Received: 5 July 2024 | Accepted: 27 August 2024

DOI: 10.1002/ueg2.12671

REVIEW ARTICLE

ueg journal WILEY

Defining mucosal healing in randomized controlled trials of inflammatory bowel disease: A systematic review and future perspective

Tommaso Lorenzo Parigi[1,2] | Virginia Solitano[1,3] | Alessandro Armuzzi[4,5] | Manuel Barreiro de Acosta[6] | Jake Begun[7] | Shomron Ben-Horin[8] | Luc Biedermann[9] | Jean-Frederic Colombel[10] | Axel Dignass[11] | Mathurin Fumery[12] | Subrata Ghosh[13] | Taku Kobayashi[14] | Edouard Louis[15] | Fernando Magro[16] | Remo Panaccione[17] | Astrid Rausch[18] | Walter Reinisch[19] | Christian Selinger[20] | Vipul Jairath[3,21] | Silvio Danese[1,2] | Laurent Peyrin-Biroulet[22]

Correspondence
Tommaso Lorenzo Parigi, Department of Immunology, Infectious Disease and Transplantation, University Vita-Salute San Raffaele, Via Olgettina 58, Milan 20132, Italy.
Email: parigi.tommaso@hsr.it

Abstract

Background: Mucosal healing (MH) is an established treatment goal in inflammatory bowel disease (IBD). However, various definitions of MH exist. We aimed to identify how MH is defined in randomized controlled trials (RCTs) in ulcerative colitis (UC) and Crohn's disease (CD).

Methods: We searched MEDLINE, EMBASE, and the Cochrane library from inception to December 2023 for phase 2 and 3 RCTs of advanced therapies in IBD.

Results: One hundred forty-four studies were included, 72 in UC and 72 in CD, published between 1997 and 2023. In UC, 64% (46/72) RCTs reported MH as an endpoint. 12 definitions of MH were found, from endoscopic assessment alone (35/46; 76%) to the more recent combination of histology and endoscopy (10/46; 22%). 96% (44/46) of studies used the Mayo Endoscopic Subscore. In CD, reporting of MH lagged behind UC, with only 12% (9/72) of trials specifically defining MH as an endpoint, 7 as "absence of ulceration," 2 as Simplified Endoscopic Score for CD score ≤2 or 0. Histological assessment was performed in 3 RCTs of CD. Centralized reading of endoscopy was used in 48% (35/72) of RCTs of UC and 22% (16/72) of CD. Only 1 RCT included transmural healing as an endpoint.

Conclusions: A standard definition of MH in IBD is lacking. Definitions have evolved particularly in UC, which now includes the addition of histological evaluation. Transmural healing holds promise as a future target in CD. We support a greater standardization of definitions as we expect endpoints to become increasingly stringent and multimodal with computers automating the assessment.

KEYWORDS
clinical trials, Crohn's disease, deep remission, endoscopy, histologic healing, histological healing, IBD, neutrophils, pathology, ulcerative colitis

INTRODUCTION

Randomized controlled trials (RCTs) are pivotal for the approval of novel agents and should serve as the highest level of evidence to guide clinical decision making. The endpoints of these RCTs are often used by policy makers in determining cost-effectiveness, reimbursement, and establishing health policy. In inflammatory bowel disease (IBD), the correlation between clinical and endoscopic indices has long been known to be weak,[1] but it was the availability of effective maintenance therapies, such as biologics, that spurred interest in better predictors of long-term outcomes. In 2015, the Selecting Therapeutic Targets in IBD (STRIDE) Initiative agreed on a set of objective measures of inflammation to inform clinical decision making, and the concept of mucosal healing (MH) emerged as a treatment goal.[2] MH is not synonymous with endoscopic remission or endoscopic improvement but rather aims to incorporate the strongest predictors of long-term outcome into a single item, identifying the population of patients at greater risk of relapse while overcoming some of the limitations of symptom assessment. Guidelines and consensus statements have defined MH predominantly on the basis of endoscopic, and, to a lesser degree, histologic assessment in ulcerative colitis (UC).[3] However, in the literature, a significant heterogeneity in such criteria exists. In addition, in CD, imaging complements endoscopy to assess transmural involvement and to evaluate areas inaccessible to endoscopy. Robust evidence shows how transmural response is strongly correlated to endoscopic changes and predictive of favorable long-term clinical outcomes.[4–6] Notably, while guidelines such as the updated STRIDE II[7] consensus and regulatory recommendations do not formally prioritize transmural healing, we aimed at investigating its use and definition in our systematic review.

We aimed to conduct an up-to-date systematic review of the use and the definitions of MH in RCTs of advanced treatments for UC and CD and to identify opportunities for further research.

Key summary

Summarise the established knowledge on this subject?

- Mucosal healing is a key treatment target in inflammatory bowel diseases.

What are the significant and/or new findings of this study?

- We found a great heterogeneity in the definition of mucosal healing in randomized clinical trials. In ulcerative colitis, in recent years mucosal healing evolved to include histological outcomes in addition to endoscopic ones, while in Crohn's disease the term mucosal healing is seldom used and endoscopic response and remission are preferred.
- How can this study help patient care? Endpoint definitions are crucial to the interpretation and translation of trials' results into clinical practice. Standard definitions of mucosal healing are needed.

METHODS

Search

Following the Preferred Reporting Items for Systematic Reviews and Meta-analysis recommendations, MEDLINE [Ovid, 1946], EMBASE [Ovid, 1947], the Cochrane Library [CENTRAL] were searched to identify placebo- and active-controlled trials.

Two previous searches, one in UC from Sedano et al.[8] and one in CD from Almradi et al.[9], were performed through April 2020 and March 2021, respectively. We updated these searches to 31 December 2023. In addition, because the previous systematic reviews were limited to placebo-controlled studies, we manually re-included active-controlled randomized clinical trials previously excluded. The search strategies are provided in Supplementary table 1 and 2.

Study selection and eligibility

No language restriction was applied. Citations and abstracts of potentially relevant studies were selected and screened. After automatically eliminating duplicates (Covidence systematic review software, Veritas Health Innovation), two authors (TL and VS) independently screened titles and abstracts. The full-text of potentially relevant records based on titles and abstracts was assessed for eligibility. Disagreements were resolved by consensus or by consulting a third author (SD).

Eligible studies were phase II and III placebo-controlled or active-controlled induction and/or maintenance trials of biological agents, biosimilars, or advanced small molecules in adults with moderate-to-severe CD or UC. Conference abstracts were excluded. Trials investigating efficacy on fistulising or stricturing CD, acute severe UC, hospitalized patients, or pouchitis were excluded as well as trials comparing dosing strategies and therapeutic drug monitoring, complementary therapies, or devices. Risk of bias was not

assessed as the review focused on the definitions of reported endpoints rather than the study results.

RESULTS

The updated literature search identified 8745 citations (Figure S1). After removing duplicates, 3554 records were screened for eligibility, 124 underwent full-text review, and 27 were included. In addition, 109 studies were retrieved from previous versions of the systematic review[8,9] and 8 active-controlled RCTs were manually included.

A total of 144 randomized controlled studies were included in the review, 72 in UC (Table 1) and 72 in CD (Table 2) published between 1997 and December 2023.

Mucosal healing definitions in ulcerative colitis

Overall, MH was specifically reported as a primary or secondary endpoint in 46 of 72 (64%) RCTs of UC. The term "mucosal healing" first appeared in a UC RCT in the 2005 ACT 1-2[10] trials; afterward, the proportion of RCTs mentioning MH grew, peaking in the 2010–2020 decade when 90% (34/38) of studies included it (Figure 1).

In total, 12 different definitions of MH were found in UC trials. Of the 46 RCTs reporting MH, 35 (76%) defined it by endoscopic measures only, 10 (22%) as a combination of endoscopy and histology, 1[11] (2%) included histology only.

The vast majority of studies used the Mayo Endoscopic Score (MES) (44/45, 98%) to define MH, and 1 (2%) the Baron endoscopic subscore.[12]

The most common definition of MH was a MES ≤1, chosen in 33 RCTs (33/46, 72%), 1 study as a MES improvement of at least one point, and another study[12] defined MH as a Baron endoscopic subscore of 0 or 1, which includes the same features as the MES. Friability, a feature originally included in the MES of 1, was progressively excluded from the MES 1 count following the 2016 Food and Drugs Administration (FDA) recommendations.[13,14] Only 2 studies set the bar of MH as high as MES = 0, both of which with the addition of histological remission (histo-endoscopic mucosal remission or HEMR) defined as a Geboes score <2.0.[15,16]

All of the 10 RCTs that included combined endoscopic and histological assessments in the definition of MH were published after 2019 (Figure 2). All of these studies based the histological component on the Geboes score with either a cut-off of ≤2.1 or ≤3.1, the only exceptions being VEGA[17] and UNITI[18]; the first did not specify a score, the second provided descriptive criteria and cut-offs that align with a Geboes score ≤3.1. The combination of endoscopic and histologic measures for the definition of MH in UC is consistent with the FDA's 2016 Draft Guidance for Industry recommendation, which stated that MH claims for new drugs for UC would no longer be sufficient based on endoscopic appearance endpoints alone, but would also require histologic evaluation.[14]

In two development programs, the definition of MH changed across trial phases: ozanimod and ontamalimab. In the 2016 phase 2 trial of ozanimod for UC (TOUCHSTONE),[19] MH was defined as MES ≤1, while in the phase 3 "True North"[20] trial published in 2021, the definition evolved to a combination of MES ≤1 without friability and histologic remission defined as a Geboes score <2. Similarly, in the ontamalimab development program, the Phase 3 trial definition of MH included the histologic criterion (Geboes ≤2) in addition to the endoscopic one, which remained MES ≤1 but was adjusted to exclude friability.[21,22]

Mucosal healing in Crohn's disease

Of the 71 placebo-controlled RCTs included in our review, only 9 (12%) specifically defined MH (Figure 3) using 3 different definitions. Seven trials specified it as "absence of mucosal ulceration," the remaining 2 as a Simplified Endoscopic Score for CD (SES-CD) ≤2 or 0.

MH first appeared as an endpoint in CD's in the 2006 substudy[23] of the ACCENT 1 trial defined as complete absence of ulcerations. Although the number of studies reporting MH increased in the following years, its uptake never reached that of UC. More broadly, in CD, only around one third (23/71) of RCTs evaluated endoscopic response, and one fifth endoscopic remission (15/71), with a significant overlap between the two (13 RCTs reported both), meaning that the majority of studies did not report any endpoint based on mucosal evaluation.

Some earlier trials did not require baseline endoscopic evaluation, preventing before-and-after comparisons and precluding endpoints such as endoscopic response. The few studies that measured endoscopic response between 1999 and 2010 (n = 7) evaluated changes in the Crohn's disease endoscopic index of severity score without specifying a minimum improvement. After 2010, all but one study[24] adopted the SES-CD and cut-offs of improvement were specified. Following a post hoc analysis of the SONIC trial,[25] a 50% or greater reduction from baseline scores became the standard definition of endoscopic response and indeed was used in all studies included in our review and adopted by the FDA[26] (Figure 3). Additionally, four trials also included a 25% or more decrease cut-off.[21,27–29] Endoscopic remission was based on SES-CD in all except two studies.[24,30] Compared to endoscopic response, there was more variability in the selection of cut-offs for endoscopic remission, ranging from a SES-CD ≤4 to a SES-CD of 0, and additionally different definitions for those patients with isolated ileal disease.

No study in CD included histologic remission as an endpoint and only three included histological response.[31–33] Although named differently, the three studies used very similar definitions.

TABLE 1 Phases 2 and 3 randomized clinical trials of advanced medications for ulcerative colitis included in the systematic review.

Year	First author	Study name	MH definition	Endoscopy central reading	Histology central reading
2023	Feagan	VEGA	MES ≤1 + histologic healing	Yes	Yes
2023	Atreya		MES ≤1	Yes	Yes
2023	Vermeire		MES ≤1 + geboes ≤2	Yes	
2023	D'Haens			No	Yes
2023	Peyrin-Biroulet	QUASAR		Yes	Yes
2023	D'Haens	LUCENT 1-2		Yes	Yes
2022	Chen	AMBER 2		Yes	
2022	Danese	GARDENIA		Yes	
2022	Danese	U-ACCOMPLISH	MES = 0 + geboes <2	Yes	NA
2022	Ferrante			No	
2022	Matsuoka			Yes	
2022	Peyrin-Biroulet	HICKORY		Yes	NA
2022	Rubin	HIBISCUS 1		Yes	NA
2022	Sandborn	ELEVATE UC 12	MES ≤1 (without friability) + geboes <2	Yes	NA
2022	Sandborn	VIBRATO	MES ≤1 (without friability) + geboes ≤3.1	Yes	NA
2022	Vermeire	ABX464/ Obefazimod	MES = 0 + geboes <2	Yes	No
2022	Vermiere	LAUREL		Yes	NA
2023	Chen		MES ≤1	Yes	
2021	Feagan	SELECTION	MES ≤1 (without friability) + geboes <2	Yes	Yes
2021	Kita			No	
2021	Sandborn	PROPEL		Yes	Blinded pathologist
2021	Sandborn	True North	MES ≤1 (without friability) + geboes <2	Yes	Yes
2021	Vermeire			Yes	
2021	Weisel			No	
2020	Atreya	CONDUCT		Yes	Yes
2020	Danese		MES ≤1 + geboes <2	Yes	NA
2020	Kierkus		MES ≤1 without friability	Yes	
2020	Radeke		Baron ≤1 with no bleeding	No	
2020	Sandborn	I6T-MC-AMAC		Yes	Yes
2020	Sandborn	OASIS		Yes	Yes
2020	Sandborn	U-ACHIEVE (substudy 1 [I])	MES ≤1	Yes	Yes
2020	Sandborn	VISIBLE 1	MES ≤1	Yes	NA
2019	Hibi		MES ≤1	No	
2019	Motoya		MES ≤1	No	
2019	Sands	VARSITY	MES ≤1	No	No
2019	Sandborn		MES ≤1	Yes	No

(Continues)

TABLE 1 (Continued)

Year	First author	Study name	MH definition	Endoscopy central reading	Histology central reading
2019	Sands	UNIFI	MES ≤1 + neutrophil infiltration in <5% of crypts, no crypt destruction, and no erosions, ulcerations, or granulation tissue	Yes	NA
2018	Sandborn		Histologic remission	Yes	NA
2018	Sands		MES ≤1	Yes	
2017	Hibi	PURSUIT-J	MES ≤1	No	
2017	Sandborn	OCTAVE	MES ≤1	Yes	
2017	Vermeire	TURANDOT	MES ≤1	Yes	
2016	Atreya	COLLECT	MES ≤1	No	Yes (single pathologist)
2016	Sandborn	TOUCHSTONE	MES ≤1	Yes	Yes
2016	Sandborn		MES ≤1	No	No
2015	Danese		Improvement of MES from 3 or 2 to 1, or from 1 to 0	No	No (only baseline inclusion centralized)
2015	Jiang		MES ≤1	No	
2015	Reinisch		MES ≤1	No	
2015	Rutgeerts	PURSUIT-IV	MES ≤1	No	
2015	Yoshimura		MES ≤1	Yes	Yes
2014	Mayer		MES ≤1	No	Yes (single pathologist)
2014	Sandborn	PURSUIT-M	MES ≤1	No	
2014	Sandborn	PURSUIT-SC	MES ≤1	No	
2014	Suzuki		MES ≤1	No	
2014	Vermeire		MES ≤1	No	NA
2013	Feagan	GEMINI 1	MES ≤1	No	
2012	Sandborn	ULTRA 2	MES ≤1	No	
2012	Sandborn		MES ≤1	No	Yes (single pathologist)
2012	Sandborn			No	
2012	Sands		MES ≤1	No	
2011	Leiper		MES ≤1	No	No
2011	Reinisch	ULTRA 1	MES ≤1	No	
2008	Lewis			No	
2007	Schreiber			No	
2006	van assche	PROSPECT		No	Yes (single pathologist)
2006	van Deventer	ISIS 2302-CS27	MES ≤1	No	
2005	Feagan			No	
2005	Rutgeerts	ACT 1	MES ≤1	No	
2004	van Deventer			No	
2003	Nikolaus			No	
2003	Probert			No	
2003	Sandborn			No	NA

TABLE 2 Phase 2 and 3 randomized clinical trials of advanced medications for Crohn's disease included in the systematic review.

Year	First author	Study name	MH definition	Endoscopy central reading	Histology central reading
2023	D'Haens	DIVERGENCE 1	None. 1st RCT with transmural healing	No	No
2023	Vermeire	VISIBLE 2		No	
2023	Kita			No	
2023	Vermeire		SES-CD ≤2	No	
2023	Sanborn	BERGAMOT		Yes	
2023	Allez	TRIDENT	Absence of mucosal ulcerations	Yes	Yes
2023	Loftus	EXCEL EXCEED		Yes	
2022	Berera			No	
2022	D'Haens			No	
2022	Sands	SEAVUE		Yes	
2022	D'Haens	ADVANCE		Yes	
2022	Sandborn	GALAXI-1	Absence of mucosal ulcerations	Yes	
2022	Sands			Yes	
2020	Sandborn			Yes	
2020	Watanabe			No	
2020	Sands			Yes	
2020	Chen			No	
2019	Danese	ANDANTE		No	
2018	Sandborn	OPERA		No	
2018	Schreiber			Yes	
2017	Sandborn			Yes	
2017	Feagan		Absence of mucosal ulcerations	Yes	
2017	Panés			No	
2017	Sands			No	
2017	Vermeire	FITZROY	SES-CD = 0	Yes	
2016	Targan			No	
2016	Feagan	UNITI 1-2		No	
2018	Rutgeerts	UNITI substudy	Absence of mucosal ulcerations	Yes	
2015	Panaccione			No	
2014	Sands			No	
2014	Sandborn			No	
2013	Sandborn			No	
2012	Hueber			No	
2012	Rutgeerts	EXTEND	Absence of mucosal ulcerations	Yes	
2012	Sandborn	CERTIFI		No	
2012	Sandborn	*CD-IP arm		No	
2012	Watanabe			No	
2011	Sandborn			No	
2010	Colombel	SONIC	Absence of mucosal ulcerations	No	
2010	Reinisch			No	

(Continues)

TABLE 2 (Continued)

Year	First author	Study name	MH definition	Endoscopy central reading	Histology central reading
2010	Sands			No	
2010	van der Woude			No	
2008	Feagan			No	
2008	Sandborn			No	
2007	Colombel	CHARM		No	
2007	Sandborn	CLASSIC-2		No	
2007	Mansfield			No	
2007	Sandborn	GAIN		No	
2007	Sandborn	PRECISE		No	
2007	Targan	ENCORE		No	
2007	Yacyshyn			No	
2006	Rutgeerts	ACCENT 1 substudy	Absence of mucosal ulcerations	Yes	
2006	Hanauer	CLASSIC-1		No	
2006	Hommes			No	
2006	Lemann			No	
2006	Reinisch			No	
2006	Rutgeerts			No	
2005	Sandborn	ENACT		No	
2005	Feagan			No	
2005	Schreiber			No	
2004	Ito			No	
2004	Mannon			No	No
2004	Sandborn			No	
2004	Winter			No	
2003	Ghosh			No	
2002	Hanauer	ACCENT 1		No	
2001	Gordon			No	
2001	Sandborn			No	
2001	Sandborn			No	
1999	D'Haens			No	Yes (single pathologist)
1997	Stack			No	
1997	Targan			No	

Central reading of endoscopy in clinical trials

Central reading is the independent, off-site, blinded review or reading of imaging endpoints. In IBD, the central reading of endoscopy has two main purposes: to ensure inclusion criteria are met and to independently assess changes in disease activity. Both FDA and European Medicines Agency recommend the use of central reading of endoscopy videos in clinical trials of IBD.[14,34] Furthermore, the FDA endorses centralized histological scoring of biopsies in UC studies.

The first use of a centralized reading process in IBD was in 2006 in the ACCENT-1 endoscopic substudy where the first author, blinded from study data, reviewed the recordings of all ileocolonoscopies to assess efficacy endpoint.[23] Years later, in the EXTEND trial of adalimumab in CD central reading was used again.[30] The importance of central review gained further traction after a landmark study in 2013 showed how enrolling patients based on the local endoscopists' assessment led to the erroneous conclusion that a mesalazine formulation was not superior to

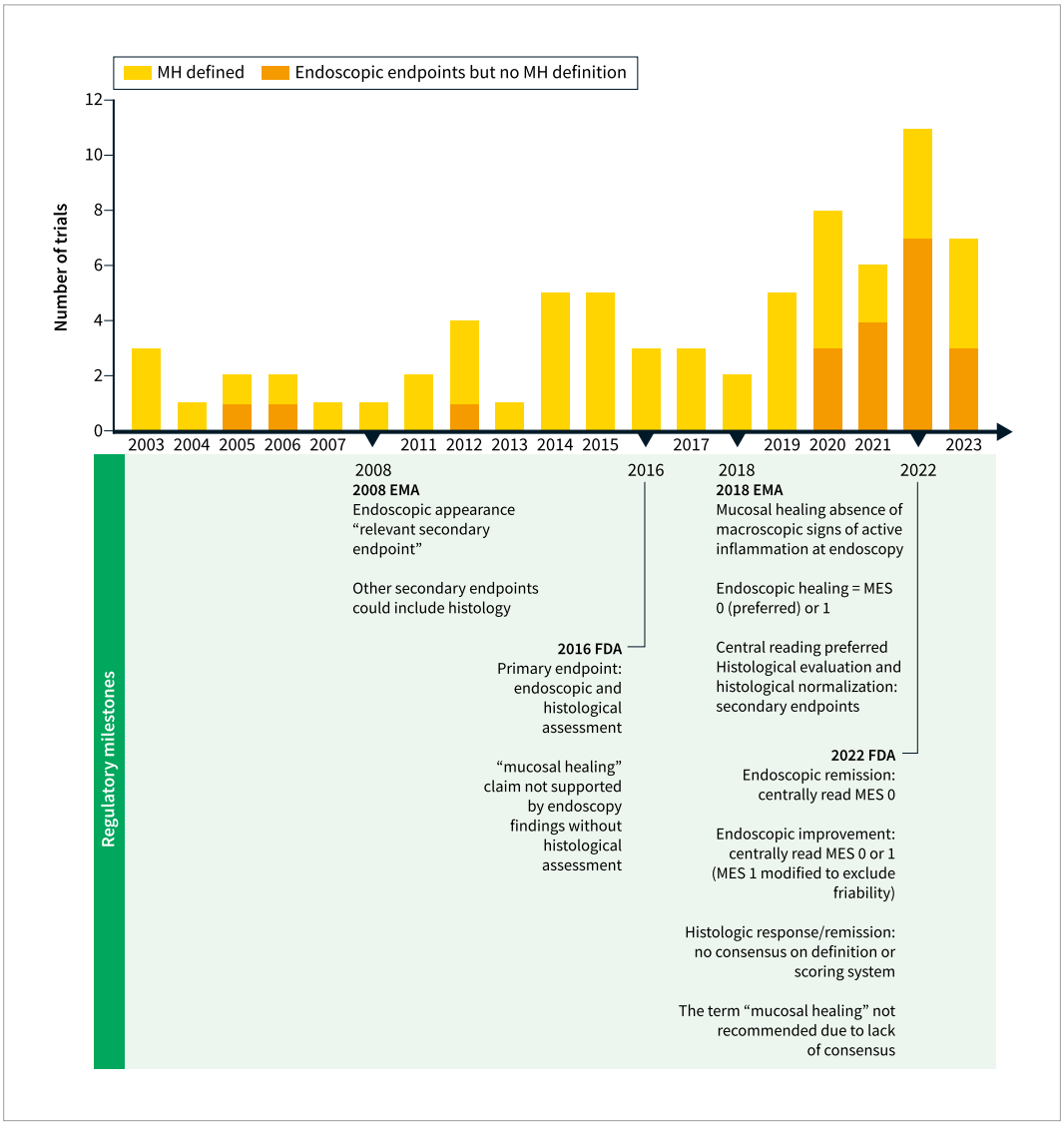

FIGURE 1 Reporting of mucosal healing as an endpoint in randomized controlled trials of new agents for ulcerative colitis. EMA, European medicines agency; FDA, food and drugs administration; MES, mayo endoscopic subscore; MH, mucosal healing.

placebo in UC. Instead, if enrollment had been verified independently, the difference would have been significant.[35] In UC RCTs, the assessment of drug response through central reading was deployed for the first time only in 2015,[36] but despite the initial delay, it took hold more than in CD, 68% (35/51) of UC studies published after 2015 compared to 48% (14/29) in CD.

Blinded evaluation of endoscopy has shown to decrease placebo response rates, thereby reducing the sample size required. For example, in the phase 2 RCT of ontamalimab, an anti-MADCAM-1 antibody, central reading assessment more than halved the MH rate of placebo, from 21.9% to 8.2%.[22] However, central reading remains far from perfect. Inconsistencies among central readers have been demonstrated,[37] and pre-scoring factors such as the quality of the video, of the bowel preparation, and of the overall endoscopy impact the ability of external reviewers to assess the severity of disease.

Centralized reading of histology in clinical trials

In UC, 50% (18/36) of RCTs that included some histological evaluation reported a central reading although whether this was performed on-site or off-site was not always specified. In CD, of the only 3 RCT evaluating histological endpoints, 2 (67%) reported a centralized reading, one of which was performed on-site by a single pathologist also investigator of the trial, although blinded.[32]

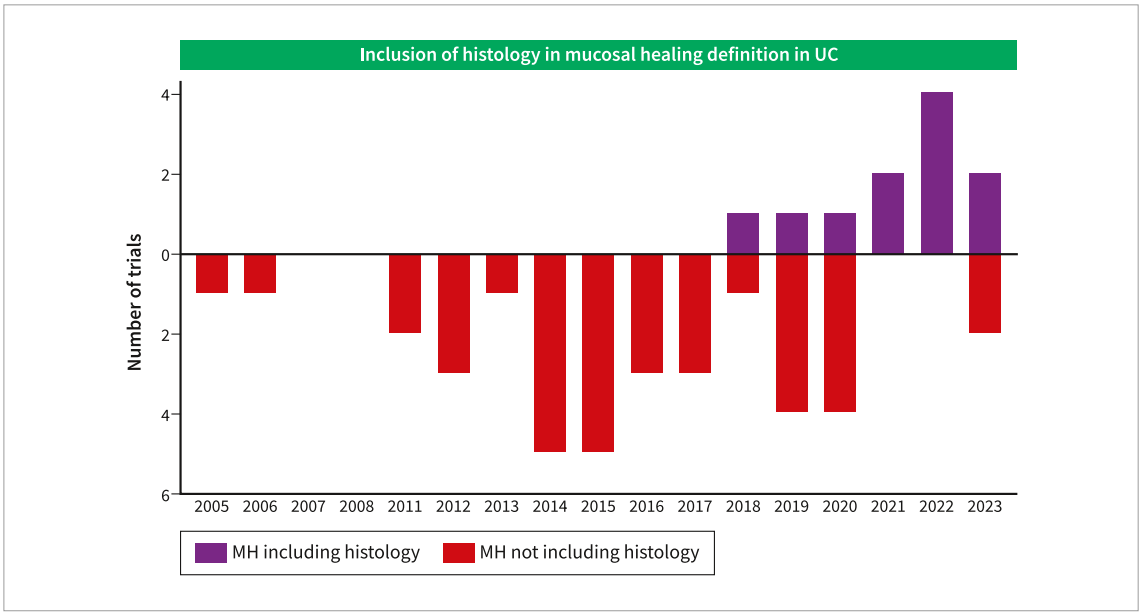

FIGURE 2 Inclusion of histological assessment in the definition of mucosal healing in randomized controlled trials of ulcerative colitis. MH, mucosal healing.

Transmural healing

In our systematic review, only 1 RCT, the DIVERGENCE 1 phase 2 study of filgotinib for small bowel CD included transmural assessment as secondary endpoint. Transmural healing was defined as a centrally read Magnetic Resonance Index of Activity score <7 in all small bowel segments.[38]

DISCUSSION

Mucosal healing is an important treatment target in both UC and CD. It differentiates symptom control from disease control, which is a critical concept, because it is disease control that has been associated with improved outcomes in observational studies.[39,40] It is therefore logical that MH, or at least improvement of endoscopic activity, should be of paramount importance in assessing the efficacy of drugs. Hence, the definition, as well as the timing, of MH is central to the interpretation of trial results. Here we systematically review the definitions of MH used in RCTs in UC and CD. Interestingly, there has been an evolution of the concept of MH over the years and even within individual drug development programs. In UC, the definition has become more stringent, while in Crohn's disease, the original concept of MH has given way to definitions of endoscopic response and remission.

A great heterogeneity exists in definitions of MH, even considering UC and CD separately. This heterogeneity limits drug comparison through meta-analysis and generates confusion to the point that FDA in 2022 suggested to stop using the term MH in UC trials due to the lack of consensus on its definition.[41] In UC, most studies used a Mayo score, that includes the endoscopic subscore, to assess efficacy but in older studies, subscores were not reported separately nor there was a clear cutoff of MH. In the studies that did report MH definition, until recently, this was based only on endoscopic appearance. Afterward, the awareness that subtle mucosal changes could be missed by endoscopy and mounting evidence on benefits of histological remission expanded the concept of MH to include histological assessment.[7,42,43] Nevertheless, most studies still consider mild inflammatory changes such as erythema (for example in the MES 1) compatible with MH, implicitly suggesting that complete restoration is beyond the reach of available therapies or not providing sufficient additional benefits. Indeed, the clinical significance of mild inflammatory features is probably best captured over long follow-up periods that exceed the duration of clinical trials. Real world studies, which could fill this evidence gap, are complicated and often less rigorous in their assessment.

In CD, although the discrepancy between symptoms and objective measures of severity is even greater than in UC, the concept of MH has trailed the field of UC. This is due to several reasons. Firstly, in CD, mucosal damage is typically patchy, complicating endoscopic score calculations and limiting histologic assessment with sampling variability; indeed, the prognostic implication of microscopic inflammation in CD remains unclear.[44] Secondly, endoscopy and histology do not adequately capture the transmural extent of the disease, and even when this is visible, it is unclear whether few deep ulcers carry worse prognostic value than many shallow aphthous ones.

Importantly, endoscopic measures of disease activity were included in more trials than those that provided a precise definition of MH. In several studies, the endpoints were even more stringent, combining both endoscopic and histological improvement. This reflects a growing interest in a deeper assessment of the mucosa, yet also suggests a move beyond the term MH. In line with this, the

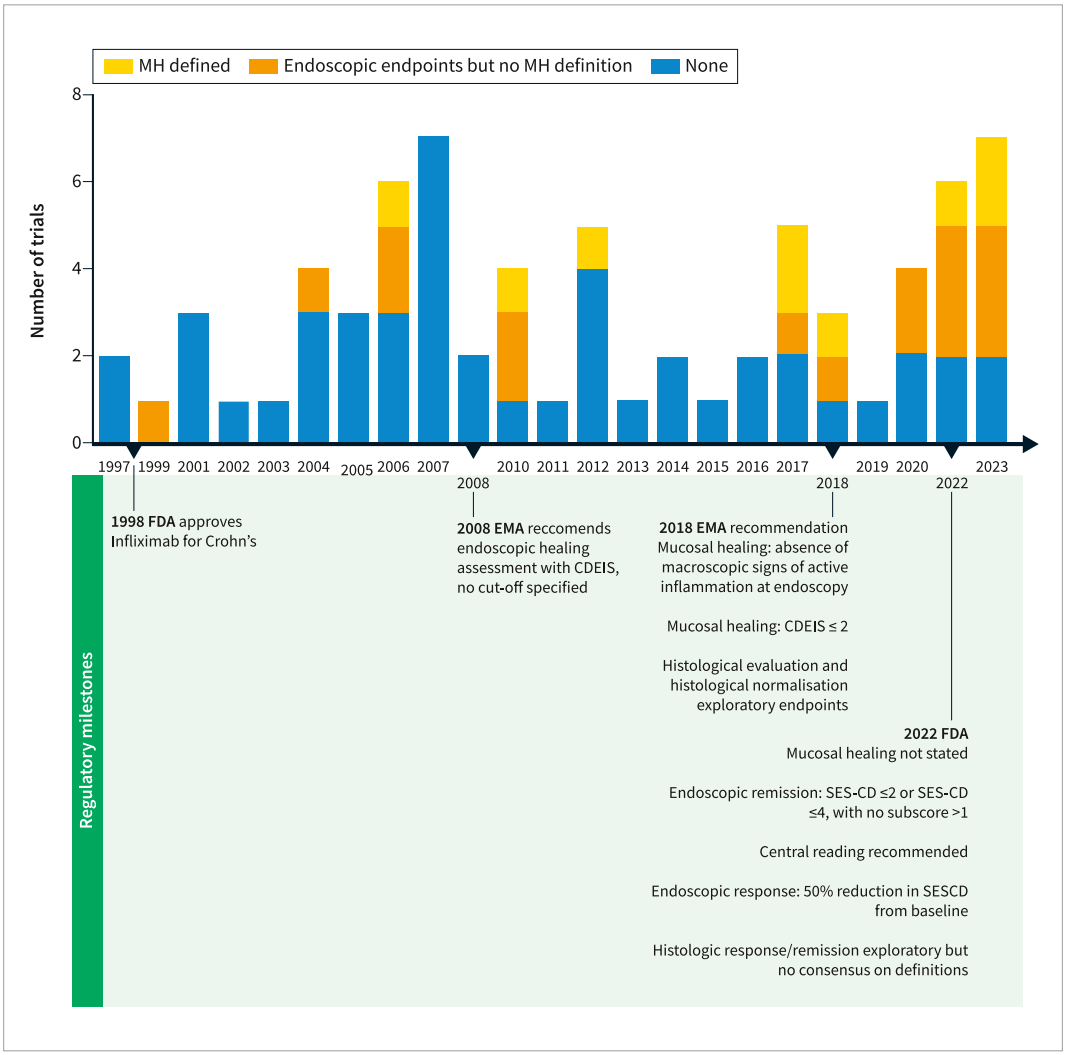

FIGURE 3 Reporting of mucosal healing as endpoint in Randomized Controlled Trials of Crohn's disease. CDEIS, Crohn's disease endoscopic index of severity; EMA, European medicines agency; FDA, food and drugs administration; MH, mucosal healing; SES-CD, simplified endoscopic score for Crohn's disease.

FDA's 2022 guidance on clinical trial endpoints for UC recommended discontinuing the use of the term 'MH' due to its ambiguous definition, a shift from its 2016 guidance.[41] Regulatory changes are summarized in supplementary Tables S3 and S4.

Transmural assessment is just beginning to be implemented in CD RCTs. In addition to the DIVERGENCE 1 trial,[38] two sub-studies, one of the VERSIFY phase 3 trial[45] and the other of the STURDUST trial,[46] recently assessed transmural healing with MRI and intestinal ultrasound, respectively. Furthermore, other studies are ongoing to assess treatment impact on transmural healing (NCT06408935) and transmural healing itself as a treatment target (NCT06257706). Thus far, all completed and ongoing studies employed central reading of imaging.

Our systematic review has several strengths. It includes the first exhaustive literature search with the identification of all definitions of MH used in RCTs of IBD, their assessment through local or centralized reading, and their changes over time. Nevertheless, there are some limitations to our work. First, endpoints used in RCTs might differ from the goals of physicians in real-world clinical practice. Secondly, our work does not address the relationship of the different thresholds of MH with the risk of disease progression. Although less inflammatory activity is clearly desirable, the optimal compromise between more stringent endpoints, trial success rates and measurable clinical benefits is still a matter of discussion.

Future perspectives

Studies show that recurrent inflammatory episodes may occur in IBD even when MH is achieved, meaning that MH does not equate to full disease resolution and additional healing layers are needed for prolonged remission.[43] In UC, an ambitious outcome of "disease clearance" has been proposed, defined as complete normalization of symptoms, endoscopy, and histology.[47] Retrospective data show that

patients achieving disease clearance have better long-term outcomes than those in remission alone. However, prospective validation is missing, and importantly, only a small minority achieve disease clearance with current treatments. More broadly, stricter endpoints in clinical trials risk reducing effect size and increasing sample size requirements, making recruitment more difficult.

To improve disease assessment, several approaches have been proposed. Advanced endoscopy techniques, such as virtual chromoendoscopy and high-magnification scopes, provide detailed mucosal views, detecting subtle inflammatory changes better than conventional white-light.[48,49] Confocal endomicroscopy, combining high magnification with intravenous contrast, evaluates intestinal barrier permeability, a relapse predictor potentially more accurate than endoscopy and histology in UC.[50] Despite their promise, these techniques have been tested only in cohort studies, not in RCTs, and their widespread use could be limited by technology and expertise availability.

Another rapidly developing area is artificial intelligence. Several machine learning systems have proved to assess endoscopic and histological healing with accuracies in the range of 90% compared to humans.[51–53] These advances are particularly relevant for clinical trials where centralized human reading, the current gold standard, has many inefficiencies. Furthermore, computational tools may enhance the quantification of inflammatory burden. Most endoscopic scores for UC consider only the most affected segment and thus limit the index responsiveness. While a human segment-by-segment assessment is cumbersome and time-consuming, an automated "cumulative" disease score could provide a more granular quantification of the disease, improving the responsiveness of the endoscopic outcomes and reducing sample size requirements.[54] Finally, since in real world the adoption of standard scores remains suboptimal[55] automation could facilitate the uptake.

All these approaches require endoscopies that are unpleasant for patients. Next-generation biomarkers based on transcriptomics[56] and proteomics[57] analysis of circulating RNA and proteins show promise in determining inflammation and healing. A more available solution could come from cross-sectional imaging, especially intestinal ultrasound. Radiation-free imaging with blinded central reading and potential AI enhancement could reduce endoscopies.[58] Successful applications of AI evaluation of transmural damage[58,59] could support the adoption of transmural endpoints. Given the limitations of current options, holistic strategies combining available modalities are reasonable while awaiting more accurate techniques.

CONCLUSION

The concept of MH in IBD has evolved, but there is no consensus on its definition. In UC, histology complements endoscopy in defining MH, whereas in CD, endoscopic appearance remains primary. Transmural assessment using cross-sectional imaging may be a major turning point in CD. Future endpoints are expected to be more stringent and multimodal with AI-derived automated assessments.

AUTHOR CONTRIBUTIONS

Study concept and design: Tommaso Lorenzo Parigi, Silvio Danese, Laurent Peyrin-Biroulet. Acquisition of data Tommaso Lorenzo Parigi and Virginia Solitano. Analysis and interpretation of data Tommaso Lorenzo Parigi and Virginia Solitano. Draft of the manuscript Tommaso Lorenzo Parigi. Critical revision of manuscript: all authors. All authors have approved the final version of this manuscript.

AFFILIATIONS

[1]Division of Immunology, Transplantation and Infectious Disease, Università Vita-Salute San Raffaele, Milan, Italy

[2]Department of Gastroenterology and Endoscopy, IRCCS Ospedale San Raffaele, Milan, Italy

[3]Division of Gastroenterology, Department of Medicine, Western University, London, Ontario, Canada

[4]IBD Center, IRCCS Humanitas Research Hospital, Milan, Italy

[5]Department of Biomedical Sciences, Humanitas University, Milan, Italy

[6]Gastroenterology Department, Hospital Clínico Universitario de Santiago de Compostela, Santiago, Spain

[7]Faculty of Medicine, Mater Research Institute University of Queensland, Brisbane, Queensland, Australia

[8]Sheba Medical Center, Tel Aviv, Israel

[9]Department of Gastroenterology & Hepatology, University Hospital Zurich, Zurich, Switzerland

[10]The Henry Janowitz Department of Gastroenterology, Icahn School of Medicine at Mount Sinai, New York, New York, USA

[11]Department of Medicine and Agaplesion Markus Hospital, Goethe University, Frankfurt am Main, Germany

[12]Gastroenterology Department, Centre Hospitalier Universitaire d'Amiens, and PeriTox, Université de Picardie Jules Verne, Amiens, France

[13]University College Cork, Cork, Ireland

[14]Center for Advanced IBD Research and Treatment, Kitasato University Kitasato Institute Hospital, Tokyo, Japan

[15]Department of Gastroenterology, Liège University Hospital, Liege, Belgium

[16]Hospital de Sao Joao, Porto, Portugal

[17]Inflammatory Bowel Disease Unit, University of Calgary, Calgary, Alberta, Canada

[18]Hospital Britanico de Buenos Aires, Buenos Aires, Argentina

[19]Division Gastroenterology & Hepatology, Department of Internal Medicine III, Medical University of Vienna, Vienna, Austria

[20]Leeds Gastroenterology Institute, Leeds Teaching Hospitals NHS Trust, Leeds, UK

[21]Alimentiv Inc, London, Ontario, Canada

[22]Department of Gastroenterology, INFINY Institute, FHU-CURE, Nancy University Hospital, and INSERM, Nutrition-Genetics and Environmental Risk Exposure, University of Lorraine, Vandœuvre-lès-Nancy, France

ACKNOWLEDGMENTS

AbbVie funded this systematic literature review as part of a consensus activity and had the opportunity to review and comment on the publication prior to submission. However, AbbVie did not

contribute to medical writing support or journal fees, and decisions regarding final content were made solely by the authors.

Open access funding provided by BIBLIOSAN.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

The data supporting this study are provided in summary form in the tables and results of the manuscript. The full dataset is available on request from the corresponding author.

ORCID

Manuel Barreiro de Acosta https://orcid.org/0000-0001-5915-1477
Shomron Ben-Horin https://orcid.org/0009-0001-1586-6056
Taku Kobayashi https://orcid.org/0000-0002-2073-4234
Fernando Magro https://orcid.org/0000-0003-2634-9668
Christian Selinger https://orcid.org/0000-0003-2022-5859
Vipul Jairath https://orcid.org/0000-0002-1092-0033
Laurent Peyrin-Biroulet https://orcid.org/0000-0003-2536-6618

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Parigi TL, Solitano V, Armuzzi A, Barreiro de Acosta M, Begun J, Ben-Horin S, et al. Defining mucosal healing in randomized controlled trials of inflammatory bowel disease: A systematic review and future perspective. United European Gastroenterol J. 2024;12(9):1266–79. https://doi.org/10.1002/ueg2.12671