MUCOSAL HEALING IN ULCERATIVE COLITIS – THE FOUNTAIN OF YOUTH?

Ulcerative colitis (UC) and Crohn’s disease (CD) are two distinct pathologies commonly described as inflammatory bowel disease (IBD). UC is a chronic condition with frequent episodes of acute exacerbations and remissions. Its etiology and pathogenesis are still poorly characterized, although an aberrant immune response in individuals with a genetic predisposition is recognized (1).

Advances in the diagnosis and treatment of IBD have led to new perspectives on potential therapeutic targets. Recently, the therapeutic objectives have become more ambitious, going beyond clinical and biological remission, and aiming for mucosal healing, deep remission and even histological remission (2). In this way, clinicians aim for the modification of the natural history of the disease and an improvement in the quality of life.

Mucosal healing (MH) is not a new concept. A number of chronic pathologies, such as chronic duodenal ulcers, have MH as their therapeutic endpoint. Relatively recently Korelitz (3) used for the first time the term MH in the context of IBD.

The definition of MH is not universally accepted. In UC this can be either complete or partial (4):

- **Complete MH** involves the absence of friability, ulcerations and erosions in the rectum or colon (Mayo score 0).
- **Partial MH** involves an improvement in endoscopic appearance and the absence of ulcerations with a Mayo score of 1.

These definitions are however imperfect as they rely to a great extent on the endoscopist’s experience and the methods used to improve endoscopic visibility (chromoendoscopy, high contrast imaging which amplifies mucosal details, etc.). Furthermore, there is no consensus regarding the optimal time interval from the commencement of therapy to the assessment of MH (8, 12 or 24 weeks), as well as the interval at which follow-up assessment takes place (5).

MH (the absence of erosions, ulcerations and friability) is a separate concept from „deep remission”, which is defined as the absence of clinical, biological and imaging evidence of inflammation (6). **Histological remission** does not have a standardised definition; histological changes in remission include architectural changes of the crypts and a residual inflammatory infiltrates – a key diagnostic aspect being the absence of neutrophil infiltration (6). A frequently asked question is whether MH can exist without a normal microbiota. Nevertheless, the answer to this requires further investigation and research.

In UC, MH is determined by colonscopic means. The most frequently used endoscopic score is the Mayo score (score 0 = MH / inactive disease; score 1 = the presence of slight erosions or friability) and UCEIS (Ulcerative Colitis Endoscopic Activity Index or the Travis score). The latter has the advantage of a more detailed
assessment of the severity of endoscopic lesions, with more reproducible results (5). Although invasive, endoscopic assessment is relatively cheap and remains the principal method of evaluating and stratifying the activity of the disease, monitoring its evolution and assessing treatment response.

An alternative non-invasive method of assessing MH is the measurement of fecal calprotectin. This correlates not only with the extent of UC (higher values in pancolitis and left-sided colitis compared to proctitis) but also with the activity of the disease. Thus, calprotectin values under 50 μg/g suggest “deep remission”; an average value of 477 μg/g correlates with an acute exacerbation whilst two levels above 300 μg/g predict a future episode of acute flare (6). Many studies have demonstrated the role of calprotectin as a prognostic factor for MH (7,8). Roseth et al (7) demonstrated that a normalization in calprotectin levels correlates with endoscopic healing. Rikanek et al (8) demonstrated that the level of fecal calprotectin correlates not only with endoscopic, but also with histological healing.

The concept of MH as an ideal and final therapeutic target is extremely controversial. MH varies depending to the medical therapy used: infliximab 42-62%, adalimumab 25-47%, golimumab 42-45% and vedolizumab 52-56% (9). In some ways, MH has proven its benefits: a rise in quality of life, sustained clinical remission, a reduction in the use of steroids and immunosuppressants, length of hospital stay, colectomy rates and risk of colorectal cancer down to similar rate to that in the general population (4,10). These would justify the adjustment in medical therapy to reach MH.

In contrast, an escalation in treatment exposes patients to side effects. According to the most comprehensive analysis published in 2016 (11), there is an increased risk (19%) for infections (not necessarily severe as patients are under surveillance) as well as a two-fold rise in the rate of opportunistic infections. This meta-analysis did not identify a rise in the risk of malignancy (possibly due to a short follow-up period) and did not identify significant differences between the different types of biological therapies concerning side-effects.

An additional controversial matter is whether the attainment of MH allows the cessation of medical therapy. The risk of recurrence at 1 year is 58% for patients in clinical remission, 36% in those with incomplete MH and 28% in those with complete MH (6). It is known that the episodic use of anti-TNF agents (‘holiday drug administration’) is associated with a raised risk of immunization, hypersensitivity and loss of effect (12). In contrast, the possibility of attaining an ‘indefinite remission’, the risk of side-effects and raised costs are justifications for cessation of biologic therapy in patients with MH. Recent studies (13) suggest that the treatment of a new flare episode with the same anti-TNF alpha agent that had been interrupted is efficient, leading to remission in 80-92% of cases. A possible explanation for this high remission rate could be the use of an anti-TNF agent in a selected group of patients that are responders to anti-TNF.

In conclusion, MH represents a therapeutic target with multiple benefits in clinical practice. There is insufficient data to make firm recommendations, with the decisions to increase (in order to achieve MH) or interrupt therapy (after complete MH) being case
Mucosal healing in ulcerative colitis – the fountain of youth?

specific, dependent on a risk-benefit analysis and taking in account the patient’s choices. Complete MH does not however signify complete healing of the patient, mandating ongoing careful monitoring efforts. Despite all the recent advances, clinicians must have the wisdom to understand that they continue to treat IBD, not heal it.

Prof. Dr. Cristina Cijevschi Prelipcean, MD, PhD
Lecturer Cătălina Mihai, MD, PhD
"Grigore T. Popa" University of
Medicine and Pharmacy - Iaşi, Romania

REFERENCES

1. Lichtenstein GR, Rutgeerts P. Importance of mucosal healing in ulcerative colitis. *Inflamm Bowel Dis* 2010; 16(2): 338-346.