Achieving Remission in IBD: Looking to Novel Agents to Update Management Paradigms

Defining the Burden of IBD

Inflammatory bowel disease (IBD) is a chronic, relapsing disorder of the gastrointestinal (GI) tract that affects more than 1.5 million Americans. Patients with IBD are significant users of health care resources, representing an excess of 1.8 million visits to ambulatory care facilities and more than 75,000 visits to the emergency room each year. As a result, the direct and indirect medical costs associated with IBD are substantial. Moreover, patients with IBD are at increased risk of colon and biliary cancers, and immunosuppressive therapies have been associated with increased risks of lymphomas and skin cancers.

Management Strategies in IBD: Where Are We Now?

Ulcerative Colitis

For patients with moderate to severe ulcerative colitis (UC), therapeutic options include systemic corticosteroids and immunosuppressive therapy or biologic therapy with anti-tumor necrosis factor alpha (TNF-α) agents. Systemic corticosteroids are effective at inducing remission, but adverse effects limit long-term use, and 1 year after starting corticosteroids, up to 60% of patients become corticosteroid dependent or require colectomy. Thiopurines are modestly effective at maintaining corticosteroid-induced remissions but are associated with the need for therapeutic monitoring, risk of infections, and neoplasias.

Infliximab, adalimumab, and golimumab are now all approved for UC by the US Food and Drug Administration (Figure 1). In the ACTIVE ULCERATIVE COLITIS TRIAL (ACT) 1 and ACT 2 trials, infliximab induced healing in 46% to 57% of patients at week 30, and 45% at week 52. Remission, a secondary endpoint, was attained at week 30 in 26% to 37% of patients. In extensively pretreated patients with severe disease,

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Studies have assessed the role of anti-TNF-α and co-therapy with an immunosuppressant such as azathioprine to reduce patient immune responses to therapy. Although the combined therapies were more effective than the individual components, the combination regimen is complex, and long-term safety is a concern for all but the most severe patients.

TREATMENT FAILURE
Although anti-TNF-α agents have shown clear benefits over conventional treatments for inducing and maintaining clinical remission in IBD, approximately one-third of patients with CD are primary nonresponders to induction therapy. Moreover, in a systematic review of adalimumab studies, the risk for loss of response was 20% per patient year, with other studies reporting similar results.

Loss of response may be due to immunogenicity, pharmacology, or loss of mechanism. Both serum drug levels and the presence of anti-drug antibodies (ADAs) can be determined with commercial assays. In addition, inflammation plays a lesser role in established disease, and longer duration of disease is less responsive to anti-TNF-α therapy.

In the case of true “primary failures,” several factors need to be considered, including whether the patient has received an adequate dose and duration of treatment. Maintaining adequate serum levels of monoclonal antibodies is critical to both short-term and long-term effectiveness. The development of ADAs increases the clearance of monoclonal antibodies and lowers trough levels and, therefore, the clinical effectiveness of anti-TNF-α therapy.

Currently, primary nonresponse or secondary failure with anti-TNF-α therapy is treated empirically, with dose escalation being a common “first step,” particularly for secondary failure after an initial response (or for insufficient response). A substantial proportion of patients on anti-TNF-α therapy (25%) require dose escalation per year to overcome rapid drug clearance due to pharmacokinetics or ADAs. Although it has been shown that low titers of ADAs can be transiently “overcome” by repeated, higher dosing, the efficacy of this strategy is likely to be short lived, with the need for continued dose increases. In addition, corticosteroid-free remission is often not achieved.

Prior anti-TNF-α exposure appears to be a risk factor for dose escalation within 1 year of adalimumab therapy, whereas prior combined immunosuppressive therapy associated with lower rates of discontinuation of anti-TNF-α therapy. Patients who develop immunogenicity to one agent are likely to develop immunogenicity to a subsequent biologic; therefore, it is usual to add an immunosuppressant if the patient has been treated previously with anti-TNF-α monotherapy.

It is now possible to simultaneously measure ADAs and drug levels. In a retrospective study of 155 patients who had had infliximab and anti-infliximab antibodies measured, the results impacted treatment decisions in 73% of patients. Patients who fail therapy because of the development of ADAs are excellent candidates for a switch to an alternative anti-TNF-α agent (Figure 2).

Failing with documented treatment failure despite the presence of adequate serum concentrations are unlikely to respond to switching to an alternative anti-TNF-α agent. These individuals will usually require therapies with a different mechanism of action. Options available as an alternative to anti-TNF-α therapy are currently relatively limited, for example, to general immunosuppressants.
Disease Mechanisms and Therapeutic Targets

Although the pathogenesis of IBD is not completely understood, it is thought that UC and CD occur in genetically susceptible individuals through an abnormal inflammatory response to enteric commensal bacteria. Although the clinical presentations of UC and CD can be different, they share many common pathophysiologic mechanisms, including lymphocyte-mediated immune responses. Epidemiologic data, detailed molecular studies, and recent genome-wide association studies suggest that UC and CD are related polygenic diseases that share a number of susceptible loci. For instance, they are both associated with genomic regions that implicate products of genes involved in lymphocyte trafficking.

One of the hallmarks of chronic inflammation is the rapid recruitment of circulating lymphocytes to areas of inflammation. Inhibition of lymphocyte adhesion and migration decreases the density of lymphocytes within the GI tract, reduces the secretion of proinflammatory soluble mediators, and diminishes cellular immune events, which ultimately attenuates tissue inflammation.

Integrins are a family of cell-surface glycoproteins involved in cell adhesion and immune cell migration and activation. The α4 integrin is expressed predominantly on lymphocytes, monocytes, eosinophils, and basophils and is usually undetectable on neutrophils. Both α4β1 and α4β7 play a role in migration of lymphocytes across the vascular endothelium and contribute to cellular activation and survival within the parenchyma. In addition, α4β7 appears central to lymphocyte homing to intestinal tissue via mucosal addressin cell adhesion molecule-1 (MadCAM-1). In IBD, lymphocyte trafficking plays a key role in perpetuating inflammation by allowing the capture and entry of activated lymphocytes into intestinal tissues. As such, interfering with this trafficking process is a potential target for IBD therapies. Several agents are under investigation (Figure 3).

The integrin antagonists, natalizumab and vedolizumab, both block integrins with the α4 subunit but have different specificity for the β subunit. Natalizumab has broad systemic effects on lymphocyte trafficking attributable to nonselective binding to the α4β1 subunit, which inhibits the interaction of α4β1 and VCAM-1, expressed throughout the body, as well as the interaction of α4β7 with MadCAM-1. Vedolizumab blocks only the α4β7 integrin, acting on the MadCAM-1 receptor. Because the interaction between α4β7 integrin and MadCAM-1 is particularly important for lymphocyte trafficking into the GI endothelial cells, this selective binding therefore inhibits this without impacting trafficking to the CNS.

The effect of natalizumab on immune surveillance in the CNS explains both the efficacy observed in multiple sclerosis and the increased risk of developing progressive multifocal leukoencephalopathy (PML), an opportunistic infection associated with the John Cunningham (JC) virus. Vedolizumab does not affect CD4+ and CD8+ cell counts in cerebrospinal fluid (CSF) or the CD4+/CD8+ ratio in healthy volunteers. These results are consistent with vedolizumab’s lack of effect on physiologic CNS immune surveillance and pathologic CNS inflammation in monkeys.

Integrins and Addressins in IBD: Examining the Evidence

Natalizumab was shown to be effective in maintaining remission in CD. In the Evaluation of Natalizumab as Continuous Therapy (ENACT) 1 study, natalizumab administered intravenously at a dose of 300 mg at 0, 4, and 8 weeks failed to induce clinical response at week 10. However, in ENACT 2, patients from the ENACT 1 trial who responded at weeks 10 and 12 were rerandomized to maintenance therapy with natalizumab 300 mg or placebo every 4 weeks through week 54 and were followed through week 60. Remission was maintained through week 54 in 44% of patients in the natalizumab group vs 26% of the placebo group (P=0.003). However, the risk of PML with natalizumab therapy is 1:160 to 1:10,000, dependent on risk factors—notably JC virus status, prior immunosuppressant use, and duration of therapy.

Seamless induction-maintenance phase III studies of vedolizumab in UC (GEMINI 1) and CD (GEMINI 2) were conducted. The GEMINI 1 trial found that in the vedolizumab group, the 6-week clinical response rate was 47% compared with 23% in the placebo group (P<0.001). 17% of patients receiving vedolizumab and 5% receiving placebo were in clinical remission at week 6 (P=0.001).

Patients in remission were then entered into the maintenance phase. At week 52, 42% of patients treated with vedolizumab every 8 weeks and 45% of those treated every 4 weeks remained in clinical remission, compared to 16% of placebo-treated patients (P<0.0001). In addition, significantly more patients treated with vedolizumab had a durable clinical response, durable clinical remission, and corticosteroid-free remission (Figure 4 on page 4). Mucosal healing rates were also significantly greater with vedolizumab.
The GEMINI 2 trial in patients with CD also found that vedolizumab was superior to placebo in terms of patients entering remission at 6 weeks (14% response rate at week 6 vs 7% with placebo, P=0.02); however, the rates of clinical response were not significantly different to placebo (31% at week 6 vs 26% with placebo). At week 52 of maintenance treatment, however, 39% of patients treated with vedolizumab every 8 weeks and 36% of those treated every 4 weeks were in clinical remission, compared with 22% of placebo-treated patients (P<0.001). At week 52, significantly more vedolizumab-treated patients had a Clinical Disease Activity Index-100 response, and vedolizumab treatment also resulted in an increase in corticosteroid-free remission. The proportion of patients with a durable clinical remission did not, however, differ significantly among the groups (Figure 5).

Importantly, vedolizumab appears to be effective in patients who were anti-TNF naïve and also in those who had previously been treated with anti-TNF antibodies. Therefore, vedolizumab may provide a new therapeutic option for anti-TNF–naïve patients as well as those who do not respond to or have lost response to prior anti-TNF therapy.

The safety profile of vedolizumab appears to be favorable, and, as mentioned, no cases of PML have been reported in association with vedolizumab. Therefore, in the phase III GEMINI trials, the main adverse events reported were headache, nasopharyngitis, arthralgia, and fever. Based on these studies, agents targeting gut-specific lymphocyte trafficking hold great promise for new options and safe and effective therapy in IBD.
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Release date: February 2014 • Expiration date: February 28, 2015 • Estimated time to complete activity: 0.5 hour

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For purposes of certification, please complete the following information. Note that we will not forward or sell your contact information. Please PRINT clearly.

First Name: ___________________________ Middle Initial: ______________________ Last Name: _______________________

Degree: ○ MD ○ DO ○ PharmD ○ RN ○ NP ○ PA ○ Other:

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E-mail (REQUIRED TO RECEIVE CERTIFICATE):

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○ NO, I do NOT want to be contacted in the future.

I certify my actual time spent to complete this educational activity to be (check one):

○ I participated in the entire activity and claim 0.5 credit.

○ I participated in only part of the activity and claim __________ credit.

Signature: ___________________________ Date: ___________

Only completed forms will be processed for credit. Please allow 4-6 weeks to receive your certificate. Thank you for participating in this activity.

POST-TEST QUESTIONS

Instructions: For each question circle the most appropriate response.

1. One year after starting corticosteroids, approximately what proportion of patients with ulcerative colitis (UC) become corticosteroid dependent or require colectomy?
   A. Up to 50%
   B. Up to 60%
   C. Up to 70%
   D. Up to 80%

2. A 30-year-old woman with a 5-year history of UC who was treated with anti-tumor necrosis factor-alpha (TNF-α) therapy (infliximab 5-mg/kg standard loading dose and then maintenance every 8 weeks) experienced a resolution of clinical symptoms since initiation of therapy 6 months ago but now reports recurring symptoms. Stool cultures and assessment for Clostridium difficile are negative. What is your first consideration for a patient who is losing response to anti-TNF-α therapy?
   A. Increase the dose.
   B. Shorten the dosing interval.
   C. Measure trough serum levels and anti-drug antibodies.
   D. Reassess for active inflammation.

3. A 45-year-old man with extensive small bowel nonpenetrating Crohn's disease (CD) had been treated previously with azathioprine 2 to 3 mg/kg/d. When he lost response, adalimumab was added in standard loading (160/80 mg) and maintenance 40 mg every other week. After 1 year, he experienced complete loss of response and did not respond to empiric dose escalation to weekly dosing. He is now being considered for treatment with natulizumab. Which of the following is NOT true about this patient’s risk of progressive multifocal leukoencephalopathy (PML) on natulizumab?
   A. The risk of PML is increased because of prior use of azathioprine.
   B. The risk is increased if the patient is seropositive for John Cunningham virus.
   C. The risk increases with a treatment duration of natulizumab longer than 2 years.
   D. The risk is increased because the patient is male.

4. MAdCAM-1 is the addressin to which the integrin α4β7 binds. What is MAdCAM-1?
   A. Membrane addressin cell adhesion molecule-1
   B. Mucosal addressin cell adhesion molecule-1
   C. Mucosal activated cell addressin molecule-1
   D. Membrane attached cell addressin molecule-1

5. Vedolizumab exerts its effect by binding to which integrin?
   A. α4β1
   B. α4β7
   C. MAdCAM-1
   D. VCAM-1

6. In the GEMINI I trial in UC, significantly more patients treated with vedolizumab had a durable clinical response, durable clinical remission, and corticosteroid-free remission than did patients treated with placebo; true or false?
   A. True
   B. False
**ACTIVITY EVALUATION FORM AND APPLICATION FOR CONTINUING MEDICAL EDUCATION CREDIT**

We greatly value your opinion. Please complete this evaluation and return it, along with the post-test, to Global Education Group. Your responses will be used in future planning of activities and materials.

I am a(n): ☐ MD ☐ DO ☐ PharmD ☐ RN ☐ NP ☐ PA ☐ Other: _________________________________________________________________

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<th>Upon completion of this activity, participants will be able to:</th>
<th>Strongly Disagree</th>
<th>Disagree</th>
<th>Agree</th>
<th>Strongly Agree</th>
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<td>Summarize the role of lymphocytes in the pathogenesis of inflammatory bowel disease (IBD) and the shared pathophysiology of ulcerative colitis (UC) and Crohn’s disease (CD)</td>
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<td>Explain the efficacy and limitations of current therapy for moderate to severe IBD and the impact of unmet medical needs</td>
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<td>Review the identification of treatment failure and the options available for patients who do not respond to current therapy</td>
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<td>Describe the mechanism of action of integrin inhibitors in IBD and how integrin inhibitors could be integrated into clinical care paradigms for IBD</td>
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Please indicate the extent of your agreement with the following statements:

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<th>The faculty for this activity were effective</th>
<th>Strongly Disagree</th>
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Overall, was this activity free from bias?
☐ Yes  ☐ No

Of the patients you will see in the next week, about how many will benefit from the information you learned today?
☐ More than 50 patients
☐ 26 to 50 patients
☐ 11 to 25 patients
☐ 1 to 10 patients
☐ Not applicable

Based on what I learned today, I will improve my practice by incorporating the following (check all that apply):
☐ Improved diagnosis/patient assessment
☐ Useful therapies and appropriate uses
☐ Cutting-edge science in this therapeutic area
☐ Best practices of my colleagues and leaders
☐ Other (explain): ____________________________________________________________

Please rate the professional practice value of each of the following in terms of improving your practice:

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<th>The professional practice value of each of the following</th>
<th>Least Valuable</th>
<th>Somewhat Valuable</th>
<th>Valuable</th>
<th>Most Valuable</th>
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<td>This CME activity</td>
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<td>Direct-to-consumer advertising</td>
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Based on your experience, which of the following are the primary barriers to implementing changes in practice (check all that apply):
☐ Lack of knowledge regarding evidence-based strategies
☐ Lack of convincing evidence to warrant change
☐ Lack of time/resources to consider change
☐ Insurance, reimbursement, or legal issues
☐ Other (explain): ____________________________________________________________

What motivated you to participate in this activity?
☐ CME credits
☐ Faculty
☐ Topic or therapeutic area
☐ Format type

Please rate your level of agreement with the following statement:

A substantial proportion of patients with moderate to severe IBD in whom anti-TNF-α therapy is indicated do not enter long-term (>1 year) complete remission with anti-TNF-α therapy.

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<th>Reject completely</th>
<th>1 2 3 4 5</th>
<th>Accept completely</th>
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How confident are you that you can identify and manage primary or secondary nonresponse to anti-TNF-α therapy?
☐ Not confident
☐ Some confidence
☐ Confident
☐ Very confident

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