ADVANCES IN IBD

Current Developments in the Treatment of Inflammatory Bowel Disease

Section Editor: Stephen B. Hanauer, MD

Highlights From the New ACG Guideline on Crohn's Disease Management

Gary R. Lichtenstein, MD
Professor of Medicine
Director, Center for Inflammatory Bowel Disease
Perelman School of Medicine of the University of Pennsylvania
Philadelphia, Pennsylvania

G&H When and why was the new guideline released?

GL The new American College of Gastroenterology (ACG) guideline for managing adult patients with Crohn's disease was published in the April issue of *The American Journal of Gastroenterology* (with the full text of the guideline available for free download at https://www.nature.com/articles/ajg201827.pdf). This guideline was commissioned because older guidelines no longer reflected the current standards of practice for Crohn's disease management. In addition, although there were various guidelines available for different aspects of treatment of patients with Crohn's disease, there was no large, all-encompassing guideline for appropriate management of these patients. This comprehensive, inclusive update on how to diagnose and treat patients with Crohn's disease consists of 60 recommendations (the strength of which were evaluated according to the Grading of Recommendations Assessment, Development, and Evaluation [GRADE] system) and 53 summary statements (which are descriptive and are not rated according to evidence).

G&H How was the new ACG guideline developed?

GL Five gastroenterologists with expertise in Crohn's disease who are from different institutions across the United States were asked by the ACG to write the guideline (Drs Edward V. Loftus Jr, Kim L. Isaacs, Miguel D. Regueiro, Bruce E. Sands, and myself). Dr Lauren B. Gerson, who is since deceased, was the GRADE methodologist, which means that she assessed the level of the evidence of each recommendation using the GRADE system.

G&H In the new ACG guideline, what are the most significant changes involving the diagnosis of Crohn's disease and the use of endoscopy?

GL One diagnostic change is that fecal calprotectin has been advocated to be a useful tool for differentiating inflammatory bowel disease from irritable bowel syndrome. This was graded to be a strong recommendation with a moderate level of evidence. With regard to endoscopy and diagnosis, the SCENIC consensus (Surveillance for Colorectal Endoscopic Neoplasia Detection and Management in Inflammatory Bowel Disease Patients: International Consensus Recommendations) had suggested that all patients should undergo chromoendoscopy. The new ACG guideline stresses that patients who are at high risk for colorectal neoplasia, such as those with a history of dysplasia and those with primary sclerosing cholangitis, should consider use of chromoendoscopy. In individuals with conventional risk factors, high-definition white-light endoscopy is similar to chromoendoscopy for detection of dysplasia. Additionally for chromoendoscopy, the new ACG guideline states that targeted biopsies could be used instead of random surveillance biopsies when endoscopists have training in and comfort with chromoendoscopy.

As for other endoscopic modalities, the new ACG guideline found that there was inadequate evidence to support the use of narrow-band imaging on a routine basis when evaluating patients for surveillance. This was designated as a conditional recommendation with a low level of evidence, so it may change in the future, but at the present time, narrow-band imaging has not conclusively demonstrated to add any surveillance benefit over conventional high-definition white-light endoscopy.

G&H How does the ACG guideline reflect new knowledge of Crohn's disease activity and prognosis?

GL Since the publication of prior editions of Crohn's disease guidelines, our understanding of disease activity has evolved. Patients with Crohn's disease are often now classified based upon their prognosis and disease activity. Disease activity is a combination of symptoms and endoscopic findings, whereas prognosis involves predictive factors of a benign or a more virulent course of disease, with the more virulent course possibly resulting in disease-related disability or mandating surgery. Thus, disease activity and prognosis define the patient's need for the use of biologic therapy; the patient no longer has to go through the conventional step-up treatment approach (in which the health care provider would first try treatment with a corticosteroid, then an immune modulator, and finally a biologic agent). In this new treatment approach, the health care provider would immediately use a biologic agent at the outset of treatment if the patient's disease activity and/or prognosis warrants it. This evolution in treatment parallels what is currently being done in clinical practice based upon good-level evidence.

G&H What are the most significant changes involving medical treatment of Crohn's disease?

GL Vedolizumab (Entyvio, Takeda) and ustekinumab (Stelara, Janssen) have been approved since the prior edition of the ACG guideline, so the new guideline discusses appropriate use of these agents and the supporting data. Another particular focus involves which patients with Crohn's disease should consider biologic therapy. Twenty percent to 30% of Crohn's disease patients have disease that does not mandate the use of a biologic agent, as the disease may not progress. Thus, the new guideline notes that health care providers may choose not to treat some low-risk patients with Crohn's disease and can just follow them (both with cross-sectional imaging and endoscopy) to ensure that their disease does not progress.

G&H What are some other medical therapies that are discussed in the new guideline?

GL Research has shown that oral mesalamine is not consistently effective vs placebo to induce short-term symptomatic remission in patients who have active Crohn's disease. Therefore, the new guideline states that this treatment should not be used in patients who have active Crohn's disease. This was deemed to be a strong recommendation with a moderate level of evidence.

However, although azathioprine and 6-mercaptopurine are not good inductive agents, they are good maintenance agents. In addition, these agents have demonstrated to be corticosteroid-sparing agents. The new guideline advocates thiopurine methyltransferase testing prior to the initial use of these agents to treat Crohn's disease.

In addition, the new guideline states that methotrexate can be considered to maintain remission and improve the signs and symptoms of Crohn's disease patients who are corticosteroid-dependent.

The guideline also states that sulfasalazine can effectively treat symptoms of colonic, mild to moderately active Crohn's disease. Therefore, sulfasalazine can be considered in these patients, although it is not strongly recommended due to the lack of data assessing its ability to induce mucosal healing.

Additionally, the new guideline notes that antimycobacterial therapy is not effective to induce or maintain remission or mucosal healing in Crohn's disease patients. Therefore, it does not have a role as a primary therapy in these patients. This was deemed to be a conditional recommendation with a low level of evidence; given the data currently available and the potential adverse events, this treatment is not recommended.

G&H According to the new guideline, what is the role of combination therapy?

GL The new guideline notes that combination therapy lessens immunogenicity and increases trough levels of a biologic agent. If a patient has a poor prognosis and significant disease activity, it is important to consider the use of combination therapy with a biologic agent and an immunomodulator. In so doing, it is important to assess the risks vs benefits, given that azathioprine and 6-mercaptopurine have the potential for malignancy (lymphoma in particular) after treatment for 1 year. Thus, combination therapy should be considered as a treatment option for patients with appropriately active disease or in individuals with a poor disease-related prognosis. The health care provider may elect to withdraw azathioprine or lessen the dose in the future; this was not detailed in the new guideline, but it is commonly done in clinical practice.

G&H How does the new guideline address therapeutic drug monitoring?

GL Therapeutic drug monitoring is advocated, particularly for patients who have experienced a secondary loss of response. This is new since the last edition of the ACG guideline. Therapeutic drug monitoring should be used in clinical practice to better understand whether loss of response can be explained by a low drug level or by immunogenicity (or a combination thereof).

G&H Does the new guideline address the use of biosimilars?

GL The new guideline suggests that there are data supporting a single switch from an originator to a biosimilar, but there are not adequate data to support multiple switches between an originator and a biosimilar or a second biosimilar. No controlled trials in inflammatory bowel disease have yet looked at this issue directly.

G&H What are the key points of the new guideline in terms of surgical treatment of Crohn's disease?

GL According to the new guideline, the presence of an abdominal abscess should lead to the consideration of surgery, although some patients may respond to medical therapy after drainage guided by radiology. However, this is only a summary statement because there is not enough evidence to make a recommendation. The guideline also discusses how surgery could be required for patients who have complications of disease, such as intractable hemorrhage, perforation, obstruction, abscess, dysplasia, cancer, or disease that is medically refractory. Also discussed is the potential for strictureplasty in the appropriate patient population.

G&H How does the new guideline address postoperative management of Crohn's disease?

GL The new guideline recommends that all Crohn's disease patients stop smoking because active tobacco smoking, especially in women and heavy smokers, has been identified to increase the likelihood of postoperative recurrence.

In terms of preventing Crohn's disease recurrence following surgery, the guideline notes the limited benefit of mesalamine, although this treatment (or no treatment at all) may be used in patients who have undergone isolated ileal resection and do not have any risk factors for Crohn's disease recurrence. This is a change in the guideline, as mesalamine was previously widely used for preventing recurrence. In addition, recurrence may be prevented with the use of metronidazole and ornidazole (the latter of which is not available in the United States), administered at doses of 1 to 2 g/day, in Crohn's disease patients who have undergone ileocecal resection. This was determined to be a conditional recommendation with a low level of evidence. Additionally, clinical and endoscopic recurrence may be prevented with thiopurines, which are more effective than mesalamine (although not effective enough for preventing severe recurrence). This was graded to be a strong recommendation with a moderate level of evidence. To prevent postoperative recurrence in patients at high risk, anti–tumor necrosis factor (TNF) therapy should be considered within 4 weeks of surgical intervention. Despite a lack of data in postoperative Crohn's disease, anti-TNF therapy might be considered in combination with an immune modulator to lessen immunogenicity and reduce loss of response. This was deemed to be a conditional recommendation with a low level of evidence.

G&H What issues were pointed out for future research?

GL The new ACG guideline points out that the current medical therapies do not result in adequate response in a sizeable number of patients and it is still not possible to predict whether a particular patient will respond to treatment. Future research should explore the prediction of response and nonresponse with various mechanisms of action and predictive models. It would be helpful and a welcome addition to patient management to have readily available, easy-to-use, validated metrics in which doctors could plug in certain parameters and then be able to predict events, such as the likelihood of hospitalization, surgery, and future need for corticosteroids.

Dr Lichtenstein has consulted for Abbott Corporation/AbbVie, Actavis, Alaven, Celgene, CellCeutix, Ferring, Gilead, Hospira, Janssen Orthobiotech, Luitpold/American Regent, Pfizer Pharmaceuticals, Prometheus Laboratories, Romark, Salix Pharmaceuticals/Valeant, Santarus/Receptos/Celgene, Shire Pharmaceuticals, Takeda, and UCB; conducted research for Celgene, Janssen Orthobiotech, Salix Pharmaceuticals/Valeant, Santarus/Receptos/Celgene, Shire Pharmaceuticals, and UCB; received honorarium (CME Program) from Ironwood, Luitpold/American Regent, Merck, and Romark; and received funding to the University of Pennsylvania (IBD Fellow Education) from Janssen Orthobiotech, Pfizer Pharmaceuticals, and Takeda.

Suggested Reading

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