ADVANCES IN IBD

Current Developments in the Treatment of Inflammatory Bowel Disease

Section Editor: Stephen B. Hanauer, MD

Mucosal Healing with Infliximab: Results From the Active Ulcerative Colitis Trials

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G&H How does infliximab cause mucosal healing?

WJS Research has shown that tumor necrosis factor (TNF) is overexpressed in patients with moderate-to-severe ulcerative colitis (UC); this proinflammatory cytokine can be measured in blood, stool, and colon biopsies. Infliximab (Remicade, Janssen Biotech) is a monoclonal antibody that binds TNF; this binding inactivates TNF and prevents its proinflammatory effects. However, researchers do not yet know whether anti-TNF therapy is uniquely effective in terms of its ability to achieve high rates of mucosal healing, or whether some of the same intracellular pathways that lead to clinical improvement also lead to mucosal healing. We know that mesalamine can induce mucosal healing in patients with mild-to-moderate UC, and steroids can also induce mucosal healing to some extent; whether steroids can induce mucosal healing as effectively as anti-TNF therapy is not clear. In Crohn's disease (CD), steroids appear to be considerably less effective for inducing mucosal healing than anti-TNF therapy; azathioprine is also less effective than anti-TNF therapy for inducing mucosal healing in the CD population.

G&H What was the rationale for conducting the Active Ulcerative Colitis Trials?

WJS The original Active Ulcerative Colitis Trials (ACT 1 and ACT 2) were designed to demonstrate that infliximab is effective for induction and maintenance of remission in patients with UC. These trials were initiated in 2002 and completed in late 2004, and they led to the US Food and Drug Administration's approval of infliximab in 2005 for induction and maintenance of remission in UC. In addition to demonstrating infliximab's clinical efficacy, these trials also showed that infliximab could induce mucosal healing in patients with UC.

An enormous amount of data was generated in ACT 1 and ACT 2, and subsequent studies have used that data to better understand UC and how to treat it. A paper published in *Gastroenterology* in 2009 compared infliximab versus placebo for the prevention of colectomy in patients with UC. More recently, my coworkers and I conducted another analysis of the ACT 1 and ACT 2 data. This latter paper, which was published in *Gastroenterology* in 2011, sought to examine mucosal healing and its impact on long-term treatment outcomes; specifically, it assessed whether infliximab therapy that achieved mucosal healing led to better long-term outcomes than treatment that improved clinical symptoms but did not achieve mucosal healing.

G&H Can you briefly review the design and results of this study?

WJS ACT 1 and ACT 2 included patients who were receiving outpatient treatment for moderate-to-severe UC after having failed therapy with immunosuppressant medications and/or steroids. In order to qualify for ACT 1 or ACT 2, patients had to have moderate-to-severe disease on endoscopy, as well as moderate-to-severe disease overall. Patients were randomized to induction and maintenance therapy with infliximab or placebo. Patients underwent an

endoscopy (either flexible sigmoidoscopy or colonoscopy) at baseline and again at Weeks 8 and 30; patients in ACT 1 also underwent a final endoscopy at Week 52. These endoscopies were scored using the Mayo Clinic scoring system; endoscopy subscores ranged from 0 to 3, with 0 denoting normal bowel, 1 denoting mild findings, 2 denoting moderate findings, and 3 denoting severe findings. For our study, we defined mucosal healing as a subscore of 0 or 1. We then correlated Week 8 endoscopy subscores with subsequent clinical findings.

Our analysis found that patients who had a Week 8 endoscopy subscore of 0 or 1 had much lower rates of hospitalization or surgery and higher rates of steroid-free remission over the next 6–12 months. There was little difference in colectomy rates between patients who had an endoscopy subscore of 0 versus those with a subscore of 1 at Week 8, as both groups had fairly low colectomy rates. Conversely, patients who did not achieve mucosal healing at Week 8 (ie, endoscopy subscore ≥2) had considerably higher rates of subsequent colectomy.

Interestingly, when we looked at more sensitive outcome measures such as steroid-free clinical remission, we did find differences between patients with a Week 8 endoscopy subscore of 0 versus those with a subscore of 1. Steroid-free remission rates were approximately 20% higher in patients who had a subscore of 0 compared to patients with a subscore of 1 at Week 8; these latter patients showed dramatic endoscopic improvement from baseline but not complete normalization of the mucosa. This finding provides clinicians with a critical piece of information because it shows that a spectrum of clinically important outcomes are possible, depending on the degree of mucosal healing after the induction period.

G&H Did ACT 1 and ACT 2 have any major limitations? What about your subsequent analysis?

WJS ACT 1 and ACT 2 were prospective, randomized, double-blind trials, so the findings of the original studies are quite robust. However, these trials were not specifically designed to answer the question of whether achieving mucosal healing leads to better outcomes than treating to clinical endpoints. Because the current study is a secondary analysis, its conclusions are not as robust as if we had conducted a prospective, randomized trial specifically designed to answer this question.

G&H How might the findings from your recent study impact clinical practice?

WJS In my opinion, this study provides additional pieces of useful information that add to an accumulating body of literature showing that mucosal healing changes the course of UC and CD, reduces the need for surgery, and may reduce the occurrence of colorectal dysplasia and cancer. Overall, data suggest that mucosal healing is a desirable outcome and should be considered as a goal of therapy. In my practice, I frequently, if not almost uniformly, re-evaluate patients with UC using flexible sigmoidoscopy at the end of induction therapy to ascertain whether they have achieved mucosal healing. If they have not achieved mucosal healing, I often escalate their therapy in an attempt to reach this goal, even if the patients are feeling well. There is now a fairly large body of data to suggest that this approach is a good strategy, but a definitive prospective trial has not yet been conducted to prove its benefit. Thus, I am hesitant to state that all practitioners should aim to achieve mucosal healing. However, practitioners should be aware of the evolving data, and they may want to consider aiming for mucosal healing in patients who are at higher risk for poor outcomes. I believe treating to mucosal healing is now within the spectrum of standard clinical practice, although I do not think it can be called a mandatory standard of care at this time.

G&H Are there less invasive alternatives to endoscopy that could be used to detect mucosal healing?

WJS The search for alternatives to endoscopy is still evolving. A subgroup of patients have elevated serum levels of C-reactive protein (CRP); in these patients, normalization of CRP levels might correlate with and potentially be a surrogate for endoscopic improvement. There are also tests that measure stool calprotectin or stool lactoferrin; these proteins are produced by white blood cells that are present in stool. There is evolving experience using these fecal biomarkers of inflammation in UC, and testing for one or both of these biomarkers might eventually serve as an alternative to endoscopy. These biomarkers have not yet been sufficiently validated to replace endoscopy in clinical practice, but such validation might occur within the next 1–2 years.

G&H Has mucosal healing been studied in patients being treated with anti-TNF agents other than infliximab?

WJS Mucosal healing has not been very well studied in trials of certolizumab pegol (Cimzia, UCB). However, mucosal healing has been studied in CD and UC patients treated with adalimumab (Humira, Abbott). The EXTEND trial examined mucosal healing in CD patients who were treated with adalimumab; data from this study have been published in abstract form, and the full study will be published soon. In addition, 2 studies are examining the efficacy of adalimumab in patients with UC; a study assessing adalimumab

for induction therapy has already been published, and a study assessing adalimumab for induction and maintenance therapy is currently in press in *Gastroenterology*. These studies all include mucosal healing endpoints; however, like the original infliximab studies published in 2005, these studies are not designed to examine the relationship between mucosal healing and long-term outcomes.

G&H What further studies are needed to explore the relationship between mucosal healing and long-term outcomes in UC?

WJS Prospective studies are needed to better understand this relationship. The REACT II study is currently being planned to assess the use of different treatment algorithms for CD; in this study, treatment will involve a series of drugs used in a predefined sequence. Patients in the experimental arm of the study will undergo colonoscopy at baseline and approximately every 4 months thereafter until mucosal healing is achieved or the clinician runs out of options in the treatment algorithm; the control arm of this study will consist of a treatment algorithm based on clinical endpoints. This trial will then compare the 2 groups in terms of outcomes such as occurrence of disease complications, need for surgery, and need for chronic steroid use. While I am not aware that such a trial is being planned for UC, I imagine that researchers will consider it once the CD trial has been launched.

G&H Overall, why is mucosal healing an important treatment endpoint?

WJS I think that mucosal healing is a measure of the underlying inflammation that causes the disease, whereas clinical symptoms are more of a secondary surrogate. Thus, the idea of treating the disease to resolution, as measured by mucosal healing, is very appealing. Clinical symptoms are important, but treating the underlying inflammatory condition is likely the more critical factor. Over the next few years, I suspect that therapy for inflammatory bowel disease will transition from treating clinical endpoints to treating the underlying disease.

Suggested Reading

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