REVIEWS

Mucosal healing in Crohn's disease: Relevance and controversies in real life clinical practice

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ABSTRACT

Mucosal healing is a recent and emerging concept in Crohn's disease management that has been associated to a good prognosis and therefore it has been also proposed to be a clinically relevant therapeutic endpoint. On the other hand, there are many controversial aspects about this concept, and some clinically relevant difficulties that may preclude clinicians from moving this concept from clinical trials to clinical practice in many cases. This review is focused on both aspects of mucosal healing in day-to-day real life clinical practice.

Key words: Crohn's disease. Inflammatory bowel disease. Mucosal healing.

INTRODUCTION

Digestive endoscopy has always been an essential tool in the diagnosis and monitoring of inflammatory bowel disease (IBD), including Crohn´s disease (CD) and ulcerative colitis, by the nature of both the disease and the physicians who, as gastroenterologists, usually have a quick and easy access to endoscopic procedures.

However, the role of endoscopy in the management of CD has not been entirely clear for many years, since more importance has been given to the clinical features.

The mere presence or absence of symptoms has classically been considered as the treatment goal, used to make decisions regarding treatment changes, and it has also been considered as an endpoint for clinical research; moreover, current definitions of response, relapse or recurrence are based only on clinical features (1). The emerging relevance of endoscopic monitoring of CD is a recent approach to the disease management. During the last decade, biologic therapies have brought to clinicians new scenarios and new concepts about the disease and its management, including "mucosal healing" (MH) as a new item to be taken into account. Disappearance of the mucosal lesions that do define the disease can be achieved in a significant proportion of patients receiving biologic therapies. Research has been conducted during the last years to clarify the clinical relevance of MH, highlighting the importance of an early and aggressive therapeutic approach in order to have the opportunity of changing the natural course of the disease (2,3). Interestingly, biologics are not the only group of drugs that can provide MH. This feature has been shown to happen in a variable proportion of cases treated with methotrexate, thiopurines or even steroids (4-8).

Evolving concepts about CD management have been rapidly moving from paying attention to symptoms or complications of the disease, to a proactive attitude in order to prevent those symptoms and complications by aiming steroid-free clinical remission and, later on, searching for a truly deep remission that includes not only the already mentioned steroid-free clinical remission, but also some other relevant items like MH, but also normalization of C-reactive protein or other serological surrogate markers of inflammation, improvement in quality of life, growth in children or decrease in hospitalizations or surgeries (9-11).

Despite it seems true that the achievement of MH is an important landmark, and that it should be considered as a necessary endpoint for clinical research, including

clinical trials designed to prove the efficacy of pharmacological treatments for CD, it is also true that it is hard to move this concept of MH into day-to-day clinical practice (11,12).

The purpose of this review is not only to address the benefits of the achievement of MH that could justify a therapeutic effort or even a MH targeted therapeutic approach for CD (13), but also to address the difficulties that the clinicians face when trying to incorporate the concept of MH into daily clinical practice.

MUCOSAL HEALING IS IMPORTANT IN CROHN'S DISEASE MANAGEMENT

An effort should be made to avoid addressing this issue from a merely endoscopic point of view, or even focused only on the results of the different clinical trials that have added relevance to the concept of MH. It is necessary to put MH in its proper clinical context to understand its importance in the management of CD.

Crohn´s disease is a chronic and disabling condition, and the current knowledge about its natural history shows that the intestinal inflammatory activity leads to structural damage that can be irreversible despite an adequate control of the acute inflammation. Since clinical outcomes are poorly correlated with endoscopic features, the mere control of the symptoms may not be enough to keep the patient away from the long term consequences of the disease (14-16). Moreover, early stages of the disease are predominantly acute and inflammatory instead of chronic and fibrotic, and that justifies the current thinking about a more precocious and intensive treatment that may have greater therapeutic impact and perhaps the possibility of changing the course of the disease by preventing bowel damage, functional impairment, or complications such as fistula, perforation, abscess or stenosis (9,15,17,18). As a matter of fact, current recommendations emphasize the importance of identifying those patients who are at risk of a poor outcome to be treated early and aggressively (1). Interestingly, currently available tools to predict the outcome of the disease in each case are scarce and clinically based variables, such as the age or the presence of perianal disease, and even though they should be taken into account when determining the initial therapeutic strategy, it seems clear that clinicians are in the need of better tools to monitor activity of the disease, response to therapies or even to be able to predict the outcome of the disease in a single patient (1,3,19).

Mucosal healing and clinical outcome

Data suggesting that MH is associated with better outcome are easy to find. Moreover, data regarding the correlation between the therapeutic approach and the likelihood of achieving MH and steroid-free clinical remission is also of the highest quality and reliability, and suggest that early and aggressive treatment in CD is associated with higher rates of clinical remission and MH.

A European trial followed 133 patients recently diagnosed with CD; they were distributed in two cohorts: The first one received conventional and stepwise therapeutic approach ("Step-Up" cohort) and the second one received combined therapy with thiopurines and anti-TNFα biologic therapy from diagnosis ("Top- Down" cohort). After 2 years of follow-up, patients in the "Top-Down" cohort achieved better control of the disease, not only in terms of steroid free clinical remission; those patients who received the earlier and more intensive treatment strategy achieved very high rates of MH that were around 70 % (20). Interestingly, the follow-up of these two cohorts was prolonged for two years more, up to four years. This extension study reveals that patients who reached MH had a better outcome and were able to remain in steroid free clinical remission in a much higher proportion. In fact, MH at second year of treatment was the only predictive factor for steroid free clinical remission at the fourth year of follow up (21). This data suggests that MH is a useful marker of good prognosis in both short and long term.

Another international and multicenter clinical trial called SONIC randomized more than 500 patients recently diagnosed with CD to receive monotherapy with infliximab, azathioprine or combination of both. After 26 and 50 weeks of follow up, it was found that those patients receiving the most aggressive and early treatment were most likely to achieve better control of the disease, in terms of steroids-free clinical remission, and that happened in more than a half of the patients in this combotherapy group. Moreover, this group of patients was more likely to achieve MH, and almost half of the patients who received the combo therapy achieved it in contrast with both monotherapy groups (30 % in the infliximab group, 16 % in the azathioprine group). In other words, a more aggressive early therapeutic approach was followed by a better control of the disease and a higher probability of achieving MH (22). A recently published *post-hoc* analysis of the same trial showed that not only MH, but also endoscopic response (defined as a decrease from baseline in endoscopic activity scores of at least 50 %) at week 26 of treatment identified those patients who were most likely to be in steroid-free clinical remission at the end of the follow up. Even though this cut-off value should still be validated, it seems that a significant improvement in the mucosal lesions is enough to be a marker of good prognosis (23).

On the other hand, it is important to acknowledge that symptoms relief is not a useful tool to identify those patients who have achieved MH. In fact, the correlation between MH and clinical features is known to be poor. Some previously performed studies failed to find a signifi-

cant correlation between different endoscopic scores of inflammatory activity of the disease and the clinical features (24-26). Moreover, a recent *post-hoc* analysis of the SONIC study showed that the currently used and widely accepted score to assess CD activity from a clinical point of view (Crohn's disease activity index, CDAI) is not a reliable measure of the underlying endoscopic inflammation. In fact, the positive and negative predictive value of CDAI to detect MH using 150 as a cut-off for CDAI (which is the commonly used threshold for clinical remission) were only 65 % and 53 %, respectively (16).

Mucosal healing, hospitalizations and surgery

Data suggesting that MH, beyond mere clinical response, changes the course of the disease are available since the early nineties, even before biologics were available. The IBSEN study, a Norwegian cohort of 354 patients with ulcerative colitis and 141 patients with CD were followed for 5 years, between 1990 and 1994, concluded that MH was a marker for good prognosis since MH was associated with less hospitalizations or surgeries (27). Later on, a *post-hoc* analysis of the ACCENT trial tried to assess the impact of infliximab in the mucosal lesions and the impact of the MH achievement in the disease outcome. Patients that achieved MH at week 10 did not need to be hospitalized during the follow up, while up to 46 % of those patients who did not reach MH needed to be admitted to the hospital at some point during the follow up (28,29).

Some other studies, carried out in real life clinical practice, have yielded results that reinforce this idea from different points of view. Thus, the Belgian experience from a single center in the use of infliximab in clinical practice includes 614 consecutive patients with a mean follow up of 55 months, and showed not only the usefulness of this treatment to induce MH, but also that MH is a marker of good prognosis that is associated with lower rates of hospitalizations and surgeries. On the other hand, 39 % of the patients who did not achieved MH underwent surgery compared with 14 % surgical rate of the group of patients who did achieve MH or at least endoscopic response (30,31).

Mucosal healing, quality of life and costs concerns

Taking into account the patients perspective, and that the achievement of MH may need patients' acknowledgement and collaboration regarding increase of endoscopic procedures or immunosuppressive load, it seems reasonable to address the impact of MH in the quality of life of the patients. Even though the health related quality of life is deeply influenced by some other items that have been already addressed in this text, such as hospitalizations, surgeries or symptoms, there are some studies focused on

other areas of the quality of life by measuring *ad-hoc* predefined and validated scores like the inflammatory bowel disease questionnaire (IBDQ).

The EXTEND trial was designed to evaluate the impact of adalimumab on mucosal lesions in CD patients. A sub-analysis of this trial showed that those patients who achieved early deep remission (clinical remission and MH at week 12) did better until the end of the follow up at week 54, and needed less hospitalizations, treatment adjustments or surgeries. Moreover, those patients who reached early deep remission obtained better figures in the IBDQ: At the end of the follow up, 2/3 of the patients who achieved early deep remission at week 12 showed a significant improvement in the IBDQ score, compared with 1/3 of the patients who did not achieve the early deep remission (32,33). This study also included a costs analysis concluding that those patients who achieved early deep remission cost less money at the end of the follow up, since the costs of hospitalizations, surgeries, etc. overwhelmed the pharmacological expenditures in the other group. This means that, in addition to the clinical benefits for patient, early deep remission represented a mean of 10,360 $ saving per patient between weeks 12 and 54 (34) . This economic issue has been specifically addressed in a decision analytic model comparing two alternative treatment strategies in the United States: In the clinical response arm, patients not in clinical remission at year 1 are dose-escalated. In the MH arm, patients with persistence of mucosal ulcerations at year 1 are escalated irrespective of clinical symptoms. Patients remained at risk for hospitalization and surgeries while they had active disease, and the horizon examined was 2 years. This theoretical model demonstrate that MH as an endpoint is a cost-effective strategy in CD initiating biologics. Whether or not these conclusions can be assumed in other countries with different health care systems should be individually evaluated (35).

A recently published Spanish study was specifically designed to assess the impact of MH in the quality of life; it was a prospective study that enrolled 115 patients, and the health-related quality of life score (HRQOL) was used to evaluate if the achievement of the MH was followed by a normalization of the IBD patients' perception of health. Finally, this study showed that as much as 80 % of patients normalized HRQOL score when MH was achieved. Therefore, MH by itself is associated with a normalization of the perception of health by most IBD patients independently of treatment. However, a significant group of patients did not achieve restoration of HRQOL, which reinforces the necessity of a global care addressed to all patient concerns to achieve patients' complete health restoration (36).

Mucosal healing and risk of relapse after drug withdrawal

Given the hard economic situation that triggers the health care system of many countries, payers and gov-

ernments claim for a more affordable way of using anti-TNFα biologic therapies, which may include stopping them once the clinical remission has been achieved and maintained for a reasonable period of time. On the other hand, clinicians are in the need of some kind of data supporting a more restrictive use of different therapies. Unfortunately, data regarding safety of drug withdrawal in this clinical setting is scarce (37). The most reliable data comes from a randomized clinical trial in which authors assessed the risk of relapse after infliximab therapy was discontinued in patients on combined maintenance therapy with antimetabolites and identified factors associated with relapse. One of the factors that can predict the outcome after infliximab withdrawal was the presence of MH. As a matter of fact, as much as half of the patients enrolled suffered a clinical relapse, although patients at low risk of relapse could be identified according to a number of risk factors that include MH among others such as the absence of previous surgical resections, the male sex, anemia, high leukocyte count, elevated CRP, high fecal calprotectine or infliximab trough levels above 2 mg/L. Patients with no more than 2 of those risk factors had 15 % of relapse within one year (38). Taking into account the most important limitation of this study, which is the lack of endoscopic follow-up, the reliability of this strategy in maintaining long term deep remission cannot be evaluated.

Mucosal healing and post-surgical recurrence

Post-surgical scenario is, by far, the clinical setting in which MH has the most clearly defined role, clinicians acknowledge its relevance and systematic performance of an endoscopic procedure to verify MH after a surgical resection is widely spread; moreover, a MH based strategy is currently accepted in this post-surgical clinical setting.

The Rutgeerts score classifies patients who have undergone an ileocecal resection according to their risk of clinical relapse and based on endoscopic findings in the neo-terminal ileum six months after surgery. Thus, it considered that those patients with no lesion in the neo-terminal neoileon (i0) or with few lesions (< 5 aphthous ulcers, i1) have less than 10 % likelihood of clinical recurrence in 10 years (39). On the other hand, patients who have severe endoscopic lesions like aphthous diffuse ileitis (i3) or the presence of diffuse mucosal inflammation with ulcers, nodules or stenosis (i4), are the most likely to suffer clinical recurrence (up to 70 % in the first year) or to be reoperated. Intermediate stages, like the presence of more than 5 isolated aphthous lesions on unaffected mucosa, or the presence of skip areas of larger lesions on unaffected mucosa, or even the presence of ulcers at the anastomotic ring (i2), seem to have up to a 40 % probability of clinical recurrence at five years. Taking all of that into account, and despite this Rutgeerts score has never been

validated or evaluated in any other clinical scenario, it is accepted that those patients who present the more severe endoscopic findings should receive immunosuppressive therapy, even in the absence of symptoms (40,41).

MUCOSAL HEALING IS NOT AN EASY ENDPOINT IN CLINICAL PRACTICE

Even though literature about MH and its beneficial effects is profuse, and that the clinical relevance of MH is widely accepted from a clinical point of view, there are many limitations and controversial aspects that preclude clinicians from incorporating the MH concept into current daily clinical practice. In fact, and in spite of all the favorable data that has been previously described, MH concept has not been incorporated to the current guidelines of management of the disease. Despite the already known poor correlation between clinical and endoscopic outcomes, no other therapeutic goal beyond the mere clinical remission has been clearly and universally accepted.

Discordance between mucosal healing and clinical symptoms

One of the reasons that may explain that MH remains far from the clinical practice in many cases could be the puzzling lack of correlation between clinical and endoscopic activity: There is a group of patients that improve from a clinical perspective although mucosal lesions remain present; this group of patients are similar to those that, in clinical trials, achieve clinical remission but not MH (22,31,42). Moreover, this group of patients with symptoms relief but with no endoscopic improvement can be found in observational studies and some of them showed lack of correlation between endoscopic and clinical activity indices or CRP as a serum surrogate marker for active intestinal inflammation (24,25). One of the most outstanding evidence about the lack of usefulness of clinical assessment of the disease to predict the achievement of MH comes from a sub-analysis of the SONIC trial, that included 188 patients with endoscopic activity that were randomized to receive either infliximab monotherapy, azathioprine monotherapy or combo of both; after 26 weeks, only approximately half of the patients in clinical remission (CDAI < 150) also had normal CRP or MH, and the positive or negative predictive value of CDAI 150 to predict MH were between 50 and 60 % (AUC = 0.5), showing the lack of reliability of the clinical evaluation as a surrogate marker for intestinal inflammation (16). On the other hand, it is also true that there are patients who remain symptomatic regardless of having achieved MH. In the previously mentioned "Top-Down/Step-Up" study, the number of patients in clinical remission was higher than those with MH in the "Step-

Up" cohort, while in the "Top-Down" cohort the number of patients with MH was higher than the number of patients in clinical remission (20).

Therefore, discordance between clinical and endoscopic situation may be patent and bewildering, makes it hard to understand the impact of both therapies and MH by clinicians who may keep far from adopting the MH concept as a rational therapeutic goal for daily practice.

Definitions of mucosal healing

The great diversity of MH definitions that can be found in literature may be another aspect that may preclude clinicians from moving MH concept from clinical trials to clinical practice. This lack of uniformity in defining what should be a therapeutic goal reduces the reliability of those studies that highlight MH as a marker of good prognosis. The most widely accepted definition of MH is the absence of ulcerated lesions (43), although this definition does not take into account other kind of lesions, slighter but certainly related to IBD such as edema, erythema or stenosis. On the other hand, other studies define MH as low figures in endoscopic activity scores, usually MH is considered if the CD Endoscopic Index of Severity (CDEIS) remains below 4 points; even though this is a very low value, this approach also has some limitations: Endoscopic scores are not easy to perform, are time-consuming and can not be routinely calculated in clinical practice, and that keeps MH far from clinical practice again. Moreover, this cut-off value is arbitrary and accepts the presence of some lesions that can even be somehow ulcerated. Finally, due to the characteristics of endoscopic activity scores in IBD, they tend to under-estimate the severity of the findings when they are short in extent, or over-estimate it when the disease extension is large (26,32,43,). Taking all of this into account, an endoscopic index based definition of MH could not be easily adopted for daily use in clinical practice.

Practical issues in mucosal healing applicability

There are many practical issues regarding MH applicability in real life clinical practice that remain unclear; most importantly, both how and how often MH should be monitored need to be addressed before incorporating MH to clinical algorithms or decision analysis. These two aspects could be of special interest in those symptom-free patients who are investigated to elucidate if they have achieved MH or not, and may directly affect the feasibility of a MH-based approach in clinical practice.

Ideally, conventional colonoscopy should be the preferred method to monitor the presence or even the persistence of MH through time, but it is an invasive, risky and expensive procedure that could be hardly accepted by patients or payers. Capsule endoscopy could be an alternative for those cases in which CD affects the small bowel, but there is no validated activity index for capsule endoscopy of the small bowel, and its role for colonic disease is still undefined. It is also an expensive procedure that may have the risk of capsule retention; it is also acknowledged that capsule endoscopy may detect slight lesions that are undetectable by other procedures, but the clinical relevance of these kinds of minor findings remains unclear (24,44-48). A rational alternative to endoscopy could be radiologic procedures, particularly magnetic resonance of the intestine: It is a non-invasive procedure that has shown to have good correlation with endoscopic findings and it has shown to be useful in detecting extra-luminal complications of CD or in those cases of CD with incomplete colonoscopies; its correlation with the CDEIS has led to design and validate an *ad-hoc* radiological activity index of CD. On the other hand, clinical applicability of magnetic resonance of the intestine in this specific clinical setting has still not been addressed, although it is very likely that the widespread of its use would provide more data about its reliability and clinical impact in this particular scenario (19,50). Finally, fecal markers may correlate with clinical course of the disease and detect subclinical inflammation and can be useful in detecting, monitoring or even in predicting response or outcomes in IBD (3,51). Moreover, fecal calprotectine has been suggested to be a good surrogate marker for detecting MH, although the numbers for positive or negative predictive values are relatively low for CD, and those beneficial features of fecal calprotectine should still be confirmed in clinical practice (52-54).

The other practical issue regarding real life applicability of MH is the periodicity of screening; in other words, how often should the asymptomatic patient undergo an imaging procedure to rule out the presence of asymptomatic activity of the disease. Obviously, it would depend on the selected procedure and its associated risks, tolerability and acceptance.

Until these two issues are clearly defined, it will be hard for clinicians to discuss with the patient or to adopt an MH targeted strategy.

Mucosal healing and safety concerns

Finally, other issues that also limit the adoption of MH as a therapeutic goal in real life clinical practice are safety concerns associated to the increase of immunosuppressive load. Even though MH has been achieved with mainly most of the available therapeutic alternatives, not only biologics, it is also true that no therapeutic option guarantees the achievement of MH since MH rates reached with every different pharmacological alternative is far from 100 % (3).

Once again, this controversial issue is especially relevant in those asymptomatic patients whose immunosup-

pressive load could be enhanced seeking for MH, since the risks of therapy related complications raise but the probabilities of achieving MH may remain uncertain. A recently published retrospective study about this specific issue showed that a MH-based approach only achieved this goal in a limited proportion of patients (55).

The higher immunosuppressive load is associated with a higher risk of developing opportunistic or serious infections (56). Regardless of the fact that clinical trials assessing the usefulness and safety of all different biological therapies in CD, irrespectively of the association of immunosuppressants, showed no increased risk of serious infections, it is also true that all these trials are short termed, and this data is hardly applicable to a life-long disease (57). Moreover, both patients and clinicians are concerned about the risk of malignancies that may be associated to immunosuppressive drugs used in IBD. It is true that neither thiopurines nor biologics increase the risk of solid tumors in both randomized controlled trials and observational studies including registry studies (58-61). In spite of that, it is also known that the higher immunosuppressive load may be associated to the higher risk of malignancies, and recent data suggest that combo therapy could be associated with a higher risk of developing any kind of tumours (62). As a matter of fact, there is no doubt about this association regarding lymphoproliferative or myeloid disorders (63,64), non-melanoma skin cancer (65-69) and probably abnormal cervical cytology or cervical dysplasia (58,70,71). A rare and fatal type of lymphoma, the hepato-splenic-T-cell lymphoma, has been reported mainly in young males under combo therapy, and that is the reason why the European Crohn's and Colitis Organization advocates for monotherapy in those cases (1).

In summary, trying to achieve MH may be risky, and there are many safety concerns and recommendations that should be considered when thinking about increasing the immunosuppressive load in the search for MH (19,72).

THE NEAR FUTURE ABOUT MUCOSAL HEALING IN CROHN'S DISEASE

Taking into account not only the referred data about the relevance that MH should have in clinical practice, but also the described limitations that may preclude from moving MH concept from clinical trials to clinical practice as a marker of good prognosis or even as a therapeutic goal by itself, it seems clear that some piece of information is still lacking.

Probably, a more simple and reasonable approach based on endoscopic response, mucosal improvement instead of mucosal complete healing may be enough to provide a better prognosis or to change the course of the disease as it has recently been pointed out: A recently published sub-analysis of the previously mentioned SONIC trial that included 172 patients with mucosal lesions found in the initial endoscopy and who underwent another colonoscopy at the 26th week, showed that a 50 % reduction in the SES-CD may be enough to predict good outcome (steroid free remission at 50th week) (23). Endoscopic response seems a more realistic and feasible therapeutic goal, that is already in the mind of many gastroenterologists since it may help to avoid some of the bewildering and confusing facts regarding MH that have been previously addressed in this text.

Moreover, the correlation between the endoscopic response or remission and the serum levels of biologic drugs may be the key for clinicians to design a rational, individualized and affordable targeted therapeutic strategy (73).

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