

ADVANCES IN IBD

Current Developments in the Treatment of Inflammatory Bowel Disease

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Histologic Healing in Inflammatory Bowel Disease



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G&H How can histologic healing be best defined in patients with inflammatory bowel disease?

BC This is a complex question to answer. Despite increasing evidence suggesting additional clinical benefits in achieving histologic healing in inflammatory bowel disease (IBD), particularly ulcerative colitis, there is little consensus on the exact definition of this target and there is no standardized reporting method. In the most simplistic terms, histologic healing can be defined as the microscopic normalization of mucosal biopsies. However, chronic histologic changes often persist long term. Therefore, histologic healing is also often described as the absence of acute inflammation, defined by the presence of intraepithelial neutrophils. A recent position paper from the European Crohn's and Colitis Organisation affirms this, stating that the absence of intraepithelial neutrophils, erosions, and ulceration should be the minimal requirement to classify a patient as having achieved histologic remission or healing. This definition is practical, and therefore often used in clinical practice.

For clinical trials, well-validated and reliable measuring tools that can standardize outcomes are desirable. For ulcerative colitis, the Robarts Histopathology Index (RHI) and the Nancy Index (NI) are the most accepted and well-validated measures. RHI assesses chronic inflammatory infiltrates, lamina propria and epithelium neutrophils, and whether any erosion or ulceration is present. Similarly, the NI scores ulceration, acute inflammatory cell infiltrate (neutrophils), and chronic inflammatory infiltrate (lymphocytes, plasmacytes). The NI is quite a simple index to score and can also be applied to clinical practice. For Crohn's disease, there are currently no

validated histologic indices. Some evidence is emerging that the RHI and NI can be used for Crohn's disease as well, but further research is required.

G&H What is the clinical importance of histologic healing in patients with IBD?

BC The importance of histologic healing in predicting clinical outcomes in IBD has recently emerged. Patients who achieve histologic healing have less long-term disease complications and are less likely to develop bowel dysplasia. The role of histologic assessment in ulcerative colitis is now evident. In ulcerative colitis patients who achieve endoscopic mucosal healing, histologic healing is further protective against disease flares, medical escalation, hospitalization, surgery, and corticosteroid use. The role of histology in clinical practice in Crohn's disease, however, is less clear. The reasons for this are multifactorial. Inflammation in Crohn's disease is patchy, making assessment challenging. In addition, histologic healing is achieved in a minority of patients; in one clinical trial, only 13% of patients achieved histologic healing on long-term anti-tumor necrosis factor regimens. Finally, as previously mentioned, there are no validated scoring systems. My colleagues and I studied the prognostic role of histology in patients with ileal Crohn's disease in clinical remission. On multivariate analysis, we found that histologic activity on ileal biopsies, but not endoscopic healing, was significantly associated with decreased risk of clinical relapse, reduced medication escalation, and reduced corticosteroid use.

Owing to the growing evidence demonstrating that patients with mucosal healing are more likely to relapse if they still have histologic activity, there is growing debate

regarding whether histologic healing should be incorporated as a treatment target. The difficulty with this idea is that the current IBD medications struggle to achieve even endoscopic mucosal healing, which is an earlier and usually easier target to attain than histologic healing. Therefore, there is concern that if histologic healing is taken on as a treatment target, patients would burn through medications very quickly and their treatment would be deemed a failure. With this in mind, I currently view histologic healing as a prognostic tool. If patients achieve both mucosal healing and histologic healing, it can be assumed that they have a high probability of doing very well clinically on follow-up. These patients may benefit from less-intense monitoring. However, if patients have histologic activity despite mucosal healing, physicians may keep a closer eye on them. Furthermore, because these patients have a higher risk of relapse, the physician might consider optimizing any current medical therapy they are taking. For example, if a patient is taking 5-aminosalicylic acid (5-ASA) agents at a low or maintenance dose but has ongoing histologic inflammation, the physician may increase that dose to try to achieve histologic healing.

G&H Can histologic healing ultimately be attained in most patients with ulcerative colitis and Crohn's disease?

BC Unfortunately, no. Many patients cannot even achieve mucosal healing. Mucosal healing rates of 40% are considered impressive in large biologic and small molecule clinical trials. Rates can be higher in the real world, particularly if patients are treated with a biologic early in their disease course; however, there remains a significant treatment gap. Furthermore, even among patients who achieve mucosal healing, a percentage will still have ongoing histologic activity. These numbers vary, but histologic healing rates in clinical trials usually range between 20% and 30%. Thus, histologic healing is optimistically achieved in only approximately one-third of patients. This is a major reason that histologic healing should not be incorporated as a treatment target in IBD.

G&H Is it possible to predict which patients will achieve histologic healing?

BC Markers and predictive algorithms are not yet available, but certain factors, such as disease severity in both Crohn's disease and ulcerative colitis, are known to be associated with unfavorable outcomes. Patients who are less likely to achieve either mucosal healing or histologic healing include those who are diagnosed at a younger age, have deep ulcers on diagnosis, and have a long duration of disease. Among Crohn's disease patients, those who

smoke, have stricturing or fistulizing disease, and have ileal involvement have a worse prognosis. Thus, it would be assumed that these patients are less likely to achieve histologic normalization or healing. In a study that my colleagues and I conducted, only proctitis, which is associated with favorable longer-term outcomes, predicted normalization in patients with ulcerative colitis.

There are also several blood markers that can predict worse outcomes in IBD, but they have not been studied for the prediction of histologic healing.

G&H Do more aggressive treatments lead to better rates of histologic healing?

BC That is the hope, and there is emerging evidence to support this. We know that rates of histologic healing are greater with biologics and small molecules compared with immunomodulators, which are superior to corticosteroids and 5-ASA medications. In addition, there is evidence that early aggressive therapy, or a top-down approach, leads to improved rates of mucosal healing and hence, presumably, histologic healing in IBD. Targeting objective markers and escalating therapy based on these findings appears to improve longer-term outcomes, especially in Crohn's disease. In particular, the CALM study demonstrated that a treat-to-target algorithm using objective monitoring and escalating therapy accordingly was superior at achieving endoscopic mucosal healing in 12 months compared with relying on reactive monitoring in which therapy was changed only when patients experienced symptoms. A prospective study is currently underway in ulcerative colitis patients that is comparing the targeting of mucosal healing vs histologic healing vs clinical symptoms. The results of this trial are highly anticipated and much needed.

G&H Do patients who achieve histologic healing require less rigorous monitoring?

BC That is how I use histology in clinical practice. There are no prospective studies on this topic, but there is good evidence, particularly in ulcerative colitis, that histologic healing is associated with improved prognosis and decreased risk of flare, corticosteroid use, and hospitalization. Therefore, if, for instance, a patient is taking 5-ASA tablets and has achieved both mucosal and histologic healing, I may see him or her only once a year and, for example, perform an intestinal ultrasound to make sure the patient is staying in deep remission. However, if a patient achieves mucosal healing but has ongoing histologic activity, I may see if there is a way to optimize his or her medications, and I would see him or her every 6 months with closer objective monitoring, including

fecal calprotectin and intestinal ultrasound. If a patient has both histologic activity and mucosal activity, I would see him or her more frequently and escalate therapy where appropriate to try to achieve mucosal healing at a minimum.

G&H Is histologic assessment necessary in all patients with IBD?

BC Many doctors do not see the utility of histologic assessment in patients with IBD and do not obtain biopsies. They may think that once mucosal healing is achieved, patients do not need to be monitored closely for other targets. However, I think histologic assessment is still important even in the setting of longstanding remission, particularly in ulcerative colitis patients. Biopsies are required in longstanding ulcerative colitis as part of dysplasia assessment to either look for dysplasia or to confirm disease extent. To verify the extent of histologic disease, I obtain a biopsy in every segment for histologic assessment even if the patient has achieved mucosal healing. I then use this information as a prognostic marker to guide future dysplasia assessment. Patients with ongoing histologic activity have a greater risk of developing dysplasia in the future and flaring, so they also need to be monitored more closely.

G&H What are the priorities of research in this area?

BC There are still many research gaps in this area. Better prospective studies are needed to determine which

patients and how many can achieve histologic healing. Histologic healing is a good prognostic marker, but it is not clear how achievable it is as a treatment target. As mentioned, there is a study currently underway on this issue comparing treatment targets of histology, mucosal healing, and clinical symptoms in ulcerative colitis, but not yet in Crohn's disease. Validated histologic scores are also needed in Crohn's disease. Several groups are currently working on this issue. In addition, it is unclear how many biopsies should be taken and from where. There is some evidence in ulcerative colitis that only a few biopsies are needed from each segment, but it is not certain how accurate this notion is and only small studies have been conducted. Finally, more research is needed to determine whether artificial intelligence has a role in IBD to help predict outcomes and histologic healing as well as help determine who needs escalation of therapy.

Disclosures

Dr Christensen has no relevant conflicts of interest to disclose.

Suggested Reading

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