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Review Article

Clinical implications of mucosal healing in the management of patients with inflammatory bowel disease

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ABSTRACT

The natural history of Crohn's Disease and ulcerative colitis is characterized by repeated episodes of inflammation and ulceration of the bowel. This results in complications implying a worse quality of life and significant healthcare costs, due to hospitalization, surgery and an escalation of therapy.

The main goal of the therapy in inflammatory bowel disease is to achieve and maintain disease remission, with an improved health-related quality of life, less hospitalization, and less surgery. The concept of remission has changed in the recent years. In fact the concept of clinical remission, where only the patients' symptoms are in remission, has been replaced by the new concept of deep remission. This implies not only sustained clinical remission but also complete mucosal healing, with the normalization of serological activity indexes.

Mucosal healing, rarely achieved with traditional drugs, can now be achieved and maintained by means of biological drugs. Current evidence suggests that the achievement of mucosal healing might significantly change the natural course of inflammatory bowel diseases and should represent an objective end point of future therapeutic trials, particularly for colonic diseases.

1. Introduction

Inflammatory Bowel Disease (IBD), which includes both Crohn's Disease (CD) and ulcerative colitis (UC), is a chronic idiopathic inflammatory disorder affecting the gastrointestinal tract [1]. CD and UC affect more than 1 million people in the United States, with thousands of new diagnoses annually [2,3]. The natural history of CD and UC is characterized by repeated episodes of inflammation and ulceration of the bowel. This results in complications implying a worse quality of life and significant healthcare costs, due to hospitalization, surgery, and an escalation of therapy [4–6]. The main goal of the therapy in IBD is to achieve and maintain disease remission, with an improved health-related quality of life, less hospitalization, and less surgery [7]. The concept of remission has changed in recent years. The concept of clinical remission, where only the patients' symptoms are in remission, has been replaced by the new concept of deep remission. This implies not only a sustained clinical remission but also a complete mucosal healing (MH), together with the normalization of serological activity indexes (C-reactive protein, CRP). MH is thought to be an important prognostic feature for the efficacy of treatment in IBD. MH is assessed by endoscopy and is a component of intestinal healing, which determined by endoscopic healing, histological healing, transmural healing and fistula healing [8].

In this article we review the clinical relevance and the clinical implications of MH, discussing its role in predicting the course of IBD and its impact on decisions regarding medical strategies.

2. Definition of MH

2.1. Crohn's Disease

Currently, there is no validated gold standard definition of MH in CD. Historically, endoscopy, rather than histology, has been the focus of mucosal assessment in CD patients for several reasons.

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Because of the segmental nature of CD, which can lead to sampling error when biopsies are performed, and the predilection of CD for the ileum, histological scoring is inherently difficult [9,10]. Also, despite a number of histological activity indices have been developed, none of them has been prospectively validated. In addition, endoscopic assessment of disease activity in CD has been shown to be better correlated with transmural inflammation and therefore to the actual severity of the disease [11]. Finally, there is a paucity of data evaluating the impact of histological healing on clinical outcomes.

At the moment, there are 2 validated indices for assessing endoscopic activity in CD: CDEIS and SES-CD.

Both are too complex and cumbersome to be used routinely in clinical practice. Clinical trials examining endoscopic MH as a secondary or even primary end point in CD have really only begun in the last decade, corresponding to the era of both antitumor necrosis factor alpha (anti-TNFα) therapy and recognition of MH as a potentially important treatment end point. In the 1990 the study of the Groupe d'Etude Therapeutique des Affectiones Inflammatoires du Tube Digestif (GETAID) showed no significant correlations between the clinical activity of the disease and the endoscopic activity after treatment with steroids. In addition, they also showed the low impact of endoscopic improvement in the long-term prognosis, and the ineffectiveness of steroid treatment intensification to obtain further endoscopic improvement [12]. With the use of Infliximab, for the first time a significant correlation between the variations in the CDAI score and the CDEIS endoscopic score has been demonstrated.

Regarding surgery for CD, Rutgeerts showed that the presence of mucosal lesions with increasing severity predicts a high probability of post-surgical recurrence [13]. Furthermore, Allez et al. showed that patients with active CD having deep and extensive ulcerations, are, over a long period of time, at a greater increased relative risk of undergoing colectomy compared to patients free of such lesions. The presence of deep ulcers and other severe endoscopic lesions was an independent risk factor for colectomy, together with CDAI > 288 and the absence of immunosuppressive treatment [14]. Similarly, in a Norwegian population-based cohort study, 11% of CD patients with MH at 1 year needed surgical resection within 5 years compared to 20% of patients without MH [15].

Many different definitions of MH have been used over the years and, unfortunately, none of them has been validated or even universally accepted. A recent expert consensus report defined MH in CD as the "restoration of normal mucosal appearance by endoscopy of a previously inflamed region and the complete absence of ulceration and macroscopic and histological signs of inflammation" [16]. This rigorous combined endoscopic and histologic definition has not yet been applied to clinical trials, which have primarily used endoscopic indices to define MH [10].

2.2. Ulcerative colitis

Similarly to CD, there is no validated goldstandard definition of MH in UC. Numerous endoscopic and histological indices have been developed to measure disease activity in UC. All these indices include overlapping endoscopic mucosal features, such as vascularity, granularity, erythema, friability, bleeding, and ulceration. However, in many of these indices, clinically meaningful cut-off scores for endoscopic remission or improvement have not been defined, and none has been prospectively validated. The development of the new UCEIS was a collaborative effort involving 40 IBD specialists from 13 countries. It has been found that 3 endoscopic features are the most discriminating: vascular pattern (score 1–3), bleeding (score 1–4), and erosions and ulcers (score 1–4) [17]. UCEIS is currently undergoing independent validation. More recently, another index was developed and validated: the UC Colonoscopic Index of Severity (UCCIS), which provides reproducible results in endoscopic scoring of patients with UC [18].

The importance of achieving MH in UC patients was long ago underscored by Wright and Truelove, who showed that UC patients not achieving MH under oral and rectal steroids relapsed more frequently during a follow-up period of 1 year compared to patients who did achieve it (40% vs. 18%, respectively) [19].

A number of recent clinical trials of various medications for the treatment of active UC have examined endoscopic MH as a secondary end point but have used different definitions of MH.

Similar to CD, there is much heterogeneity in the way MH has been defined in UC, and none of these definitions has been validated or universally accepted. The challenge lies in collectively interpreting the results of studies that use different definitions of MH.

3. Clinical implications of MH

3.1. Hospitalizations and surgery

The analysis of the significance of MH requires evaluation of the therapeutic results in relation to the drivers of the direct costs of IBD, mainly meaning hospitalization and surgery. Therefore, those factors that may affect the therapeutic results of these patients will have significant impacts in terms of reducing the social cost of this disease [20]. Also, in the CHARM study it was possible to demonstrate a significant reduction in the number of hospitalizations of CD patients treated with adalimumab versus placebo. The relative risk reduction is of 78% at 3 months, and 57% at 1 year in patients treated with adalimumab compared to those treated with placebo [21].

An observational cohort study of Norwegian IBD patients (IBSEN cohort) showed that after a 1-year follow-up 38% of CD patients and 50% of UC patients had evidence of MH; after 1 year these patients had fewer colectomies for UC than at 5 years of follow-up (2% vs. 7%, $p = 0.02$); however, these findings refer to an earlier cohort of patients followed up during the pre-biological treatment era, when MH was not yet considered a routine endpoint for clinical trials [15]. Similarly, the study performed by Schnitzler et al. [22], which is a "real-life" experience that highlights how MH predicts long-term outcome of maintenance therapy with infliximab in Crohn's Disease, showed that MH was associated with a significantly lower need for major abdominal surgery during long-term follow-up (14.1% of patients with MH needed major abdominal surgery vs. 38.4% of patients without MH, $p = 0.0001$).

With regard to the surgical setting in UC, a French study performed in order to evaluate the value of colonoscopy for the assessment of colonic ulcerations, enrolling 118 patients with steroid-refractory UC, showed that the presence of severe endoscopic lesions was an independent factor predictive of colectomy [23]. Similarly, a prospective study by Solberg et al., performed to evaluate the course of UC in a population-based inception cohort and to identify prognostic risk factors, showed that patients who presented with MH within 1 year of diagnosis, independently of the therapeutic regimen, had a significantly lower risk of colectomy [24].

3.2. Relapse rates after drug withdrawal

Among other clinical implications of MH, we should consider the relapse rate of the disease after drug withdrawal. The results from the GETAID trials are contrasting. In this regard, Louis et al. recently performed a study [25,26] to assess the risk of relapse after discontinuation of infliximab in patients on combined maintenance therapy with immunosuppressors. By multivariate analysis

complete MH was among the factors strongly associated with a decreased risk of clinical relapse after infliximab withdrawal; this finding is in contrast with an older study by Lèmann (a randomized, double-blind, controlled, non-inferiority withdrawal trial in CD patients in long-term remission on azathioprine), in which the presence of ulcerations at ileocolonoscopy, before discontinuation of azathioprine, was not predictive of clinical relapse [27].

3.3. Quality of life

Similarly, another end point that needs to be taken into account is quality-of-life benefit. A sub-study of the EXTEND trial (a randomized, double-blind, placebo-controlled trial that was performed to evaluate adalimumab for induction and maintenance of MH in 135 adults with moderate to severe ileocolonic CD) showed, at multivariate analysis, the significant predictive effects of week 12 endoscopic assessment scores for quality-of-life outcomes at week 52 [28]. Interestingly, the EXTEND trial had MH as primary end point of the study.

3.4. Colorectal cancer

Finally, particularly for UC, it is important to consider that there is a clear relationship between the grade and chronicity of the inflammation in the colon and the risk of colorectal cancer. Indeed, greater reduction of inflammation, as demonstrated by MH, may be associated with a decreased risk of colorectal cancer [29]. In this regard, in a study of patients with long-standing UC who were undergoing surveillance colonoscopy, in univariate analysis the degree of colonoscopy and histologic inflammation correlated with the risk of developing colorectal neoplasia. By contrast, in multivariate analysis only histological inflammation was an important determinant of risk [30]. In the follow-up study, the multivariate analysis also showed that UC patients who had a macroscopically normal colon had a colorectal cancer risk similar to that of the general population [31].

3.5. Ability of a drug to induce MH: is it the only parameter to impact the clinical course of IBD?

Three recent studies on endoscopic MH have provided strong evidence that the attainment of this end point leads to improved clinical outcomes [32–34]. The first study, by Ardizzone et al. [32], was a 5-year natural history study of 157 UC patients who were part of a 25-year hospital-based inception cohort and treated with their first course of corticosteroids. The authors used a modified Baron index to assess baseline endoscopic activity (with MH defined as a score of 0) and reported that a lack of MH at 3 months after commencement of the first course of corticosteroids was the only variable associated with an increased risk of use of immunosuppressive therapy, hospitalization, and colectomy at 5 years of follow-up at multivariate analysis.

3.6. Altogether, corticosteroids in IBD appear incapable of maintaining clinical remission and, even more, to maintain MH

The second study, a combined analysis of ACT 1 and 2, as well as the ACT 2 extension study by Colombel et al. [33], addressed the impact of the degree of endoscopic MH at week 8, as defined by the Mayo endoscopic sub-score, on a variety of future clinical outcomes among both infliximab-treated ($n = 484$) and placebo-treated ($n = 244$) patients. For the end point of time to colectomy, infliximab-treated patients with lower endoscopy sub-scores at week 8 were more likely to be colectomy-free by week 54 (95% for a score of 0, 95% for 1, 87% for 2, and 80% for 3; $p = 0.004$); however, this trend was not observed in placebo-treated patients. For symptomatic remission at week 30 or 54, there was a clear and highly significant separation between all 4 strata of endoscopic sub-scores among both infliximab-treated and placebo-treated patients, with lower endoscopic sub-scores leading to higher rates of symptomatic remission [week 30: infliximab-treated patients (71% for 0, 51% for 1, 23% for 2, 10% for 3) and placebo-treated patients (55% for 0, 38% for 1, 15% for 2, 6% for 3); week 54: infliximab-treated patients (73% for 0, 47% for 1, 24% for 2, 10% for 3) and placebo-treated patients (67% for 0, 39% for 1, 9% for 2, 4% for 3); $p < 0.0001$ for all analyses]. Similar results with a highly significant separation between all 4 strata of endoscopic sub-scores among both infliximab-treated and placebo-treated patients were observed for the outcomes of corticosteroid-free remission, corticosteroid-free symptomatic remission, median corticosteroid dose at week 30 or 54, MH at week 30, and sustained MH at weeks 30 and 54. Interestingly, although these analyses restricted to infliximab-treated patients who achieved a clinical response at week 8 yielded similar trends in terms of outcomes, restricting the analyses to infliximab-treated patients who achieved clinical remission at week 8 revealed no difference in the outcomes between patients with an endoscopic sub-score of 0 or 1.

The third study, by Meucci et al. [34], followed 61 patients who achieved clinical remission after 6 weeks of combined oral and rectal mesalazine therapy for up to 1 year and defined MH as a Mayo endoscopic sub-score of r1. The authors observed rates of clinical relapse at 1 year of 80% versus 23% in patients without and with MH. Furthermore, MH was the only independent predictor of clinical relapse. It is worth noting that in this study the 1-year clinical relapse rates were similar for patients with endoscopic sub-scores of 0 or 1.

As underscored by the authors of the studies here mentioned, the simple description of the ability of a drug to induce MH is not the only parameter to impact the clinical course of the patient's disease and of the various forms of disease to be managed. The fact is that no controlled studies are available on the outcome of different therapeutic strategies based on clinical versus endoscopic parameters. In particular, for example, the achievement of early endoscopic response to corticosteroids can be used to predict the risk of negative clinical outcomes, such as hospitalizations, immunosuppressor use, and even colectomy; it also may suggest routine monitoring of endoscopic response after the end of treatment for active disease and early introduction of more aggressive treatments, such as immunosuppressors, in those patients who do not achieve MH, although this approach requires validation in prospective trials.

3.7. Endoscopic assessment of MH: a helpful tool to guide therapeutic decision-making?

It is certainly useful to consider the endoscopic assessment of MH to guide therapeutic decision-making, especially before starting, altering the dose, switching or stopping expensive anti-TNFα therapy. In this context, a cross-sectional cohort study was performed to assess the frequency and determinants of management change in all children who underwent endoscopy for the surveillance or evaluation of established IBD. The study showed that patients with mucosal injury were more likely to have a management change than those with MH (80% vs. 20%; $p < 0.001$), while blood work and patient's symptoms before the procedure did not predict management outcome [35].

More recently, the STORI trial, mentioned above, focused on the (endoscopically-guided) decision making in stopping anti-TNFα therapies. This prospective study was performed to assess the risk of relapse after infliximab therapy was discontinued in patients on combined maintenance therapy with antimetabolites.

At multivariate analysis, risk factors for relapse included male sex, the absence of surgical resection, leucocyte counts >6.0 × 10(9)/L, levels of haemoglobin ≤145 g/L, CRP ≥5.0 mg/L, and faecal calprotectin ≥300 μg/g. Patients with no more than 2 of these risk factors (approximately 29% of the study population) had a 15% risk of relapse within 1 year. In this context, the same multivariate analysis showed that endoscopic MH, assessed through CDEIS (=0), identified a subgroup of patients in whom, when combined with a low CRP, normal haemoglobin and clinical history, endoscopic MH could predict sustained remission in about 80% of them [25,26].

Finally, the endoscopic evaluation is already commonly performed within a year of ileocolic resection and recommended by some guidelines to guide prophylaxis in the setting of the postsurgical recurrence of CD [36].

Some studies pointed out that the severity of the endoscopic lesions at the start is more relevant than MH in affecting the clinical implications of the end points. In fact, a recent phase IIIB, multicentre, open-label clinical trial, performed to evaluate the efficacy of certolizumab pegol in improving endoscopic lesions in patients with active ileocolonic CD, showed that the rate of complete MH was relatively low (8% at week 54), because of the severity of the intestinal lesions at baseline (more than 90% of patients having deep ulcerations) [37].

Furthermore, it is important to consider that patients understandably dislike invasive procedures such as endoscopic procedures. At present, the assessment of MH represents a target difficult to be reached, which either way provides better support for a therapeutic decision than does clinical judgement alone.

3.8. Advanced endoscopic imaging to assess MH

Considering the importance of endoscopy in assessing MH in order to assist therapeutic decision-making, it becomes obvious that there is a need for new and more advanced endoscopic imaging techniques for better characterization of mucosal inflammation.

With regard to the screening for colorectal cancer, pancolonic chromoendoscopy and targeted biopsies of suspicious lesions represent already a more effective surveillance method in IBD than taking only multiple non-targeted biopsies; similarly, magnification chromoendoscopy improves the detection of pre-neoplastic and neoplastic mucosal changes [38].

On the other hand, in the context of the assessment of mucosal inflammation, magnification endoscopy has the potential to predict relapse in patients with quiescent disease [39]. Furthermore, dyeless chromoendoscopy offers the potential to replace conventional dye-based chromoendoscopy for lesion detection and assessment of disease severity in IBD: i-scan significantly improves the diagnosis of severity and extent of mucosal inflammation in patients with IBD [40].

Confocal laser endoscopy can also detect more neoplasms in surveillance colonoscopy of patients with IBD and can predict neoplastic changes with high accuracy; furthermore, it has been demonstrated that confocal laser endoscopy can reliably predict inflammatory activity in IBD during ongoing endoscopy, even in patients with macroscopically uneventful mucosa [41,42]. Endocytoscopy harbours the potential to accurately determine various inflammatory mucosal cells during ongoing endoscopy in IBD and thus the severity of the inflammation [43].

These emerging imaging modalities enable the endoscopist to detect and characterize more pre-neoplastic and neoplastic lesions and to predict mucosal inflammation more precisely as compared to conventional white-light endoscopy, thus opening new avenues for diagnostic and therapeutic strategies in IBD.

4. Future perspectives: from mucosal healing to deep remission

4.1. The new concept of "deep remission"

A new therapeutic target that is emerging in the scientific community is the concept of deep remission, which has already been defined as the combination of clinical remission (CDAI < 150) in the absence of the residual use of steroids, along with more objective variables, such as negativity of the indexes of biological activity of the disease (CRP), and in association with MH.

While deep remission is an emerging concept in IBD, in rheumatoid arthritis, treatment goals no longer include symptom control alone but also alteration of the biological processes underlying synovial inflammation and progressive structural destruction, thereby preventing structural joint damage and functional decline [44]. Achieving deep remission (clinical remission and MH) might be the only way to alter the course of the disease in IBD patients.

4.2. Deep remission and Crohn's Disease

From the EXTEND study, post hoc data about deep remission in CD, defined here as clinical remission (CDAI > 150) together with MH, can be derived. Deep remission at 1 year was significantly more common in patients treated continuously with adalimumab than in those treated with placebo, although only recorded in 19.4% of patients. Quantifying the magnitude of the difference at 1 year corresponds to an OR of 30.4; in the third month, however, there is a carry-over effect of induction, so that even in the arm maintaining placebo 9.8% patients meet the criteria for deep remission [28]. In EXTEND, patients achieving deep remission at week 12 had reduced rates of hospitalization, fewer dose escalations, better quality of life and improved work productivity and activity [45].

Therapeutic interventions in the past, considering those provided in the pivotal trials for approval of biologic drugs, were aimed at the advanced stages of CD. In this context the possibility of a striking impact on long-term disability is reduced, because complications and disability in advanced diseases are in fact already present, and even the most effective drug is likely to have little effect and little capacity to change the clinical course of the disease. Recent evidence suggests that when therapeutic intervention occurs early in the disease, it is more likely that the disease can be treated positively [46].

On the other hand, the selection of patients and treatment is flexible and should always take into account the history and total weight of disease, in the light of a perspective which includes the following: considerations of the risk/benefit ratio, preference and expectations of the patient, and the ratio between these elements and the severity and complexity of the disease.

The top-down strategy, evaluated in the "step-up/top-down" trial, has proven to be more effective than the step-up strategy in inducing and maintaining remission in steroid-free patients 1 and 2 years after enrolment. In this study, 2 years after randomization, complete MH was observed in 73% of patients in the top-down group compared with only 30% of those in the step-up group [47].

Similarly, major effectiveness in the early phases of the disease (as identified in the subgroups with shorter duration of disease at diagnosis) has been demonstrated by post hoc analysis of the CHARM study, including adalimumab. In fact, in this study, patients with duration of disease of less than 2 years presented a remission rate of 51% in the treatment arm vs. 17% in the placebo arm ($p = 0.014$), while in patients with a disease duration between 2 and 5 years the remission rate was 44% in the treatment arm vs. 11% in the placebo arm. Finally, in patients with disease duration of more than 5 years the remission rate was 35% in the treatment arm vs. 11% in the placebo arm [21]. The same results were replicated,

despite the small numbers and the evaluation of a more difficult target to achieve than MH, in post hoc analysis of the EXTEND trial with adalimumab. In this study the reduction of risk of relapse compared to placebo is lost for groups with longer duration of disease and the results are strongest for diseases of less than 2 years.

In this study, the MH rate was 44% in the group with duration of disease of less than 2 years, 40% in the group with disease duration between 2 and 5 years, and 21% in the group with disease duration greater than 5 years [48]. Also regarding deep remission, another post hoc analysis of the EXTEND study shows a trend towards a significant reduction in frequency, going from the group of subjects with disease duration of less than 2 years (deep remission in 33% of patients) to those with over 5 years of disease duration (deep remission in 16% of patients) [20].

4.3. The "Lèmann Score"

CD may have an extremely variable course, and therefore an instrument to measure cumulative structural damage, predicting long-term disability, is needed. Beaugerie et al. in 2006 identified prognostic factors associated with a more disabling course of disease [49]. Recently, IPNIC [50] developed a score, called "Lèmann score", which should take into account damage location, severity, extent, progression and reversibility, as measured by diagnostic imaging techniques and history of surgical resection. This score is expected to be able to portray a patient's disease course on a double axis graph, with time as the *x*-axis, bowel damage severity as the *y*-axis, and the slope of the line connecting data points as a measure of disease progression. This instrument could be used to assess the effect of various medical therapies on the progression of bowel damage, i.e. using accelerated step care in the case of severe CD.

Sustained deep remission is an important goal for improving outcomes in this chronic, progressive disease, and it is an achievable goal in today's clinical practice. We can already tailor our approach to each patient, for optimum, individualized management. In the near future, we will be further guided by new treatment strategies and indices of prognosis and damage.

4.4. Deep remission and ulcerative colitis

With regard to UC, MH is also an important predictor of long-term as well as of short-term outcomes. Sandborn et al. [51] demonstrated that infliximab-treated patients with endoscopic scores of 2 or 3 at week 8 were significantly more likely to progress to colectomy at week 54. Colectomy-free probability at week 54 was 95%, 95% and 80% in patients with week 8 endoscopic scores of 0–1, 2, and 3, respectively. These findings are supported by the previous work by Froslie et al. [15], in which patients with MH at 1 year were less likely to undergo colectomy during the subsequent 5-year follow-up period.

The achievement of deep remission might be the only way to alter the course of IBD. However, there is no validated definition of deep remission in IBD, even though an attempt was made recently for CD. In UC, deep remission could be defined as clinical remission associated with complete MH. In the near future, the concept of deep remission may evolve, with the inclusion of histological remission in UC and transmural healing in CD. However, the ability of the available drugs to induce and maintain deep remission in IBD needs to be assessed in large disease-modification trials.

5. Conclusion

It is becoming clear that treatment for clinical remission alone may not be an adequate approach for IBD in the long term. There is a growing body of evidence that the attainment of MH in IBD is auspicious, as it leads to a number of improved clinical outcomes. MH, which is a new concept concerning the goal of deep remission, and rarely achieved with traditional drugs, can now be achieved and maintained by means of biological drugs. Current evidence suggests that the achievement of MH might significantly change the course of the natural history of IBD and should represent an objective end point of future therapeutic trials, particularly for colonic diseases.

However, until future prospective studies identify and validate a single gold standard MH scoring system (separately for CD and UC) that is relatively easy to use and predictive of clinical outcomes, establishing a critical time point for measuring MH, and demonstrating that treatment to MH can change the natural history of these diseases, MH will remain an admirable secondary goal in the treatment of IBD patients.

Conflict of interest

None declared.

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