Editorial

The Concept of Mucosal Healing in Ulcerative Colitis: Time and Reasons for a Reappraisal

Antonio Lopez-Sanroman

Gastroenterology and Hepatology Department and Universidad de Alcalá, Hospital Ramon y Cajal, Madrid, Spain

Corresponding author: Professor Antonio Lopez-Sanroman, PhD, Gastroenterology and Hepatology Department and Universidad de Alcalá, Hospital Ramon y Cajal, E28034 Madrid, Spain. Email: alsanroman@salud.madrid.org

Scientific research has to create labels to define and designate categories; once these categories exist in the intellectual level, they allow us in turn to sort and understand the real world. Scientific language used in these labels has to be precise and needs to be created swiftly, and confusion sometimes will arise during their development. This sense of urgency results occasionally in the selection of inexact or ambiguous terms. It is important to be vigilant and prevent their imprecisions from standing in the way of science.

With the advance of therapeutic devices in inflammatory bowel disease [IBD], measurement of treatment effect has sometimes been arbitrary. Many activity indices were developed without a sound scientific basis, but then rose to become the international standard and to be employed by numerous researchers, if not by all. This success was sometimes due to the simplicity of the indices themselves, or to the lack of better alternatives.

Biological therapies represented a new paradigm in IBD therapy. They proved their ability to induce changes that had not been previously described or appreciated with classic drugs. A new jargon appeared to designate these changes, and was enthusiastically adopted and disseminated by marketing experts. In previous times, patients either did or did not get better; but now new concepts such as ‘deep remission’ or ‘mucosal healing’ suddenly got all the attention. Terminology comes of age when drugs leave behind the artificial world of pivotal studies and come down to the arena of actual patient care. When remission is defined in ulcerative colitis, this clearly marks, both for patients and for caregivers, the ideal target. To achieve remission is the perfect goal of therapy, and any self-respecting drug has to prove its ability to attain remission in a consistent and predictable way.

Endoscopy describes in a more or less standardised way a series of objective and reproducible changes; however, this is not as easy as it sounds, and agreement between endoscopic descriptions is not always straightforward. In the first trials of anti-tumour necrosis factor [TNF] in ulcerative colitis [UC], the index chosen to gauge the endoscopic effects of these powerful drugs in the management of treatment-refractory cases was the one designated the Mayo index, described in the 1980s for a study on salicylates in mild to moderate UC. In its endoscopic sub-index, this index defines Mayo 0 as normal mucosa, and Mayo 1 as the persistence of mild friability, reduced vascular pattern, and mucosal erythema. Endoscopic remission, if understood literally, cannot be anything but the restitution of colonic mucosa to its original aspect. Few war wounds can be accepted, such as fibrous scars, mucosal bridges, or even pseudopolyps, but mucosal elasticity, shine, resilience, and vascular pattern have to come back to normal. However, in the anti-TNF pivotal trials the bar went down, and both Mayo 0 and Mayo 1 were considered to represent mucosal healing. Maybe it was important to ensure that the efficacy of biologicals was adequately represented, but the message sunk in and conventions initially defined and accepted for the initial stages of clinical research, reached real life and went ahead unquestioned.

Nevertheless, something stood out in all these pivotal studies: although it would make sense to consider endoscopic remission as a more difficult target than clinical remission, this was not the case in either the ACT, the ULTRA, or the PURSUIT studies. Also, clinicians very soon started appreciating differences between Mayo 0 endoscopic remission and Mayo 1 endoscopic remission: the latter was a predictor of a higher probability of clinical recurrence.

In this issue of the Journal of Crohn’s and Colitis, Barreiro and coworkers contribute with an elegant prospective longitudinal cohort study in which patients with UC in remission were followed up for 1 year. The authors clearly showed that the probability of relapse diverged significantly between Mayo 0 and Mayo 1 patients, both at 6 and at 12 months of follow-up. This was true for any extension of disease, and was supported by a more frequent need of treatment escalation in the Mayo 1 subgroup. Their methodology is precise, and conforms to the requirements defined both by the original Mayo index description and by ECCO consensus on the definition of relapse. The lack of histological correlation and of calprotectin determinations is a limitation of this study, but is not likely to substantially affect conclusions, and instead opens ways for further research.

In a smaller, retrospective study, also included in this issue of ECCO-JCC, Beal Carvalho et al. describe similar findings, although in their experience this could not be representative of patients with minimal extension of disease [E1-proctitis]. Their definition of relapse was different [need for induction treatment, treatment escalation, hospitalisation, or surgery], which probably explains this minor divergence.
We think that Barreiro et al. are right when they state that their findings ‘support the concept of mucosal healing being defined as an endoscopic Mayo score of 0’. Thus Mayo 1 could be a minimal requirement, but the significance of achieving a Mayo 0 restitution deserves a specific discussion. An additional issue to discuss is that mucosal changes are not always uniform, even less so in treated or long-standing colitis. In general the worst-affected segment is evaluated, as done by Barreiro et al. The recent contribution by Lobatón et al. is an important step in this direction.

Recent consensuses on activity measurement in IBD are still considering traditional indexes, but the importance assigned to other measures, such as patient-reported outcomes and objective measures of activity [including endoscopy], is continuously growing. Although inter-observer correlation is far from optimal, endoscopy is a semiquantifiable exploration, reproducible and accessible to centralised reading. New indexes, such as the Ulcerative Colitis Endoscopic Index of Severity [UCEIS], have to be explored. Medical societies could help ensure their uniform application; in this sense, ECCO will soon include in its website a workshop on UCEIS, which could be an important step towards this objective.

In conclusion, this controversy teaches us a lesson: we should not immediately transfer definitions adopted in pivotal trials, which might be more exploratory than clinically significant, to daily clinical practice. Our patients are not similar to those included in pivotal trials, and neither are our follow-up schedules, our concomitant medications, or our definitions [and the patients’ perceptions] of response, remission, and treatment success. Studies such as those published in this issue of ECCO-JCC show us that clinical judgement is best applied before accepting the hot results of clinical research as the ultimate guides or translating their concepts and jargon into daily practice.

**Funding**

This work was not supported by any funding source.

**Conflict of Interest**

In the past 3 years, the author has served as lecturer, adviser, or both for the following companies: Abbvie, MSD, Ferring, FAES Farma, Shire, Chiesi, Tillots, Falk, and Takeda. In the same period, the author has received research grants from Abbvie, Tillots, and MSD.

**References**

11. Barreiro
13. Boal