Assessment of Endoscopic Disease Activity in Ulcerative Colitis: Is Simplicity the Ultimate Sophistication?

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Key Messages

- Current endoscopic scores for UC have important limitations at assessing endoscopic remission. Further validation and adoption of newer endoscopic scores could be advantageous.

Keywords

Ulcerative colitis · Mayo Endoscopic Score · Endoscopy · Mucosal healing

Abstract

Background: Endoscopic remission is an increasingly recognized important therapeutic endpoint in the management of patients with UC. **Summary:** The Mayo Endoscopic Score (MES) remains the most common endoscopic index recommended in guidelines and widely used in clinical trials and in clinical practice. The MES is easy, simple, and practical but is suboptimal at providing an accurate depiction of segmental healing and/or at measuring a substantial but incomplete response across the spectrum of endoscopic inflammation. Other endoscopic scores have been proposed but have not received wide recognition or adoption.

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Introduction

Endoscopic improvement (Mayo Endoscopic Subscore 0 or 1) and endoscopic remission (Mayo Endoscopic Subscore 0) are recognized as important treatment endpoints in ulcerative colitis (UC). Endoscopic improvement is associated with reduced risk of relapse, hospitalization, dysplasia, cancer, and need for colectomy [1–5]. The importance of endoscopic improvement as a target has been highlighted by the Selecting Therapeutic Targets in Inflammatory Bowel Disease (STRIDE) initiative of the International Organization for the Study of Inflammatory Bowel Diseases (IOIBD) [6]. The endoscopic target recommendation for endoscopic improvement in UC was defined as resolution of friability and ulceration at flexible sigmoidoscopy or colonoscopy, which is to be assessed within 3–6 months after the start of therapy. In line with these guidelines, all recent clinical trials in UC have incorporated endoscopic improvement as an element of the primary endpoint of clinical remission (total Mayo score ≤ 2 and none of the subscores > 1) and endoscopic im-

Fig. 1. Mayo Endoscopic Score (MES). **a** MES 0 (no friability and granularity and intact vascular pattern). **b** MES 1 (mild erythema or decreased vascular pattern). **c** MES 2 (marked erythema, absent vascular pattern, friability, and erosions). **d** MES 3 (spontaneous bleeding and ulceration) (reprint with permission from Takaneka et al., Sci Rep. 2019;9:17751; <https://doi.org/10.1038/s41598-019-54369-7>).

Fig. 2. a, b Right and left colon endoscopic images showing erythema, absent vascular markings, granularity, friability, and diffuse ulcerations consistent with MES = 3. MES, Mayo Endoscopic Score.

provement (Mayo Endoscopic Subscore 0 or 1) or endoscopic remission (Mayo Endoscopic Subscore 0) as a leading secondary endpoint. The recent update from the STRIDE II trial also referred to the association between superior disease outcomes and endoscopic remission [7]. Although not validated, the Mayo Endoscopic Score (MES) (Fig. 1) remains the most extensively used endoscopic index in clinical trials [2, 3, 5] with a score of 0 or 1, previously defined as mucosal healing [1] but nowadays defined as endoscopic improvement. As a result, the assessment of endoscopic activity with

the MES is essentially binary in nature (≤ 1 vs. ≥ 2 or 0 vs. ≥ 1). The MES is easy, practical, and provides a simple conceptual visual framework of the degree of endoscopic inflammation in UC [1]. Importantly, it is somewhat reproducible with good predictive value and reasonable agreement between central readers [8]. However, the FDA decision to score clear friability without erosions, ulceration, or spontaneous bleeding as a Mayo Endoscopic Subscore of 2 demonstrated the different interpretations of this “simple” scoring system. Other recent UC endoscopic scores include the UI-

Fig. 3. **a** Right colon showing scarring and endoscopic remission (MES = 0). **b** Sigmoid colon showing punctate erythema and minor erosions (MES = 2). **c** Rectum showing erythema and multiple linear ulcerations (MES = 3). MES, Mayo Endoscopic Score.

cerative Colitis Endoscopic Index of Severity (UCEIS) and the Ulcerative Colitis Colonoscopic Index of Severity (UCCIS) – both of which have been validated – and the more recent Modified Mayo Endoscopic Score (MMES) [9]. UCEIS has a better discriminate value than the Mayo score with a clear correlation with disease severity and response to treatment [10]. However, of all UC endoscopic scores, only the UCCIS and MMES take into consideration the extent of endoscopic inflammation with segmental scoring of disease activity [9]. While it stands to reason to use the highest score for endoscopic inflammation in UC (independent of location and extent) at initial diagnosis or during disease flare, it is unclear if this holds true for accurate assessment of endoscopic response to treatment initiation or escalation, especially when such response is significant albeit less than complete.

Illustrative Case

Our patient is a 52-year-old male with a history of ulcerative proctitis for 17 years maintained in remission with topical 5-ASA therapy. One month prior to presentation, he developed increasing tenesmus, bloody and mucoid diarrhea reaching ≥ 20 bowel movements per day including at night. Stool tests including microscopy, culture, and *Clostridium difficile* toxin were negative. He received oral prednisone 50 mg/day for 2 weeks without any notable clinical response. Ileocolonoscopy revealed a normal terminal ileum and extensive colitis with diffuse ulcerations throughout the whole colon for a Mayo Endoscopic Score (MES) of 3 (Fig. 2). He was started on oral tofacitinib 10 mg BID resulting in rapid improvement, steroid withdrawal, and complete resolution of clinical symptoms. Repeat ileocolonoscopy after 24 weeks showed near complete endoscopic remission with the exception of the distal 20 cm of the colon, which exhibited patchy mucosal erythema and linear ulcerations consistent with Mayo 3 (Fig. 3). Table 1 shows the different UC endoscopic scores for this patient at baseline and after treatment.

Table 1. Endoscopic score of the case study at baseline and on treatment

Endoscopic score	Baseline	Week 24
MES	3	3
UCEIS	6	5
UCCIS	106.6	46.1
MS	15	5
EMS	135	10
MMES	27	5

MES, Mayo Endoscopic Score; UCEIS, UC Endoscopic Index of Severity; UCCIS, UC Colonoscopic Index of Severity; MMES, Modified Mayo Endoscopic Score; MS, Modified Score; EMS, Extended Modified Score. For week 0 (all segments MES 3, 90 cm involved): MES only evaluating the most affected area: 3; MS calculated by adding up the individual MES of all 5 segments: 15; EMS obtained by multiplying the MS by disease extent in decimeters: 135 (15 × 9 dm); MMES obtained by dividing the EMS by the number of segments with active inflammation: 27 (135 ÷ 5). For week 24 (sigmoid minor erosions up to 20 cm and superficial ulcers in the rectum): MES: 3; MS: 5; EMS: 10; MMES: 5 (10 ÷ 2).

Discussion

The above case illustrates the existing problem with endoscopic scores of disease activity that do not take into consideration disease extent and segmental scoring. Based on the MES, this patient would not have met the endoscopic improvement target in clinical trials (Mayo 0 or 1) despite a remarkable and near-complete endoscopic response calculated at 80% on MMES and approximately 60% on UCCIS. According to the STRIDE guidelines [6], “only a Mayo subscore of 0–1 can be systematically recommended in clinical practice.” This was also stressed in the recent STRIDE II update with endoscopic healing as the preferred long-term goal [7]. Although endoscopic remission (Mayo Endoscopic Subscore or UCEIS score of 0) is associated with better outcomes and lower risk of relapse [7, 11], the use of a highly stringent endoscopic goal may further accentuate this spread by minimizing the observed benefit of endoscopic improvement (e.g., a change from Mayo Endoscopic Subscore 3 to 1). Some therapies may result in partial but substantial endoscopic response over time, and it would be incorrect to misclassify such patients as nonresponders because of a less than optimal tool for assessment of endoscopic activity. The potential for this misclassification may be further exaggerated in clinical practice where an unmet endoscopic improvement endpoint may lead to a change or switch in therapy when one is not necessary. Tables 2 and

3 [12–18] show the endoscopic improvement rates following induction and maintenance from registration trials of currently approved treatments for moderate to severe UC. As discussed above and given the potential for overscoring with the MES, it is conceivable that the rates of significant endoscopic improvement are in fact higher than those reported using the existing definition.

The UCCIS developed in 2013 is calculated by evaluating segmental scores using 4 different variables (granularity, vascular pattern, ulceration, and bleeding/friability) [4]. It has been validated and has high interobserver agreement. However, obtaining the final score is complex and may not be simple to use in clinical practice [9]. Building on the simplicity, familiarity, and predictive value of the original Mayo Endoscopic Score (MES), the Leuven group developed the Modified Mayo Endoscopic Score (MMES) by first calculating the Modified Score (MS) which is the sum of Mayo Endoscopic Subscores (MES) of each of the 5 colon segments (ascending, transverse, descending colon, sigmoid, and rectum) [3] on a 15-point scale. The Extended Modified Score (EMS) is then obtained by multiplying the MS by the maximal extent of inflammation (in decimeters). Finally, the Modified Mayo Endoscopic Score (MMES) is calculated by dividing the EMS by the number of segments with active inflammation [3]. The MMES score is easy to calculate and use but – similar to its ancestor the MES – has not been validated, although it has been shown to correlate well with clinical, biological, and histological disease activity [9]. The main limitation of both the UCCIS and the MMES is that one should perform a complete colonoscopy to calculate the score reliably, a procedure that is not always preferable in case of acute severe colitis or short-term follow-up after treatment initiation. Furthermore, the predictive value of a clear decrease in the number and extent of ulcerative lesions (as assessed in both UCCIS and MMES) without achieving endoscopic improvement (Mayo Endoscopic Subscore 0 or 1) still needs to be demonstrated in clinical trials and supported by real-world evidence.

The advent of effective biologic drugs and new small molecules has transformed the treatment landscape in UC. The assessment of endoscopic improvement to therapy is an important central target in management of patients in clinical trials and in real life. In patients with treated UC, patchy distribution of inflammation and histologic rectal sparing has been demonstrated [19]. Further studies are needed to address the predictive value of a segmental endoscopic improvement as depicted by the MMES and the UCCIS. For this purpose, clinical trials

Table 2. Endoscopic improvement (defined as endoscopic Mayo subscore of 0 or 1) in ulcerative colitis induction trials

Author (trial)	Year	Treatment	Comparator	Endoscopic assessment, weeks	N (treatment)	N (placebo)	Endoscopic improvement treatment group, N (%)	Endoscopic improvement placebo group, N (%)
Rutgeerts (ACT 1)	2005	Infliximab	Placebo	8	121	121	75 (62.0)	41 (33.9)
Rutgeerts (ACT 2)	2005	Infliximab	Placebo	8	121	123	73 (60.3)	38 (30.9)
Sandborn (ULTRA 1)	2012	Adalimumab	Placebo	8	248	246	102 (41.1)	78 (31.7)
Sandborn (PURSUIT)	2014	Golimumab	Placebo	6	253	251	107 (42.3)	72 (28.7)
Feagan (GEMINI 1)	2014	Vedolizumab	Placebo	6	225	149	92 (40.9)	37 (24.8)
Sandborn (OCTAVE 1 and 2)	2017	Tofacitinib	Placebo	8	905	234	271 (29.9)	32 (13.6)
Sands (UNIFI)	2019	Ustekinumab	Placebo	8	322*	319	87 (27.0)	44 (13.8)

* Ustekinumab weight-range-based dose that approximated 6 mg/kg.

Table 3. Endoscopic improvement (defined as endoscopic Mayo subscore of 0 or 1) in ulcerative colitis maintenance trials

Author (trial)	Year	Treatment	Comparator	Endoscopic assessment, weeks	N (treatment)	N (placebo)	Mucosal healing treatment group, N (%)	Mucosal healing placebo group, N (%)
Rutgeerts (ACT 1)	2005	Infliximab	Placebo	54	121*	121	55 (45.5)	22 (18.2)
Rutgeerts (ACT 2)	2005	Infliximab	Placebo	30	121*	123	56 (46.3)	37 (30.1)
Sandborn (ULTRA 2)	2012	Adalimumab	Placebo	52	248	246	62 (25.0)	38 (15.4)
Sandborn (PURSUIT-M)	2014	Golimumab	Placebo	54	151 [†]	154	64 (42.4)	41 (26.6)
Feagan (GEMINI 1)	2014	Vedolizumab	Placebo	52	122 [‡]	126	63 (51.6)	25 (19.8)
Sandborn (OCTAVE sustain)	2017	Tofacitinib	Placebo	52	395	198	164 (41.5)	26 (13.1)
Sands (UNIFI)	2019	Ustekinumab	Placebo	44	176 [§]	175	90 (51.1)	50 (28.6)

* Infliximab 5 mg/kg body weight. [†] Golimumab 100 mg every 4 weeks. [‡] Vedolizumab 300 mg every 8 weeks. [§] Ustekinumab 90 mg every 8 weeks.

should include full colonoscopies both at baseline and after induction. Although this will clearly be more cumbersome for the patients and more costly for the sponsor, it will be the only way to demonstrate the superiority of the MMES and the UCCIS over the Mayo and UCEIS scoring.

Histologic remission has been associated with increasing the odds of relapse-free survival [20]. The adoption of a novel endoscopic score with or without a histologic score for assessment of both disease severity and extent is timely given the often-patchy response noted in many patients and the critical therapeutic decision process that hinges on this assessment. This will transform this endpoint evaluation from a binary to a continuous model of endoscopic response. Using the MMES might be cumbersome in daily practice outside the research purposes. A potential alternative might be the modified score which offers the simplicity of the original Mayo Endoscopic Score (with segmental

scoring) as well as a proven correlation with disease activity and may arguably be adopted and further validated in clinical trials and clinical practice including the assessment of the predictive value. The use of machine learning algorithms and recurrent neural networks may facilitate and standardize the task [21]. In addition to endoscopic improvement, other factors that should be explored as markers of response include histological predictive values (distal histological activity vs. proximal disease activity), fecal calprotectin as a measure of “whole bowel” inflammation as a marker of response to therapy, and possibly the use of artificial intelligence to define the best and most practical tool for evaluating disease activity.

Statement of Ethics

The patient mentioned in the illustrative case has given consent for publishing.

Conflict of Interest Statement

No conflicts of interest exist.

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Author Contributions

Ala I. Sharara contributed to acquisition of data; analysis and interpretation of data; drafting of the manuscript; and final approval of the version; Maher Malaeb contributed to acquisition of data; analysis and interpretation of data; drafting of the manuscript; and final approval of the version; Matthias Lenfant contributed to acquisition of data; analysis and interpretation of data; drafting of the manuscript; and final approval of the version; Marc Ferrante contributed to acquisition of data; analysis and interpretation of data; drafting of the manuscript; and final approval of the version.

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