

ADVANCES IN IBD

Current Developments in the Treatment of Inflammatory Bowel Diseases

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Utilizing Mucosal Healing as a Treatment Goal in Ulcerative Colitis

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G&H Is there currently a working definition of mucosal healing, as it relates to ulcerative colitis, that can be utilized as a treatment endpoint?

DR Providing a consistent definition of mucosal healing that can be used in study protocols and clinically initially appears simple, but it becomes more complicated with discussion. An experienced clinician will say, “I know it when I see it,” and describe intact bowel mucosa with no erosions and no friability. However, in designing a research protocol, it becomes much more difficult to quantify and standardize the meaning of the term.

Usually, mucosal healing is designated as a secondary endpoint in clinical trials, and the established measures of disease control, including symptom management and cessation of bleeding, remain the primary measures. Once these other endpoints have been achieved, we may examine the bowel and define mucosal healing retroactively, based on how much healing we have achieved in correlation with our primary goals. Investigators have embraced a secondary endpoint of mucosal healing, but as described in the published studies, the endpoint ends up being, in some cases, mucosal improvement, which becomes equated with mucosal healing. Mucosal healing is also sometimes designated as including an inflammation score of 1 on a 4- or 5-point scale. As a result, when we talk about the available evidence for mucosal healing, we need to acknowledge that our current definitions are not consistent and have resulted, to some extent, in flawed data and data analyses.

G&H How can these inconsistencies be addressed for future research protocols?

DR When considering other immune-mediated diseases treated with anti-inflammatories, such as psoriasis, there is no guessing regarding healing. When the skin heals from psoriasis, it is easily recognized, and psoriasis treatments have very little placebo response. In rheumatoid arthritis, researchers employ the Sharp scoring system, which is a measurement of joint degeneration on radiographic imaging.

Measures of mucosal healing in ulcerative colitis (UC) and Crohn’s disease need to reach the same levels of consistency and objectivity, and we need to define what is reproducible and can be measured in some way that we do not end up in confusion. We then need to teach our colleagues how to utilize that endpoint and to incorporate it into clinical trials. Many investigators, myself included, have attempted to do this. Going forward, a society or group of thought leaders will need to develop a consensus statement that explicitly outlines the requirements for the term colonic mucosal healing, as well as features that disqualify findings from being termed healed. I think there is a mandate at this point to make these distinctions and agree on them. If we are to move the field forward in this area, we need to embrace a uniform set of criteria and then study them.

G&H Assuming the definition of mucosal healing is standardized and studies show that it correlates with better outcomes in UC patients, how will it affect day-to-day clinical practice?

DR If the properly designed studies were conducted, showing that achievement of mucosal healing is associ-

ated with better short-term outcomes (defined as stable disease control through 2 years), then it would become the standard of care for treatment of UC. The mandate for treating physicians would no longer be symptom control, but some confirmatory evidence of healed mucosa.

Ideally, mucosal healing would be determined in the clinical setting through a noninvasive sample of a fecal or serum marker that is both sensitive for and specific to healed colonic mucosa. Although research is ongoing, this marker has yet to be found. In its absence, monitoring for mucosal healing will require treatment for a determined period of time, followed by colonoscopy to determine the state of the mucosa. This would increase the incidence of procedures and the cost of care. With these increases, the questions of payment and justification to the payer are raised. Further, patients will need to be on board with these examinations. If the patient is feeling well, will they be willing to undergo additional colonoscopies on a regular basis, solely to monitor for mucosal healing?

Similarly, the physician will need to be committed to the concept of mucosal healing as a valid endpoint. There is no point in performing colonoscopy if the physician is not willing to embrace the next level of therapy based on colonoscopic findings. In other words, if the patient feels better on their 5-aminosalicylic acid (5-ASA) therapy and the clinician does not feel that mild inflammation will justify therapeutic escalation, then there is no point in looking for it.

G&H Do you see potential difficulty for community physicians and patients in accepting these concepts?

DR Earlier, I noted that demonstrated short-term improvement would be the key to accepting mucosal healing as a treatment endpoint. I do not believe that physicians are as excited about the idea of mucosal healing achieving long-term improved outcomes, partially because I think that it is difficult to think about the long term when the patient is feeling fine, symptomatically, now. Historically, we have not taken a long-term approach in our general management of these patients. For the most part, physicians say, and patients agree, that “you’re better now, let’s just keep doing what we’re doing.” Physicians do not say, “The fact that you are better now and we’ve achieved this level of mucosal healing through therapy escalation likely means that you’ll be in better shape in 10 years.” Therefore, I think that in order to change practice, physicians and patients will need to see the short-term results and understand that with a healed mucosa, they will be less likely to relapse or to require surgery in the following 2 years.

G&H How might the clinical goal of mucosal healing change the way UC therapy is administered?

DR First, we need to determine those therapies that can achieve mucosal healing and those that cannot. Again, we currently have only indirect evidence of mucosal healing as a secondary endpoint, with a definition of healing that may or may not be valid.

Once we have validated data on mucosal healing associated with specific therapies, then we will need to develop an algorithm that describes what therapy will be attempted first. The first therapy will be utilized until the patient achieves symptomatic remission. If they do not achieve symptomatic remission with this therapy, we will escalate therapy without checking for mucosal healing. If the therapy does provide symptomatic remission, then we will perform colonoscopy (or sigmoidoscopy), most likely after 3 months of therapy, to confirm mucosal healing and stable remission. If, at this point, the patient feels fine but their bowel is still inflamed, we will escalate therapy.

This is where the commitment to mucosal healing as a valid treatment endpoint is most critical. It is unlikely that physicians would argue with the idea of moving up within a class of therapy. Increasing the 5-ASA dose in order to achieve mucosal healing is a totally reasonable thing to do. Adding rectal 5-ASA to treat distal inflammation is a reasonable thing to do. However, patients and physicians have doubts when we say that we need to go from this 5-ASA, which has achieved symptomatic remission, to an immunomodulator that has associated risks of infection and lymphoma. If the bowel remains inflamed on the immunomodulator, then we consider a biologic, and a whole new series of risks and benefits need to be weighed.

G&H Can you describe the specific risks and benefits that would need to be discussed?

DR It is important to understand what is a concern and what is a real statistical risk because when we weigh the relative benefits against a poorly defined risk, we make decisions based on fear rather than fact. We know for a fact that prednisone, azathioprine/6-mercaptopurine, and most likely the anti-tumor necrosis factor biologics all increase the risk of bacterial infection. Azathioprine, across numerous studies and numerous disease states, also doubles the relative risk of lymphoma, which is a real risk with a real definition, but the absolute risk remains quite small. With regard to biologic therapies, there is a risk of hepatosplenic T-cell lymphoma, which, although of concern, is still poorly defined and very rare.

Regardless, no clinician will argue that the patient who is symptomatic and has an immediate need to escalate therapy has a complicated risk/benefit ratio to consider. We all agree that symptomatic UC and an actively inflamed rectum are terrible things.

However, when we see the not uncommon situation where the patient feels fine, but they have inflammation on colonoscopy when scoped, the risk/benefit ratio is more complicated. This is where the doctor needs to believe, and the patient needs to be convinced, that changing therapy will result in better short- and long-term outcomes.

G&H Should mucosal healing become the accepted standard of care, how would you approach this discussion with patients?

DR Many physicians raise the issue of cancer prevention when discussing both therapeutic adherence and mucosal healing with their patients. In truth, the incidence of colorectal cancer is so rare, that from the absolute point of view, it may not be the best thing to emphasize with patients. I believe that mucosal healing should be portrayed as the best way to save the patient's colon by presenting the idea that, if they are more likely to relapse, they are more likely to require surgery. When I do have that discussion with patients, my emphasis is on the goal of disease control and quality of life rather than crisis management, and on being proactive, not reactive, about symptoms. If proven definitively, mucosal healing should be presented as a necessary step in proactively controlling the disease and avoiding hospitalization and surgery. Cancer prevention comes along with that goal but may not be as compelling a reason.

G&H Can you discuss the emerging concept of deep mucosal or histologic healing?

DR So-called deep mucosal healing is based on the idea that histology is more predictive than endoscopy. Litera-

ture published by Alain Bitton and colleagues has demonstrated that the presence of lymphocytes in the rectal mucosa on biopsy is predictive of relapse in UC. These findings are based solely on biopsy of the rectum. Thus, we have known that histology may be more predictive than endoscopy for some time.

As discussed above, the definition of mucosal healing based on endoscopy has yet to be firmly established, which makes histologic sampling an appealing idea. However, histology scores are potentially equally confusing. If biopsies are obtained by the gastroenterologist, what is the protocol for where to biopsy? Right now, the endoscopist would biopsy where their eye takes them, which is biased. The pathologist has a glimpse into the bowel, but they are only seeing what the gastroenterologist chooses to show.

Thus, we return to surrogate marker research as the best way forward. A fecal or serum marker that is more reflective of the entire colon, as opposed to a targeted biopsy, would be a better objective measure of inflammation. Unfortunately, the currently utilized fecal markers of calprotectin and lactoferrin have not been as specific and sensitive as we would like. We await future research into new markers that will allow for better standardized inflammatory measures and aid in consistently defining the endpoint of mucosal healing.

Suggested Reading

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