The Importance of Mucosal Healing in Ulcerative Colitis

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Anthony M. Sofia, Sarah R. Goeppinger, and David T. Rubin

Keywords
Mucosal healing • Ulcerative colitis • Inflamed rectum • Tenesmus • Incomplete evacuation • Urgency • Bleeding • Hematochezia • Prognostic marker inflammatory damage • Colorectum

Introduction

Ulcerative colitis (UC) is an idiopathic condition of the colon, in which acute and chronic inflammation results in an injured bowel. Chronic inflammatory damage, confined exclusively to the mucosa of the colorectum, is the hallmark of the disease. The inflammation is characteristically superficial in nature and appears to begin in the rectum with variable extension to more proximal portions of the colon. This inflammation, and subsequent loss of function, is the mechanism underlying the typical symptoms of UC. Although there may be more systemic symptoms, the majority of the symptoms of UC are derived from an inflamed rectum and due to loss of compliance of the rectum, loss of sensation of stool, as well as symptoms of tenesmus incomplete evacuation, urgency, and bleeding with hematochezia. The healed bowel can result in the resolution of symptoms and has been associated with disease control and resolution, but traditional clinical assessment of UC involves symptom management primarily, with the assumption that when bleeding and urgency are improved, adequate disease control has been achieved. However, resolution of bowel inflammation is not always manifest as improved or resolved symptoms, and improved symptoms are not always associated with a healed bowel or durable disease control. This chapter reviews the importance of musical healing as a prognostic marker and therapeutic endpoint in UC.

A.M. Sofia, M.D. (✉)
Department of Internal Medicine, University of Chicago Medicine, 165 N. Canal St. #1030, Chicago, IL 60637, USA
e-mail: masofia@uchicago.edu

S.R. Goeppinger, B.A.
Section of Gastroenterology, Department of Medicine, University of Chicago Medicine, 5841 South Maryland Avenue, MC 4080, Chicago, IL 60637, USA
e-mail: goeppinger@medicine.bsd.uchicago.edu

D.T. Rubin, M.D.
Section of Gastroenterology, Department of Medicine, University of Chicago, 5841 S. Maryland Avenue, MC 4076, Chicago, IL 60637, USA
e-mail: drubin@medicine.bsd.uchicago.edu

Endoscopic Scoring of Mucosal Inflammation in UC

The description of inflammation in UC varies from mild mucosal disruption with loss of vascularity and some edema to more significant diffuse inflammation, with mucopus or even diffuse ulcerations and areas of complete loss of the mucosa. An additional feature of active mucosal inflammation in UC is contact friability or spontaneous bleeding. Although traditionally described as diffuse in its extent and involvement, some patchiness to the endoscopic appearance may be seen during disease onset or with partial treatment by medical therapy (Fig. 5.1).

In an effort to quantify the degree of inflammation, a number of different clinical, endoscopic, and composite scoring systems have been developed over time (Table 5.1). Most frequently embraced is the so-called Mayo endoscopic subscore, which was developed from the previously published "Baron score" and modified in order to be part of a

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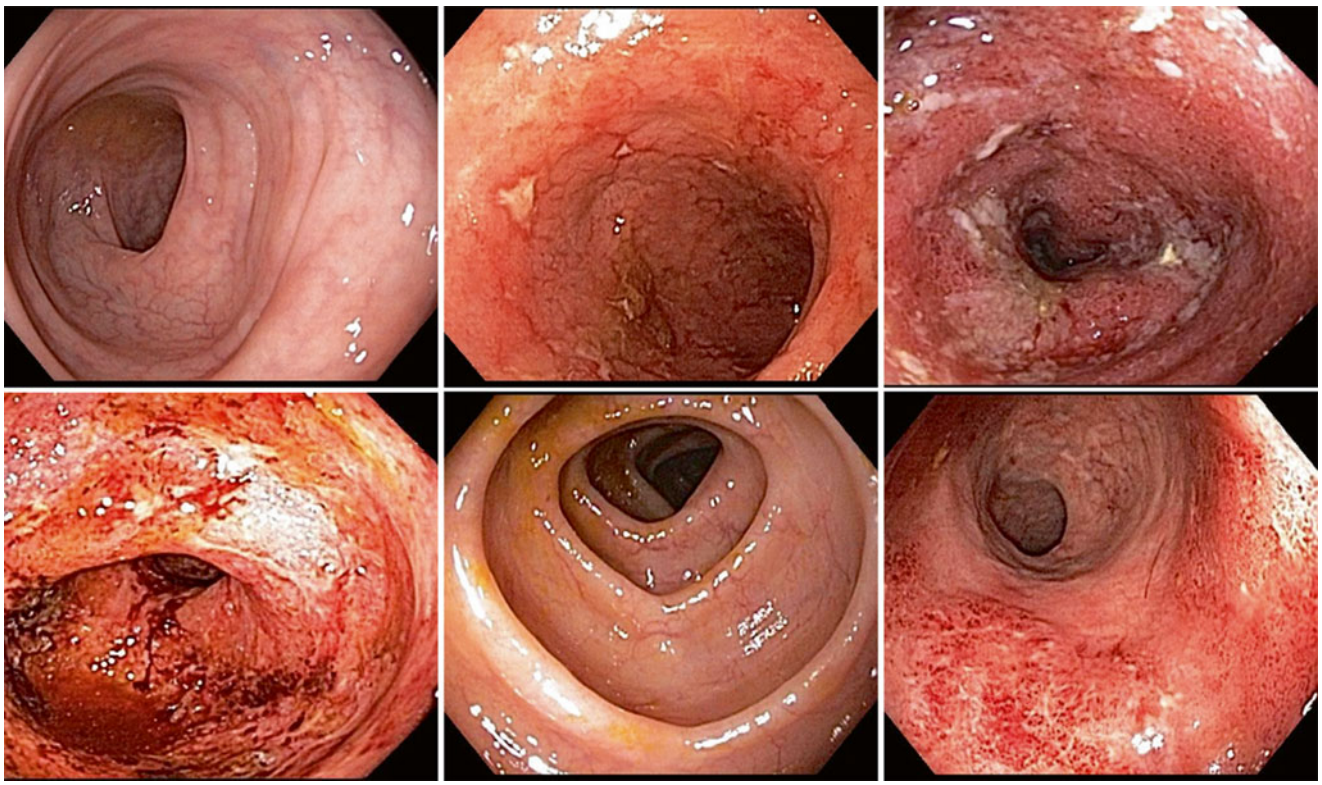

Fig. 5.1 Variable appearances of mucosa in ulcerative colitis

Table 5.1 Measuring disease activity in ulcerative colitis

Based on clinical and biochemical disease activity	Based on endoscopic disease activity	Composite clinical and endoscopic disease activity
Truelove and Witts severity index (TWSI)	Truelove and Witts sigmoidoscopic assessment	Mayo score (DAI)
Powell-Tuck index	Baron score	Sutherland index (DAI, UCDAI)
Clinical activity index (CAI)	Powell-Tuck sigmoidoscopic assessment	
Activity index (AI or Seo index)	Rachmilewitz endoscopic index	
Physician global assessment	Sigmoidoscopic index	
Lichtiger index (mTWSI)	Sigmoidoscopic inflammation grade score	
Investigators global evaluation	Mayo score flexible proctosigmoidoscopy assessment	
Simple clinical colitis activity index (SCCAI)	Sutherland mucosal appearance assessment	
Improvement based on individual symptom scores	Modified Baron score	
Ulcerative colitis clinical score (UCCS)	UC endoscopic index of severity (UCEIS)	
Patient-defined remission		

Adapted from D'Haens G, Sandborn WJ, Feagan BG, Geboes K, Hanauer SB, Irvine EJ, Lémann M, Marteau P, Rutgeerts P, Schölmerich J, Sutherland LR. A review of activity indices and efficacy end points for clinical trials of medical therapy in adults with ulcerative colitis. Gastroenterology. 2007 Feb;132(2):763–86 [47]

composite index (the "Mayo score") for the clinical trials of delayed-release mesalamine [1]. In the Mayo endoscopic subscore, the endoscopic appearance is rated from 0 to 3 (Fig. 5.2). A score of 0 is termed "normal," which is defined as an intact mucosa with a preserved vascular pattern and no friability or granularity. A score of 1 represents an abnormal appearance but is not grossly hemorrhagic. The mucosa may appear erythematous and edematous, and the vascular pattern may appear blunted. A score of 2 is moderately hemorrhagic, with bleeding to light touch but without spontaneous bleeding seen ahead of the instrument on initial inspection. In the traditional Mayo scoring, friability is part of a score of 1, but in the modified Mayo scoring (as in the clinical trials with MMX mesalamine), friability is part of a score of 2.

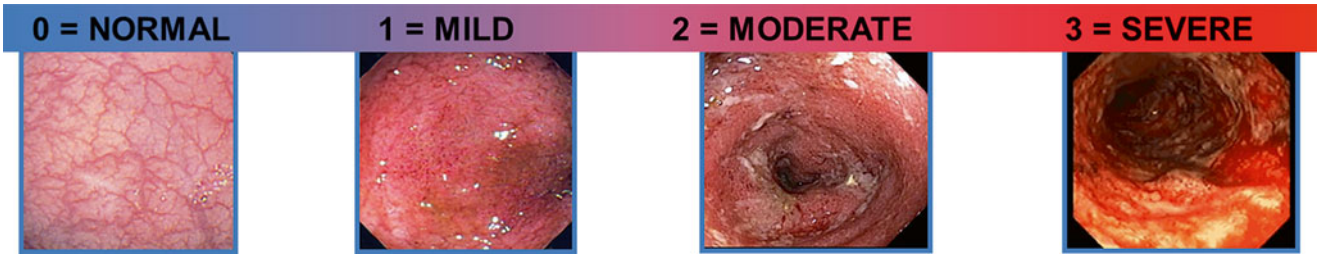

Fig. 5.2 Representative photos of the Mayo endoscopic subscore. Schroeder KW, Tremaine WJ, Ilstrup DM. Coated oral 5-aminosalicylic acid therapy for mildly to moderately active ulcerative colitis. A randomized study. N Engl J Med. 1987 Dec 24;317(26):1625–9 [46]

A score of 3 is termed "severe," which is defined as having marked erythema, absent vascular markings, granularity, spontaneous bleeding, and ulcerations. In most clinical trials, the term "mucosal healing" has been defined as a Mayo subscore of 0 or 1. The prior definitions of mucosal healing have had limitations, and there has been interest in clarifying endoscopic and histologic definitions for future clinical trials and disease management paradigms. Therefore, in 2007, the International Organization for the Study of Inflammatory Bowel Disease (IOIBD) defined mucosal healing as an absence of friability, blood, erosions, or ulcerations [2, 3].

Most recently, Travis and colleagues have described a novel UC scoring index of severity, the UCEIS (Ulcerative Colitis Endoscopic Index of Severity). In the two-phase development study, a library of 670 video sigmoidoscopies from patients with composite Mayo scores between 0 and 11 were supplemented by 10 videos from 5 people without UC and 5 patients hospitalized with severely active disease. In phase 1, 10 investigators each viewed 16/24 videos to determine agreement on the Baron score with a central reader and agreed definitions of 10 endoscopic descriptors. In phase 2, 30 investigators each rated 25/60 videos for said descriptors and assessed overall severity on an analog scale that ranged from 0 to 100. The study found a 76 % agreement for severe and a 27 % agreement for normal endoscopic appearances. It was concluded that the UCEIS accurately predicted the overall assessment of endoscopic severity in UC; however, additional testing and further validity are needed before use in clinical practice.

For clinical trials, the use of a centralized reader for endoscopic scoring is of interest and has demonstrated significant impact on clinical trial outcomes. Further training of gastroenterologists in particular will be necessary in order to develop reliable approaches to the use of endoscopic mucosal healing as a clinical practice treatment endpoint [4, 5].

Histologic scoring of mucosal healing in UC notably, histologic findings previously have not been part of these definitions of mucosal healing in UC. The IOIBD also defined the two histologic patterns that are consistent with remission. The first is demonstration of chronic inflammation in the lamina propria with regular or irregular glands. The second is a lack of inflammation with an atrophic glandular pattern with short crypts, glands with lateral buddings, dichotomic glands, or an apparently normal glandular pattern [3]. Numerous methods of classifying histologic activity have been proposed, but despite emerging interest by regulatory bodies, these scales have not been validated as clinical trial endpoints or for clinical practice [6]. There remain numerous unanswered questions about whether histologic healing or remission can be a realistic treatment goal for the majority of patients [6, 7].

Why Mucosal Healing Is Important in UC

Although the obvious connection between the status of the mucosal inflammation and the condition of the patient with UC has long been recognized, it has only been in recent years that a therapeutic goal of mucosal healing could be entertained. This is due to the ability to measure mucosal injury in easier ways, emerging data on clinical outcomes associated with degrees of mucosal inflammation, and the development of many therapies that offer methods of healing the mucosa in patients with UC [2]. It is also due to the appreciation that symptoms similar to active UC can be mimicked by the presence of irritable bowel syndrome or, possibly, injury to the mucosa and submucosa from prior inflammation and chronic changes that occur. In addition, the emerging clinical goal of endoscopic mucosal healing enables further distinction from other conditions such as infections, which also may produce confounding symptoms. Therefore, the adoption of mucosal healing as a therapeutic goal theoretically can reduce the diagnostic reliance on subjective clinical characteristics. Such a therapeutic endpoint also clarifies response to therapy, so that therapeutic adjustments are made with more accurate information. Finally, emerging evidence demonstrates that endoscopic mucosal healing is associated with improved short- and long-term outcomes in UC (Table 5.2).

Table 5.2 Possible primary and secondary benefits of mucosal healing in ulcerative colitis

Reduction of clinical relapse
Reduction in surgical rates
Reduction in hospitalization
Reduction in neoplasia
Improvement in quality of life

Histologic and endoscopic inflammatory activity has been shown to be associated with higher rates of disease relapse in UC. Riley and colleagues evaluated 82 ulcerative colitis patients who were in remission to see if histologic inflammation during remission predicted relapse. Each of the 82 patients were in clinical remission and had rectal biopsies obtained at the beginning of the trial. They were then maintained on sulfasalazine or mesalamine and followed for clinical relapse. The investigators found that a number of histologic findings predicted clinical relapse. The histologic findings predictive of clinical relapse at 12 months were acute inflammatory cell infiltrate, crypt abscesses, mucin depletion, and breached surface epithelium [8]. A more recent study by Meucci and colleagues determined that endoscopic mucosal inflammation during clinical remission predicted disease relapse. The investigators induced clinical remission in ulcerative colitis patients with mesalazine and then performed colonoscopy at 6 weeks of treatment. Patients who had achieved both endoscopic and clinical remission by week 6 had a significantly lower rate of disease relapse in the following 12 months (23 %) than patients who achieved clinical remission alone (80 %, $p<0.01$) [9].

Active endoscopic inflammation and mucosal healing are also predictive of rates of surgery. Carbonnel and colleagues performed endoscopy on 85 patients with active UC. They found that 93 % of patients with endoscopically severe disease (defined as deep/extensive ulcers, mucosal detachment, large mucosal abrasions, or well-like ulcers) required subsequent colectomy compared to 23 % of the patients with endoscopically moderately active disease (superficial ulcers, deep but not extensive ulcers) [10]. Additional evidence was described by Frøslie and colleagues in the study of a Norwegian observational cohort. Patients were enrolled and had follow-up colonoscopies 1 and 5 years after enrollment. Of the 354 patients who completed the follow-up, those who had achieved mucosal healing after the 1-year colonoscopy were less likely to undergo colectomy by the 5-year follow-up, regardless of treatment exposure (in other words, the healing itself was predictive of the outcome, not how they achieved it). The relative risk of having a colectomy in the patients with mucosal healing was 0.22 (95 % CI: 0.06–0.79) [11].

Increased histologic inflammatory activity is also associated with a higher risk of cancer and dysplasia. Rutter and colleagues first published a case-control study to evaluate the association between severity of inflammation on surveillance colonoscopy and later development of colonic dysplasia. Univariate analysis demonstrated that both endoscopic and histologic inflammation were associated with an increased risk for dysplasia and colorectal cancer. After controlling for other explanatory variables, only histologic inflammation was significantly associated with an increased risk for dysplasia or colorectal cancer. For each one-unit increase in the histologic score, the odds of colorectal neoplasia increased by a factor of 4.69 (95 % CI: 2.10–10.48, $p<0.001$) [12]. Gupta and colleagues also reviewed a cohort of 418 patients and assessed their histologic activity scores, as reported by their pathologists. Univariate analysis found that mean, maximal, and cumulative severity of histologic inflammation was associated with significant risk for developing advanced neoplasia [13]. Rubin and colleagues performed a case-control study with 59 cases of colorectal neoplasia matched to 141 controls, with prospective regrading of the degrees of histologic inflammation by two expert pathologists. We created a novel expanded histologic grading scale, in order to capture more detail at the lower end of the scale, and included "normalization" of biopsies as well. On multivariate analysis, mean histologic activity index score over the surveillance period was significantly associated with colorectal neoplasia risk (as was male sex). For each one-unit increase in histologic activity index score, there was an adjusted odds ratio of 3.68 (95 % CI, 1.69–7.98; $p=0.001$) [14]. These studies all demonstrate that increased inflammation over time is a specific and independent risk factor for neoplasia in UC. However, while these studies suggest that altering the course of inflammation may change the likelihood of cancer, there is no direct evidence of this point, and prospective studies to measure such an endpoint will be difficult to perform. Nonetheless, the British Society of Gastroenterology has incorporated a stratification scheme for intervals of surveillance colonoscopy based on the presence of inflammation during the exam [15].

Achieving Mucosal Healing with Therapy in UC

There are multiple therapeutic avenues by which to achieve mucosal healing in UC. The available therapies for UC include corticosteroids, 5-aminosalicylic acid derivatives, immunomodulators, and biological agents.

Interestingly, corticosteroids have been shown to have some mucosal healing effect for decades. In 1955, Truelove and Witts reported on the use of cortisone in UC. They identified a significant difference between the group treated with oral cortisone and the placebo group, with treated patients having a higher likelihood of achieving a normal or near-normal appearing bowel on sigmoidoscopy [16]. In a later

report, they found similar results with intravenous steroids on inducing clinical remission but they did not report on sigmoidoscopic appearance [17]. More recent studies of oral glucocorticoids include a study by Lofberg and colleagues which compared oral budesonide and prednisolone. They used the Mayo endoscopic subscore to determine mucosal response to therapy. They found that 12 % of patients on budesonide and 17 % of patients on prednisolone achieved complete endoscopic remission and there was no significant difference between the two groups [18]. These findings must be interpreted with the additional knowledge that steroids are not effective maintenance therapies in UC and the understanding of the mechanism of steroids on the mucosa of UC, including the inhibition of prostaglandin synthesis, which may in fact impair healing.

Many studies have shown that 5-aminosalicylate therapy can achieve mucosal healing in UC and the majority have used the prior definition of a Mayo endoscopic subscore of 0 or 1. Kamm and colleagues studied mesalazine with Multi Matrix System (MMX) technology (Cosmo, Lainate, Italy) in patients with mild to moderate ulcerative colitis. They determined that 77.6 % of patients on 4.8 g of MMX mesalazine daily, 69.0 % of patients on 2.4 g of MMX mesalazine daily, and 61.6 % of patients on 2.4 g delayed-release mesalamine three times daily were able to achieve mucosal healing at 8 weeks of treatment. This was compared to 46.5 % of patients on placebo, and mucosal healing was defined as a modified Sutherland index less than or equal to 1 [19]. A similar study by Lichtenstein and colleagues studied the percentage of patients who received clinical and endoscopic remission in 8 weeks on MMX mesalamine at a dose of 2.4 g twice per day ($n=93$), 4.8 g once per day ($n=94$), or placebo ($n=93$). This study reported similar results with remission achieved by 34.1 % of patients on a twice-daily dose of MMX mesalamine 2.4 g, 29.2 % on 4.8 g once daily, and 12.9 % on placebo [20]. The combined rate of mucosal healing in both of these studies was 32.0 % of patients on MMX mesalazine 2.4 g daily and 32.2 % of patients on MMX mesalazine 4.8 g daily, compared 15.8 % of patients in the placebo group [21].

In the ASCEND I study, Hanauer and colleagues reported that oral delayed-release mesalamine induced complete remission in 46 % and 36 % of patients with mild to moderate ulcerative colitis for 4.8 g daily and 2.4 g daily, respectively [22]. The ASCEND II study again compared delayed-release mesalamine in 4.8 g daily or 2.4 g daily formulations, limited to patients with moderately active ulcerative colitis. The study found that 20.2 % of the patients on 4.8 g daily and 17.7 % of the patients on 2.4 g daily were able to achieve complete remission [23]. These studies reported patients who achieved complete remission, which required both endoscopic and clinical remission, but did not report on the subset that achieved mucosal healing. A combined analysis of patients with moderate ulcerative colitis from ASCEND I and ASCEND II showed mucosal healing (a score of 0 or 1) at week 3 in 65 % of patients receiving 4.8 g daily of delayed-release mesalazine and 58 % of patients receiving 2.4 g daily. At week 6 they found that mucosal healing rates were significantly higher in patients receiving 4.8 g daily than 2.4 g daily (80 % vs. 68 %, $p=0.012$) [24]. In a subsequent post hoc analysis, Lichtenstein and colleagues reviewed the mucosal healing rates of the ASCEND trials when a Mayo endoscopic subscore of 0 was used and found that the healing rates were substantially lower in those treated with delayed-release mesalamine 2.4 g per day versus 4.8 g/day [24].

In another report, Kruis and colleagues studied once-daily dosing of mesalazine versus three times daily dosing in patients with ulcerative colitis [25]. In this study they measured mucosal healing by a Rachmilewitz endoscopic index of less than 4. Patients achieved mucosal healing in 71 % with once-daily dosing of mesalazine and 70 % of patients with three times daily dosing. These studies show that 5-ASA compounds, despite their different formulations, are capable of inducing mucosal healing (albeit with variable definitions) at significant rates for mild to moderate ulcerative colitis.

There is much less evidence regarding the immunomodulators, azathioprine and 6-mercaptopurine. Ardizzone and colleagues compared the efficacy of azathioprine to oral 5-aminosalicylic acid for inducing remission in steroid-dependent ulcerative colitis. They found that 53 % of patients taking azathioprine achieved both clinical and endoscopic remission compared to 19 % of patients taking oral 5-aminosalicylic acid ($p=0.006$). Additionally, they found that the mean Baron index score for endoscopic activity was significantly lower in the azathioprine group compared to the 5-aminosalicylic acid group at the 3- and 6-month follow-up [26]. Paoluzi and colleagues also performed a trial of azathioprine without a comparison group. They found that 68.7 % of patients achieved endoscopic remission as defined by a Baron index score of 0 [27]. These studies suggest that mucosal healing is achievable with azathioprine, but the results are not directly comparable to other therapies and the exact rate of healing is not known.

The clinical trials of tumor necrosis factor alpha inhibitors have shown that they are capable of inducing mucosal healing (Table 5.3). In contrast to the varied definitions of mucosal healing that studies of the other classes have used, the biologic therapy trials used a Mayo endoscopic subscore of 0 or 1 to define mucosal healing. Infliximab was found in the ACT 1 and ACT 2 trials to achieve mucosal healing at week 8 at rates of 16.5 % on adalimumab versus 9.3 % on placebo. Among those who were anti-TNF-α naïve compared to those who had previously received anti-TNF agents, the rates of remission at week 8 were 21.3 % on adalimumab and 11 % on placebo, and 9.2 % on adalimumab and 6.9 % on placebo, respectively. The significant difference between

Table 5.3 Mucosal healing rates from trials of biologic therapies for ulcerative colitis

Drug	Clinical trial		Reported rates of mucosal healing[a]		
Infliximab	ACT1		5 mg	10 mg	Placebo
		8 weeks	62.00 %	59.00 %	33.90 %
		p value	<0.001	<0.001	
		30 weeks	50.40 %	49.20 %	24.80 %
		p value	<0.001	<0.001	
		54 weeks	45.50 %	46.70 %	18.20 %
		p value	<0.001	<0.001	
	ACT2		5 mg	10 mg	Placebo
		8 weeks	60.30 %	61.70 %	30.90 %
		p value	<0.001	<0.001	
		30 weeks	46.30 %	56.70 %	30.10 %
		p value	0.009	<0.001	
Adalimumab	ULTRA2		160 mg/80 mg/40 mg		Placebo
		8 weeks	41.10 %		31.70 %
		p value	0.032		
		52 weeks	25.00 %		15.40 %
		p value	0.009		
Golimumab	PURSUIT-SC		400 mg/200 mg	200 mg/100 mg	Placebo
		6 weeks	45.10 %	42.30 %	28.70 %
		p value	<0.0001	0.0014	
	PURSUIT-M		100 mg	50 mg	Placebo
		54 weeks	43.50 %	41.80 %	26.90 %
		p value	0.002	0.011	
Vedolizumab	GEMINI-1		300 mg		Placebo
		6 weeks	40.90 %		24.80 %
		p value	0.001		
		52 weeks, dosing every 8 weeks	41.80 %		15.90 %
		p value	<0.001		
		52 weeks, dosing every 4 weeks	44.80 %		15.90 %
		p value	<0.001		

[a]Mucosal healing was defined as a Mayo endoscopic subscore of 0 or 1 for each study included. Dosing schedules are indicated by the first dose, followed by the second and third doses if necessary as reported in the individual studies. Results are reported at various time points after initiating therapy and are accompanied below by their respective *p* value for comparison with placebo

infliximab dosed at 5 mg/kg, 10 mg/kg, and placebo was also demonstrated at weeks 30 and 54 [28]. In a follow-up post hoc analysis, Colombel and colleagues showed that achieving Mayo endoscopy score of 0 or 1 was associated with a reduction in colectomy [29].

There is also evidence that adalimumab can induce mucosal healing. The ULTRA 1 study was a randomized controlled trial of adalimumab in moderate to severe ulcerative colitis. The results of the induction phase were reported by Reinisch and colleagues. They found that there were no statistically significant differences between the rates of mucosal healing for adalimumab dosed 160 mg followed by 80 mg, adalimumab dosed 80 mg followed by 40 mg, and placebo [30]. This negative result was likely due to an unexpectedly high rate of mucosal healing in the placebo group. In the follow-up study of ULTRA 1, all patients were placed on adalimumab following induction, whether or not they had received adalimumab or placebo. They found that 36.5 % of all patients in the study achieved mucosal healing by week 52 [31]. The ULTRA 2 study was a double-blinded, randomized, placebo-controlled trial of adalimumab. Mucosal healing was achieved in 41.1 % of patients receiving adalimumab at week 8, compared to 31.7 % of patients receiving placebo ($p=0.032$). At week 52, 25 % of patients receiving adalimumab had achieved mucosal healing, compared to 15.4 % of patients receiving placebo ($p=0.009$) [32]. In addition to infliximab and adalimumab, a recent phase 2/3 randomized, placebo-controlled trial of golimumab showed that patients were able to achieve mucosal healing using this new TNF-inhibitor therapy. Sandborn and colleagues reported in the PURSUIT-SC study the results of golimumab induction. They found a significant difference in the rate of mucosal healing with 42.3 % of patients receiving the 200 mg/100 mg induction dosing ($p=0.0014$) and 45.1 % of patients

receiving the 400 mg/200 mg induction dosing ($p<0.0001$) compared to 28.7 % of patients receiving placebo had achieved mucosal healing at week 6 [33]. In the follow-up PURSUIT-M study, Sandborn and colleagues reported significantly higher rates of patients achieving mucosal healing at both 30 and 54 weeks for golimumab than placebo [34]. The patients on golimumab 100 mg achieved mucosal healing at a rate of 42.4 % compared to 26.6 % with placebo ($p=0.002$). As well, patients on golimumab 50 mg achieved mucosal healing at a rate of 41.7 % ($p=0.011$).

A new class of biologic medication for ulcerative colitis blocks the leukocyte trafficking from the endothelium to the bowel. Vedolizumab is a humanized monoclonal antibody against the alpha-4-beta-7 integrin. In the GEMINI 1 trial, vedolizumab was found to be capable of inducing mucosal healing in ulcerative colitis [35]. The definition of mucosal healing was the same as in the prior studies of TNF inhibitors, a Mayo endoscopic subscore of 0 or 1. After induction with vedolizumab, 40.9 % of patients achieved mucosal healing, compared to 24.8 % of patients in the placebo arm ($p=0.001$). Maintenance with vedolizumab was also found to have higher rates of mucosal healing. Vedolizumab dosed every 8 weeks achieved mucosal healing in 51.6 % at 52 weeks of treatment, compared to 56.0 % if it was dosed every 4 weeks, and 19.8 % of the patients in the placebo arm. Both dosing regimens were significantly different from placebo ($p<0.001$ and $p<0.001$, respectively), but not statistically significant between each other.

Challenges to the Adoption of Mucosal Healing into Clinical Practice

The next challenge in mucosal healing is incorporating this new knowledge into clinical practice and addressing barriers to adopting mucosal healing as a goal for therapy. The evidence presented in the previous sections supports the idea that those who achieve mucosal healing would have better outcomes. However, these studies were not performed to compare therapeutic strategies. Currently, there is no prospectively collected evidence that targeting mucosal healing provides a benefit over treating to symptoms and only some emerging information that it can be systematically achieved as a desired clinical endpoint. Additionally, there are important management concerns that have yet to be answered. First, it is unclear if mucosal healing is an achievable endpoint for the majority of patients. Second, there is unclear risk or cost to performing serial endoscopic exams to determine response to therapy. And, importantly, patients' willingness to undergo more frequent invasive testing has not been investigated.

One of the challenges is that the correlation between mucosal healing and clinical remission is not perfect. Mismatch between symptoms and endoscopic appearance can occur when a patient feels well but has endoscopic inflammation greater than a Mayo endoscopic subscore of 1 or when a patient is still experiencing symptoms despite a Mayo endoscopic subscore of 1 or 0. The choice to adjust therapy based on endoscopic appearance when a patient feels well requires consideration of the risks incurred by the change in therapy and the risk of not achieving mucosal healing despite such therapy adjustments. While there is retrospective evidence to support the long-term benefits of having achieved mucosal healing during the course of treatment, there is not a complete understanding of the near-term risks associated with this pursuit. More frequent invasive testing to assess the status of the mucosa and increased exposure to higher intensity therapies and their side effects are primary concerns that may adversely affect quality of life in the near term, particularly if the patient is symptomatically well. The converse may have implications for management too, although scoping a patient who is still symptomatic but is found to have mucosal healing is the standard of practice in the course of evaluating an actively symptomatic patient.

There is evidence that mismatch between symptoms and mucosal healing is a common clinical problem. The ACT1 trial found a poor correlation between mucosal healing and clinical remission [28]. There are two potential explanations for this observation. First is that the use of a broader definition of mucosal healing (a Mayo endoscopic subscore of 0 or 1) leads to inclusion of patients in the mucosal healing group who actually have clinically active disease. The groups might have appeared more similar if mucosal healing was defined as a Mayo endoscopic subscore of 0 rather than 0 or 1. The second potential explanation is that patients who achieved mucosal healing were experiencing overlap symptoms from irritable bowel syndrome, the side effects from therapy, or another diagnosis, all of which may confound their clinical appearance.

The gold standard for determining the presence or absence of mucosal healing remains endoscopic evaluation. Endoscopy is an invasive test that can provide significant information about the activity of a patient's disease. However, endoscopy requires significant resources, entails risk of patient morbidity, and is limited by interoperator variability [36].

Alternatives to endoscopy for the detection of mucosal healing are being investigated and becoming more widely available to practitioners. The most commonly encountered is a stool test for the quantity of calprotectin. Calprotectin is a prevalent cytosolic protein in granulocytes. The presence of calprotectin in the stool is proportional to neutrophil migration to the gastrointestinal tract and also proportional to the degree of inflammation [37]. Lobaton and colleagues tested a quantitative test for fecal calprotectin and investigated its correlation with endoscopic inflammation. Using a

280 microgram per gram level, they found a sensitivity of 75.4 % and a specificity of 89.1 % for the presence of mucosal healing [37].

Another noninvasive and easily accessible test is the measurement of serum C-reactive protein (CRP) levels. CRP production by hepatocytes increases under conditions of infectious stimuli, inflammatory diseases, neoplasia, and stress among others. While a strong CRP response has been seen in certain inflammatory conditions such as Crohn's disease and rheumatoid arthritis, other conditions like ulcerative colitis produce a much milder effect [38]. The reason for this discrepancy is not yet known. Therefore, the assessment of CRP levels should not be solely used to determine the severity of mucosal inflammation.

Because of its utility as a noninvasive marker of inflammation and the studies showing that mucosal healing can predict clinical course, investigators have been testing the ability of calprotectin levels to make similar predictions. Recently, Lasson and colleagues tested fecal calprotectin levels in the stool of patients at 3 months after being diagnosed with ulcerative colitis and starting treatment. They found that a fecal calprotectin level of 169 micrograms per gram at 3 months after diagnosis predicted those patients who would have more active disease over the following year with a sensitivity of 64.4 % and a specificity of 70.8 %. Similarly, a fecal calprotectin level of 262 micrograms per gram predicted those patients who would have more active disease over the 2- and 3-year follow-up period. The sensitivity and specificity of a cutoff of 262 micrograms per gram were 51 % and 81.8 % at 2 years and 52.2 % and 85.9 % at 3 years [39]. As well, elevated fecal calprotectin levels seem to be able to predict patients at higher risk of disease relapse [40, 41]. De Vos and colleagues studied fecal calprotectin levels in patients receiving treatment with infliximab. Patients with an 80 % decrease in fecal calprotectin level between the baseline measurement and the measurement at 2 weeks or a calprotectin level of less than 50 mg/kg at 2 weeks after initiating therapy were found to have achieved mucosal healing at week 10 of therapy with infliximab with a sensitivity of 54 % and specificity of 67 % [42]. In a separate study of patients receiving infliximab, they found that those patients who achieved deep remission at 52 weeks had consistently very low levels of fecal calprotectin throughout the follow-up period. Additionally, two consecutive fecal calprotectin levels greater than 300 micrograms per gram 1 month apart was predictive of disease relapse while on treatment with a sensitivity of 61.5 % and specificity of 100 % [43].

Fecal calprotectin is an important addition to the management of ulcerative colitis, but it does have limitations. The ability to distinguish active ulcerative colitis from irritable bowel syndrome symptoms is one of the important strengths of using endoscopy to monitor for mucosal healing. Studies have shown that fecal calprotectin is not able to differentiate irritable bowel syndrome symptoms from ulcerative colitis [44, 45]. As well, as demonstrated by the study by Lobaton and colleagues, the test characteristics are good, but the test is not completely able to rule in the presence of mucosal healing or rule out its absence [37]. As a result, if one were to use fecal calprotectin instead of endoscopic evaluation for monitoring disease activity, there would be patients who have achieved mucosal healing that have a negative test and patients who have not achieved mucosal healing who have a positive test. Additionally, the various test characteristics of fecal calprotectin for predicting clinical course are not strong enough to be relied upon with complete certainty [40–43]. They may be able to help guide physician expectations but should be considered within the clinical context.

Integrating Mucosal Healing into Current UC Management

With the therapeutic goal of mucosal healing, an efficient, practical algorithm for assessing disease response begins with baseline assessment of disease activity. This can be done with the initial endoscopic evaluation. This baseline evaluation can be paired with a surrogate marker, such as CRP if the patient manifests an elevated level, or fecal calprotectin.

After the initial assessment, the first choice of therapy can be based on existing practices and standards for starting medical management of the disease. The therapeutic trial of this initial management is monitored for approximately 3–6 months, with the time to reassessment varying based on the clinical trial data (approximately 3 months for anti-TNF therapies or mesalamine and 6 months for azathioprine/6-mercaptopurine). After this monitoring period, the disease activity is reassessed with either endoscopic evaluation or with surrogate marker testing.

If the endoscopy does not reveal mucosal healing, or the surrogate marker is not consistent with mucosal healing, the next steps are discussed with the patient in a shared decision-making approach. As was previously discussed, the decision to change management based on objective findings can be complicated when the subjective disease activity is discordant. In a subset of patients who do not achieve mucosal healing but who do have symptomatic relief, there may be resistance to escalating beyond therapy that the patient perceives as being effective. For these patients, a comprehensive evaluation of their comorbidities, disease course, and psychosocial factors will help guide discussion. For some patients, the potential reduction in colorectal dysplasia or potential for reduction in hospitalizations may be significant enough to outweigh the risks of increasing medical therapy.

If the endoscopic evaluation reveals mucosal healing, or the surrogate marker is consistent with mucosal healing, then

regular clinical follow-up is recommended. During these follow-up visits, disease stability can be measured using standard clinical criteria. After a period of 6–12 months of disease monitoring, the next step is reassessment of disease activity by endoscopy or surrogate marker. Clinical disease monitoring may be complicated by scenarios in which the patient has objectively achieved mucosal healing, but the disease symptoms are still present. Similar to the converse situation, this will require the clinician to pursue alternative diagnoses that can complicate UC. As well, the clinician must have a discussion with the patient about therapeutic options and the reasoning for not escalating therapy in the face of significant symptoms.

Summary

Objective assessment of mucosal inflammation is clearly associated with improvement in short-term and long-term clinical status of patients with UC and can be obtained with currently available therapies. Emerging indices of inflammatory activity and paradigm shifts in our management strategies are making the adoption of mucosal healing as an endpoint a practical reality. The practicing clinician and clinical scientist need to incorporate this rapidly moving field into their current work.

References

1. Schroeder KW, Tremaine WJ, Ilstrup DM. Coated oral 5-aminosalicylic acid therapy for mildly to moderately active ulcerative colitis. A randomized study. N Engl J Med. 1987;317:1625–9.
2. Pineton de Chambrun G, Peyrin-Biroulet L, Lemann M, Colombel JF. Clinical implications of mucosal healing for the management of IBD. Nat Rev Gastroenterol Hepatol. 2010;7:15–29.
3. D'Haens G, Sandborn WJ, Feagan BG, et al. A review of activity indices and efficacy end points for clinical trials of medical therapy in adults with ulcerative colitis. Gastroenterology. 2007;132:763–86.
4. Feagan BG, Sandborn WJ, D'Haens G, et al. The role of centralized reading of endoscopy in a randomized controlled trial of mesalamine for ulcerative colitis. Gastroenterology. 2013;145:149–57.e2.
5. Rubin DT. What you see is not always what you get: raising the bar on clinical trial methodology in ulcerative colitis. Gastroenterology. 2013;145:45–7.
6. Peyrin-Biroulet L, Bressenot A, Kampman W. Histologic remission: the ultimate therapeutic goal in ulcerative colitis? Clin Gastroenterol Hepatol. 2013;12:929–34.e2.
7. Cooney RM, Warren BF, Altman DG, Abreu MT, Travis SP. Outcome measurement in clinical trials for Ulcerative Colitis: towards standardisation. Trials. 2007;8:17.
8. Riley SA, Mani V, Goodman MJ, Dutt S, Herd ME. Microscopic activity in ulcerative colitis: what does it mean? Gut. 1991;32:174–8.
9. Meucci G, Fasoli R, Saibeni S, et al. Prognostic significance of endoscopic remission in patients with active ulcerative colitis treated with oral and topical mesalazine: a prospective, multicenter study. Inflamm Bowel Dis. 2012;18:1006–10.
10. Carbonnel F, Lavergne A, Lemann M, et al. Colonoscopy of acute colitis. A safe and reliable tool for assessment of severity. Dig Dis Sci. 1994;39:1550–7.
11. Froslie KF, Jahnsen J, Moum BA, Vatn MH. Mucosal healing in inflammatory bowel disease: results from a Norwegian population-based cohort. Gastroenterology. 2007;133:412–22.
12. Rutter M, Saunders B, Wilkinson K, et al. Severity of inflammation is a risk factor for colorectal neoplasia in ulcerative colitis. Gastroenterology. 2004;126:451–9.
13. Gupta RB, Harpaz N, Itzkowitz S, et al. Histologic inflammation is a risk factor for progression to colorectal neoplasia in ulcerative colitis: a cohort study. Gastroenterology. 2007;133:1099–105. quiz 340–1.
14. Rubin DT, Huo D, Kinnucan JA, et al. Inflammation is an independent risk factor for colonic neoplasia in patients with ulcerative colitis: a case-control study. Clin Gastroenterol Hepatol. 2013;11(12):1601–8.e1–4.
15. Cairns SR, Scholefield JH, Steele RJ, et al. Guidelines for colorectal cancer screening and surveillance in moderate and high risk groups (update from 2002). Gut. 2010;59:666–89.
16. Truelove SC, Witts LJ. Cortisone in ulcerative colitis; final report on a therapeutic trial. Br Med J. 1955;2:1041–8.
17. Truelove SC, Jewell DP. Intensive intravenous regimen for severe attacks of ulcerative colitis. Lancet. 1974;1:1067–70.
18. Lofberg R, Danielsson A, Suhr O, et al. Oral budesonide versus prednisolone in patients with active extensive and left-sided ulcerative colitis. Gastroenterology. 1996;110:1713–8.
19. Kamm MA, Sandborn WJ, Gassull M, et al. Once-daily, high-concentration MMX mesalamine in active ulcerative colitis. Gastroenterology. 2007;132:66–75. quiz 432–3.
20. Lichtenstein GR, Kamm MA, Boddu P, et al. Effect of once- or twice-daily MMX mesalamine (SPD476) for the induction of remission of mild to moderately active ulcerative colitis. Clin Gastroenterol Hepatol. 2007;5:95–102.
21. Sandborn WJ, Kamm MA, Lichtenstein GR, Lyne A, Butler T, Joseph RE. MMX Multi Matrix System mesalazine for the induction of remission in patients with mild-to-moderate ulcerative colitis: a combined analysis of two randomized, double-blind, placebo-controlled trials. Aliment Pharmacol Ther. 2007;26:205–15.
22. Hanauer SB, Sandborn WJ, Dallaire C, et al. Delayed-release oral mesalamine 4.8 g/day (800 mg tablets) compared to 2.4 g/day (400 mg tablets) for the treatment of mildly to moderately active ulcerative colitis: the ASCEND I trial. Can J Gastroenterol. 2007;21:827–34.
23. Hanauer SB, Sandborn WJ, Kornbluth A, et al. Delayed-release oral mesalamine at 4.8 g/day (800 mg tablet) for the treatment of moderately active ulcerative colitis: the ASCEND II trial. Am J Gastroenterol. 2005;100:2478–85.
24. Lichtenstein GR, Ramsey D, Rubin DT. Randomised clinical trial: delayed-release oral mesalazine 4.8 g/day vs. 2.4 g/day in endoscopic mucosal healing—ASCEND I and II combined analysis. Aliment Pharmacol Ther. 2011;33:672–8.
25. Kruis W, Kiudelis G, Racz I, et al. Once daily versus three times daily mesalazine granules in active ulcerative colitis: a double-blind, double-dummy, randomised, non-inferiority trial. Gut. 2009;58:233–40.
26. Ardizzone S, Maconi G, Russo A, Imbesi V, Colombo E, Bianchi PG. Randomised controlled trial of azathioprine and 5-aminosalicylic acid for treatment of steroid dependent ulcerative colitis. Gut. 2006;55:47–53.
27. Paoluzi OA, Pica R, Marcheggiano A, et al. Azathioprine or methotrexate in the treatment of patients with steroid-dependent or steroid-resistant ulcerative colitis: results of an open-label study on

efficacy and tolerability in inducing and maintaining remission. Aliment Pharmacol Ther. 2002;16:1751–9.
28. Rutgeerts P, Sandborn WJ, Feagan BG, et al. Infliximab for induction and maintenance therapy for ulcerative colitis. N Engl J Med. 2005;353:2462–76.
29. Colombel JF, Rutgeerts P, Reinisch W, et al. Early mucosal healing with infliximab is associated with improved long-term clinical outcomes in ulcerative colitis. Gastroenterology. 2011;141:1194–201.
30. Reinisch W, Sandborn WJ, Hommes DW, et al. Adalimumab for induction of clinical remission in moderately to severely active ulcerative colitis: results of a randomised controlled trial. Gut. 2011;60:780–7.
31. Reinisch W, Sandborn WJ, Panaccione R, et al. 52-Week efficacy of adalimumab in patients with moderately to severely active ulcerative colitis who failed corticosteroids and/or immunosuppressants. Inflamm Bowel Dis. 2013;19:1700–9.
32. Sandborn WJ, van Assche G, Reinisch W, et al. Adalimumab induces and maintains clinical remission in patients with moderate-to-severe ulcerative colitis. Gastroenterology. 2012;142:257–65. e1–3.
33. Sandborn WJ, Feagan BG, Marano C, et al. Subcutaneous golimumab induces clinical response and remission in patients with moderate to severe ulcerative colitis. Gastroenterology. 2014;146(1):85–95. quiz e14–5.
34. Sandborn WJ, Feagan BG, Marano C, et al. Subcutaneous golimumab maintains clinical response in patients with moderate-to-severe ulcerative colitis. Gastroenterology. 2014;146:96–109.e1.
35. Feagan BG, Rutgeerts P, Sands BE, et al. Vedolizumab as induction and maintenance therapy for ulcerative colitis. N Engl J Med. 2013;369:699–710.
36. Chen SC, Rex DK. Endoscopist can be more powerful than age and male gender in predicting adenoma detection at colonoscopy. Am J Gastroenterol. 2007;102:856–61.
37. Lobaton T, Rodriguez-Moranta F, Lopez A, Sanchez E, Rodriguez-Alonso L, Guardiola J. A new rapid quantitative test for fecal calprotectin predicts endoscopic activity in ulcerative colitis. Inflamm Bowel Dis. 2013;19:1034–42.
38. Vermeire S, Van Assche G, Rutgeerts P. C-reactive protein as a marker for inflammatory bowel disease. Inflamm Bowel Dis. 2004;10:661–5.
39. Lasson A, Simren M, Stotzer PO, Isaksson S, Ohman L, Strid H. Fecal calprotectin levels predict the clinical course in patients with new onset of ulcerative colitis. Inflamm Bowel Dis. 2013;19:576–81.
40. D'Inca R, Dal Pont E, Di Leo V, et al. Can calprotectin predict relapse risk in inflammatory bowel disease? Am J Gastroenterol. 2008;103:2007–14.
41. Gisbert JP, Bermejo F, Perez-Calle JL, et al. Fecal calprotectin and lactoferrin for the prediction of inflammatory bowel disease relapse. Inflamm Bowel Dis. 2009;15:1190–8.
42. De Vos M, Dewit O, D'Haens G, et al. Fast and sharp decrease in calprotectin predicts remission by infliximab in anti-TNF naive patients with ulcerative colitis. J Crohns Colitis. 2012;6:557–62.
43. De Vos M, Louis EJ, Jahnsen J, et al. Consecutive fecal calprotectin measurements to predict relapse in patients with ulcerative colitis receiving infliximab maintenance therapy. Inflamm Bowel Dis. 2013;19:2111–7.
44. Jonefjall B, Strid H, Ohman L, Svedlund J, Bergstedt A, Simren M. Characterization of IBS-like symptoms in patients with ulcerative colitis in clinical remission. Neurogastroenterol Motil. 2013;25:756–e578.
45. Jelsness-Jorgensen LP, Bernklev T, Moum B. Calprotectin is a useful tool in distinguishing coexisting irritable bowel-like symptoms from that of occult inflammation among inflammatory bowel disease patients in remission. Gastroenterol Res Pract. 2013;2013:620707.