ADVANCES IN IBD

Current Developments in the Treatment of Inflammatory Bowel Disease

Section Editor: Stephen B. Hanauer, MD

Residual Inflammation and Ulcerative Colitis in Remission

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G&H How is remission of ulcerative colitis defined?

AM Remission of ulcerative colitis (UC) is somewhat in the eye of the beholder. What patients consider remission might be different from what the average physician or the US Food and Drug Administration (FDA) considers remission. For patients and many gastroenterologists, remission simply means that the symptoms of UC resolve, the patient feels well, and the disease is not interfering with activities of daily living.

From a research and regulatory point of view, no single unified definition for remission of UC exists. Remission can be described in terms of symptoms, endoscopic appearance, or histologic features. There are different methods to define clinical, endoscopic, and histologic remission in UC. Several indices of clinical disease activity have been used in different clinical trials over the years, such as the Mayo Score or Seo Index, and each of these has its own criteria for "remission." This makes for a confusing situation when comparing studies, being akin to using inches, centimeters, or paper clips to measure the length of an item. For example, endoscopic remission might be defined as a completely normal-appearing mucosa in one trial and as mucosa that has no ulcers but mild erythema in another trial.

A workshop titled Gastroenterology Regulatory Endpoints and the Advancement of Therapeutics was recently held among representatives from the FDA and experts in inflammatory bowel disease to come up with a universal definition or criteria to define remission in UC for future clinical trials (http://great2.org).

G&H How best is remission of UC achieved and maintained?

AM A number of agents, including mesalamine, thiopurines, and anti–tumor necrosis factor (TNF) antibodies, have been shown to maintain remission in patients with UC. One-year clinical remission rates of 40% to 60% are typically reported in trials of these agents. Patients with more severe disease at baseline, such as those enrolled in recent trials of anti-TNF regimens, usually have lower rates of maintenance of remission than those with mild disease at enrollment. Once a patient achieves remission with a particular agent, he or she is kept on it indefinitely, as these agents only maintain remission as long as they are used.

G&H Why do some patients with UC still experience gastrointestinal symptoms even when UC is considered to be in remission?

AM This is now recognized as a common limitation of measuring remission based on symptoms alone. Some patients in whom colonic mucosa has healed still report diarrhea or abdominal pain. This is usually due to overlap functional symptoms or, sometimes, infections. The converse is also true; many patients considered to be in clinical remission based on their symptoms have persistent endoscopic or histologic evidence of inflammation. A study published last year and conducted by my colleagues and I examined the endoscopy findings of 100 patients with UC in clinical remission and found endoscopic evidence of inflammation in 45% of the patients. The inflammation was mild in most of these patients but was at least moder-

ate in 13% even though, based on their symptoms, these patients met the criteria for clinical remission. These results were similar to those of a Dutch study, also published in the past year; about 30% of patients had endoscopic inflammation despite having no symptoms.

When we went "deeper" and examined biopsy findings, 54% of the patients in our study had histologic inflammation even though they had no symptoms. The issue of identifying residual histologic inflammation is quite important in the long term because these patients are at higher risk for colon cancer as well as disease relapse and need for hospitalization or surgery. Independent of other factors, patients who have residual histologic inflammation, even if they feel well, are more likely to have worse long-term outcomes.

G&H Is there a way to predict which patients may be prone to residual inflammation once clinical remission is ostensibly achieved?

AM The most obvious way to screen for residual inflammation is sigmoidoscopy, but this modality is costly and presents some inconvenience for the patient. In our study, a serum C-reactive protein (CRP) level greater than 10 mg/L was shown to have a positive predictive value of 86% for at least moderate histologic inflammation among patients with UC in clinical remission. These findings suggest that a CRP blood test may be an alternative to identify patients who may warrant more invasive procedures, such as sigmoidoscopy, to confirm if residual inflammation is present.

A question of interest is whether the dosage or type of therapy should be increased or otherwise modified in patients who have no symptoms but persistent residual inflammation. Findings from one recent study suggest that if treatment is adjusted in response to endoscopic findings, regardless of whether the patient has symptoms, resolution of the inflammation is more likely than if only symptoms are responded to. The challenge is to convince a patient who feels well that it is in his or her best interest to start more potent or invasive treatments with potential for serious adverse effects. I often have to explain to the patient that if residual inflammation is present, clinical relapse, colon cancer, and need for colectomy are more likely. This argument is convincing, but a lot of the presumptions are based on indirect evidence rather than randomized controlled trials.

G&H What can be further done to reduce the inflammatory process in the patient at risk for residual inflammation and other changes associated with UC?

AM The "ideal" agent for inducing and maintaining mucosal healing in UC would be safe, convenient to administer, inexpensive, and associated with high adherence rates. No currently approved agent meets all these criteria. No comparative studies among all the available therapies have been done to show which provides the highest mucosal healing rate in similar populations with ongoing inflammation. If a patient is on drug A and does not have endoscopic healing, then I will make the case that a different, more aggressive treatment should be tried in an effort to induce mucosal healing. It becomes a trade-off of risk to benefits; the more aggressive treatment may have higher mucosal healing rates but be associated with rare but more serious adverse effects. If the medication that the patient is taking fails to induce healing or endoscopic remission, then it is at least worthwhile to have a conversation with him or her about trying a different medication to achieve that goal.

G&H In addition to mesalamine, which adjunctive or alternative management strategies can help ameliorate residual symptoms of UC?

AM A number of complementary therapies have been shown, in clinical trials, to be beneficial. Curcumin, the probiotic VSL#3, and aloe vera have all been shown to at least induce a response in controlled trials in patients with mild UC who are already using mesalamine. The data on maintenance of remission in the long term, and whether these complementary therapies induce mucosal or histologic healing, are sparse, although there are some data that VSL#3 can induce mucosal healing and improve symptoms. Patients who do not wish to start a more aggressive immunosuppressive therapeutic regimen may add these agents to their mesalamine regimen instead.

G&H What research on UC management and remission specifically needs to be done?

AM We need studies that compare different agents in their ability to maintain both endoscopic and histologic remission in patients with colitis. We also need prospective studies to learn whether patients in clinical but not endoscopic remission achieve overall benefit in the long term from switching from mesalamine to a thiopurine or anti-TNF agent.

G&H How can a clinician relay the importance of therapy adherence to the patient with UC?

AM Adherence to medications is probably the greatest challenge in relation to maintenance of remission in patients with UC. Studies that my colleagues and I and others have performed report that only about half of patients prescribed mesalamine actually take their medication as prescribed. This lack of adherence is both intentional and unintentional; some patients decide to stop

taking their medication, and others forget to take their 4 to 6 pills a day. A study that was recently completed by my colleagues and I found that a patient's lack of belief in the need for maintenance therapy once he or she felt well and the patient's concerns about adverse effects both influenced the likelihood of refilling the mesalamine prescription over 6 to 12 months. This suggests that gastroenterologists need to do a better job of educating patients about the benefits of sticking to their medication regimen even if they are feeling healthy.

G&H Do you have any recommendations for office-based gastroenterologists?

AM The message that I would convey is that speaking directly to patients about adherence to therapy is a worthwhile exercise. This might be as simple as asking a patient whether he or she skipped taking pills during the past week. A recent study showed that very few gastroenterologists do this, but emphasizing the benefits of adherence, even when patients feel well, may play a role in reducing patients' risk of relapses and complications in the long term.

Also, patients who are in clinical remission after a change in therapy should be assessed after 3 or 6 months to determine if they have obtained mucosal healing. If we can get patients into both clinical and endoscopic remission, they may do far better in the long term.

Dr Moss has previously served on advisory boards for Janssen, Abbott, and UCB and is an investigator on research grants to Beth Israel Deaconess Medical Center from Pfizer, Shire, and Salix.

Suggested Reading

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