ADVANCES IN IBD

Current Developments in the Treatment of Inflammatory Bowel Disease

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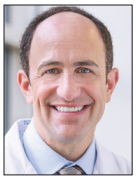
Transmural Healing in Inflammatory Bowel Disease



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G&H How can transmural healing be defined?

DR Transmural healing refers to evidence of healing of all layers of the bowel, with the recognition that inflammation in Crohn's disease, and very likely in ulcerative colitis as well, goes beyond the mucosal surface. A variety of definitions have emerged, usually using either cross-sectional imaging with magnetic resonance (MR) enterography, computed tomography enterography, or, more recently, intestinal ultrasound. Transmural inflammation causes the bowel wall to thicken and in some cases (but not all) the lumen to narrow, and proposed definitions have involved normalization of the bowel wall thickness of the inflamed sections.

In an excellent systematic review and expert consensus published in *The Lancet Gastroenterology & Hepatology* in 2021, Geyl and colleagues proposed definitions of transmural remission in Crohn's disease and ulcerative colitis. The authors described transmural remission based upon bowel wall thickness below a certain parameter—in Crohn's disease, less than 3 mm for the small bowel and less than 4 mm for the colon. The authors also described transmural remission as potentially being defined using both endoscopic and radiologic imaging. In other words, the physician needs to examine the inside of the bowel endoscopically and then examine the full thickness of the bowel using other technology (eg, cross-sectional imaging or intestinal ultrasound), and both sets of findings have to be considered together for a patient to demonstrate that level of healing.

Similarly, in ulcerative colitis, transmural remission was defined as bowel wall thickness less than or equal to 3 mm for the large intestine and sigmoid colon, as well as less than or equal to 4 mm for the rectum. The authors acknowledged that there may be some enlargement of the muscularis propria that is not inflammation. This can be assessed with cross-sectional imaging or intestinal ultrasound, the latter of which is an excellent approach.

The definition of transmural healing is evolving and based upon expert consensus, but the available evidence supports the implementation of this assessment in practice in the near future. However, the definition still needs further prospective validation, and there are ongoing studies to determine important issues such as how often transmural healing can be achieved and what clinical outcomes are associated with this concept.

G&H How and when can transmural healing be best evaluated?

DR Transmural healing can be evaluated in a variety of ways. For example, it can be assessed by intestinal ultrasound performed by the treating physician in his or her office, or the patient can be referred to another provider who can perform the procedure. Magnetic resonance imaging (MRI) can be used, even in a patient who is feeling better or who has endoscopic improvement, to assess deep layers of bowel inflammation. However, one of the issues is not which procedure should be used but the timing of when it should be performed. The systematic review of available data and expert consensus suggested that evaluation should be performed in ulcerative colitis no later than week 12 or 14 and may be performed even sooner to assess early response to therapy. Recognizing that Crohn's disease is generally thought to take longer to heal, the suggestion was to assess patients at week 26

or 52, although some patients may have earlier or more rapid response.

As physicians incorporate treat-to-target management strategies and acknowledge that deeper levels of control are associated with better outcomes, the important question is whether the assessment of transmural healing can provide impactful information even when a patient is already feeling better, his or her endoscopy looks better, or even his or her calprotectin level decreases. If physicians are going to try to treat to this level of healing, they need to make sure that it is incrementally better than the standard approach of treating to symptom improvement or, preferably, to endoscopic healing.

In Crohn's disease, it has been demonstrated that patients who achieve transmural healing ... have a substantially lower likelihood of surgery, hospital admission, and therapy escalation.

G&H What is the impact of achieving transmural healing on disease-related outcomes?

DR In Crohn's disease, it has been demonstrated that patients who achieve transmural healing, as defined as normal MR enterography findings and a healed bowel on endoscopy, have a substantially lower likelihood of surgery, hospital admission, and therapy escalation. These findings are in comparison with patients who only achieve endoscopic mucosal healing, with persistent active inflammation and thickening on MRI, or patients who have no obvious healing on either endoscopy or MRI. In addition, transmural healing is thought to be a more stable clinical outcome than endoscopic mucosal healing and is associated with a lower likelihood of relapse and adverse events, as shown in studies by Fernandes and colleagues and Castiglione and colleagues.

In ulcerative colitis, data are evolving and there is ongoing research to elucidate the answer to this question, which was recently explored by the BRIDGe Group. It is presumed that the findings may be similar to those in Crohn's disease, but the nature of transmural healing in ulcerative colitis is not fully defined yet. The hypothesis is that some patients who have persistent symptoms, whether these involve the bowel or are more systemic symptoms such as fatigue, may have transmural inflammation or even fibrosis associated with their rectum or colon from their ulcerative colitis.

STRIDE-II, the consensus statement on treatment targets that was published in 2021, acknowledged that transmural healing is an evolving consideration in Crohn's disease. The consensus statement notes that experts acknowledge that transmural healing might be on the list for consideration in ulcerative colitis but that the evidence was not there yet. In fact, the consensus on ulcerative colitis focused more on histologic healing at that time. Thus, there is still work that needs to be done, and this concept needs to be better understood. This is an area on the cutting edge for research.

G&H How well can transmural healing be achieved with the current therapies for inflammatory bowel disease?

DR As new treatments have become available, therapeutic goals have evolved to deeper levels of healing. There is some evidence suggesting that transmural healing can be achieved with advanced therapies for inflammatory bowel disease. The VERSIFY trial demonstrated that patients who received vedolizumab (Entyvio, Takeda) for the treatment of Crohn's disease were more likely to have MRI improvement if they were tumor necrosis factor (TNF) inhibitor–naive than if they were TNF inhibitor–experienced. In addition, a substudy of the STARDUST treat-to-target study of ustekinumab (Stelara, Janssen) used dose escalation based on endoscopy. The substudy looked at intestinal ultrasound in patients with Crohn's disease and demonstrated that ustekinumab could achieve transmural healing in a number of patients.

G&H Would you like to highlight any other studies involving transmural healing?

DR A recent study from my institution led by my colleague Dr Noa Krugliak Cleveland demonstrated that patients with ulcerative colitis had diminished compliance of their rectum. We hypothesized that this might be owing to transmural involvement of the colitis that restricts the rectum's ability to stretch and squeeze properly. She is performing additional work now to better characterize the presence and responsiveness of transmural alterations in ulcerative colitis. If it is recognized and accepted that ulcerative colitis may be transmural in many or most patients, this idea may change the way that

ulcerative colitis is thought about; for years, ulcerative colitis has been considered to be a mucosally confined disease.

G&H In your opinion, should patients with inflammatory bowel disease be treated to transmural healing?

DR Patients who are at high risk for relapse or disease-related complications should be monitored appropriately to achieve objective measures of disease control. Given what is being learned about transmural healing in Crohn's disease, it appears to be quite an important parameter and should be considered in patients who have risk factors for complications and progression, such as younger age of diagnosis, previous or known penetrating complications, and history of 1 or more surgeries.

The adoption of point-of-care intestinal ultrasound for the assessment of Crohn's disease is making it much easier to determine whether patients have achieved transmural healing. I believe this will facilitate the incorporation of transmural healing into routine clinical practice.

G&H What questions need to be answered before transmural healing can be incorporated more widely into routine clinical practice?

DR Several important questions remain unanswered. One is whether more studies can demonstrate that transmural healing is better than the current standard of endoscopic healing. Another question is whether transmural healing represents a deeper level of control, such that some patients can even de-escalate therapy once this target has been achieved. In addition, the timing for complete transmural healing needs to be determined. Even though the consensus statement suggested when this endpoint should be assessed, the reality is that physicians do not know the details of how the bowel heals and whether healing may occur faster or slower in some patients. Other questions are whether transmural healing in the small bowel is different from transmural healing in the colon, and whether transmural inflammation in the colon or rectum is associated with neoplasia more than just histologic inflammation. It also needs to be determined whether symptoms correlate better to transmural healing than to endoscopy or histology. Finally, further research is needed regarding fibrosis of the bowel that is presumed to occur in some (or many) patients with transmural alterations, and whether achieving improvement or healing of transmural disease may result in bowel remodeling or regaining of function. That is a difficult but important question that could change the way patients experience inflammatory bowel disease.

In order to move this field forward, these questions need to be studied. Further research is also needed with therapies to better understand timing and incorporate transmural healing as a real endpoint in clinical trials and real-world evidence. It is important to educate and disseminate information about the definitions of transmural healing and the available evidence of clinical correlations between transmural healing and outcomes of interest. It is also important to make sure that the available tools are sensitive and reliable. That includes developing a workforce of colleagues who can perform intestinal ultrasound and educating radiologists how to properly interpret and read the required level of detail. Finally, consensus statements and guidelines need to be developed. There is much work left to be done. The ultimate measure of success is whether transmural healing improves quality of life and disease control in patients with inflammatory bowel disease.

Disclosures

Dr Rubin has been a consultant to Janssen and Takeda and a speaker for Samsung/Biomedica. He has an investigator-initiated research grant from Takeda.

Suggested Reading

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