ADVANCES IN IBD

Current Developments in the Treatment of Inflammatory Bowel Disease

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Mucosal Healing in Crohn's Disease and Ulcerative Colitis

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G&H How has the definition of mucosal healing evolved?

LP-B For many decades, mucosal healing equaled endoscopic healing. The main change is that, for several years now, histology has been included in the definition of mucosal healing. Thus, mucosal healing is now considered to be endoscopic healing plus histologic healing.

G&H How well does mucosal healing correlate with disease activity in Crohn's disease and ulcerative colitis?

LP-B For decades, we have noticed that there is a large disconnect between symptoms and mucosal healing in Crohn's disease. We know that approximately half of the patients who achieve endoscopic healing will still have some symptoms. In ulcerative colitis, there was a perception that rectal bleeding was very well correlated with mucosal healing. However, symptoms were only very well correlated with endoscopic improvement, which is an endoscopic Mayo score of 0 or 1. On the other hand, if a clinician is more ambitious and is looking at complete endoscopic healing, which is endoscopic remission and an endoscopic Mayo score of 0, or if the clinician is looking at histologic healing, then the same disconnect observed in Crohn's disease is seen in ulcerative colitis, with approximately half of patients having very good endoscopic healing but still having some symptoms.

G&H Overall, what is the current role of mucosal healing in Crohn's disease and ulcerative colitis?

LP-B It is agreed that the presence of severe endoscopic lesions is associated with a poor outcome, although this is supported mostly by indirect evidence. Randomized, controlled trials, which produce the strongest level of evidence, are needed to show whether it makes a difference to use treatment based on symptoms vs treatment based on mucosal healing. Cohort studies and long-term follow-up of randomized, controlled trials have shown that a patient with Crohn's disease or ulcerative colitis who still has endoscopic lesions has a worse outcome than if the patient has endoscopic healing. More data will likely be available within the next few months, as trials addressing this issue have just been completed. One such trial is the STARDUST study, which is comparing a treat-to-target strategy with early endoscopic evaluation vs a routine care maintenance strategy in patients with Crohn's disease who are receiving ustekinumab (Stelara, Janssen).

In summary, I think that all clinicians agree that we should look beyond symptoms and that it is not acceptable anymore to treat only symptoms. However, the key question is whether clinicians should optimize medical treatment to achieve mucosal healing in all patients. Clinicians are starting to do this because it appears that mucosal healing is associated with a worse outcome, such as more surgery and hospitalization.

G&H Should complete mucosal healing be the ultimate treatment goal?

LP-B The importance of treating very severe endoscopic lesions is well known. However, we do not know whether complete endoscopic healing (macroscopically normal mucosa) is needed even though evidence is accumulating to support this target. For this reason, clinicians currently do not systematically optimize treatment in patients with Crohn's disease or ulcerative colitis who have some mild endoscopic lesions. Thus, although mucosal healing is being considered as a target more and more in both clinical trials and clinical practice, so far treating and removing only the most severe lesions is accepted. This means the absence of ulcerations in Crohn's disease and an endoscopic Mayo score of 0 or 1 in ulcerative colitis. In parallel, both the US Food and Drug Administration and the European Medicines Agency require clinical trials to include mucosal healing as a treatment target because that is the most effective way to see whether a drug works and has a real anti-inflammatory effect.

> … in ulcerative colitis, a patient likely already has good mucosal healing after at least 2 months with all agents, whereas in Crohn's disease, clinicians likely need to wait at least 4 months for optimal mucosal healing.

It is also important to keep in mind that mucosal healing is associated with a worse outcome only if it cannot be achieved by medical treatment. If mucosal healing can be achieved with treatment, the patient will have an improved outcome. In the prebiologic era, if a Crohn's disease patient had severe endoscopic lesions before starting treatment, the patient had a worse outcome than a patient without such lesions. However, that does not matter anymore in the biologic era; what matters is whether the patient achieves endoscopic healing or not with his or her treatment. In other words, the presence of endoscopic lesions prior to starting treatment is not important because if the treatment works and heals the mucosa, the patient will have a good outcome.

G&H Are there any predictors of mucosal healing?

LP-B There are no strong independent predictors of mucosal healing, which would essentially be predictors of drug response. We simply know that it is more difficult to achieve mucosal healing in late Crohn's disease. In addition, many studies have shown that it is much more difficult to achieve mucosal healing in the terminal ileum than in the colon.

G&H How can mucosal healing be assessed?

LP-B Currently, endoscopy is not always used, as it is a relatively invasive procedure and is not well tolerated by patients. Thus, clinicians are using many different tools, such as C-reactive protein, calprotectin, ultrasound, magnetic resonance imaging (MRI), and capsule endoscopy. The tools that are chosen depend on reimbursement, access, and disease phenotype. For instance, monitoring of ileal disease and colonic disease is not the same. The decision also depends on the country. Inflammatory bowel disease centers in Germany and Italy often use ultrasound, whereas centers in France frequently use MRI. The main take-home message, however, is that clinicians need to monitor mucosal healing repeatedly and have different options to do so.

G&H What is the optimal time for evaluating mucosal healing?

LP-B After 20 years of experience with anti–tumor necrosis factor (TNF) agents, we know that mucosal healing should be assessed 6 to 9 months after starting treatment for Crohn's disease and 3 to 6 months after starting treatment for ulcerative colitis. However, this guideline, which came from the STRIDE program, was tailored to patients treated with anti-TNF agents. Now that new drugs such as vedolizumab (Entyvio, Takeda), ustekinumab, and tofacitinib (Xeljanz, Pfizer) are available, the optimal timing for evaluating mucosal healing has to be determined for these agents. No trial has compared different timings to assess mucosal healing, and it takes a long time to determine when a patient has reached the peak for such evaluation, as clinicians need to accumulate experience with any new drug. What we know is that in ulcerative colitis, a patient likely already has good mucosal healing after at least 2 months with all agents, whereas in Crohn's disease, clinicians likely need to wait at least 4 months for optimal mucosal healing.

G&H Should mucosal healing be used systematically in clinical practice now? Is it attainable in all or most patients?

LP-B There is enough evidence that shows that leaving severe intestinal lesions is not beneficial, but it is unclear whether one erosion or tumor cell can be left. However, it is agreed that mucosal healing should be assessed in clinical practice for both ulcerative colitis and Crohn's disease. More and more clinicians are assessing mucosal healing; in fact, all clinicians now check it at some point, although we still do not know whether this should be done every 2, 3, or 6 months or even every 1 or 2 years.

The key question is whether mucosal healing can be reached in all patients. Unfortunately, the answer is no. One of the main lessons that we have learned from the last decade is that we are becoming very ambitious in terms of therapeutic goals, but because we are more ambitious, the therapeutic failure rate is increasing. For instance, the maximum rate of complete mucosal healing that can be achieved with the most potent drugs currently available is 15% to 20%. Thus, the vast majority of patients will fail if treatment success is defined as mucosal healing.

G&H How do the current inflammatory bowel disease drugs compare in terms of inducing and maintaining mucosal healing?

LP-B The drugs currently being used can be divided into 2 categories. One consists of corticosteroids, which are used mostly for symptoms rather than for endoscopic healing. All of the other agents being used in clinical practice—including 5-aminosalicylic acid, thiopurine, methotrexate, anti-TNF agents, vedolizumab, ustekinumab, and tofacitinib—are induction and maintenance agents, and so can induce and maintain mucosal healing. Overall, when considering moderate to severe inflammatory bowel disease, immunosuppressants (thiopurine, methotrexate) are less effective than biologics and tofacitinib to achieve mucosal healing. Endoscopic improvement can be achieved in approximately one-third of patients treated with biologics or tofacitinib.

G&H What are the next steps in research?

LP-B One of the next steps in research is to define the optimal target in terms of mucosal healing. Two validated scores, the Nancy Index and the Robarts Histopathology Index, can be used to assess histologic healing in routine practice and clinical trials. Should clinicians always look beyond endoscopic healing and consider histologic healing? In other words, does mucosal healing mean the removal of severe endoscopic lesions, does it mean a normal endoscopy, or does it mean both (ie, normal endoscopy plus normal histology)? This question will be addressed in ongoing trials.

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Suggested Reading

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