

Table 1. Select Endoscopic Disease Activity Scores for Ulcerative Colitis

Index	Variables
Truelove and Witts score[14]	Mucosal assessment (granularity, hyperemia)
Baron score[15]	Bleeding, vascular pattern
Powell-Tuck score[16]	Bleeding
Sutherland score[17]	Bleeding, friability
Mayo endoscopic subscore[18]	Vascular pattern, erythema, friability, erosions and ulcerations, bleeding
Rachmilewitz score[19]	Granulation, mucosal damage, vascular pattern, bleeding
Modified Baron score[20]	Vascular pattern, friability, ulcerations, bleeding

response to intestinal microbes in a genetically susceptible host.[1] In a population-based study in Olmsted County, Minnesota, the adjusted prevalences of Crohn's disease and UC in 2001 were 174 cases per 100,000 persons and 214 cases per 100,000 persons, respectively. Extrapolation of these study results to the US population in 2000 (approximately 281 million people) suggests that there were approximately 489,000 patients with Crohn's disease and 601,000 patients with UC among US residents at that time.[2] The natural history of Crohn's disease and UC is characterized by repeated episodes of inflammation and ulceration of the intestine, resulting in complications requiring hospitalization, surgery, and escalation of therapy.[3,4]

Assessment of disease activity is a challenging aspect of IBD, not only for the management of patients with IBD but also for the design and conduct of clinical trials. The National Cooperative Crohn's Disease Study Group created the Crohn's Disease Activity Index (CDAI), which has been used in clinical trials to define the activity, remission, and relapse of Crohn's disease.[5] This index has been recommended by the International Organization for the Study of Inflammatory Bowel Disease (IOIBD) and the European Crohn's and Colitis Organization for defining Crohn's disease activity.[6,7] For UC, however, there is no consensus on a validated scale to define disease activity, and combinations of endoscopy and clinical disease activity indices have been used.[8]

The idea of using mucosal healing as an endpoint for assessing disease activity and remission in IBD patients started gaining traction with the demonstration that treatment with azathioprine and then infliximab (Remicade, Janssen Biotech; a chimeric monoclonal antibody against tumor necrosis factor–α [TNF-α]) could induce not only symptomatic improvement but also endoscopic remission in patients with Crohn's disease.[9-11]

What Is Mucosal Healing?

There is no validated definition of what constitutes mucosal healing in IBD.[6,12] An IOIBD task force proposed defining mucosal healing in UC as the absence of friability, blood, erosions, and ulcers in all visualized segments of gut mucosa.[12] Similarly, for Crohn's disease, the IOIBD put forward a consensus definition of mucosal healing that includes the absence of ulcers. However, the panel rightly alludes to this definition as an evolving standard that needs validation.[13] Simply stated, mucosal healing should imply the absence of ulcerations and erosions. Does this statement mean that all patients should have complete absence of ulcers and erosions? Not necessarily. Studies have not yet determined what minimum degree of endoscopic improvement is associated with improved clinical outcomes—in other words, what constitutes a clinically meaningful improvement in endoscopic appearance.

Mucosal healing has traditionally been assessed by endoscopy in patients with IBD. With the advent of capsule endoscopy, less invasive mucosal assessment of the small bowel in Crohn's disease patients is possible.

Ulcerative Colitis

There are numerous endoscopic indices that have been used to assess disease activity in clinical trials of UC.[14-20] Clinicians need to remember this point when comparing the rates of mucosal healing across studies, since minor changes in the definition of mucosal healing may result in considerable differences in healing rates. Table 1 summarizes some of the commonly used indices. Of note, none of these indices have been fully validated in prospective studies. In an exhaustive review, D'Haens and colleagues summarized the different endpoints currently used for the indications of treatment, induction of remission, maintenance of remission, and endoscopic remission in UC patients.[12] Table 2 shows the Mayo UC endoscopic score, which is an endoscopic index that is commonly used in both clinical trials and clinical practice.[18]

Crohn's Disease

In contrast to the lack of validated endoscopy indices for UC, there are validated endoscopy indices for measurement of Crohn's disease activity (Table 3). The gold standard is the Crohn's Disease Endoscopic Index of Severity (CDEIS).[21] This index is a validated and reproducible scale that was prospectively developed but is somewhat cumbersome to use and requires training. A simplified version of this scale is the Simple Endoscopic Score for

Table 2. Mayo Endoscopic Score

Score	Disease activity	Endoscopic features
0	Normal or inactive	None
1	Mild	Erythema, decreased vascular pattern, mild friability
2	Moderate	Marked erythema, absent vascular pattern, friability, erosions
3	Severe	Spontaneous bleeding, ulceration

Table 3. Select Endoscopic Disease Activity Scores for Crohn's Disease

Index	Variables
Crohn's Disease Endoscopic Index of Severity[21]	Superficial and deep ulceration, ulcerated and nonulcerated stenosis, surface area of ulcerated and diseased segments*
Simple Endoscopic Score for Crohn's Disease[22]	Ulcer size, ulcerated surface, affected surface, presence of narrowings
Rutgeerts score[23]	Aphthous ulcerations, inflammation, ulcers, nodules, narrowing

*Gold standard.

Crohn's Disease (SES-CD).[22] In addition, the Rutgeerts score is commonly used for estimating the severity and recurrence of Crohn's disease in the neoterminal ileum following resection.[23]

Induction and Maintenance of Mucosal Healing

Numerous trials in IBD patients have assessed mucosal healing as one of the study endpoints. This review will focus on prospective studies or randomized trials that have used established endoscopic criteria or a strict definition of mucosal healing as an index for assessment of disease activity. When no randomized clinical trial is available, we have described the best available prospective study (Tables 4 and 5). An exhaustive review by Pineton de Chambrun and colleagues has covered the studies in IBD that have included assessment of mucosal healing.[24]

Ulcerative Colitis
The ASCEND trials showed that an oral delayed-release mesalamine formulation can induce mucosal healing in patients with mildly to moderately active UC. ASCEND I enrolled patients with mildly to moderately active UC, and ASCEND II enrolled patients with moderately active

UC.[25,26] A post–hoc combined analysis of the 2 studies showed that the rate of mucosal healing (endoscopy sub-score of 0 or 1) at Week 6 was 80% among patients who received the 4.8-g/day dose and 68% among patients who received the 2.4-g/day dose (P=.012).[27]

The ASCEND III study was conducted to determine the best initial dose of mesalamine (4.8 g/day vs 2.4 g/day) in patients with moderately active UC.[28] This study used a modified sigmoidoscopy score that included assessment of mucosal friability by biopsy forceps in addition to the endoscopic scores used in earlier studies. The investigators did not specify a definition of mucosal healing, but they did report a decrease in modified sigmoidoscopy score at Week 6 in 30.2% of patients (105 of 348) receiving the 4.8-g/day dose of mesalamine versus 30.7% of patients (106 of 345) who received the 2.4-g/day dose (P=.88).

Sandborn and colleagues published a post–hoc analysis of 2 placebo-controlled, randomized trials in which patients received 8 weeks of multimatrix (MMX) mesalamine (Lialda, Shire)—2.4 g/day (once daily or 1.2 g twice daily) or 4.8 g/day (once daily)—or placebo; a modified Sutherland endoscopy score was used to assess mucosal healing.[29] Complete mucosal healing (defined as a sigmoidoscopy score of 0) was achieved in 32% of patients (55/172) in the 2.4-g/day group, 32.2% of patients (56/174) in the 4.8-g/day group, and 15.8% of patients (27/171) in the placebo group. When a similar definition of mucosal healing was applied to the combined post–hoc analysis of ASCEND I and II, 32% of patients in the 4.8-g/day group and 24% of patients in the 2.4-g/day group (P=.125) had a sigmoidoscopy score of 0 at Week 6, which is closer to the mucosal healing rates seen in the ASCEND III and MMX mesalamine studies.[27] This finding highlights the need for a consistent definition of mucosal healing across trials.

Corticosteroids are able to induce and maintain mucosal healing in subsets of patients with UC. In a randomized, double-blind, placebo-controlled clinical trial, Gross and coworkers showed that 2 formulations of topical budesonide (ie, foam [2 mg] and liquid enema [2 mg]) taken once daily for 4 weeks by patients with active UC or proctosigmoiditis induced mucosal healing as assessed by the Rachmilewitz index.[30] Fifty-two percent of patients receiving budesonide foam and 54% of patients receiving budesonide enema achieved mucosal healing.

In a randomized trial of azathioprine (2 mg/kg daily) versus mesalamine (3.2 g daily) for the treatment of steroid-dependent UC, induction of clinical and endoscopic remission (Baron index of 0 or 1) with steroid discontinuation occurred at 6 months in 53% of patients receiving azathioprine versus 19% of patients receiving mesalamine (P=.006).[31] Two randomized, double-blind, placebo-controlled studies—ACT 1 and ACT 2—evalu-

Table 4. Characteristics of Select Studies of Inflammatory Bowel Disease Medications That Have Assessed Mucosal Healing

Study	Medication	Disease	Study design	Endoscopic index (definition of mucosal healing)
Lichtenstein GR, et al[27]	Delayed-release mesalamine	UC	ASCEND I and II post–hoc analysis	Mayo score (endoscopy score of 0 or 1)
Sandborn WJ, et al[29]	Multimatrix mesalamine	UC	Post–hoc analysis	Modified Sutherland score (sigmoidoscopy score of 0)
Gross V, et al[30]	Topical budesonide	UC	Double-blind, randomized, noninferiority study	Rachmilewitz index (<4)
Modigliani R, et al[37]	Prednisolone	CD	Open-label prospective study	CDEIS (no lesions or scars)
Ardizzone S, et al[31]	AZA	UC	Randomized trial	Baron index (remission: score of 0 or 1)
Mantzaris GJ, et al[38]	AZA	CD	Randomized trial	CDEIS* (complete and near-complete mucosal healing)
Ogata H, et al[36]	Oral tacrolimus	UC	Randomized trial + open-label extension	Mayo score + Sutherland score (endoscopy score of 0 or 1)
Rutgeerts P, et al[32]	IFX	UC	Double-blind, randomized, controlled trials	Mayo endoscopic score (0 or 1)
Colombel JF, et al[41]	IFX + AZA	CD	Double-blind, randomized, controlled trial	No index (complete absence of mucosal ulceration)
Reinisch W, et al[33] Sandborn WJ, et al[34]	ADA	UC	Double-blind, randomized, controlled trial	Mayo score (endoscopy score of 0 or 1)
Rutgeerts P, et al[42]	ADA	CD	Open-label + randomized trial	SES-CD (absence of mucosal ulceration)
Colombel JF, et al[44]	Certolizumab pegol	CD	Open-label trial	CDEIS (complete endoscopic remission: CDEIS <3)

*Complete mucosal healing was defined as disappearance of all pathologic findings; near-complete healing was defined as occasional aphthae, residual superficial erosions, or thickened folds.

ADA=adalimumab; AZA=azathioprine; CD=Crohn's disease; CDEIS=Crohn's Disease Endoscopic Index of Severity; IFX=infliximab; SES-CD=Simple Endoscopic Score for Crohn's Disease; UC=ulcerative colitis.

ated the efficacy of infliximab for induction and maintenance of remission in adults with moderately to severely active UC.[32] In ACT 1, induction therapy with infliximab (administered at 0, 2, and 6 weeks) resulted in Week 8 mucosal healing as assessed by a Mayo endoscopic score of 0 or 1 in 62% of patients in the 5-mg/kg infliximab group, 62% of patients in the 10-mg/kg infliximab group, and 33.9% of patients in the placebo group (*P*<.001). At Week 54, 45.5% of patients in the 5-mg/kg group had achieved mucosal healing, compared to 18.2% of placebo-treated patients (*P*<.001). In ACT 2, 60.3% of patients

treated with infliximab at a dose of 5 mg/kg achieved mucosal healing, compared to 30.9% of patients in the placebo group (*P*<.001).[32] At Week 30, 56% of patients in the 5-mg/kg infliximab arm had maintained mucosal healing, compared to 37% of patients in the placebo arm. The ACT trials showed that infliximab can induce and maintain mucosal healing over a period of up to 1 year in UC patients.

A randomized controlled trial assessed adalimumab (Humira, Abbott) for induction of clinical remission in moderately to severely active UC (defined as a Mayo score

Table 5. Results of Select Studies of Inflammatory Bowel Disease Medications That Have Assessed Mucosal Healing

Study	Medication	Mucosal healing rates		P-value
Lichtenstein GR, et al[27]	Delayed-release mesalamine	Week 6:	80.8% in 4.8-g/day group 68% in 2.4-g/day group	.012
Sandborn WJ, et al[29]	Multimatrix mesalamine	Week 8:	32.2% in 4.8-g/day group 32% in 2.4-g/day group 15.8% in placebo group	NR
Gross V, et al[30]	Topical budesonide	Week 4:	52% in budesonide foam group 54% in budesonide enema group	NR
Modigliani R, et al[37]	Prednisolone	By Week 7:	13% of 92% who achieved clinical remission on prednisolone	NA
Ardizzone S, et al[31]	AZA	6 months:	53% in AZA group 19% in mesalamine group	.006
Mantzaris GJ, et al[38]	AZA	1 year:	83% in AZA group 24% in budesonide group	.0001
Ogata H, et al[36]	Oral tacrolimus	Week 2:	43.8% in tacrolimus group 13.3% in placebo group	.012
Rutgeerts P, et al[32]	IFX	Week 8: Week 54:	62% in 5-mg/kg/day group, 62% in 10-mg/kg/day group, 33.9% in placebo group 45.5% in 5-mg/kg group 18.2% in placebo group	<.001 .001
Colombel JF, et al[41]	IFX + AZA	Week 26:	43.9% in IFX + AZA group (group 1) 30.1% in IFX group (group 2) 16.5% in AZA group (group 3)	1 vs 3, P<.001; 2 vs 3, P=.02
Reinisch W, et al[33] Sandborn WJ, et al[34]	ADA	Week 8: Week 52:	46.9% in ADA 160/80 group 37.7% in ADA 80/40 group 41.5% in placebo group 25% in ADA 160/80 group 15.4% in placebo group	NS <.01
Rutgeerts P, et al[42]	ADA	Week 12: Week 52:	13.1% in ADA induction group 27.4% in continuous ADA group 0% in ADA induction group 24.2% in continuous ADA group	.056 <.001
Colombel JF, et al[44]	Certolizumab pegol	Week 10: Week 54:	11.5% on certolizumab pegol 18.9% on certolizumab pegol	NR

ADA=adalimumab; AZA=azathioprine; IFX=infliximab; NA=not applicable; NR=not reported; NS=not significant.

≥6 and endoscopic subscore ≥2).[33] The primary endpoint of this study was clinical remission (Mayo score ≤2 with no individual subscore >1); mucosal healing (endoscopy subscore of 0 or 1) was one of the secondary endpoints. Under the original study protocol, 186 patients were randomized to subcutaneous treatment with adalimumab 160/80 (160 mg at Week 0, 80 mg at Week 2, and 40 mg at Weeks 4 and 6) or placebo. A second induction group (adalimumab 80/40: 80 mg at Week 0; 40 mg at Weeks 2, 4, and 6) was later included at the request of European regulatory authorities. At Week 8, 41.5%, 37.7%, and 46.9% of patients achieved mucosal healing in the placebo (n=130), adalimumab 80/40 (n=130), and adalimumab 160/80 (n=130) groups, respectively. The differences in rates of mucosal healing were not statistically significant. In a 52-week follow-up study, the results

of which were published in abstract form only, induction and maintenance of clinical remission were assessed at Weeks 8 and 52 in the placebo group and the adalimumab 160/80 group (which received 160 mg at Week 0, 80 mg at Week 2, and 40 mg every other week starting at Week 4).[34] Mucosal healing at Week 52 was seen in 15.4% of patients (38/246) in the placebo group compared to 25% of patients (62/248) in the adalimumab group (*P*<.01).

Ogata and colleagues performed a randomized, placebo-controlled trial of oral tacrolimus (FK506) administered for 2 weeks with target trough concentrations of 10–15 ng/mL (high trough) and 5–10 ng/mL (low trough) in patients with moderately or severely active UC.[35] The 2-week trial was followed by a 10-week, open-label extension study in which all patients received oral tacrolimus. The investigators used a disease activity index that included assessment of mucosal healing using an endoscopic score that combined aspects of the Schroeder and Sutherland scores. Mucosal healing rates at Week 2 in the high trough, low trough, and placebo groups were 78.9%, 44.4%, and 12.5%, respectively. In the open-label extension study, mucosal healing was seen in 72.7% of patients receiving tacrolimus. In a more recent randomized controlled trial, these investigators used oral tacrolimus for 2 weeks to achieve a target blood concentration of 10–15 ng/mL, and they showed mucosal healing in 43.8% of patients in the tacrolimus group versus 13.3% of patients in the placebo group (*P*=.012).[36] At Week 2, 20 of 62 patients were transitioned to azathioprine, and the remaining 42 patients were placed in the open-label tacrolimus arm. Among patients who received tacrolimus from the beginning of the study, the rate of mucosal healing increased from 66.7% at Week 2 to 85.7% at Week 12.

Crohn's Disease

Most of the Crohn's disease treatment trials have used a CDAI score less than 150 points as the endpoint for evaluation of remission. The subjective nature of much of the CDAI score (eg, stool frequency, degree of abdominal pain, and overall sense of well-being)—which are not necessarily sensitive or specific for the presence of bowel inflammation—is cited as one of the main reasons for the high placebo response rates seen in many clinical trials.

In a seminal trial performed by Modigliani and colleagues of Groupe d'Etude Thérapeutique des Affections Inflammatoires Digestives, patients were started and then maintained on prednisolone at a dose of 1 mg/kg body weight per day until clinical remission was achieved (at least 3 weeks and at most 7 weeks).[37] Among the 92% of Crohn's disease patients who achieved clinical remission, 29% achieved endoscopic remission per CDEIS cri-

teria by the end of 7 weeks, with 13% achieving complete mucosal healing (no lesions or scars).

In a randomized controlled trial, Mantzar and coauthors compared the efficacy of azathioprine (2.0–2.5 mg/kg daily) versus budesonide (6–9 mg daily) in patients with steroid-dependent Crohn's ileocolitis or proximal colitis who were in clinical remission; this study evaluated mucosal healing at 1 year using the CDEIS.[38] Eighty-three percent of the azathioprine-treated patients achieved complete or near-complete mucosal healing, compared to only 24% of patients treated with budesonide (*P*=.0001).

The era of biologic treatment for IBD began with a study by Van Dullemen and colleagues that showed that mucosal healing (as assessed by the CDEIS) occurred in 9 of 10 patients 4 weeks after a single infusion of infliximab.[9] The ACCENT I study was a randomized, multicenter, controlled trial that evaluated the benefit of maintenance infliximab therapy in patients with active Crohn's disease who responded to a single infusion of infliximab.[39] An endoscopic substudy of the ACCENT I trial assessed mucosal healing in 99 patients. Twenty-nine percent of Crohn's disease patients who received 3 infliximab infusions at a dose of 5 mg/kg (at Weeks 0, 2, and 6) showed evidence of mucosal healing at Week 10, compared to 3% of patients who received only 1 infliximab infusion (*P*<.006). In the same study, 44% of patients who were on regularly scheduled maintenance therapy with infliximab achieved mucosal healing, compared to 18% of patients who received episodic infliximab infusions. The main drawback of this analysis was that only 75% and 59% of patients had endoscopies at Weeks 10 and 54, respectively.[40]

The SONIC study was a randomized, double-blind clinical trial that assessed the efficacy of infliximab monotherapy, azathioprine monotherapy, and the 2 drugs combined in 508 adults with moderate-to-severe Crohn's disease who were naïve to immunosuppressive or biologic therapy.[41] Mucosal healing, defined as the complete absence of mucosal ulceration in the colon and terminal ileum, was seen in 30.1% of patients assigned to infliximab monotherapy at Week 26, compared to 16.5% of patients assigned to azathioprine monotherapy (*P*=.02) and 43.9% of patients in the combination therapy group (*P*=.06 for combination therapy vs infliximab monotherapy; *P*<.001 for combination therapy vs azathioprine monotherapy).

In the EXTEND trial, patients with moderately to severely active ileocolonic Crohn's disease (defined as a CDAI score of 220–450 points) and baseline mucosal ulceration (defined as a SES-CD score of 2 or 3 in >1 colon segments) received open-label adalimumab induction therapy consisting of 160 mg at Week 0 and 80 mg at Week 2.[42] At Week 4, patients were randomized to receive maintenance therapy with adalimumab

(40 mg every other week) or placebo through Week 52. This study was the first biologic study in which the primary endpoint was complete mucosal healing (determined by the review committee's visual assessment of Week 12 endoscopies). In the intent-to-treat population, complete mucosal healing was achieved at Week 12 in 13.1% of patients (8/61) in the induction-only group and 27.4% of patients (17/62) in the group receiving continuous adalimumab (P=.056). At Week 52, rates of complete mucosal healing were 0% (0/61) and 24.2% (15/62) in the 2 treatment groups, respectively (P<.001).

MUSIC was a 54-week, open-label trial that evaluated the efficacy of certolizumab pegol (Cimzia, UCB) for healing mucosal lesions (measured using the CDEIS) in patients with moderate-to-severe Crohn's disease (defined as a CDAI score of 220–450 points and CDEIS score ≥8 points).[43,44] Like the EXTEND trial, the primary endpoint of this study was mucosal healing, defined by a change in the CDEIS from baseline to Week 10. Secondary endpoints included endoscopic remission (CDEIS score <7 points) and response (≥4-point change in CDEIS score). Certolizumab pegol at a dose of 400 mg was administered subcutaneously in 89 subjects at Weeks 0, 2, and 4, after which it was administered every 4 weeks. At Week 10 (n=78), 61.5% of patients achieved an endoscopic response and 11.5% of patients achieved complete endoscopic remission (CDEIS <3 points). In the 53 patients who completed 54 weeks of treatment and provided endoscopic data at baseline, Week 10, and Week 54, the rates of endoscopic response, remission (CDEIS score <7 points), and complete endoscopic remission (CDEIS <3 points) were 62.2%, 28.3%, and 18.9%, respectively.[44]

Why Is Mucosal Healing Important?

The main hypothesis in support of mucosal healing is that achieving mucosal healing may improve quality of life, prevent IBD relapses, minimize hospitalizations, and alter the natural history of the disease to prevent complications such as fistulae, colorectal cancer, and need for surgery.

Colorectal Cancer and Ulcerative Colitis

In a study of patients with longstanding UC who were undergoing surveillance colonoscopy, a univariate analysis by Rutter and coworkers showed that the degree of colonoscopic and histologic inflammation correlated with risk of colorectal neoplasia; however, in the multivariate analysis, only histologic inflammation was an important determinant of risk.[45] In a follow-up study, the same group showed that UC patients who had a macroscopically normal colon had a colorectal cancer risk similar to that of the general population.[46]

Mucosal Healing and Long-Term Outcomes

A prospective, population-based study of the Inflammatory Bowel South-Eastern Norway Study cohort evaluated the impact of mucosal healing on long-term outcomes in UC and Crohn's disease patients before the advent of biologic therapy.[47] In UC patients, mucosal healing was associated with a low risk of future colectomy. In Crohn's disease patients, mucosal healing was associated with decreased need for future corticosteroid treatment and less inflammation. In the initial cohort of 227 Crohn's disease patients, 141 underwent repeat colonoscopy at 1 year. On re-evaluation at the end of 5 years, 23 of 71 patients with endoscopic activity at 1 year were on oral corticosteroids, compared to 6 of 48 patients who had achieved mucosal healing at 1 year (P=.02). Among those in the UC cohort (n=513) with 1-year follow-up endoscopy (n=354), 3 patients in the mucosal healing group were recorded as having undergone surgery at 5 years, compared to 13 patients in the group without mucosal healing at 1 year (P=.02). One of the main drawbacks of this study was that endoscopies were performed by many different gastroenterologists, and no kappa value (a measure of interobserver validity) was provided.

In a recently published study, members of an inception cohort of newly diagnosed patients in Italy with moderately to severely active UC were given corticosteroids and were evaluated clinically (Powell-Tuck index) and endoscopically (Baron index) after 3 months, 6 months, and every 6 months thereafter for 5 years; patients were designated as having complete response (Baron score of 0) or partial response (Baron score 1–3).[48] This study showed that patients who achieved a complete response at 3 months had lower rates of hospitalization (25% vs 49%; P<.01), less use of immunosuppressive therapy (5% vs 26%; P<.003), and lower rates of colectomy (3% vs 18%; P<.0265) compared to patients with a partial response. In a study by Ferrante and colleagues that evaluated long-term outcomes in UC patients receiving infliximab, absence of short-term mucosal healing as defined by a Mayo endoscopy score of 0–1 was a predictor of need for colectomy.[49] In a post–hoc analysis of the ACT trials for UC, Colombel and colleagues showed that infliximab-treated patients who had a lower Mayo endoscopy score at Week 8 were less likely to undergo colectomy by Week 54 (P=.0004).[50] These patients were also more likely to be in corticosteroid-free symptomatic remission at Week 30 (P<.0001) and Week 54 (P<.0001). Both infliximab-treated and placebo-treated patients who had lower endoscopy scores at Week 8 were more likely to be in symptomatic remission at Week 54. However, more infliximab-treated patients were in symptomatic remission overall, compared to those treated with placebo.

The ACCENT I endoscopic substudy found a numerical trend toward a lower rate of Crohn's disease–related

hospitalizations among patients with better mucosal healing, although this trend was not statistically significant.[40] In an observational study of Crohn's disease patients by Schnitzler and coworkers, mucosal healing was seen in 124 of 183 patients (initial responders) on long-term infliximab maintenance treatment.[51] Patients who achieved mucosal healing had a 14.1% rate of major abdominal surgery compared to a rate of 38.4% among patients who did not achieve mucosal healing (*P*<.0001) after a median of 22.3 months (interquartile range, 2.2–50.6) after the follow-up endoscopy, which was performed a median of 6.7 months after starting treatment with infliximab. Mucosal healing was also associated with a significantly better disease-free survival (logrank: *P*<.001). In addition, 42.2% of patients who achieved mucosal healing required hospitalization during the follow-up period versus 59.3% of patients without mucosal healing (*P*=.0018).[51]

Clinical trials in UC and Crohn's disease have significant placebo response and remission rates.[52,53] A meta-analysis of clinical trials of UC showed that studies that included endoscopic mucosal healing (defined by an endoscopic score of 0) as part of the definition of remission had a lower placebo remission rate (odds ratio, 0.4; 95% confidence interval, 0.2–7; *P*=.02).[53] The authors hypothesized that this finding resulted from a more stringent definition of remission in studies that included endoscopic assessment; therefore, the placebo-treated patients were less likely to be judged as having achieved spontaneous clinical remission. This finding was further validated by the fact that the studies included in this meta-analysis that used more stringent definitions of response and remission (such as a Ulcerative Colitis Disease Activity Index score of 0 or absence of rectal bleeding) had lower placebo rates. This meta-analysis also showed that clinical remission rates were strongly correlated with endoscopic remission rates (r=77; *P*=.001). However, this meta-analysis (of all studies) had significant heterogeneity (test of heterogeneity, *P*<.001), and the findings should be interpreted with caution.

Surrogate Markers of Mucosal Healing

Biomarkers like fecal calprotectin, fecal lactoferrin, serum C-reactive protein (CRP), and fecal S100A12 have been shown to correlate with disease activity in UC and Crohn's disease patients.[54-57] In a retrospective study conducted at Mayo Clinic, CRP elevations in Crohn's disease patients were associated with moderate-to-severe clinical activity, active disease at colonoscopy, and histologically severe inflammation.[58] In UC patients, CRP elevations were significantly associated with severe clinical activity and active disease at ileocolonoscopy. In a study by Sipponen and colleagues that assessed patients who were treated with

anti-TNF agents, 11 patients achieved partial or complete endoscopic response and had significant decreases in fecal calprotectin and lactoferrin levels. No significant decreases in fecal calprotectin and lactoferrin concentrations were seen in the 3 nonresponders.[59]

Computed tomography enterography (CTE) and magnetic resonance enterography (MRE) are newer modalities for diagnosing and assessing disease activity in IBD patients.[60] A study by Wold and coauthors showed the sensitivity and specificity of CTE to be 75% and 100%, respectively, compared to fluoroscopic small bowel examination and terminal ileoscopy to detect active small bowel inflammation in patients with Crohn's disease.[61] Recent studies indicate that both CTE and MRE might be useful to monitor disease activity in patients who have been started on anti-TNF therapy.[62,63]

A prospective, cross-sectional study of 164 Crohn's disease patients who underwent colonoscopy showed that serum high-sensitivity CRP (hsCRP), serum interleukin (IL)-6, fecal calprotectin, and fecal lactoferrin concentrations were significantly higher in patients with more severe endoscopic disease activity (ie, SES-CD score >7; *P*<.001).[56] On the other hand, no significant association was seen between CDAI and SES-CD scores. Interestingly, CDAI score did not correlate with either serum hsCRP (both phenotype and genotype) or IL-6 concentrations, nor did it correlate with fecal calprotectin and lactoferrin concentrations.

Future Directions

Mucosal healing as assessed by endoscopy is a useful tool for evaluating and guiding response to therapy in patients with IBD. However, performing endoscopy on a frequent, regular basis may have drawbacks. Patient discomfort and compliance are both issues. Also, while generally considered to be a low-risk procedure, diagnostic endoscopy still carries risks of perforation, bleeding, and cardiovascular risks due to sedation. In addition, endoscopy is an expensive test, and frequent endoscopy may not prove to be cost-effective in an environment of healthcare reform and an era of comparative effectiveness research. Finally, colonoscopy without biopsy may not be able to completely assess treatment response and predict long-term outcomes.

On the other hand, newer clinical trials are incorporating mucosal healing as an endpoint for evaluation of efficacy in an effort to better define appropriate patients and reduce placebo response rates. However, we do not yet have prospective trials demonstrating that escalation of therapy to achieve mucosal healing can alter long-term outcomes such as hospitalizations and surgeries. A European Crohn's and Colitis Organization consensus conference on

mucosal healing in IBD concluded that mucosal healing is important, but this conference highlighted the need for large, prospective studies assessing the impact of mucosal healing and histologic healing on the natural course of this disease.[64] Further, researchers still face the problems associated with use of different endoscopic assessment scales.

Overall, mucosal healing is an admirable goal that we should strive to achieve in our patients on a regular basis. However, until clinicians have a standard definition of mucosal healing and a consistently used, prospectively validated measurement scale with good interobserver agreement, mucosal healing alone will be insufficient to guide therapy.

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