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Mucosal Healing in Ulcerative Colitis – When Zero is Better

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Abstract

Background and aims: Extensive evidence has underlined the importance of mucosal healing as a treatment aim for ulcerative colitis (UC). We aimed to assess differences in the incidence of clinical relapse at 12 months between UC patients with Mayo endoscopic scores (MES) 0 and 1.
Methods: This retrospective study included consecutive patients in corticosteroid-free remission between 2008 and 2013 and with follow-up of at least 1 year, with MES 0 or 1 in complete colonoscopy. Clinical relapse was defined as need for induction treatment, treatment escalation, hospitalization or surgery. A p value <0.05 was considered statistically significant.
Results: The study included 138 patients, 72 (52.2%) female, with mean age of 49 (±14) years. Inflammatory activity was classified as MES 0 in 61 (44.2%) patients and MES 1 in 77 (55.8%) patients. Clinical relapse during follow-up was significantly more frequent in patients with MES 1 than MES 0 (27.3 vs 11.5%, $p = 0.022$), and in the multivariate analysis MES 1 was the only factor significantly associated with an increased risk of relapse (odds ratio 2.89, 95% confidence interval 1.14–7.36, $p = 0.026$). This association was encountered in the subgroup of patients with left-sided/extensive colitis (29.7 vs 11.1%, $p = 0.049$), but not proctitis (25.0 vs 12.0%, $p = 0.202$).
Conclusions: In patients with UC in corticosteroid-free remission, particularly those with left-sided colitis or extensive colitis, MES 1 was significantly associated with a 3-fold increased risk of relapse compared with endoscopic MES 0. Our results support the use of endoscopic MES 0 as the most suitable treatment endpoint to define mucosal healing in patients with UC.

Key Words: Ulcerative colitis; mucosal healing; Mayo score; inflammatory bowel diseases

1. Introduction

Ulcerative colitis (UC) is a chronic inflammatory bowel disease of unknown aetiology, with an increasing prevalence, reaching up to 505 per 100 000,[1,2] characterized by periods of remission and periods of relapse.[3]

Traditionally, UC treatment was aimed at the relief of disease-related signs and symptoms, such as diarrhoea, rectal bleeding, abdominal pain, weight loss and malaise.[4] However, the correlation between symptoms and endoscopic findings is imperfect,[5] and almost half of all patients in clinical remission present with colonic mucosal inflammation.[6] Moreover, drugs such as corticosteroids have been shown to significantly improve clinical symptoms but provide modest benefits in improving mucosal lesions.[7] In recent years, prospective studies have associated mucosal healing with reduced rates of disease relapse, hospital admission and surgery,[8–12] as well as a lower cumulative risk of dysplasia and colorectal cancer progression.[11,13,14] Current treatment strategies are aimed at achieving mucosal healing in UC patients,[3,13] which is widely considered the gold standard

for assessing disease activity. Several indices were developed to more accurately define and evaluate mucosal healing in UC,[13,15–18] of which the most often used in clinical trials is the Mayo endoscopic score (MES).[8,9] The MES is a component of the Mayo score,[19] and classifies mucosal inflammation from 0 to 3 on the basis of the vascular pattern, erythema, friability, erosions and ulcers.

Currently, accepted endpoints for mucosal healing in UC include MES 0 (normal mucosa) and MES 1 (erythema and decreased vascular pattern may be present),[9,12,20] but some authors have suggested a more restricted definition of mucosal healing: an MES of 0.[8,21,22]

The aim of this study was to compare clinical outcomes in UC patients in sustained corticosteroid-free remission with MES 0 and MES 1.

2. Methods

We performed a retrospective single-centre study including consecutive UC patients in sustained corticosteroid-free remission (≥6 months) undergoing endoscopic evaluation between January 2009 and December 2013. Patients having a complete colonoscopy with MES 0 or MES 1 were included. All patients had a previously established diagnosis of UC, were followed as outpatients and were receiving UC medication. Patients with absence of follow-up, medication adjustment or loss of compliance between endoscopic evaluation and outcome assessment, colorectal cancer or pregnancy were excluded.

Clinical disease activity was evaluated using the partial Mayo score, previously used in several clinical trials,[20,23,24] including the rectal bleeding and stool frequency subscales only, as this score has shown a good correlation with the Mayo score and eliminates the potentially confounding physician's global assessment variable (subjective assessment, prone to interobserver variability).[23] Clinical remission was defined as a rectal bleeding subscore of 0 (no rectal bleeding) and a stool frequency subscore of either 0 (normal stool frequency for the patient) or 1 (1 or 2 more daily stools than normal).

Bowel preparation was achieved with a polyethylene glycol-based electrolyte solution, and patients with incomplete colonoscopy or inadequate bowel preparation were excluded.

Endoscopic evaluation was performed by a single gastroenterologist with significant inflammatory bowel disease experience (>15 years of practice), using the Montreal classification[25] for disease extent (E1, proctitis, disease limited to the rectum; E2, left-sided colitis, disease involvement proximal to the rectosigmoid junction and distal to the splenic flexure; E3, extensive colitis, disease involvement proximal to the splenic flexure) and a modified MES[20] for disease inflammatory activity, where the presence of any friability is considered MES 2. Patients were considered to have MES 0 if there was normal mucosa in all colonic segments and MES 1 if erythema or a decreased vascular pattern was observed.

Laboratory data were obtained at the time of the colonoscopy, including complete blood count, C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), iron, total iron-binding capacity, ferritin, total proteins and albumin.

Clinical data were analysed for a defined period of 12 months of follow-up after total colonoscopy, and clinical relapse during this period was considered as the need for intensification or modification of medication, UC-related hospital admission or surgery. A secondary analysis was performed for the incidence of adverse events during follow-up, defined as the need for corticosteroid therapy or immunosuppressants, as well as UC-related hospitalization or surgery.

Statistical analysis was performed using SPSS 21.1™ (WinWrap Basics™). Univariate analyses were performed using the independent samples *t* test for continuous variables and the χ^2 test for categorical variables, and multivariate analysis was performed using a logistic regression model with calculation of odds ratios and 95% confidence intervals. A Kaplan–Meier curve for duration of clinical remission during follow-up was generated for patients with MES 0 and MES 1, and compared with a 2-side log-rank test. A Cox hazard regression model was used to calculate hazard ratios for disease relapse. Statistical significance was defined as $p < 0.05$ and quantitative variables were presented as mean ± SD.

3. Results

One hundred and thirty-eight patients were included during the 5-year period, with a mean age of 49 ± 14 years); 52% ($n = 72$) were female. Most patients (67.4%, $n = 93$) were non-smokers, and 8 (5.8%) had a family history of inflammatory bowel disease. The majority of the patients (78.3%; $n = 108$) were being treated with aminosalicylates alone, while 21.7% ($n = 30$) were under immunosuppressant/immunomodulator therapy; of these, 7.2% ($n = 10$) were treated with azathioprine in monotherapy, 12.3% ($n = 17$) with azathioprine and aminosalicylates, and 2.2% ($n = 3$) with azathioprine and the anti-tumour necrosis factor α (TNFα) agent infliximab.

Mean haemoglobin (14.1 ± 1.6 g/dL), leucocyte ($7.0 \pm 2.1 \times 10^3$/μL), platelet ($239 \pm 59 \times 10^3$/μL), CRP (3.1 ± 3.1 mg/L), ESR (14.1 ± 11.3 mm/h) and albumin (4.4 ± 0.5 mg/dL) serum levels were within the normal range.

Disease distribution was limited to the rectum in 46.4% ($n = 64$) of the patients, while 27.5% ($n = 38$) had left-sided colitis and 26.1% ($n = 26$) had extensive colitis; in the assessment of disease activity, MES 0 was observed in 44.2% ($n = 61$) patients and MES 1 in 55.8% ($n = 77$). Table 1 summarizes the patients' clinical, laboratory and endoscopic characteristics.

The two groups of patients with MES 0 and MES 1 were homogeneous, with no statistically significant differences between them in either clinical or laboratory variables (Table 2).

During the 12-month follow-up period, clinical relapse was observed in 20.3% ($n = 28$) of the patients, with a mean interval between colonoscopy and relapse of 5.6 (SD ± 2.9) months. In these 28 patients, intensification of the current therapy was needed in 16 (57.1%), corticosteroids were started in 6 (21.4%), a decision to start azathioprine was made in 5 (17.9%), and in 2 (7.1%) patients an anti-TNFα agent was added to azathioprine; finally, 3 (10.7%) of the patients with clinical relapse had a hospital admission and were started on systemic corticosteroids, and in one of them an anti-TNFα drug was started.

In the univariate analysis, younger age at colonoscopy (44.2 ± 12.7 vs 50.1 ± 14.0 years, $p = 0.045$) and MES 1 (27.3 vs 11.5%, $p = 0.022$) were associated with an increased risk of clinical relapse, but MES 1 was the only variable associated with an increased risk of clinical relapse in the multivariate analysis (MES 1: odds ratio 2.89, 95% confidence interval 1.137–7.358, $p = 0.026$). The Kaplan–Meier curves of recurrence-free survival for patients with MES 1 and MES 0 are shown in Figure 1.

The incidence of relapse during follow-up in patients with MES 1 when compared with MES 0 was also significantly superior in the subgroup of patients with left-sided/extensive colitis (29.7 vs 11.1%, $p = 0.049$), but not in patients with disease limited to the rectum (25.0 vs 12.0%, $p = 0.202$). The interval between colonoscopy and clinical relapse was not significantly different between patients with MES 1 and MES 0 (4.0 ± 2.0 vs 6.1 ± 3.1, $p = 0.105$).

Overall, MES 1 was significantly associated with an increased risk of adverse outcomes (13.0 vs 3.3%, $p = 0.044$), although we

Table 1. Patient characteristics (global).

Female (%)	52.2
Age at colonoscopy, y (mean ± SD)	48.9 ± 13.9
Age at diagnosis, y (mean ± SD)	40.9 ± 13.8
Disease duration, y (mean ± SD)	8.0 ± 6.7
Smoking status (%)	
Former smoker	27.9
Smoker	9.8
Non-smoker	62.3
Family history of inflammatory bowel disease (%)	5.8
Medication (%)	
5-ASA	78.7
5-ASA + immunosuppressants	9.8
Immunosuppressants	11.5
Haemoglobin, g/dL (mean ± SD)	14.1 ± 1.6
Leucocytes, 10^3/μL (mean ± SD)	7.0 ± 2.1
Platelets, 10^3/μL (mean ± SD)	239 ± 59
ESR, mm/h (mean ± SD)	14.1 ± 11.3
CRP, mg/L (mean ± SD)	4.1 ± 3.8
Ferritin, ng/mL (mean ± SD)	138 ± 113
Albumin, mg/dL (mean ± SD)	4.5 ± 0.5
Disease distribution (%)	
Proctitis (E1)	46.4
Left-sided colitis (E2)	27.5
Extensive colitis (E3)	26.1
Disease activity (%)	
MES 0	44.2
MES 1	55.8

5-ASA, 5-aminosalicylates; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; MES, Mayo endoscopic score.

Table 2. Patient characteristics.

	MES 0	MES 1	*p*
Female (%)	50.8	53.2	0.777
Age at colonoscopy, y (mean ± SD)	49.8 ± 14.3	48.1 ± 13.7	0.477
Age at diagnosis, y (mean ± SD)	42.5 ± 14.2	39.7 ± 13.5	0.239
Disease duration, y (mean ± SD)	7.4 ± 6.0	8.5 ± 7.2	0.345
Smoking status (%)			
Former smoker	27.9	18.6	0.206
Smoker	9.8	12.0	
Non-smoker	62.3	69.4	
Family history of inflammatory bowel disease (%)	4.9	6.5	1.000
Medication (%)			
5-ASA	78.7	77.9	0.914
5-ASA + immunosuppressants	9.8	9.1	
Immunosuppressants	11.5	13.0	
Haemoglobin, g/dL (mean ± SD)	14.2 ± 1.5	14.1 ± 1.7	0.728
Leucocytes, 10^3/μL (mean ± SD)	7.0 ± 2.8	7.0 ± 2.3	0.901
Platelets, 10^3/μL (mean ± SD)	247 ± 56	234 ± 61	0.195
ESR, mm/h (mean ± SD)	16.4 ± 13.7	13.9 ± 13.6	0.093
CRP, mg/L (mean ± SD)	4.1 ± 3.8	4.2 ± 4.4	0.642
Ferritin, ng/mL (mean ± SD)	138 ± 113	123 ± 100	0.435
Albumin, mg/dL (mean ± SD)	4.5 ± 0.5	4.4 ± 0.6	0.491
Disease distribution (%)			
Proctitis (E1)	41.0	51.3	0.369
Left-sided colitis (E2)	32.8	23.7	
Extensive colitis (E3)	26.2	25.0	

5-ASA, 5-aminosalicylates; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; MES, Mayo endoscopic score.

encountered no differences between patients with MES 1 and MES 0 regarding each individual outcome: need for corticosteroid therapy (5.2 vs 3.3%, $p = 0.584$), immunosuppressants (9.1 vs 3.3%, $p = 0.170$) or hospitalization (2.6 vs 1.6%, $p = 0.702$). No patient was submitted to surgery during follow-up.

4. Discussion

In this study we demonstrated that in UC patients in sustained corticosteroid-free remission with MES ≤1, more than one-fifth will present with clinical relapse during 12 months of follow-up. Additionally, we encountered a 3-fold risk of clinical relapse in patients presenting with MES 1 compared with MES 0.

Both UC and CD are inflammatory bowel diseases, characterized by periods of remission and periods of relapse, carrying a significant morbidity burden,[11] directing previous treatment goals towards achieving symptom remission.[26] However, correlation between symptoms and inflammatory activity in UC is poor, and clinical assessment is often insufficient for a precise treatment approach.[22,27,28]

The concept of mucosal healing has been discussed for over 60 years,[15] and has recently become a preferred treatment endpoint for UC patients.[3,13]

The importance of mucosal healing was shown in two landmark studies using the MES. In the IBSEN Group study, performed in the pre-anti-TNFα era, mucosal healing was significantly associated with a reduced risk of colectomy,[10] and in the combined analysis of ACT 1 and ACT 2 trials, patients with MES ≤1 at week 8 of infliximab treatment were significantly less likely to present with clinical relapse or need for corticosteroids at weeks 30 and 54, and progressed less frequently to colectomy.[8] Other authors have shown mucosal healing to be associated with lower risks of clinical relapse,[7,9,24] hospitalization,[7,13] immunosuppressant use[7] and colectomy,[7,29,30] and long-term follow-up of UC patients demonstrated a lower risk of dysplasia and colorectal cancer,[31] often undistinguishable from the normal population risk, in the presence of colonic mucosal healing.[14] Finally, a negative correlation between endoscopic inflammatory activity and patients' quality of life has been reported.[32]

Nevertheless, the definition of mucosal healing in UC patients is still a contentious topic; it was considered in 2007 by the International Organization for the Study of Inflammatory Bowel Disease as the absence of friability, blood, erosions and ulcers in all segments of gut mucosa.[28] The endoscopic component of the Mayo score, created in 1987,[19] included the variables erythema, decreased vascular pattern, friability, erosions and ulcers, and has become the most often employed score in clinical trials,[13] particularly the modified MES, where mild friability is considered MES 2 and not MES 1.[8,9] Current ECCO guidelines define endoscopic remission as MES ≤1 and complete endoscopic remission is considered for MES 0 only.[13]

In our study, MES 1 was significantly associated with an increased risk of clinical relapse compared with MES 0 (27.3 vs 11.5%, $p = 0.022$), as well as an increased risk of hospitalization or the need for corticosteroid or immunosuppressant drugs (13.0 vs 3.3%, $p = 0.044$). Very few studies have reported differences in clinical outcomes between patients with MES 0 and MES 1. Our results are in line with those obtained by Colombel et al.,[8] where patients with MES 0 at week 8 of infliximab were significantly more often in corticosteroid-free remission after 1 year of follow-up than patients

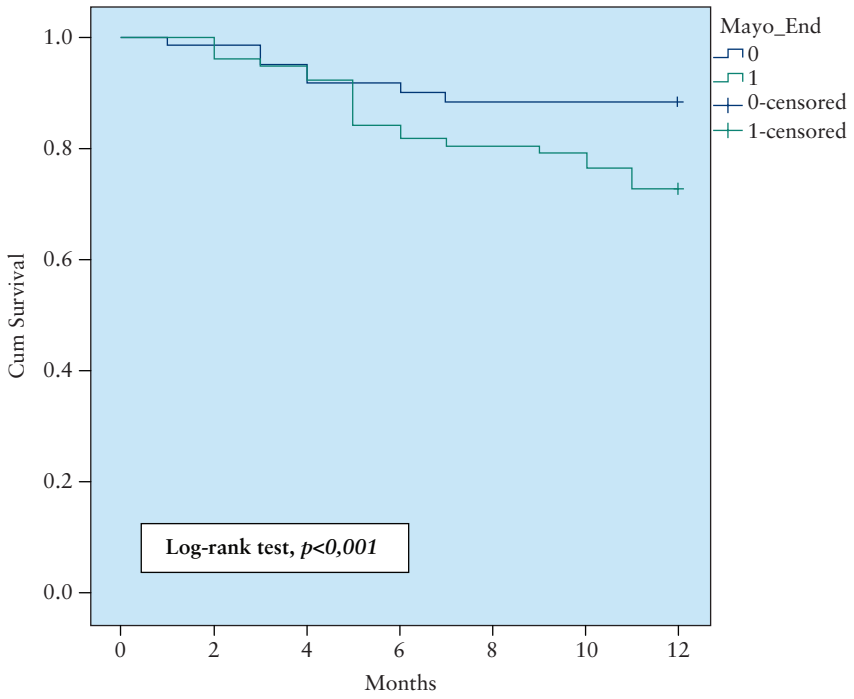

Figure 1. Kaplan–Meier curves of recurrence-free survival for patients with Mayo endoscopic score 0 and 1, using the log-rank test.

with MES 1 (73 vs 47%, $p < 0.001$); Nakarai et al.,[24] who reported significantly increased risks of clinical relapse, need for corticosteroids and hospitalization in MES 1 patients in clinical remission when compared with MES 0; and Yokoyama et al.,[33] who demonstrated significant differences in long-term maintenance of remission between patients with MES 0 and MES 1 (93 vs 70%, $p < 0.001$). In contrast, Meucci et al.[9] reported no differences in the maintenance of remission with mesalamine in patients with MES 0 and MES 1, while MES 2 was associated with an increased risk of relapse.

We report as well a significantly higher risk of relapse in patients with MES 1 in the subgroup of patients with left-sided or extensive colitis (29.7 vs 11.1%, $p = 0.049$), but no significant differences were observed in those patients presenting with proctitis (25.0 vs 12.0%, $p = 0.202$). This new evidence may be explained by a heightened importance of complete mucosal healing in a colon with extensive inflammatory tissue damage and increased complexity in adequately differentiating MES 0 and MES 1 in the rectal mucosa, but because clinical relapse was twice as frequent with MES 1 than it was with MES 0 in patients with proctitis, a type II error may not be safely excluded. Further studies with larger sample sizes may be warranted to clarify this topic. New technologies, such as narrow-band imaging and magnifying endoscopy, may also allow greater detail during mucosal observation and assist in identifying patients with a superior risk of relapse.[34]

Histological healing as a target in UC is increasingly a topic of discussion, and markers of histological inflammation, such as basal plasmacytosis[35] and an elevated Geboes score,[36] have been associated with a higher incidence of clinical relapse. In our study no histological analysis was performed, but Guardiola et al.[37] demonstrated that only 7% of patients with MES 0 had significant histological inflammatory activity compared with 52% of those with MES 1 ($p < 0.001$), and Lemmens et al.[38] reported that MES 0 accurately reflected normal histology in biopsies. Nevertheless, using histological healing as an endpoint in UC is still hindered by the following: a validated and easily reproducible histological index is needed for clinical practice; few studies have evaluated the impact of current drugs, particularly anti-TNFα agents, in achieving histological healing; and data regarding long-term outcomes, such as disease progression, hospitalization and surgery, are still insufficient.[22,28,39]

The prognostic use of serum or faecal markers in patients with UC has been studied extensively as a potential technique to reduce the need for costly and invasive endoscopic procedures, but recent studies have shown inconsistent results, both for CRP[6,35,40,41] and for ESR.[40,41] In our work, neither inflammatory marker was associated with an increased risk of adverse outcomes and neither correlated with endoscopic inflammatory activity, but, unlike other studies, our analysis was restricted to patients in corticosteroid-free remission with MES ≤1. The modest correlations between serum markers and UC endoscopic activity when compared with CD patients may be explained by the fact that CD is a transmural disease, leading to higher serum concentrations of the pro-inflammatory interleukin IL-6.[42]

Finally, calprotectin is a faecal biomarker showing a good correlation with endoscopic inflammation in both CD and UC and demonstrated promising results in predicting clinical relapse,[43,44] but its use in clinical practice is limited by both inter- and intra-assay variability and lack of defined cutoff levels.[45,46]

Our work has some limitations: it was a unicentric retrospective study using the Mayo endoscopic score and had a short follow-up period. Nonetheless, the short period of follow-up and the fact that it was an observational study based on prospectively collected data reduced the risk of intervention bias. The limitations of the Mayo score, a non-validated score with significant inter-observer variability,[22] were partially attenuated by excluding the physician's global assessment, a subjective variable that is prone to bias, particularly in retrospective studies,[8,20] and by considering mucosal friability in the exclusion criteria (MES 2) and restricting the realization of colonoscopies by a single gastroenterologist. Moreover, because mucosal healing often lags behind the achievement of clinical remission,[11] the strict inclusion criteria of patients with at least 6 months

of corticosteroid-free remission allows for exclusion of patients who might have MES 1 at the time of endoscopic evaluation but who are still progressing to complete mucosal healing.

In conclusion, in our study, patients with MES 1 were at a statistically significant 3-fold increased risk of clinical relapse during follow-up and significantly more likely to need corticosteroids, progress to immunosuppression therapy or warrant hospitalization. In particular, patients with left-sided or extensive colitis benefited the most from complete mucosal healing. These results support the importance of endoscopic assessment of patients in clinical remission and the use of endoscopic Mayo score 0 as the most suitable treatment endpoint to achieve mucosal healing in UC patients.

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Conflict of Interest

No authors report conflict of interest.

Author Contributions

All authors contributed to and agreed on the content of the manuscript. P. Boal Carvalho carried out the study and data analysis, searched the literature and drafted the manuscript; F. Dias de Castro performed data and statistical analyses; B. Rosa revised the manuscript and performed data analysis; M. J. Moreira participated in the design of the study and performed the endoscopic procedures; J. Cotter critically revised the manuscript and approved the final version to be submitted.

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