

# ADVANCES IN IBD

Current Developments in the Treatment of Inflammatory Bowel Diseases

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## Mucosal Healing as a Treatment Goal in Crohn's Disease

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**G&H** Can you provide a working definition of mucosal healing as it applies to Crohn's disease patients?

**GVA** In Crohn's disease, we recommend the single criterion of the disappearance of mucosal ulceration, as established by complete ileocolonoscopy, to indicate mucosal healing. This is the most easily measured and relevant criterion and the one utilized in clinical trials of anti-tumor necrosis factor biologic therapies. It correlates well with levels of C-reactive protein (CRP) as well as clinical disease severity scores. It also provides a very hard endpoint in trials and is easily recorded. However, it is an all-or-nothing observation. Patients either achieve it or they do not, which provides little quantitative information in the clinical trial setting. Nonetheless, it remains the most workable definition for clinicians.

**G&H** How does this definition differ from the emerging concept of deep mucosal, or histologic, healing?

**GVA** Histologic healing usually lags behind mucosal healing in both ulcerative colitis and Crohn's disease. In patients with endoscopically healed mucosa, pathology from colonic biopsy can still show mildly active Crohn's disease, as opposed to complete remission. A lack of deep histologic healing indicates continued inflammation. By examining the level of inflammation deeper in the colonic lamina propria, we can gauge the likelihood of disease recurrence. A lack of histologic healing may be a sign that

tapering or cessation of therapy, with either immunosuppressants or biologic therapy, is not currently advisable. However, data from controlled trials are lacking.

**G&H** How can mucosal healing be assessed and applied in patients with disease that extends beyond the colon, into the small bowel?

**GVA** Utilizing ileocolonoscopy, we can observe only 10–15 centimeters of the terminal ileum. Crohn's disease patients with upper intestinal disease or ileitis extending up from the region of the endoscopic view are more problematic in terms of visualization. Moving forward, computed tomography or magnetic resonance enteroclysis will likely become the standard procedures for assessing these patients, rather than capsule endoscopy. Capsule endoscopy is highly sensitive for visualizing ulcers, but all of the ulcers visualized may not be specific for Crohn's disease. A recent trial from a Greek center evaluated mucosal healing with capsule endoscopy and showed that only the relatively large ulcers were disappearing after therapy with steroids or biologics. Smaller ulcers, for which capsule endoscopy is very sensitive, did not disappear after therapy. More data are needed to determine the significance of these findings. Enteroclysis procedures also have the advantage of providing a transmural image that allows for the evaluation of bowel-wall thickening and fistulas.

**G&H** How closely can mucosal healing in Crohn's disease be correlated with the treatment goal of symptom relief?

**GVA** Symptom relief is, of course, of primary concern to the patient as well as the physician and presents something of a disconnect when evaluated in relation to mucosal healing. Some patients report symptoms, such as diarrhea and abdominal pain, and those symptoms are not related to mucosal ulcerations or active inflammation. They could be due to a number of comorbidities, ranging from increased bile acids to intestinal stricture. Mucosal

healing correlates very well with symptoms that are due to inflammation but poorly with those that do not.

In the SONIC trial, it was demonstrated that patients with no mucosal lesions on colonoscopy or evidence of CRP elevation did not benefit from biologic therapy with infliximab or immune modification with azathioprine. This further indicates that only symptoms that are due to inflammation will respond to biologic therapy. In the future we will likely not be inclined to treat symptomatic patients who do not have elevated CRP, endoscopic lesions, or lesions in the upper gastrointestinal tract, with powerful biologic therapies, given their associated toxicities.

### **G&H** What evidence exists to associate mucosal healing with longer-term goals such as the avoidance of hospitalization or surgery?

**GVA** There are indications from different sources that some correlation exists among mucosal healing, hospitalization, and the need for surgery. Data from the IBSEN cohort in Norway demonstrate very clearly that ulcerative colitis patients who achieve healing have fewer colectomies and that Crohn's disease patients are more likely to avoid surgery as well. Steroid therapy, which can interfere with mucosal healing, was associated with a greater likelihood of surgery in this study. There is additional evidence from trials of infliximab that there is an association between mucosal healing and surgery avoidance, but whether it is a causal relationship cannot be determined. Regardless, post-hoc analysis shows that patients who achieved mucosal healing with infliximab therapy had a lower likelihood for hospitalization and surgery. Finally, our group published evidence this month showing a clear link between avoidance of surgery and mucosal healing in a large, single-center clinical practice cohort.

### **G&H** Should mucosal healing be pursued as a treatment goal in asymptomatic patients with ulceration?

**GVA** No prospective clinical trials have yet been designed to consider patients who report freedom from symptoms but appear severely inflamed on colonoscopy. Whether

their long-term outcomes will be improved by stepping up therapy in pursuit of mucosal healing remains an open question, and any current recommendation can only be based on expert opinion or cohort studies. However, we do have evidence that patients under consideration for tapering or cessation of therapy are more likely to experience symptom relapse if they have not previously achieved mucosal healing. This has been shown in preliminary data from the French STORI trial, in which patients with active endoscopic lesions, who were receiving treatment with infliximab, had treatment withdrawn. It was found that these patients relapsed and required re-treatment more rapidly than those who had previously achieved mucosal healing.

### **G&H** How could a trial be designed to evaluate the validity of mucosal healing as a guide for treatment course?

**GVA** A trial to answer this question definitively would be very helpful. It would require taking a group of patients with new disease onset and stepping up treatment to relieve symptoms. A subset would be allowed further intensification of treatment in order to achieve and maintain mucosal healing based on endoscopic appearance. In current clinical practice, it has been estimated that anywhere from 50% to 70% of patients do not achieve complete healing. The challenge would come from the size and length of the trial. It would require many patients in order to achieve statistical significance. In order to evaluate accurately for hospitalization and surgery, patients would need to be followed for at least 5–6 years.

### **Suggested Reading**

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