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Review Article

Definition and evaluation of mucosal healing in clinical practice

Silvia Mazzuoli[a], Francesco W. Guglielmi[a,*], Elisabetta Antonelli[b], Marianna Salemme[c], Gabrio Bassotti[b], Vincenzo Villanacci[c]

[a] Gastroenterology and Artificial Nutrition Department, "San Nicola Pellegrino" Hospital Trani, BT, Italy
[b] Gastroenterology and Hepatology Section, Department of Clinical & Experimental Medicine, University of Perugia, Italy
[c] Department of Pathology, Spedali Civili of Brescia, Italy

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ABSTRACT

Since the introduction of biological therapy, endoscopic and histological remission, i.e. mucosal healing, has become an important therapeutic goal in Crohn's Disease and Ulcerative Colitis. Mucosal healing is associated with lower rates of hospitalization and surgery, although its role in preventing progression and changing the natural history of the disease has not been clearly demonstrated. A precise definition of mucosal healing has not yet been established, although the concept used in clinical trials is the "complete absence of all inflammatory and ulcerative lesions in all segments of gut" at endoscopy. This definition does not include mucosal improvement and does not distinguish among grades of mucosal healing. In both Crohn's Disease and Ulcerative Colitis trials, several qualitative and quantitative numeric endoscopic indices have been proposed to measure and distinguish endoscopic changes. In addition, the microscopic features associated with inflammatory bowel diseases are considerably modified by the course of the disease and the treatments adopted. However, it is not yet clear whether microscopic healing should be a primary endpoint in clinical trials. In this paper we discuss endoscopic and histological findings and the limitations of the endoscopic and histological indices as a basis for a standardised diagnosis of mucosal healing.

1. Introduction

In recent years the management of inflammatory bowel diseases (IBD) has substantially changed, due to the fact that the new treatments with anti-TNFα drugs induce not only clinical remission but also a significant endoscopic improvement, or even a total disappearance of the intestinal lesions [1]. Although conventional therapies with 5-aminosalicylic acid (5-ASA), oral steroids and immunomodulators may lead to mucosal healing (MH), the MH rate with these agents is lower than that obtained with anti-TNFα [2–7]. At present, there is significant evidence that the use of anti-TNFα drugs, such as infliximab, adalimumab, and certolizumab pegol, can induce and sustain endoscopic healing [8,9]. The mechanisms of action of the anti-TNFα therapies are largely unknown. Very recently, in 2 in vivo models Fischer found that adalimumab prevents intestinal barrier dysfunction and antagonises distinct effects of TNF on tight junction proteins and signalling pathways in intestinal epithelial cells. All these events may therefore represent a novel mechanism of action whereby antiTNF drugs participate in epithelial and tissue repair in CD and UC [10].

MH has now become an important endpoint to assess the therapeutic effect in IBD [11–13]. The definition of MH currently used in CD and UC clinical trials is the *"complete absence of all inflammatory and ulcerative lesions"*, but this definition lacks validation and does not include mucosal improvement and grading of MH [11,14–16]. Furthermore, in most studies the definition of MH in UC includes the presence of *"persistent erythema and friability at endoscopy"* without ulceration or erosions [14].

The aim of this paper is to review different definitions of endoscopic healing and to describe the endoscopic indices commonly used in clinical trials. We also point out the role of histological assessment and the need to use a standardised validated endoscopic score to avoid differences in MH rates among the various trials.

1.1. Controversies in MH definition

Controversies regarding the currently available definitions of MH are shown in Tables 1 and 2, reporting endoscopic indices, endoscopic features, MH definition, time/weeks between endoscopic re-evaluations and the percentage of patients showing MH. The different definitions of MH, such as "absence of ulcers" or

* Corresponding author at: Gastroenterology and Artificial Nutrition Department, "San Nicola Pellegrino" Hospital, 76125 Trani, BT, Italy. Tel.: +39 0883 483209; fax: +39 0883 483342.
E-mail address: guglielmifw@libero.it (F.W. Guglielmi).

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Table 1
Endoscopic indices used in Crohn's disease and ulcerative colitis.

	Endoscopic features	Range	Proposed MH cut-off	Validated predictive cut-off
CD endoscopic indices				
Crohn's Disease Endoscopic Index of Severity (CDEIS) (1989)	Presence or absence of ulcers (superficial or deep); percentage of ulcerated or inflamed surface, stenosis (ulcerated or non ulcerated) in five intestinal segments	0–44	CDEIS > 3 CDEIS $0_{(42–46)}$	–
Simplified Endoscopic Activity Score for Crohn's Disease (SES-CD) (2004)	Presence or absence of ulcers (size); proportion of the intestinal surface affected by ulcerations and by other inflammatory lesions; narrowing (single or multiple and permitting passage or not) in five intestinal segments	0–56	SESCD 0 SESCD < $5_{(42–46)}$	–
Rutgeert's score (1990)	Presence of ulcers, diffuse inflammation and ulcers, nodules and/or narrowing	0–4	Rutgeert 0–$1_{(42–46)}$	3–4 relapse
Lemman score (2011)	Presence of stricture lesions and presence of penetrating lesions	0–10	–	–
UC endoscopic indices				
Truelove and Witts (1955)	Hyperemia and granularity	0–3	–	–
Baron score (1964)	Severity of mucosal bleeding and friability	0–3	–	–
Modified Baron Score (1964)	Vascular pattern; mucosal granularity; bleeding, mucus, fibrin, erosions and ulcers	0–4	–	–
Powell-Tuck score (1978)	Severity of mucosal bleeding and friability	0–2	–	–
Sutherland score (1987)	Severity of mucosal bleeding and friability	0–2	–	–
Rachmilewitz score (1989)	Vascular pattern; mucosal granularity; bleeding, mucus, fibrin, erosions and ulcer	0–12	–	–
Mayo score (1987)	Erythema, vascular pattern, friability, erosions, spontaneous bleeding, ulcerations	0–3	0–1 (56)	–
Ulcerative Colitis Endoscopic Index of Severity (UCEIS) (2011)	Vascular pattern (normal, patchy obliteration, obliterated); Bleeding (none, mucosal, luminal mild, luminal moderate or severe); Lesions (none, erosions, superficial ulcers, deep ulcers)	0–3 for vascular pattern 0–4 for bleeding and lesions	–	–
Ulcerative Colitis Colonoscopy Index of Severity (UCCIS) (2013)	Vascular pattern (normal, partially visible, complete loss); Granularity (normal, fine, coarse); Ulceration (normal, erosions or pinpoint ulcerations, shallow ulcers with mucopus, deep ulcerations, diffuse ulcerated with >30% involvement); Bleeding/friability (normal, friable and bleeding on touch, spontaneous bleeding)	0–2 for vascular pattern, granularity, bleeding/friability 0–4 for ulcerations	–	–

MH, mucosal healing.

"endoscopic scores improvement", as well as the duration of the biological therapy certainly interfere with the rate of MH. In fact, in CD patients the short-term re-evaluation at 10 weeks demonstrated an "absence of ulcers" ranging between 11% and 29% of patients, and this rate rose to 45%, 44%, and 73% when patients underwent endoscopy at 24–54 and 104 weeks. Instead, when MH was considered as an "endoscopic scores improvement", the short-term MH rate at endoscopic re-evaluation ranged between 64% and 90% and remained at the same rate after medium and long-term treatment. In UC patients, the endoscopic short-term re-evaluation revealed a diagnosis of MH as "absence of ulcers" (MAYO 0) in about 27% of the patients, on the contrary when MH was considered as the "endoscopic scores improvement" (MAYO 1) the rate of MH ranged between 30% and 62% both in short- and long-term endoscopic re-evaluations.

The importance of achieving MH in clinical practice is correlated to recent evidence that shows that MH is associated with long-term symptomatic remission and a longer relapse-free interval [17], as well as with a reduction in the frequency of hospitalizations, complications and surgical resections [18–20], and with a significant improvement of quality of life [21]. Furthermore, MH is associated to a reduction of cancer risk and cancer-related mortality; data suggest that colorectal cancer in IBD patients is driven by a persistent active inflammation. Controlled prospective studies are lacking but a large cohort study indicates a lower risk of colorectal cancer in the presence of MH in patients treated with azathioprine [22] and infliximab [23]. All these events seem to have a prognostic relevance, but the role of MH in preventing progression and changing the natural history of IBD has never been demonstrated [24] probably due to the late use of anti-TNF drugs.