CLINICAL UPDATE

Advances in Inflammatory Bowel Disease From ACG 2015

Optimizing the Use of Biologic Therapies in the Management of Inflammatory Bowel Disease

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G&H Is inflammatory bowel disease an autoimmune disorder?

GD Although inflammatory bowel disease (IBD) is a chronic inflammatory disorder, it is not considered an autoimmune disorder because of the nature of the immune responses that occur. Whereas autoimmune disorders are characterized by immune responses against antigens expressed by a patient's own bodily tissues, IBD develops as a result of the immune system reacting against antigens expressed by the intestinal microbiome.

It is known that certain types of microorganisms are more likely than others to induce inflammation; thus, changes to the microbiome can influence how the body responds to the microbiome. Some dietary interventions promote inflammatory bacteria, whereas other types of diets lower inflammatory bacteria and enhance growth of *Lactobacilli*-type organisms that provide beneficial metabolic byproducts, such as butyric acid and other short-chain fatty acids, to help nourish the intestinal epithelium.

G&H What is the current understanding of how IBD develops?

GD Under normal circumstances, immune cells come into limited and controlled contact with intestinal bacterial components because they sit behind an insulating barrier made of the mucin layer and a water layer filled with bacteriocins and other antibacterial peptides. Dysbiosis, or a change in the inflammatory state, causes inflammatory cytokines that can suppress mucin production. Thus, the mucus layer thins, allowing enhanced penetration of bacterial antigens into spaces occupied by immune cells. This exposure promotes inflammation.

Bacterial products that infiltrate the lamina propria are picked up by antigen-presenting cells, which migrate into the mesenteric lymph node, where they interact with, and activate, antigen-specific T-cells. The activated T-cells traffic back to sites of active inflammation, where they receive additional stimulatory signals. These events are augmented by the release of proinflammatory cytokines (eg, tumor necrosis factor [TNF]-alpha) by epithelial cells, or other immune cells in the lamina propria, further upregulating cell adhesion molecules, which promotes trafficking of additional T-cells into the area of inflammation. This leads to a self-perpetuating cycle of inflammation.

Integrins are cell adhesion molecules widely expressed throughout the body that enable cells to bind to a specific target, such as the basement membrane or the vascular endothelium. All integrins contain an α subunit and a β subunit. Different combinations of subunits provide tissue specificity and differential binding affinity for different sites. One of the most important integrins in the pathophysiology of IBD is $\alpha 4\beta 7$, which is expressed on T-cells after activation in mesenteric lymph nodes.

The recruitment of T-cells into the inflamed gastrointestinal (GI) tissue is mediated by the interaction of integrin pairs on the T-cell surface with adhesion molecules expressed on the endothelial cell. In the setting of IBD, a central adhesion molecule is mucosal addressin cell adhesion molecule (MAdCAM-1), which is primarily expressed on the endothelial cells in organs of the GI tract (ie, the colon, small bowel, liver, biliary tree, and pancreas). This

adhesion molecule is the mechanism through which T-cells in the mesenteric lymph nodes enter the GI mucosa.

In addition to these specific interactions, there are also nonspecific ligands for the GI tract—E-selectins and P-selectins—that are expressed on the endothelial cell surface as a result of inflammatory stimuli. The E-selectins and P-selectins bind to specific T-cell receptors. This interaction actually primes the circulating T-cell to be able to interact with the cell adhesion molecules.

Once they traffic into the lamina propria, activated T-cells can reach the specific area of inflammation by following a chemokine gradient.

G&H How has the growing knowledge of IBD biology contributed to the development of new therapies?

GD Therapy for IBD has been evolving relatively dramatically over the past several years as some of these known immunologic principles have been applied to the design of specific therapies that primarily target the GI tract. In the 1940s, 5-aminosalicylic acid (5-ASA) was designed for patients with rheumatoid arthritis. It was then adapted to IBD, particularly ulcerative colitis (UC); corticosteroids were then adapted for the treatment of UC. Immunosuppressives were developed in the 1960s and were adapted to the treatment of IBD 20 to 30 years later. Approximately 10 to 20 years ago, researchers began experimenting with anti-TNFs; not long afterward, these agents were adopted into clinical practice. Anti-integrin therapies are currently gaining in popularity. New approaches are being adapted to IBD at an increasing velocity as clinicians become more comfortable with the impact of these therapies on the disease process.

Typically, biologic therapies for IBD bring to mind monoclonal antibodies. Currently used agents, as well as those in development, will likely continue to be monoclonal antibodies. However, as scientists begin to discover different targets, the definition of biologic therapy may evolve to include other approaches such as cytokine therapy, vaccine therapy, gene therapy, cellular therapy, and enhanced probiotics.

G&H Can IBD be diagnosed early in the clinical course or before symptoms develop?

GD It is possible that IBD could be detected early. Studies from the 1980s and 1990s have shown that first-degree relatives of people with Crohn's disease (CD) have an increase in intestinal permeability, which suggests that IBD may have a preclinical phase. As the condition progresses, and the inflammation perhaps increases, an early clinical phase becomes evident. Endoscopists performing screening colonoscopies, who take a peek into the terminal ileum, have likely seen a normal colon in the setting of abnormalities in the terminal ileum that resemble CD. There may be aphthous lesions or more advanced ulcerations found at the time of screening, yet the patient is completely asymptomatic.

Many people ask what to do with cases that may be in early clinical phases; a few patients have progressed from a very mild, asymptomatic state to symptomatic IBD. However, many other patients remain asymptomatic for years, and there is no clear understanding of the natural history in this group of patients.

Eventually, if a patient has enough inflammation, the condition progresses to the late clinical phase of IBD. This is where architectural changes occur in the bowel, especially in the setting of CD, where scar tissue deposition can lead to narrowing of the lumen, and deep ulcer penetration can lead to fistula formation and subsequent abdominal accesses or anorectal fistulae.

Once the patient progresses to the late clinical phase, the inflammation is not as relevant as a target as it was in the earlier clinical phase. This transition provides a warning to clinicians: there exists a window of opportunity during which the anti-inflammatory properties of some of the current therapies may make a difference in the disease course, perhaps stopping patients from moving into the late clinical phase.

G&H How often does IBD progress to the point where patients require surgery?

GD Up to 30% of patients with UC will require a colectomy during the first year of their disease process, but as many as 45% of patients may eventually require surgery at some point during the chronic phase of their illness. Over the course of 20 years after the onset of their disease, the majority of patients with CD—up to 80%—will need surgery. However, in the case of CD, even after the inflammation has been removed, studies have shown that up to 90% of patients will experience endoscopic recurrence within a year. Rates of clinical occurrence are much lower, approximately 30% in most studies. This discrepancy between the rates of clinical and endoscopic recurrence illustrates the concept of preclinical inflammation and clinical inflammation that was just discussed. There are many factors that determine whether a patient rapidly progresses to surgery or not.

G&H What are the current treatment goals for managing IBD?

GD Treatment goals may differ between the patient and the clinician. In a national survey of patients with UC, almost three-quarters of patients thought that it was

normal to experience a flare. However, clinicians would prefer patients to achieve and maintain a deep remission so that future surgery, and potentially cancer, can be avoided.

For decades, clinicians have focused on clinical parameters of IBD such as diarrhea and bleeding. There are scores that measure these outcomes somewhat accurately. However, the concept of managing other aspects of IBD to improve outcomes has since come into focus. Mucosal healing is a parameter that is receiving particular attention. However, this endpoint is not as straightforward as one might think because clinical trials have various definitions of normal. Certainly, improved quality of life is another important endpoint, but ultimately the goal is to avoid surgery and hospitalizations, which is where the bulk of the cost of IBD occurs.

Additional goals that have been entertained as relevant endpoints include the absence of mucosal lesions (via endoscopy) and the normalization of C-reactive protein. Other endpoints under evaluation include changes in fecal calprotectin and magnetic resonance imaging (MRI) findings. C-reactive protein and fecal calprotectin are relatively inexpensive and noninvasive tools; MRI is noninvasive but expensive. Colonoscopy is an expensive though reliable test with low interobserver variability, if performed correctly. A low test-to-test variability is important for measuring clinical trial endpoints.

These goals can be achieved, across the board, with different types of investigative modalities. However, it is important that a treatment goal predicts long-term outcomes, and the only goal that reliably predicts reductions in hospitalization and need for surgery is mucosal healing, which has been shown to prevent downstream complications in both CD and UC.

G&H At what point in the disease process is it appropriate to consider biologic therapies?

GD This is a question that continues to challenge clinicians. For many years, the use of biologic agents has been reserved as the last choice for patients with IBD.

For the most part, clinicians have decided that the step-up treatment algorithm is no longer appropriate and that therapy needs to be tailored to the patient's disease parameters. For example, a patient with severe inflammation would not be treated with a medication that has relatively low efficacy compared with other therapies. Therefore, the question of whether biologic therapies should be used earlier for appropriate patients with moderate to severe disease needs to be studied.

Duration of disease appears to matter. It seems that there is a window of optimal response to biologic therapy, which is when there is primarily an inflammatory component. If a point is reached where a patient develops stenotic or penetrating disease, biologic agents do not work as well. After a brief stint where biologic monotherapy was recommended, current recommendations suggest using immunomodulators in the context of biologic therapy.

Disease severity is also important. Biologic therapies are not typically used in patients with the mildest disease, but are instead reserved for patients with more significant disease. However, clinical efforts to define significant disease can be difficult; the symptom-based scoring systems that were used in the past have been shown to poorly correlate with endoscopic indicators of severity.

As more research is conducted in the area of biologic therapies, clinicians will better understand how best to use these therapies early on in the course of the disease process in order to maximize outcomes.

G&H How does the cost of biologic therapies compare with other treatment modalities?

GD Biologic therapies are typically considered to be relatively expensive, especially compared to generic 5-ASA. However, studies have shown that suboptimal therapy—manifested as using corticosteroids, switching medications, escalating doses, adding medications, or requiring disease-related hospitalization or surgery—is associated with a higher cost than in patients who seem to be maximized on their medication. These findings suggest that biologic therapies may be worth the cost if the inflammatory process can be controlled for these patients.

G&H Which biologic agent should be used first when treating a patient for IBD?

GD Researchers do not have an answer to this question yet. Hopefully in the next few years, head-to-head comparison trials of different classes of biologic agents will provide an answer. There are a number of choices among anti-TNF therapies; however, data suggest that switching from 1 anti-TNF agent to another results in lower efficacy rates with the second agent.

G&H Which prognostic factors have been found for IBD that might help identify patients who should receive biologic therapy at an earlier disease stage?

GD Early onset, defined as an age less than 40 years, is generally a poor prognostic factor for both UC and CD. Severe endoscopic lesions are also associated with a poor prognosis; the more deep ulcerations that are present, the more likely a patient is to develop complications requiring surgery. Lack of mucosal healing after induction of clinical remission also portends a bad outcome.

In patients with CD, poor outcomes have been associated with the presence of extensive disease (including upper GI tract disease) and the development of perianal disease, especially when this complication is present at the time of diagnosis; a need for corticosteroids early on in the course of treatment is also a marker in patients with CD. Smoking is a poor prognostic factor, as people who smoke are 3 times more likely to eventually require surgery. Finally, in patients with UC, the main poor prognostic indicators are the presence of pancolitis or a need for corticosteroids at the time of diagnosis.

G&H How might these prognostic factors influence the treatment strategy for a patient with IBD?

GD These factors allow clinicians to approach individualized therapy for IBD. After a patient is appropriately diagnosed, clinicians can assess risk factors. For a patient with low-risk features and milder disease, some of the less effective, but lower risk, therapies might be used first before moving up to therapies that have higher efficacy but higher risk associated with them. A patient with high-risk features or with moderate-to-severe disease may start earlier with a biologic agent in a tailored approach.

Once a patient is on medication, clinicians should assess response. Using a personalized approach, a suboptimal response would require either a dose adjustment, a switch to another drug in the same drug class, or a change in mechanism of action, depending on results of therapeutic drug monitoring. An optimal response to personalized therapy would prompt continued use of the initial drug as long as the patient responds optimally.

G&H What role does the patient have in the treatment decision-making process?

GD Patients want to be involved in making treatment decisions. Clinicians can involve patients and make the most appropriate treatment decisions by using a shared decision-making process, which includes educating patients about their options and helping them be comfortable with their treatment plan. Patients who have input into the decision and share ownership of the treatment plan are more likely to adhere to therapy.

Clinicians should discuss preference-sensitive decisions, such as the selection of a therapeutic approach (eg, monotherapy vs combination therapy), with their patients. Some patients do not want to go on either anti-TNFs or an immunomodulator. Likewise, if medication fails, clinicians and patients should consider surgery.

G&H What is the treat-to-target concept, and how is it applied to IBD management?

GD Treating to target begins with a baseline assessment. An initial target to work toward is set based on the parameters of the baseline assessment and goals of therapy. For a patient with high-risk disease, attaining the deepest mucosal remission possible is key. For a patient with relatively low-risk disease, a push in therapy to achieve mucosal remission may not be the answer; patients with no adverse prognostic factors may do very well with less aggressive therapies for the foreseeable future.

After the patient has undergone therapy, the clinician should reassess and possibly move the target based on responses. For example, if mucosal healing is not observed even after maximal combination therapy, the target could change from mucosal healing to symptom relief, or the patient could continue on-target with mucosal healing and switch drug classes. If the target is reached, the clinician should continue to assess it periodically. That way, it may be possible to avoid some of the long-term consequences of continued unmitigated inflammation.

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Suggested Reading

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