What to Do When Biologic Agents Are Not Working in Inflammatory Bowel Disease Patients

Sushila R. Dalal, MD, and Russell D. Cohen, MD

Dr Dalal is an assistant professor of medicine in the Section of Gastroenterology and Dr Cohen is a professor of medicine and director of the Inflammatory Bowel Disease Center at The University of Chicago Medicine in Chicago, Illinois.

Address correspondence to:
Dr Russell D. Cohen
The University of Chicago Medicine
5841 S. Maryland Avenue, MC 4076
Chicago, IL 60637
Tel: 773-702-0719
Fax: 773-702-2182
E-mail: rcohen@medicine.bsd.uchicago.edu

Abstract: Anti–tumor necrosis factor α and anti-integrin biologic therapies are effective for induction and maintenance of remission in moderate to severe ulcerative colitis and Crohn's disease. However, clinicians face many challenges in determining the best course of action when a patient does not respond or loses response to a biologic therapy. When patients are found to have continued active inflammation despite having undergone biologic therapy, the first determination should be whether this represents a primary nonresponse to the drug's mechanism of action or a secondary loss of response due to inadequate drug levels and/or antibody formation to the drug. Primary nonresponders may respond to a drug with a different mechanism of action. Secondary loss of response may be addressed through strategies such as dose escalation or addition of an immunosuppressant. Future options may include changing to a therapy targeting other mechanisms of immune modulation.

Keywords
Inflammatory bowel disease, Crohn's disease, ulcerative colitis, biologic therapy, anti–tumor necrosis factor α, anti-integrin

The approval of infliximab (Remicade, Janssen) to treat inflammatory bowel disease (IBD) started a revolution in IBD therapy that has led to the approval of several other anti–tumor necrosis factor (TNF) α agents (ie, adalimumab [Humira, AbbVie], certolizumab pegol [Cimzia, UCB], and golimumab [Simponi, Janssen]) and anti-integrin agents (ie, natalizumab [Tysabri, Biogen] and vedolizumab [Entyvio, Takeda]) for the treatment of Crohn's disease (CD) and ulcerative colitis (UC). However, despite the effectiveness of anti-TNF α and anti-integrin therapies in inducing and maintaining remission in IBD, patients often report symptoms that may reflect ongoing active inflammation. Determining the best course of action for a patient who does not respond or loses response to biologic therapy provides a challenge for clinicians. This article focuses on ensuring that symptoms represent continued inflammatory activity and determining whether the current therapy can be optimized or must be switched to another agent.

Determining the Source of the Symptoms

When a patient initially reports symptoms while on biologic therapy, the clinician's first objective is to ensure that the symptoms are due to active IBD. Symptoms owing to an infection or other gastrointestinal (GI) disorder cannot be treated with a biologic agent and, thus, will not respond to optimization or alteration in IBD therapy.

Two infections commonly encountered in patients with IBD are *Clostridium difficile* infection (CDI) and cytomegalovirus (CMV). The increased rate of CDI in the general population has occurred parallel with a rise in the rate of CDI in patients with IBD.[1] *C difficile* symptoms may be indistinguishable from IBD symptoms, and the endoscopic appearance of pseudomembranes is much less common in IBD patients with CDI.[2,3] The current American College of Gastroenterology guidelines, from 2013, recommend that all IBD patients hospitalized for a disease flare should be tested for CDI.[4] In addition, outpatients who do have quiescent disease or have risk factors, such as recent hospitalization or antibiotic use, and develop diarrhea should be tested for CDI. Although data are mixed on the role of immunosuppressive agents—including 6-mercaptopurine (6-MP), azathioprine, methotrexate, or corticosteroids—as risk factors for the development of CDI, the guidelines also do conditionally recommend avoidance of escalation of immunosuppressive therapy for the first 72 hours of CDI treatment when possible. The current recommendation is to maintain the existing level of immunosuppression while treating CDI.[5]

Debate has existed in the literature regarding whether CMV worsens severe colitis or is a marker of disease severity.[6] CMV infection is common in the immunocompetent population, and the initial infection is most often asymptomatic. Reactivation can occur asymptomatically in immunocompetent individuals, while immunosuppressed patients may become symptomatic. CMV colitis is usually associated with abdominal pain, fatigue, fever, diarrhea, and, occasionally, blood in the stool. Studies of patients described as having corticosteroid-refractory UC have detected CMV by immunohistochemistry in endoscopic biopsy or colectomy specimens in 20% to 40% of patients.[6] However, in many of these cases, the CMV became undetectable without the addition of antiviral therapy, and may resolve with clinical improvement. The response rate to treatment of CMV in corticosteroid-refractory patients is difficult to ascertain, as most patients studied are on concomitant IBD therapy, and determining whether the antiviral therapy or IBD therapy is responsible for the improvement may not always be easily determined.

Proving the Presence of Active Inflammation

After infection is ruled out as the source for symptoms, the decision as to whether a current therapy is effective should not be based on clinical symptoms alone. Symptoms of diarrhea, abdominal pain, or nausea may indicate other conditions, such as irritable bowel syndrome, small intestinal bacterial overgrowth, celiac disease, stricturing or scarred disease no longer responsive to anti-inflammatory therapy, or sequelae of prior surgeries, such as bile salt diarrhea. Surrogate markers, such as serum C-reactive protein (CRP) or fecal calprotectin, can be helpful indicators of inflammation. A recent meta-analysis of 19 cohort and case-control studies evaluated the accuracy of CRP and fecal calprotectin for diagnosing active disease in symptomatic patients with known IBD. Endoscopy was the gold standard comparator in these studies.[7] CRP had a low pooled sensitivity of 0.49 (95% CI, 0.34-0.64) but a high specificity of 0.92 (95% CI, 0.72-0.96). However, fecal calprotectin was more sensitive than CRP, with a pooled sensitivity of 0.88 (95% CI, 0.84-0.90) and a specificity of 0.73 (95% CI, 0.66-0.79). Notably, fecal calprotectin was more sensitive for diagnosing UC-related inflammation than CD-related inflammation. Although these markers are quick and noninvasive, they remain surrogate markers of inflammation. Endoscopic evidence of active IBD in patients with upper GI CD, ileal-colonic CD, or UC remains the gold standard for diagnosis. Cross-sectional imaging with small bowel follow-through, computed tomography enterography, or magnetic resonance enterography also provides useful indicators of inflammation, especially in patients with isolated small bowel CD.[7]

Primary Nonresponse Vs Secondary Loss of Response

Once a patient has been evaluated for infection and objective evidence of active IBD has been found, the clinician needs to determine whether the symptoms represent primary nonresponse to the biologic drug's mechanism of action or secondary loss of response. Primary nonresponders may react to a different class of drugs, whereas secondary loss of response may be addressed through dose escalation or the addition of an immunosuppressant.

Primary Nonresponse

Primary nonresponse refers to patients who do not respond adequately to the initial loading doses of a biologic agent. These patients are found to have adequate drug levels and no antibodies. Because there is a lack of response in the presence of adequate drug levels, these patients may not respond to the particular mechanism of action of the drug, and switching to a medication in a different class is recommended. Thus, when a patient has a primary nonresponse to an anti-TNF α agent, consideration can be given to a calcineurin inhibitor such

as cyclosporine or tacrolimus (in UC) or an anti-integrin agent such as natalizumab (in CD) or vedolizumab (in UC or CD). Although switching to a second anti-TNF α agent has not been shown to be particularly beneficial in this setting, it is important to realize that the vast majority of these patients in published trials and center experiences had infliximab as their initial anti-TNF α agent; there is less experience (and data) when the primary nonresponse is to a different anti-TNF α agent, where subsequent use of infliximab may be considered.

Sequential infliximab and cyclosporine in the acute setting should only be undertaken with the greatest caution, as serious infection and death have occurred.[8] A single-center study from Mount Sinai Hospital in New York evaluated 19 patients with corticosteroid-refractory UC. Ten of these patients received infliximab followed by cyclosporine within 4 weeks, while 9 patients received cyclosporine within 4 weeks of receiving infliximab.[8] Four patients (40%) of the infliximab-salvage group achieved remission, while 3 patients (33%) in the cyclosporine-salvage group achieved remission. However, 1 patient in the infliximab-salvage group died from sepsis. Within the cyclosporine-salvage group, 1 patient developed herpetic esophagitis, and another patient developed pancreatitis and bacteremia.

The University of Chicago in Chicago, Illinois reported on 49 patients with CD who received natalizumab, 47 of whom had previously failed at least 1 anti-TNF α agent.[9] Of these 49 patients, 25 patients (51%) discontinued treatment due to lack of response. Seventeen patients (35%) successfully continued treatment for longer than 12 months. Several centers in Boston, Massachusetts reported on 69 patients with CD who were treated with natalizumab, 65 of whom previously had been treated with at least 1 anti-TNF α agent.[10] Of the 62 patients who had data available to assess response, 40% successfully achieved response.

Vedolizumab was recently approved by the US Food and Drug Administration (FDA) for the treatment of moderate to severe UC and CD in patients who have failed at least 1 other agent. The GEMINI 3 (Study of Vedolizumab in Patients With Moderate to Severe Crohn's Disease) study of vedolizumab in patients with CD who had previously failed at least 1 other anti-TNF α agent found that at week 10 of treatment, a higher proportion of patients given vedolizumab were in remission (26.6%) than patients given placebo (12.1%; *P*=.001; relative risk [RR], 2.2; 95% CI, 1.3-3.6).[11]

Secondary Loss of Response

Secondary loss of response refers to patients who had previously responded to a biologic agent but then demonstrated evidence of ongoing disease activity despite continued therapy. Once ongoing inflammation has been confirmed, the drug level and antibodies to the drug should be assessed if the assay is available (as is currently the case for infliximab and adalimumab). After drug levels and antibodies are assessed, the drug dosing should be increased if drug levels are low and antibodies are not present, switched to another drug in the class if drug levels are low and antibody levels are high, or switched to another drug mechanism if drug levels are high and antibodies are not present (Table).

Table. Response to Assay of Infliximab or Adalimumab Drug Levels and Antibodies in Patients With Continued Inflammation

Drug Present?	Antibodies Present?	Action
No drug	High titer	Switch anti-TNF α agent
No drug	No antibodies or low titer	Dose increase
Inadequate	No antibodies or low titer	Dose increase
Adequate	No antibodies or low titer	Switch classes

TNF, tumor necrosis factor.

Dose Optimization of Infliximab

Adequate serum infliximab levels have been found to correlate with improved outcomes in CD and UC. A study of 105 patients with CD treated with 5 mg/kg of infliximab induction followed by scheduled interval treatment (6 to 8 weeks) or episodic-as-needed maintenance retreatment found a correlation between infliximab concentration, clinical remission, and change in endoscopic score from baseline.[12] Furthermore, there was an inverse relationship between the serum infliximab concentration and CRP. In a study of 115 patients with UC treated with 3 doses of infliximab induction followed by scheduled maintenance dosing, patients with detectable serum infliximab levels had higher rates of remission (69% vs 15%; *P*<.001) and endoscopic improvement (76% vs 28%; *P*<.001) than patients with undetectable infliximab levels.[13] An undetectable infliximab level predicted an increased risk for colectomy (55% vs 7%) as compared to patients with detectable infliximab levels. Therapeutic infliximab concentrations have been defined as greater than 12 mcg/mL at 4 weeks postinfusion or detectable infliximab (>1.4 mcg/mL) at dosing trough.[12,14] A retrospective analysis of the ACCENT (A Crohn's Disease Clinical Trial Evaluating Infliximab in a New Long-Term Treatment Regimen) I trial of moderate to severe CD patients taking infliximab 5 mg/kg or 10 mg/kg every 8 weeks found that a week 14

trough greater than 3.5 mcg/mL was significantly associated with a durable sustained response.[15] Similarly, the assessment of infliximab trough at week 14 or week 22 in 84 patients who had sustained response to infliximab demonstrated that a trough level greater than 3 mcg/mL was associated with a lower risk of treatment failure.[16] A retrospective study of patients in whom infliximab concentrations were assessed found that among 29 patients with subtherapeutic infliximab concentrations, increasing the infliximab dose was associated with a partial or complete clinical response in 86%.[17] More recently, a study of pediatric and adult patients with IBD who had suspected loss of response to infliximab at medical centers throughout Israel found that a trough level of infliximab greater than 3.8 mcg/mL identified patients who had adequate drug levels.[18] These patients failed to respond to an increase in drug dosage or to a switch to another anti-TNF α agent.

Inadequate drug levels may be achieved due to increased loss of drug. Because severe disease activity in both UC and CD causes an ulcerated and leaky mucosa and patients are known to have low serum protein levels due to loss of proteins through the gut, it has been hypothesized that the infused or injected monoclonal antibodies also leak through the gut. Infliximab was identified in 66% of the 195 fecal samples taken within the first 2 weeks of dosing from 30 patients with moderate to severe UC.[19] Nonresponse at week 2 was correlated with higher levels of infliximab in the feces (*P*=.0047). A separate analysis of the data from 728 patients enrolled in the ACT (Active Ulcerative Colitis Trial) 1 and 2 trials of infliximab showed that patients with higher serum albumin had higher levels of infliximab.[20] Below-normal serum albumin was associated with lower infliximab levels and worse response rates to the drug. A common salvage pathway for albumin and immunoglobulin G (IgG) via the neonatal Fc receptor was hypothesized to be the mechanism of this correlation. (All of the currently approved monoclonal antibodies in IBD are IgG-type.) A study of 13 patients with corticosteroid-refractory acute severe UC demonstrated that at week 10 of infliximab induction, all patients had an estimated clearance of infliximab of 2.8 days (range, 1.3-6.2 days).[21] The average half-life for infliximab is 9.5 days. Undetectable induction serum infliximab with or without a low antibody titer was associated with the development of antibodies to infliximab and treatment failure. This accelerated clearance of infliximab in severe IBD has been attributed to a high TNF α load or increased intestinal permeability.

For patients with low infliximab drug levels, dose adjustment (either through an increase in the dose given or a decrease in the dosing interval) is effective at recapturing response. Afif and colleagues reported a higher likelihood of clinical response in patients who were found to have subtherapeutic infliximab concentrations and were administered an increase in infliximab dosing.[17] In this study, 63 patients exhibited subtherapeutic infliximab levels. Twenty-five of 29 patients (86%) had complete or partial clinical response to an increased infliximab dose. Of the 6 patients who were instead switched to another anti-TNF α agent, only 2 patients (33%) had a clinical response. Yanai and colleagues also described a dose increase in 91 of 188 patients with suspected loss of response to infliximab.[18] Infliximab trough levels higher than 3.8 mcg/mL were 90% specific for failure to respond to an increased infliximab dose (with positive predictive value [PPV] of 56% and negative predictive value [NPV] of 51%) and had 86% specificity for the failure to respond to a switch to adalimumab (PPV, 72%; NPV, 43%; n=27). The TAXIT (Trough Level Adapted Infliximab Treatment) trial reported on dose optimization of CD and UC patients on maintenance infliximab therapy to infliximab trough concentrations of 3 to 7 mcg/mL, followed by 1 year of infliximab dose adjustment based on clinical symptoms or drug levels.[22] The study found that during the optimization phase, the number of CD patients in remission increased from 65% to 88% (*P*=.020) and CRP decreased from 4.3 to 3.2 (*P*<.001). Similar changes were not noted in the UC patients, likely because they were not sick at baseline. After dose optimization was achieved, continued dosing by drug level for the maintenance year of the study was not significantly different from dosing guided by clinical symptoms. Thus, dose adjustment of infliximab to a trough higher than 3 mcg/mL appears to be associated with better outcomes in several studies.

In addition to a dose increase, higher levels of drug may be obtained through the addition of an immunomodulator. In the SONIC (Study of Biologic and Immunomodulator Naive Patients in Crohn's Disease) trial of infliximab alone, azathioprine alone, or the combination for the treatment of CD, median trough levels of infliximab at week 30 were 1.6 mcg/mL in patients in the infliximab group and 3.5 mcg/mL for those in the combination therapy group *(P*<.001).[23] Corticosteroid-free remission rates were higher in patients with higher trough levels, although rates were still high among patients with lower trough levels. The UC-SUCCESS (Infliximab, Azathioprine, or Infliximab + Azathioprine for Treatment of Moderate to Severe Ulcerative Colitis) trial evaluated infliximab, azathioprine, or the combination for the treatment of UC and found that a higher percentage of patients on combination therapy (39.7%) achieved corticosteroid-free remission at week 16 compared with patients on infliximab alone (22.1%; *P*=.017) or azathioprine alone (23.7%; *P*=.032).[24] This study did not report whether this increase in remission rates was related to a

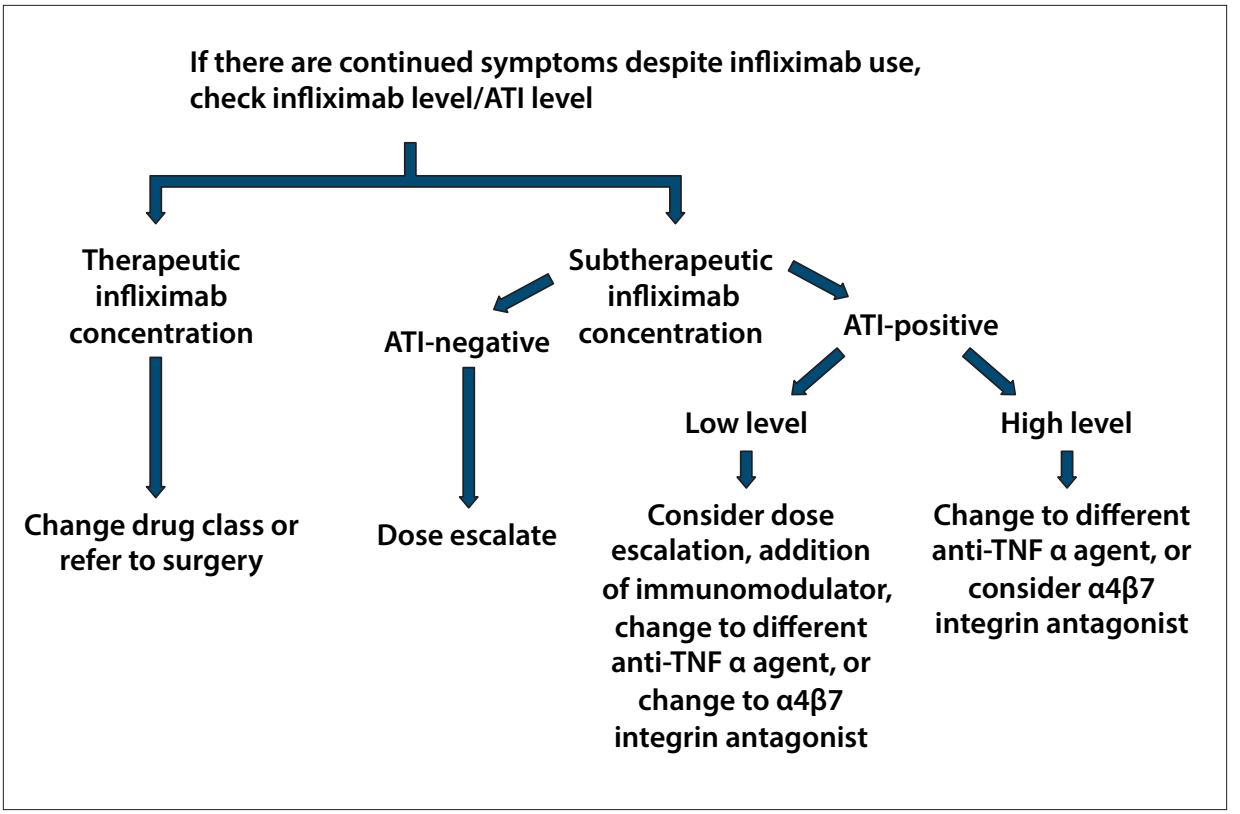

Figure 1. An algorithm for the evaluation and dose adjustment of infliximab in an inflammatory bowel disease patient with continued inflammation.

ATI, antibodies to infliximab; TNF, tumor necrosis factor.

Adapted from Khanna R, et al. *Aliment Pharmacol Ther*. 2013;38(5):447-459.

difference in infliximab levels between the combination and infliximab groups.

Secondary loss of response may also occur due to antibody formation to the drug. Baert and colleagues first demonstrated that antibodies to infliximab are associated with an increased risk of infusion reactions and a decreased duration of response.[14] In a cohort of 125 patients, the presence of antibodies at concentrations of 8 mcg/mL or higher between infusions predicted a shorter response duration (35 days vs 71 days) and a higher risk of infusion reactions (RR, 2.40; 95% CI, 1.65-3.66; *P*<.001). A systematic review of 13 studies involving 1378 patients with IBD found that the pooled risk ratio for loss of clinical response to infliximab in patients with IBD who had antibodies to infliximab was 3.2 (95% CI, 2.0-4.9; *P*<.0001) when compared with patients without antibodies to infliximab.[25] The effect estimate was mainly from 494 patients with CD (RR, 3.2; 95% CI, 1.9-5.5; *P*<.0001). Data from 86 patients with UC exhibited a nonsignificant RR of loss of response of 2.2 (95% CI, 0.5-9.0; *P*=.3).

In patients who have developed antibodies to infliximab, several strategies have been described (Figure 1). The most widely practiced strategy is to switch from infliximab to another anti-TNF α agent. However, attempts to overcome the antibodies through dose increase or the addition of an immunomodulator have also been described. Afif and colleagues reported that among patients who tested positive for antibodies to infliximab, 92% (11/12) had a complete or partial response after changing to another anti-TNF α agent. An increase in the dose of infliximab in 6 antibody-positive patients was associated with response in only 1 patient (17%).[17] In a recent analysis by Yanai and colleagues, dose escalation of infliximab or adalimumab resulted in a significantly longer response duration in patients with a low or absent antibody titer to the drugs, compared with patients with a high antibody titer.[18] Conversely, patients with a high antibody titer to the drugs had a longer duration of response when switched to another anti-TNF α agent as opposed to dose intensification.

A retrospective study of 5 patients who had developed antibodies to infliximab found that the addition of an immunomodulator, such as azathioprine or 6-MP, resulted in the gradual decrease of antibodies to infliximab, increase

in trough levels, and restoration of clinical response.[26] Although the data on adding an immunomodulator after the formation of antibodies are sparse, much more data show that the use of combination therapy with an immunomodulator from the onset of therapy helps prevent the formation of antibodies. In the SONIC trial, 0.9% of patients (1/116) receiving combination therapy had detectable antibodies to infliximab at week 30, while 14.6% of patients (15/103) receiving infliximab alone had detectable antibodies at week 30.[23] Similarly, in the UC-SUCCESS trial, 19% of patients (7/37) in the infliximab-only group had antibodies to infliximab at week 16, while 3% of patients (1/31) in the combination-therapy group had antibodies to infliximab at week 16.[24]

Dose Optimization of Adalimumab

Similar to the data for infliximab, patients on adalimumab with low drug levels also respond to dose intensification. Antibodies to adalimumab can be measured and may predict an improved response with a switch to a different agent within the class. Yanai and colleagues described a patient cohort in which adalimumab dose intensification was performed in 52 of 142 patients (37%) with suspected loss of response to adalimumab.[18] Although there was a significant difference between adalimumab levels in patients who responded to dose intensification vs those who did not (0.3 mcg/mL vs 3.2 mcg/mL, respectively; $P<.01$), there was substantial overlap between adalimumab trough levels in these 2 groups. Adalimumab trough levels were only able to modestly discriminate between response and nonresponse to dose intensification. However, adalimumab levels greater than 4.5 mcg/mL at loss of response had 90% specificity for failure to respond to dose intensification (PPV, 85%; NPV, 39.5%); therefore, 4.5 mcg/mL has been considered the adequate trough level. In terms of antibodies to adalimumab, a high antibody titer was considered greater than 4 mcg/mL; these levels had a 90% specificity for failure of early response to dose intensification (PPV, 76%; NPV, 75%) and were associated with a shorter duration of regained response. However, a low antibody titer greater than the detection limit of the assay (>1.4 mcg/mL) had only 69% specificity for failure of dose intensification.

Dose escalation has been found to be very effective with adalimumab.[27] A retrospective cohort study of CD patients requiring dose escalation for loss of response found that 24 weeks after dose escalation, 80.4% of patients (74/92) had symptomatic clinical response. Among the 74 patients who responded, the mean duration of a sustained response was 69.2 weeks. However, 56.8% of responders later experienced tertiary loss of response. A retrospective cohort study at the University of Chicago attempted to identify factors that predicted dose escalation of adalimumab; the study found that 31 of 75 patients (41%) treated with adalimumab between 2003 and 2008 required dose intensification.[28] A shorter time to dose escalation was predicted by male sex, smoking status, and colonic location of the disease. Family history of IBD predicted the need for dose intensification. The rheumatology literature has demonstrated that concomitant methotrexate increases adalimumab drug levels.[29] However, a subgroup analysis of the CLASSIC (Clinical Assessment of Adalimumab Safety and Efficacy Studied as Induction Therapy in Crohn's Disease) I trial evaluating adalimumab induction therapy did not illustrate a difference in adalimumab drug concentrations with azathioprine or 6-MP.[30]

Dose Optimization of Certolizumab Pegol and Golimumab

Although assays are not commercially available to assess drug levels or antibodies to certolizumab pegol or golimumab, clinical trial data for both agents suggest that antibodies can form to both drugs, and the incidence of antibody formation to the drugs decreases with the use of immunomodulators. Dose intensification was also allowed in the MUSIC (Endoscopic Mucosal Improvement in Patients With Active Crohn's Disease Treated With Certolizumab Pegol) trial, discussed below, and may be an option in patients who are not responding to standard dosing of certolizumab pegol.

Eighty-nine patients with CD were enrolled in the MUSIC trial, which evaluated endoscopic mucosal improvement in patients with active CD who were treated with certolizumab pegol.[31] After 10 weeks of treatment, 46 patients were dose-adjusted from 400 mg every 28 days to 400 mg every 14 days, according to the judgment of the investigator. A post hoc analysis of the trial revealed that higher serum drug concentrations of certolizumab pegol at week 8 were associated with endoscopic response and remission at week 10.[32] Therefore, in CD patients who are not responding to certolizumab pegol, dose increase to 400 mg every 14 days may be helpful in achieving higher drug levels and capturing response. In the PRECISE (Pegylated Antibody Fragment Evaluation in Crohn's Disease: Safety and Efficacy) 1 trial, 8% of certolizumab pegol–treated patients developed antidrug antibodies. Four percent of patients on concomitant immunomodulators formed antibodies vs 10% of patients on monotherapy.[33] Similarly, in the PRECISE 2 trial, antidrug antibodies were found in 8% of the certolizumab pegol–treated patients. The rate was only 2% in patients on concomitant immunomodulators vs 12% in patients on monotherapy.[34]

In a trial assessing golimumab maintenance therapy for patients with UC, the incidence of antibodies through

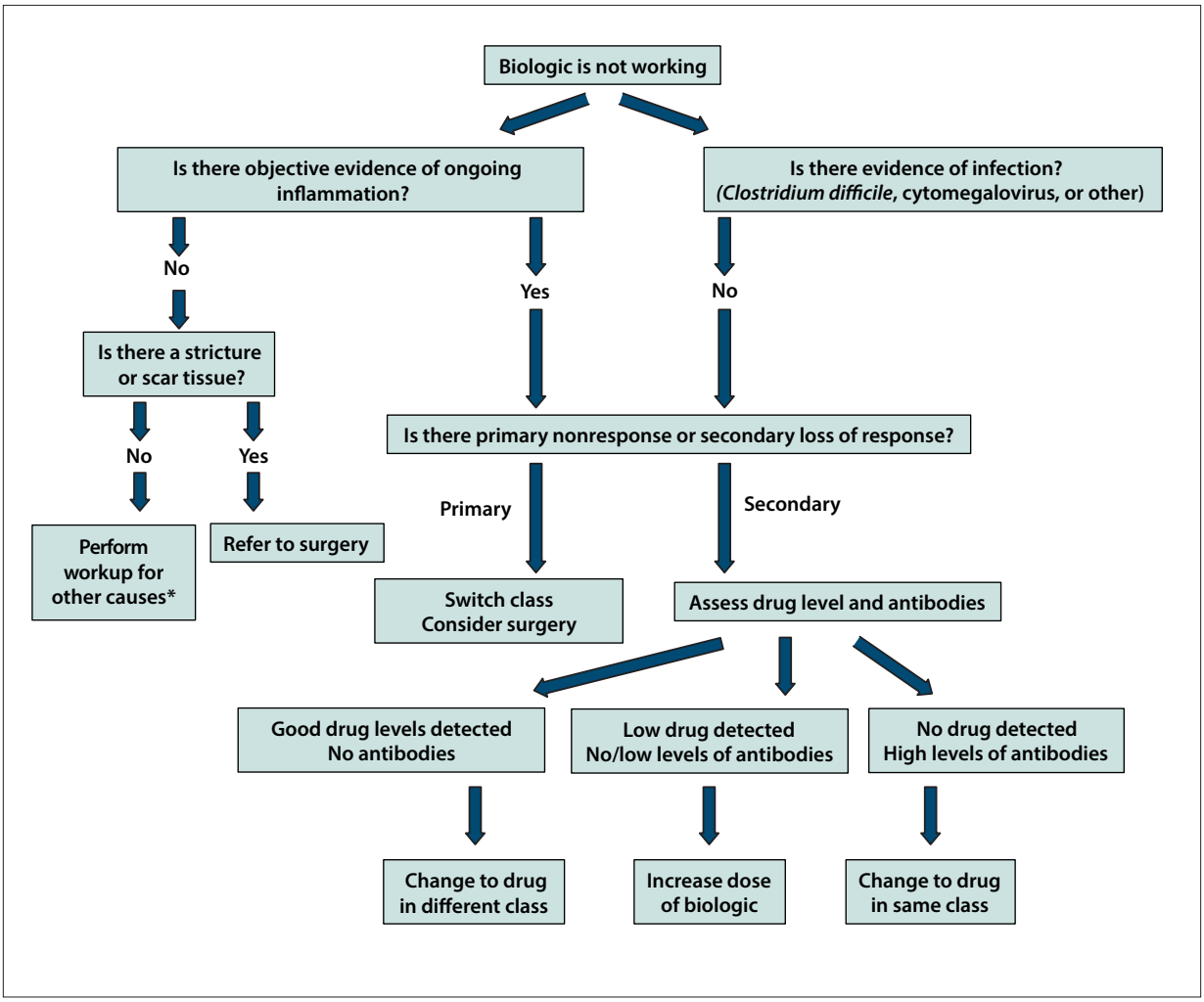

Figure 2. An algorithm for the management of patients with inflammatory bowel disease in whom biologic agents are not working.

*Other causes of symptoms can include celiac disease, small intestinal bacterial overgrowth, or irritable bowel syndrome.

week 54 was 2.9% (32/1103).[35] The rate was lower for patients who received concomitant immunomodulators vs patients who were on golimumab monotherapy (1.1% vs 3.8%, respectively).

Antibody Formation to Integrin Inhibitors

Antibody formation to integrin inhibitors (ie, natalizumab and vedolizumab) has also been described. However, dose adjustment to natalizumab has not been permitted due to safety concerns, and postmarketing experience for vedolizumab is limited thus far. The ENACT (Efficacy of Natalizumab as Active Crohn's Therapy)-1 trial evaluated natalizumab for induction of remission in CD and described antibody formation in 8% of patients (53/650) at week 12 of the study.[36] Of the patients who formed antibodies, 14% (39/286) were on natalizumab monotherapy, 6% (8/141) were on concomitant oral corticosteroids, and 3% (6/223) were on other immunosuppressants. Similarly, in the ENACT-2 trial examining natalizumab maintenance therapy, 9% of patients (36/390) developed antibodies against the drug.[36] Overall, 6% of patients (23/390) were found to have persistently positive antibodies, while 3% of patients (13/390) had transient antibodies. Although the presence of antibodies to natalizumab can be evaluated in a commercially available assay, dose adjustment and use of concomitant immunosuppression are not permissible due to the risk of progressive multifocal leukoencephalopathy, a severely debilitating and possibly fatal brain infection. Practically, the only option with loss of response to natalizumab is discontinuation of the drug. If a patient did respond to natalizumab and then had secondary loss of response due to antibody formation, switching medications within the same class (from natalizumab to vedolizumab) would be a reasonable option.

Vedolizumab, an $\alpha 4\beta 7$ integrin inhibitor, was FDA-approved for use in UC and CD in May 2014. In the

GEMINI 1 (Study of Vedolizumab [MLN0002] in Patients With Moderate to Severe Ulcerative Colitis) study of vedolizumab for UC, 3.7% of patients (23/620) had samples positive for anti–vedolizumab antibodies at any time, and 1% of patients (6/620) had samples that were persistently positive (positive on more than 2 samples) through week 52.[37] The authors report that concomitant immunosuppressive therapy was associated with decreased immunogenicity, but they did not show the data. In GEMINI 2 (Study of Vedolizumab [MLN0002] in Patients With Moderate to Severe Crohn's Disease), which evaluated samples from 814 CD patients treated with vedolizumab for antibodies against the agent, 33 patients (4.2%) had at least 1 sample with positive test results and 3 patients (0.4%) had 2 or more consecutive samples with positive results.[38] Concomitant immunosuppressive therapy was associated with decreased immunogenicity. In the GEMINI 3 study, concomitant therapy with immunosuppressants or corticosteroids led to higher rates of clinical remission at week 10 for patients who were anti-TNF α agent failures, as well as for the entire population.[11] Thus, the use of immunomodulators with vedolizumab to decrease antibody formation is advisable.

In GEMINI 1, UC patients who responded to induction therapy with vedolizumab at week 6 were randomized to receive vedolizumab every 8 weeks, every 4 weeks, or placebo.[37] Patients who failed to respond to induction therapy were placed on vedolizumab every 4 weeks. At week 52, 41.8% of patients on vedolizumab every 8 weeks were in remission, compared with 44.8% of patients receiving vedolizumab every 4 weeks and 15.9% of patients on placebo. The authors noted that patients on the 8-week and 4-week dosing schedules had saturated α4β7 integrins on peripheral lymphocytes, and no significant differences in efficacy were seen between the regimens. Similarly, in GEMINI 2, 39.0% of patients on the 8-week dosing schedule vs 36.4% of patients on the 4-week dosing schedule were in remission, compared with 21.6% of patients on placebo at week 52.[38] Patients who lost response to vedolizumab on the 8-week schedule achieved improvement in mean disease activity scores after an increase in dosing frequency to every 4 weeks without a change in adverse events.[39] Thus, consideration should be given to increasing nonresponders from dosing every 8 weeks to dosing every 4 weeks.

Summary

Loss of response to biologic agents is a common situation faced by gastroenterologists (Figure 2). The first objective when faced with a symptomatic patient on a biologic agent is to prove that the symptoms are due to active inflammation, and not due to infection or other causes. Once active inflammation is assessed, the clinician should consider whether the continued disease activity represents a primary nonresponse to the drug's mechanism of action, which would necessitate a switch to a different class of drugs, or if it is representative of secondary loss of response. Secondary loss of response may be managed through dose adjustment or use of concomitant immunomodulators to decrease antibody formation or to potentially boost drug levels; if that fails, then switching within the drug class is advised. Future therapeutic options will likely include biologic agents that use other mechanisms of action and that are currently on the market for other inflammatory conditions (eg, blockage of interleukin-12/23 with ustekinumab, interleukin-6 with tocilizumab, and janus kinase inhibition with tofacitinib), as well as other novel approaches working their way through clinical trials. The availability of multiple groups of effective immune therapies will allow for more options in the care of patients when biologic agents fail.

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