

ADVANCES IN IBD

Current Developments in the Treatment of Inflammatory Bowel Diseases

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Highlights from the Updated ACG Guidelines for Crohn's Disease Treatment

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G&H When were the latest practice guidelines for Crohn's disease published by the American College of Gastroenterology?

GL The American College of Gastroenterology (ACG) Practice Guidelines on Management of Crohn's Disease (CD) in Adults were published in February of 2009. I was an author, along with Dr. William Sandborn, Dr. Stephen Hanauer, the Practice Parameters Committee of the ACG, and select members of the editorial board of the *American Journal of Gastroenterology*. These guidelines comprise a comprehensive and concise summary for community clinicians, providing perspective on recent clinical trial data and literature and summarizing current evidence-based practice recommendations to distill the essence of current clinical care.

G&H What new diagnostic technologies are highlighted in the guidelines for CD management?

GL Diagnostic tools for CD are utilized primarily in two ways: to detect and confirm new-onset disease and to identify developing disease-related complications. The latest guidelines discuss the use of several new technologies and concepts, including serologic testing for antibodies of ASCA, pANCA, CBir1, OmpC, and I2. Monitoring of these serum markers has not proven sufficiently sensitive or specific for use as a screening tool. However, they do provide additional information to facilitate the prediction of disease course and the potential need for future sur-

gery in individual patients, and may be factored in with endoscopic evaluation, radiographic evaluation, and the patient's family history to help guide prognosis.

In addition, the utility of measuring fecal concentrations of lactoferrin and calprotectin as indicators of intestinal inflammation has received recent attention. These fecal leukocyte markers are, again, not specific enough to establish a diagnosis. However, they do provide a noninvasive indicator of the need for further evaluation in potential inflammatory bowel disease (IBD) patients.

Radiographic and endoscopic examinations remain the standard of practice and represent the gold standard by which we base our decisions.

G&H Are there any novel imaging technologies or practices that are covered in the Crohn's guidelines?

GL Wireless capsule endoscopy (WCE) has been recently introduced as a method to evaluate patients with suspected CD or those with bleeding complications of luminal disease. In individuals presenting with a suspicion of CD, who have undergone evaluation with upper endoscopy and colonoscopy but have not had any small bowel imaging study, WCE has been shown to be an effective method to image the remaining gastrointestinal tract. However, the WCE capsules do have the potential to become stuck in the small bowel. It is currently recommended that the procedure be preceded by a small bowel study to identify any stenoses before administering the capsule. Lack of stenosis can be established with computed tomography (CT) enterography or small bowel follow-through.

Capsule endoscopy may play a more prominent role in community practices where radiographic imaging is

not as specialized as in university academic medical centers and operators may not be as skilled at the detection of CD-related symptoms and complications from imaging. A naturally dissolving patency capsule is also now available, which can be passed prior to the WCE to test for any significant strictures. It is important to recognize that, currently, there is no validated standardized grading system for WCE imaging to determine whether a patient has CD. For extreme cases, the imaging is definitive but our inability to take biopsies with WCE limits its use in patients with less severe inflammation or ulceration.

The revised guidelines also highlight other imaging modalities that are relatively new. CT enterography and magnetic resonance (MR) enterography are procedures with an evolving ability to define and differentiate inflammatory from noninflammatory disease. Their usefulness can be seen in patients with confirmed CD and stricture. The question of whether the stricture should be treated with disease-modifying therapy such as an anti-tumor necrosis factor (TNF) agent or with surgery requires a determination of whether it is fibrotic or inflammatory in nature. CT and MR enterography can provide useful information to help discern if this lesion is either inflammatory or fibrotic beyond what can be seen with a standard small bowel follow-through radiograph.

G&H Do the guidelines review the research that has focused on genetic markers?

GL Yes. Since publication of the 2001 version of the guidelines and identification of the *NOD2/CARD15* gene, genetic markers of IBD have received considerable publicity. The presence of the *NOD2/CARD15* polymorphism has been associated with ileal and fibrostenotic disease, earlier onset of disease, and a family history of CD. Further, carrying a homozygote mutation versus a heterozygote portends a higher risk of developing CD. These conclusions are interesting. However, as with other genetic markers more recently associated with CD (eg, OCTN1, IL23), the same polymorphisms can be seen in the general population. This lack of specificity and incomplete understanding of their negative or positive predictive value prevents the current meaningful use of genetic markers in clinical practice.

G&H What are the current questions in disease management that are addressed in the new guidelines?

GL One question discussed in these guidelines is the definition of appropriate treatment endpoints. Should we utilize the Crohn's Disease Activity Index (CDAI), or should we look at mucosal healing, given the demon-

strated link between mucosal healing, reduced surgery, and reduced hospitalization? Should we have a mucosal damage index that considers a host of different factors, such as the location of the abnormality, presence and location of bowel dilation, intestinal fistula, and segment length? These factors might potentially be utilized in an equation and assigned a damage number. There is ongoing work on the development of a mucosal damage index and a growing recognition of the importance of mucosal healing. All of these concepts are reflected in the revised guidelines.

Further, if a medicine fails to completely heal the mucosa, should that be defined as a medical failure? Historically, the definition of remission has been linked to clinical trials and to a CDAI of less than 150, corresponding to a lack of symptoms and a lack of active inflammation or disease. As of yet, mucosal healing has not been defined as the endpoint for clinical care. A patient might receive immunomodulator therapy and remain totally asymptomatic, with 1 bowel movement daily and no flares over the course of 6 years. If, during a surveillance colonoscopy, this patient shows evidence of a 15-cm segment of inflammation with ulceration, is this an indication to switch to more aggressive therapy? Similarly, in the setting of ulcerative colitis, should a patient on mesalamine, doing well but with mild inflammation present, be switched to an immunomodulator or anti-TNF agent? Will escalation of therapy change the natural course of disease? If so, is the potential risk of escalating therapy worth the benefit that will be potentially achieved? Although these questions are not definitively answerable, they are at least discussed in the new guidelines.

Another area of significant importance is the utilization of combination therapy with an immunomodulator plus a biologic agent. Based on retrospective analyses, it has been posited that use of immunomodulators initially, with add-on of biologic therapy in those patients who cannot tolerate or gain benefit from immunomodulator use, and continuation of immunomodulators after the biologic, is not necessarily the most advantageous approach. It remains uncertain whether continuation of the immunomodulator is needed. There are secondary analyses suggesting continuation of immunomodulators is not advantageous clinically in this scenario.

A more recent study by Rutgeerts and colleagues evaluated the influence of immunosuppressive discontinuation in patients in remission with combination therapy in an open-label, randomized, controlled trial. Patients with disease controlled for 6 months or longer duration, after the initiation of infliximab (IFX) therapy combined with immunosuppressives, were randomized to continue or to interrupt immunosuppressives, while all patients received scheduled maintenance IFX therapy for

104 weeks. The primary endpoint was the proportion of patients who required a decrease in IFX dosing interval or stopped IFX therapy. Continuation of immunosuppressives beyond 6 months offered no clear benefit over scheduled IFX monotherapy. There was, however, higher median IFX trough levels and decreased serum C-reactive protein levels. The impact of these observations on long-term outcomes needs to be explored further in a larger study.

More recently, data from the SONIC trial, one of the most significant research trials in IBD within the last decade, has made an important contribution to the literature (though the full manuscript has not yet been published). SONIC was a prospective, randomized, nonplacebo-controlled trial. Patients were randomized into 1 of 3 arms. One group received a regimen of 2.5 mg/kg of azathioprine (AZA) daily after having thiopurine methyltransferase enzyme activity assessed (those that were low or intermediate [heterozygotes] were excluded). These patients were compared to groups receiving IFX (5 mg/kg) at weeks 0, 2, and 6, and every 8 weeks thereafter plus AZA or IFX monotherapy. The ability to withdraw steroids and remain in remission was considered to be the primary endpoint of the trial. Based on this endpoint, those patients receiving combination IFX/AZA performed best, whereas somewhat fewer patients in the IFX monotherapy arm achieved remission without steroids and substantially fewer in the AZA monotherapy group did. Mucosal healing was achieved and maintained in the same order. AZA monotherapy was least effective, IFX was more effective than AZA, and combination therapy was the most effective.

To some degree, these data contradict the retrospective analysis that demonstrated that continued dual therapy was not effective in individuals who had failed AZA monotherapy and then went on to biologics and immunomodulators in combination. However, these patients make up a slightly different, and possibly more refractory, population. The patients in SONIC were naive to AZA/6-mercaptopurine (6-MP)/methotrexate and biologic therapy. Thus, one might suggest that they entered the study at an earlier stage in the disease course. In this population, it would seem that more medical therapy is better. Whether this is the case remains to be seen, and per the new guidelines, this remains an open question requiring more research. Another issue that needs to be taken into context is that the use of thiopurines, whether alone or in combination with IFX or adalimumab, has been associated with the development of hepatosplenic T-cell lymphoma. Thus far, there have been a total of 32 cases of hepatosplenic T-cell lymphoma that have been described in patients with IBD. Although this is clearly

a very rare complication in all patients, young males have a higher risk, particularly those under the age of 35. Similarly, elderly patients need to be discussed when we consider using dual therapy (immunosuppressive and IFX in combination). Elderly patients have different abilities to metabolize drugs and, in general, need lower doses of medications. Thus, with a new CD presentation, an elderly patient might be at greater risk from the dual immunosuppression (ie, combination therapy). Should IFX monotherapy be the primary therapeutic agent in these populations? This has yet to be defined and will perhaps be addressed in the next iteration of the guidelines. In addition, it remains to be determined whether SONIC should be redone with other biologic therapies or if these results constitute a transferable conclusion of a class effect with all anti-TNFs.

G&H What are some of the other controversies and long-term questions pointed out for further research and discussion in the new guidelines?

GL The question of top-down versus step-up therapy is an issue of current importance in clinical management of CD. Should we start out with the most effective agents we have, anti-TNF agents, rather than attempting 5-aminosalicylic acids, steroids, and antimetabolites first? The original step-up versus top-down trial was undertaken with an on-demand approach to IFX administration, rather than the more recently favored use of scheduled maintenance. Further, the top-down arm looked at combination IFX and AZA therapy. Based on the SONIC data, this may suggest a benefit bias in these patients. Regardless, those patients who received IFX initially obtained better overall mucosal healing, when compared to those who were initially started on corticosteroids. At the end of the trial, there was similar use of IFX in the two groups and substantially less corticosteroid use in the top-down group. These advantages are very important. However, the number of patients in remission at the end of the trial remained similar across the entire study population. Based on these findings, we see a distinct advantage to top-down therapy in terms of mucosal healing and look forward to a future trial design reflecting current clinical practice, in order to better answer the question of overall advantage in terms of remission.

The optimal use of methotrexate also needs to be examined. Dose-ranging studies and long-term maintenance studies are needed, as is some consideration of using oral methotrexate as a means to reduce immunogenicity in patients using biologic therapy. Ultimately, we must determine whether methotrexate should be

used instead of antimetabolite therapy with 6-MP or AZA and if oral or subcutaneous formulations should be administered.

Finally, the controlled evaluation of surgery as a treatment option requires further attention and resources, as does the treatment of CD in pregnant patients. Although it will likely be difficult to recruit patients or to get funding for these trials, these areas remain critical for future investigation. The establishment of a pregnancy registry by the Crohn's and Colitis Foundation of America will help to facilitate further investigation of drug safety and best practice in pregnant patients.

Suggested Reading

Lichtenstein GR, Hanauer SB, Sandborn WJ, the Practice Parameters Committee of the American College of Gastroenterology. *Am J Gastroenterol.* 2009;104:465-483.

D'Haens G, Baert F, van Assche G, Caenepeel P, Vergauwe P, et al. Early combined immunosuppression or conventional management in patients with newly diagnosed Crohn's disease: an open randomised trial. *Lancet.* 2008;371:660-667.

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Critical Reading

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M. Manfredi

