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Utilizing Biologic Therapies in the Treatment of IBD: Maximizing Efficacy and Minimizing Risk in Moderate-to-Severe Crohn's Disease

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Abstract

The availability of biologic therapies has greatly expanded the treatment options for patients with Crohn's disease. The majority of the currently available biologics target tumor necrosis factor α (TNFα), a molecule important in mediating the intestinal inflammatory response. Infliximab was the first anti-TNFα agent to be approved for Crohn's disease. This was followed by the approval of both adalimumab and certolizumab pegol. Most recently, the biologic agent natalizumab gained approval for use in Crohn's disease. Natalizumab utilizes a different mechanism in that it targets the cellular adhesion molecule α4-integrin. Each of the biologic agents have shown efficacy in the setting of Crohn's disease and have relatively favorable safety profiles, although they are associated with rare but serious toxicity risks. Gastroenterologists and other clinicians who care for Crohn's disease patients are challenged with maximizing the therapeutic benefit of these biologic agents, while minimizing the associated risk to the greatest extent possible. This monograph discusses best methods for gastroenterologists and other clinicians in selecting patients for biologic treatment, timing of biologic treatment initiation, and monitoring to minimize the adverse events observed with biologics.

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Target Audience: This activity has been designed to meet the educational needs of gastroenterologists involved in the management of patients with moderate-to-severe Crohn's disease.

Statement of Need/Program Overview: The place of biologic therapies in the overall therapeutic armamentarium must be understood, in terms of sustaining treatment benefit and minimizing risk associated with combination therapies that include steroids or immunomodulators. Recent evidence regarding the use of biologic monotherapies versus combinations and top-down versus step-up strategies should be further explored and incorporated into current treatment paradigms. Until these issues have been definitively addressed, physicians need to have up-to-date information on the nuances of current controversies in order to make well-considered recommendations for ongoing treatment.

Educational Objectives: After completing this activity, the participant should be better able to:

1. Describe the current treatment guidelines including the therapeutic pyramid for moderate-to-severe Crohn's disease.
2. Cite data from recent studies of biologic and immunomodulatory agents in these patients.
3. Outline potential adjustments or revised algorithms, factoring the latest data on topics such as efficacy, safety, surgery, and quality-of-life outcomes associated with biologic therapies.

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Selecting Appropriate Crohn's Disease Patients for Biologic Therapy

Gary R. Lichtenstein, MD

Evaluating Disease Severity

When considering the initiation of biologic therapy in a patient with Crohn's disease (CD), multiple factors must be weighed. These include the severity of disease, the extent or location of disease, the presence of extraintestinal complications, and other parameters including growth and nutrition, functional ability, and the social or emotional support available to the patient.[1,2] Disease severity is used as a surrogate assessment of CD activity, due to the lack of a "gold standard" measurement. According to guidelines from the American College of Gastroenterology (ACG), CD can be clinically defined with four classifications of severity—symptomatic remission, mild-to-moderate disease, moderate-to-severe disease, and severe-to-fulminant disease (Table 1).[2] These classifications are based on the CD Activity Index (CDAI) score, and the clinical features of the patient.

Introduced in 1976, the CDAI was developed to allow uniform comparisons of patients in clinical studies.[3] The CDAI score ranges from 0 to 600, with higher values indicating more active disease. The CDAI score is a weighted calculation based on eight variables—frequency of liquid or soft stools, use of anti-diarrheal medications, the patient's general well-being, severity of abdominal pain, the presence of an abdominal mass, hematocrit levels, body weight, and the number of extraintestinal complications.[4] Although the CDAI is a frequent outcome used to assess the efficacy of a therapy in a clinical trial, it is not feasible for use in the everyday clinical setting due to the necessity for performing time-consuming, complicated, and subjective calculations. Despite this, the Food and Drug Administration (FDA) has based the approval of currently available CD biologic therapies on their ability to induce CDAI-defined clinical improvement and remission.

Most physicians instead rely on the findings of a clinical examination and their patient's clinical history in their routine practice to define the severity of disease. Classic symptoms of CD include chronic or nocturnal diarrhea, abdominal pain, unplanned weight loss, and fever.[2] Although rectal bleeding may occur, its absence is more suggestive of CD, as opposed to ulcerative colitis, when making an initial diagnosis.

Another aspect of this examination is the determination of disease location and extent. CD most frequently affects the ileum/colon (40%), although it may affect any part of the gastrointestinal system, including the small bowel (30%), the colon alone (25%), and the stomach/duodenum (5%).[5] In addition to the gastrointestinal tract, CD often has extraintestinal manifestations in the joints, eyes, or skin.[6] Other extraintestinal symptoms include pallor, cachexia,

Table 1. ACG-Defined Classification of Crohn's Disease Severity

CDAI	Remission <150	Mild-to-Moderate 150–220	Moderate-to-Severe 220–450	Severe-to-Fulminant >450
Clinical features	Asymptomatic[†]	• Ambulatory • Able to tolerate eating and drinking without dehydration • Signs of systemic toxicity (including high fevers, rigors, and prostration) • Abdominal tenderness • >10% weight loss • Painful mass or intestinal obstruction	• May have failed therapy for mild-to-moderate disease • Prominent symptoms (fever or abdominal pain and tenderness) • Significant weight loss • Substantial anemia • Intermittent nausea and vomiting	• Symptoms persist despite treatment with both conventional and biologic therapies • High fevers • Persistent vomiting • Cachexia • Significant peritoneal symptoms (including rebound tenderness or an abscess)

[†]It should be noted that a patient with steroid dependent disease is not considered in symptomatic remission.

Data from Lichtenstein et al.[2]

and fever. During the clinical examination, it is important to differentiate between those extraintestinal symptoms caused by CD-related inflammation or medications.[6]

Although laboratory tests cannot definitively diagnose CD, they may be useful in confirming the presence of inflammation as well as to monitor disease activity in response to treatment.[7] Serologic tests that reveal an elevated erythrocyte sedimentation rate (ESR) or high levels of C-reactive protein (CRP) are suggestive of inflammation, although not necessarily intestinal inflammation. The presence of neutrophil-derived proteins in the stool, including calprotectin and lactoferrin, is indicative of intestinal-specific inflammation.[8,9] One recent study suggested that elevated levels of both serum and fecal biomarkers were associated with endoscopic, but not necessarily clinical, disease activity.[10] Stool studies of diarrhea may also be helpful in the differential diagnosis of CD, as they may test for the presence of *Clostridium difficile* toxin and other enteric pathogens and parasites.[11]

An upper endoscopy or colonoscopy can confirm the diagnosis and location of CD.[2,12] In addition, endoscopy can be used to monitor intestinal mucosal inflammation in response to biologic therapy, as shown by a sub-study of the ACCENT (A Crohn's Disease Clinical Trial Evaluating Infliximab in a New Long-Term Treatment Regimen) I trial. In this substudy, colonoscopy at weeks 10 and 54 showed that a scheduled infliximab maintenance regimen was superior to an episodic regimen for inducing complete mucosal healing (50% vs 7%, P= 0.007, at week 54).[13] In a separate analysis of the ACCENT I substudy, sustained mucosal healing revealed by endoscopy was significantly associated with infliximab-induced clinical improvement.[14] Colonoscopies are only able to capture the distal region of the small bowel, representing a challenge in determining the severity and extent of small bowel-localized CD. Recent advancements in small-bowel visualization include video capsule endoscopy (VCE), which was shown in a prospective and blinded study to be superior to conventional methods (computerized tomography [CT] enterography and barium small bowel follow-through) to detect small bowel inflammation.[15] A significant complication of VCE is capsule retention within small intestinal strictures, which was found to occur in 13% of CD patients.[16] Therefore, the most recently updated ACG guidelines suggest performing a CT enterography or barium small bowel follow-through prior to VCE, in order to detect the presence of these strictures.[2]

Considering Treatment History

Historically, 5-aminosalicylates (5-ASA) have been utilized in the treatment of mild-to-moderate CD. However, increasing evidence from controlled clinical studies suggests that 5-ASA therapy has only limited benefit compared with placebo.[2,17] Instead, the localized glucocorticoid budesonide is recommended for patients with mild-to-moderate disease localized to the ileum and/or right colon. Budesonide is more effective than placebo, and as effective as corticosteroids, in this setting.[18-20]

Corticosteroids are a mainstay treatment for moderate-to-severe CD, although they have no proven efficacy as maintenance therapy.[2] In a population-based study of Olmsted County, Minnesota, corticosteroids were found to induce an immediate complete remission in 58%, a partial remission in 26%, and no response 16% of CD patients.[21] However, although the majority of CD patients initially responded to corticosteroid therapy, a 1-year follow-up demonstrated that only 32% had a prolonged response, whereas 28% became corticosteroid-dependent, and 38% required surgery. According to the ACG guidelines, over half of CD patients acutely treated with corticosteroids will eventually develop steroid-dependent or steroid-resistant disease. Interestingly, a retrospective study identified younger age, colonic localization, and smoking as significant characteristics of CD patients who become corticosteroid dependent.[22] Despite their efficacy, corticosteroids are associated with significant and multiple adverse effects.[23,24] Musculoskeletal events associated with corticosteroid use include osteoporosis and osteonecrosis. When used in children, corticosteroids have the additional effect of growth impairment. Corticosteroids may also cause adverse gastrointestinal and cardiovascular events. Patients on corticosteroid therapy may develop a sense of euphoria; however, some experience disturbing psychiatric symptoms. Corticosteroid-induced Cushingoid features, including moon face, buffalo hump, truncal obesity, and weight gain, are frequent and distressing adverse events. Importantly, corticosteroids are associated with an increased risk of serious infection and mortality in CD patients. Data from the TREAT (Crohn's Therapy Resource Evaluation and Assessment Tool) registry demonstrated that the corticosteroid prednisone, but not infliximab, was significantly associated with an increased risk of mortality (odds ratio [OR] 2.10, 95% confidence interval [CI]: 1.15-3.83, P=.16).[25] In addition, prednisone was significantly and independently associated with serious infection in infliximab-treated patients. Recently, updated results of the TREAT registry were presented at the 73rd ACG Annual Scientific Meeting, which showed that prednisone use significantly increased the risk of serious infection and mortality at a median follow-up of 4.3 years.[26]

Immunosuppressive agents, including azathioprine, 6-mercaptopurine, and methotrexate, are frequently used to maintain a steroid-induced remission of moderate-to-severe disease, or to treat steroid-dependent or steroid-refractory CD.[2] Immunosuppressant therapy is also administered concomitantly with biologic therapy, in an effort to minimize immunogenicity. Data from the ACCENT I study showed

that immunomodulatory agents administered concomitantly with infliximab did result in a decrease in the proportion of patients with detectable levels of anti-infliximab antibodies compared with no concurrent administration (16.1% vs 38%, *P*=.003).[27] However, this effect was only observed with the episodic, but not continuous infliximab regimen.

As the number of patients treated with biologic therapies continues to increase, so does the incidence of patients requiring a switch to another biologic agent. Interestingly, several clinical studies suggest that some CD patients who lose response to one biologic agent achieve a response with subsequent biologic therapy, albeit lower than biologic-therapy–naïve individuals. Specifically, the GAIN (Gauging Adalimumab Efficacy in Infliximab Nonresponders) trial showed that 21% of patients switched from infliximab to adalimumab achieved remission at week 4, compared with 7% who were switched to placebo.[28] Similarly, the CHARM (Crohn's Trial of the Fully Human Antibody Adalimumab for Remission Maintenance) trial showed that approximately one-third of patients (31–34%) switching from infliximab to adalimumab achieved remission; however, this was lower than the 42–48% of infliximab-naïve patients who achieved remission.[29]

Clinical Trial Data: Evidence to Consider When Choosing Therapy

Currently, there are two CD treatment paradigms.[30] The global standard is a step-up approach, in which patients are treated initially with corticosteroids, and are only administered biologic agents after becoming refractory or intolerant to all other conventional therapies. A top-down approach has been investigated as an alternative strategy in which patients with moderate-to-severe disease are initiated with biologic therapy. Recently, the results of a 2-year open label randomized trial which compared these two treatment paradigms in CD were published.[31] In this study, 133 patients were randomized to initiate therapy with either a conventional step-up approach (corticosteroids, followed subsequently in sequence with azathioprine and infliximab) or a top-down strategy (combined induction therapy with infliximab and azathioprine, followed by maintenance infliximab). At week 26, significantly more patients in the top-down arm achieved corticosteroid-free remission compared with the step-up arm (60.0% vs 35.9%, *P*=.0062). This significant difference was maintained at week 52, as well (61.5% vs 42.2%, *P*=.0278). Although more patients in the top-down arm experienced serious adverse events, this difference was not significant. Therefore, this study showed that the top-down treatment strategy had increased efficacy and similar safety compared with the step-up approach in CD patients.

Data from the SONIC (Study of Biologic- and Immunomodulator-Naïve Patients in Crohn's Disease) trial, which evaluated the top-down approach as well as the benefit of concomitant immunomodulators given with biologic therapy, were recently presented at the 73rd ACG Annual Scientific Meeting.[32] This study did not include patients previously treated with either immunomodulatory or biologic agents. In this study, 508 patients were randomized to three arms, receiving either infliximab in combination with azathioprine, or either agent alone. The highest rate of week 26 remission was experienced by patients in the combination group, followed by infliximab alone and azathioprine alone (57%, 44%, and 30%, respectively). Endoscopic remission rates at week 26 (43.9%, 30.1%, and 16.5%, respectively) paralleled the clinical rates of remission. Importantly, a subgroup analysis showed patients with elevated baseline CRP levels and evidence of intestinal mucosal ulceration achieved the most significant remission rates. This suggests that CD patients with a high burden of inflammation are the most likely to benefit from a top-down approach.

Another key study presented at the recent ACG meeting, the COMMIT (Combination of Maintenance Methotrexate-Infliximab Trial) study, evaluated if the addition of methotrexate to infliximab therapy was superior to infliximab monotherapy.[33] A total of 126 CD patients were randomized to receive either single-agent or combination therapy. All patients were receiving prednisone, and the primary outcome of this trial was time to treatment failure, defined as the failure to enter or maintain steroid free remission. At week 50, a similar proportion of patients in both the single-agent and combination arms experienced a treatment failure (29.8% vs 30.6%). Additionally, the investigators reported that no significant difference in changes to CDAI score. Together, this suggests the immunomodulatory agent methotrexate administered concomitantly with infliximab does not increase the efficacy of the biologic therapy alone.

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Strategies for Maximizing and Extending Response to Biologic Therapy

David T. Rubin, MD

Timing Is Everything

As biologic therapy has become more prominent in the treatment of CD, an increasing focus has been placed on identification of the patients who would most benefit from these treatments, as well as the optimal timing for treatment administration. Traditionally, biologic therapies have been used as a salvage therapy, given only after a patient has failed all conventional treatments. Indeed, this is the current FDA–approved indication for each of these biologic therapies. In this "step-up" approach, patients only begin treatment with biologic therapies after they have become refractory to 5-ASA, corticosteroids, and immunosuppressants.[1] Despite this seemingly cost-effective and safer strategy, mounting evidence argues instead for a "top-down" approach.[2] Additionally, earlier administration of biologic therapy is associated with improved long-term outcomes, including need for surgery, hospitalization, corticosteroid use, or the occurrence of CD-related disability.

Several studies demonstrate that patients with a shorter duration of disease are most likely to respond to biologic therapy. This was effectively shown in the CHARM trial,

which showed that CD patients with a disease duration of 5 years or more had a lower rate of adalimumab-induced remission compared with patients having a disease duration of less than 2 years (41% vs 59%, respectively), although still significantly increased compared with placebo (14%, $P<.001$).[3] A similar effect was observed in the PRECISE (Pegylated Antibody Fragment Evaluation in Crohn's Disease: Safety and Efficacy) 2 trial, which found remission rates dropped from 68% to 44% in CD patients who have less than 1 year and more than 5 years disease duration, respectively.[4] Other small retrospective studies also show the importance of disease duration in determining response to biologic therapy. In a retrospective study limited to 22 pediatric patients, disease activity 18 weeks following the initial infliximab infusion was significantly lower in those children with a CD duration of less than 1 year compared with a CD duration of greater than 1 year (mean PCDAI of 5.5±3 vs 18.1±14, $P<.05$).[5] In a Japanese study that compared patients with a shorter (median 3 months) and longer (median 102 months) duration of CD, those in the shorter-duration group had significantly higher rates of response (78% vs 47%, $P=.0018$) and remission (76% vs 37%, $P=.0001$).[6]

Data from the REACH (Randomized, Multicenter, Open-Label Study to Evaluate the Safety and Efficacy of Anti-TNFα Chimeric Monoclonal Antibody in Pediatric Subjects with Moderate to Severe Crohn's Disease) trial suggest that biologic therapy may be particularly active in patients with a short duration of disease.[7] This study was limited to children 6–17 years of age, who had a mean duration of disease of 1.6 years. All 112 pediatric patients received an induction regimen of infliximab (5 mg/kg) at weeks 0, 2, and 6. At week 10 following induction therapy, the majority of patients (88.4%) exhibited a clinical response, and over half (58.9%) achieved clinical remission. Those patients who showed either a response or remission were then randomized to receive an infliximab (5 mg/kg) maintenance regimen either every 8 or 12 weeks. Although the study was designed to assess the maintenance regimen in these children, it was notable that the open-label treatment with infliximab had substantially better results than that seen in the similarly designed ACCENT I study of adult CD patients.[8] At week 10 in the ACCENT I study, the response and remission rates following induction infliximab (5 mg/kg) therapy were 66.7% and 39.1%, respectively. Aside from patient age, one major difference between the two trials was the shorter duration of disease among the REACH population compared with the ACCENT I population (1.6 years vs >7 years, respectively) Another important difference in these two trials is that the REACH study required all patients to receive a concurrent immunomodulatory agent, whereas only 27.5% of the adults in the ACCENT I population received a concomitant immunomodulator.

Managing Immunogenicity

Immunogenicity, the production of antibodies against the biologic agent, can be a problem with biologic therapy. As a result of immunogenicity, patients may have an attenuated response to therapy, due to the decreased availability of the active biologic agent in their serum. Although different strategies have been attempted to manipulate the biologic agent to reduce its immunogenicity potential, it is accepted as a risk of all the biologic agents used to treat CD. In one study of 125 CD patients treated with the chimeric monoclonal antibody infliximab, 61% had anti-infliximab antibodies following an average of 3.9 infusions over 10 months.[9] This study further showed the negative impact of immunogenicity on response, as patients with a level of anti-infliximab antibodies of ≥8 µg/mL had a significantly decreased duration of response compared with patients with lower levels (35 days vs 71 days, $P<.001$). Immunogenicity to the fully human molecule adalimumab was assessed in the CLASSIC (Clinical Assessment of Adalimumab Safety and Efficacy Studied as Induction Therapy in Crohn's Disease) II trial at 2.8–3.7%.[10] Immunogenicity to the humanized Fab fragment certolizumab pegol was found to occur in 9% of patients in the PRECISE 2 trial.[4] There has not been a head-to-head trial comparing immunogenicity across agents, so comparison of the results in different trials with different agents cannot be reliably interpreted.

One possible approach for preventing immunogenicity during biologic therapy is the use of a concomitant immunomodulatory agent. The long-term safety of such an approach is under scrutiny currently. Alternatively, the method of administering the biologic agent may have an even more important role in the prevention of immunogenicity. In the ACCENT I trial, patients who were administered infliximab as an episodic regimen had a much greater incidence of immunogenicity compared with those who were administered the agent as a scheduled regimen (38% vs 8%).[11]

Approaches to Loss of Response

Lack of response to biologic therapy can be classified as either primary nonresponse or secondary loss of response, depending on whether it occurs initially or later in the course of therapy. One important factor that may have a role in a patient's primary nonresponse is prior exposure to another biologic agent. This effect can be seen when comparing results from two key adalimumab trials, CLASSIC I and GAIN, which enrolled infliximab-naïve and infliximab-nonresponding CD patients, respectively.[12,13] Despite the fact that the infliximab-nonresponding patients in the GAIN study achieved clinical remission at week 4 more frequently with adalimumab than placebo, the rate of remission was still lower than that achieved by the

infliximab-naïve patients at week 4 in CLASSIC I (36% vs 21%, respectively). Secondary loss of response, occurring after a patient initially responds to the biologic agent, may occur in up to one-third of patients receiving an anti-TNFα agent over a 6–12 month period.[8,14,15] Patients may develop a secondary loss of response for a variety of reasons, including immunogenicity or a shift in the cause of inflammation from TNFα to another mechanism (so-called "mechanistic escape").

When a patient begins to show signs of loss of response, it is important to carefully assess the patient to ascertain if it is truly a loss of response to the biologic therapy. For example, some patients who initially respond well to therapy may develop a perirectal abscess, not because of loss of response, but because they had such a robust response to the therapy that a fistula closed too rapidly. Similarly, a patient may develop an intra-abdominal complication or abdominal scarring due to rapid healing of the intestinal mucosa. Therefore, when presented with a patient who appears to have lost response to therapy, the physician should determine if the patient is actively inflamed. Once this is established, the physician should then assess if therapeutic levels of the biologic agent are actually present in the setting of the relapse. However, this assay is only presently available in the clinic for infliximab, and not adalimumab or certolizumab pegol. If a patient has active symptoms despite high levels of infliximab (measured ≥3 weeks after the last infusion), there is little evidence to support the use of another anti-TNFα agent. For these patients, another mechanism of treatment should be attempted, such as methotrexate or the biologic agent natalizumab, which targets the cellular adhesion molecule α4-integrin. Conversely, an undetectable level of infliximab suggests the patient may be clearing the drug too rapidly, possibly due to antibody formation. In this case, dosage and timing manipulation may be attempted to increase patient exposure; use of an alternative anti-TNFα agent is also warranted.

Strategies for Switching Among Biologics

Multiple studies have contributed to increasing evidence regarding the best strategies for switching among biologics. Early small studies first suggested that CD patients who were refractory to infliximab responded to adalimumab.[16,17] In the larger GAIN study, 21% of patients who had previously failed infliximab therapy achieved remission with adalimumab after 4 weeks.[12] The CHARM trial reported that approximately one third (31–34%) of infliximab-nonresponding patients achieved remission, but this was lower than the 42–48% remission rate achieved by infliximab-naïve patients in the same study.[15] Data from PRECISE 2 showed a similar pattern in response, with 44.2% of infliximab-nonresponding patients achieving a clinical response to certolizumab pegol; this was lower than the 68.7% response rate achieved by infliximab/adalimumab-naïve patients.[4]

Currently, the clinical studies available have only tested the switch from infliximab to another anti-TNFα agent. Although the switch from adalimumab to infliximab or certolizumab pegol to infliximab has not yet been evaluated in a controlled clinical setting, there is no evidence to suggest that these strategies would not work.

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Monitoring for and Avoiding Adverse Events in the Use of Biologic Therapies

Sunanda V. Kane, MD, MSPH

The best way to avoid an adverse event related to biologic therapy is to select CD patients who are good candidates for treatment with the appropriate biologic agent. When determining if a patient is an appropriate candidate for biologic therapy, individuals with an active infection or an abscess should be excluded. In addition, those with evidence of an obstruction or fibrostenotic disease that is driving the patient's symptoms should be considered for surgery.[1,2]

Monitoring Adverse Events During Therapy

A recent case at our institution highlights the need for effective monitoring in CD patients receiving biologic therapy. A well-educated male with CD, who lives approximately 100 miles from our center, presented with active disease. A prescription for a biologic was given, and the patient returned to his hometown to be followed by his primary care physician. He was instructed to contact a physician if he developed any new or unusual symptoms. Four months later, the patient's wife contacted the gastroenterologist and asked if biologics could cause snoring. Through further questioning, the gastroenterologist discovered that the patient had a persistent dry cough and requested that the patient been seen immediately for further evaluation. A subsequent chest x-ray showed a case of bilateral histoplasmosis.

This case emphasizes the importance of ensuring that patients receiving biologic therapy are routinely monitored for the development of adverse events. An important component of this monitoring is patient education emphasizing the need to inform their physician (either primary care or gastroenterologist) of the development of any new symptom of concern, such as a fever lasting more than 2 days, a persistent cough, or a sore that will not heal. This is particularly true for adalimumab, which is self-administered. Patients who receive infliximab must go to an infusion center, where they have contact with an infusion nurse who can monitor them. Similarly, CD patients who receive certolizumab pegol are administered the injection by a home health nurse. Either of these care givers can ensure that the gastroenterologist is contacted when an adverse event is suspected.

Infectious Events

One of the most significant adverse events associated with the use of biologic therapies is serious infection, primarily due to the immunosuppressant effect of the biologic agents. Two approaches may be employed to minimize the risk of developing a serious infection in CD patients. Pre-therapeutic screening is performed to identify and screen for patients with a latent infection. Vaccination prior to therapy may prevent an immunocompromised patient from acquiring a new infection.

Reactivation of latent tuberculosis (TB) is a known potential risk of biologic agents. Preclinical animal models suggest that the mechanism by which TB is reactivated by anti-TNFα agents includes a delayed immune response to sites of TB infection, a failure to form organized granulomas to contain infection, and an attenuation of the phagocytic and bactericidal characteristics of macrophages.[3-5] Multiple clinical studies, including those in patients with rheumatoid arthritis, show that patients treated with anti-TNFα biologic therapies have a 4-fold to 20-fold increased risk of developing TB.[6] However, it is important to note that among those studies limited to CD patients, the incidence of TB is lower. For example, no cases were reported in the TREAT registry of 2,850 CD patients treated with infliximab, and a Mayo study of 500 infliximab-treated CD patients also reported 0 cases.[7,8] The CHARM study reported 2 of 800 adalimumab-treated CD patients developing TB.[9] The first two clinical studies of the newest anti-TNFα agent, certolizumab pegol, reported no cases of TB among 92 and 292 CD patients.[10,11] In the PRECISE 2 trial, one case of TB was reported in 668 treated patients.[12] Due to the heightened risk of TB in CD patients, it is recommended that all patients be screened for latent TB infection prior to initiating therapy. Although a detailed history may be useful in identifying patients at an increased risk for TB, the lack of significant risk does not preclude the presence of a latent infection. Commonly used TB screening assays include a purified protein derivative (PPD) skin test and a chest x-ray.[6] Gamma interferon-based assays have demonstrated a higher specificity compared with the PPD skin test, and therefore represent a useful alternative.

A study in 2001 reported that approximately one quarter of CD patients studied (24%) were also infected with the hepatitis B virus (HBV) or hepatitis C virus (HCV), primarily due to surgical procedures and blood transfusions.[13] However, the incidence of HBV was much lower (7.5%) in a subsequent study of 80 infliximab-treated CD patients.[14] Chronic hepatitis B infection in immunocompromised infliximab-treated patients can result in enhanced viral replication and subsequent hepatitis resurgence. However, despite this risk there is currently no consensus on the pretherapeutic screening for HBV in patients receiving biologic agents.[14] Instead, physicians generally limit screening from viral hepatitis to patients whom they suspect are at increased risk for infection.[15] This includes patients who have a tattoo, a history of intravenous drug use or time in prison, received a blood transfusion prior to 1996, or who come from an area where the virus is endemic.[16]

Vaccinations prior to initiating biologic therapy are a reasonable strategy for avoiding infections in CD patients. However, it is important to note that vaccinations should only be considered in patients who are not already immunosuppressed because of receiving an immunomodulatory agent such as azathioprine, 6-mercaptopurine, or methotrexate. Vaccinations to consider include pneumococcal, influenza, or hepatitis A and hepatitis B. Recent data also suggest that vaccination against the human papillomavirus (HPV) may be important for women with CD who are receiving an immunomodulatory agent. In one study of 40 inflammatory bowel disease patients (32 of whom had CD), the rate of abnormal Pap smear results was significantly higher among these patients when compared with matched controls (42.5% vs 7%, $P<.001$).[17] In this study, the use of an immunomodulatory agent was associated with a significantly increased risk of an abnormal Pap smear (OR 1.5, 95% CI: 1.2–4.1, $P=.021$). Separately, a population-based case-control study suggested that CD itself did not increase the risk of an abnormal Pap smear, but that combined exposure to corticosteroids and immunomodulatory agents did (OR 1.41, 95% CI: 1.09–1.81).[18] It should also be remembered that patients on immunomodulators and biologics should not receive any live viruses.

Immunologic Events

As was discussed in the previous section, immunogenicity is a possible adverse event related to administration of a biologic therapy.[19] There are no guidelines regarding the use of prophylactic therapy to prevent immunogenicity and, as a result, physicians have different strategies. One approach is to use a combined regimen consisting of diphenhydramine hydrochloride, acetaminophen, and a corticosteroid just prior to administration of the biologic therapy in all patients. Another approach reserves the use of prophylactic therapy until after an immunogenic reaction is observed. The controversy regarding the use of primary versus secondary prophylaxis to prevent immunogenicity will be addressed in future clinical studies.

Infusion reactions may also occur as a result of biologic therapy. These reactions include hives, itching, rash, headache, flushing, fever, chills, nausea, tachycardia, or dyspnea.[20] In general, these reactions are only mild or moderate in severity, occur within 2 hours of initiating treatment, and rarely require discontinuation of treatment. Injection-site reactions, including erythema and/or itching, hemorrhage, pain, or swelling, tend to be more severe when associated with infliximab infusion, compared with adalimumab or certolizumab pegol.[21] The incidence of injection site reactions associated with infliximab was reported to be between 3.9% and 6.9% in clinical studies.[7,22,23]

Neoplastic Events

The increased risk of lymphoma associated with the use of biologic therapy is also of particular concern to patients. However, it is unknown if this increased risk can be attributed entirely to the biologic therapy. Other risk factors have been proposed, including CD itself, CD disease severity, and immunomodulatory agents.[24] It is important for the physician to properly explain the increased risk of lymphoma to patients, in terms that they can relate to some real level of risk. For example, a patient may interpret merely being told they have a 4-fold increased risk to develop lymphoma differently than if they were informed their risk is approximately 4 out of 100,000 compared with a baseline risk of 1 out of 100,000.[25]

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Slide Library

Biologic Therapy: Initial Steps

- Check PPD/Quantiferon Gold + CXR–Prior to therapy
  - If postive, Rx for 2 mos
  - If negative, proceed with therapy
- Exclude active infection
  - Check for perianal abscess–if pain
    - ? EUA/Pelvic MRI/Physical exam
  - Stool for Enteric Pathogen
  - Stool for *Clostridium difficile*
  - Biopsy for CMV
- Confirm active luminal inflammation or active fistula
  - ? Bile salt diarrhea
  - ? Bacterial overgrowth
  - ? Fistula

Characteristics of anti-TNFα Drugs

	Infliximab	Adalimumab	Certolizumab
Construction	25% murine	100% human	PEGylated Fab Fragment
T 1/2	7–10 days	12–14 days	14 days
Administration	IV infusion (2 hours)	Subcutaneous injection	Subcutaneous injection (nurse)
Induction	5 mg/kg weeks 0, 2, 6	160 mg week 0, 80 mg week 2	400 mg weeks 0, 2, 4
Maintenance	5 mg/kg 8 weekly	40 mg, 2 weekly	400 mg, 4 weekly

Safety and Tolerability: Anti-TNF

- Infections
  - Tuberculosis; unusual opportunistic infections
- Malignancies
  - Lymphoma
- Injection-site reactions
- Rare complications
  - Neurologic, cardiac, bone marrow suppression, hepatotoxicity

TREAT Registry

Crohn's Therapy Resource, Evaluation, and Assessment Tool
Initiated August, 2005

- 6,273-patient CD registry designed to assess long-term safety of infliximab in CD
- "Real world" experience – 80% community; 20% academic
- Treatment at the discretion of the patient's physician
- Patients are to be followed for at least 5 years
- 3,272 patients have received infliximab, usually in combination with other CD treatments (8,314 patient-years of exposure)
  - Of patients who have received infliximab, 88% have received ≥ 2 infusions
- 3,001 patients have received other CD treatments (6,596 patient-years of exposure)

Adapted from Lichtenstein GR, et al. DDW 2006, Abstract 490; Lichtenstein GR, et al. Clin Gastroenterol Hepatol. 2006;4:621–630.

TREAT: Patient Characteristics at Enrollment

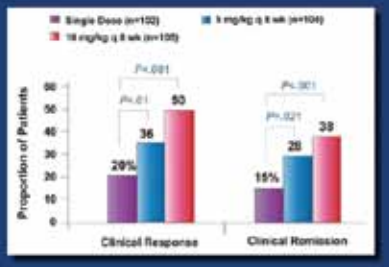
	IFX treated pts	Non-IFX	P value
Number of patients	3272	3001	—
Disease severity Moderate – severe Severe – fulminant	31.5 % 2.0 %	10.7 % 0.6 %	<.0001 <.0001
Concomitant medications Immunomodulators Prednisone	49.4 % 27.2 %	31.9 % 15.9 %	<.0001 <.0001
Hospitalization within previous year	27.4 %	19.1 %	<.0001

Adapted from Lichtenstein GR, et al. DDW 2006, Abstract 490; Lichtenstein GR, et al. Clin Gastroenterol Hepatol. 2006;4:621–630.

Discussing Risks and Benefits of a Second Biologic

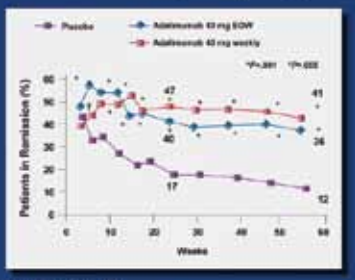
- Importance of steroid cessation
- Safety and tolerability
- Efficacy
  - Patients previously exposed to infliximab
  - Patients not on immunomodulators
- Reduction in hospitalizations and surgeries

ACCENT I: Maintenance Infliximab
Clinical Response and Remission at Week 54



Adapted from Hanauer SB et al. Lancet. 2002;359:1541.

CHARM: Clinical Remission of Crohn's Disease Over Time With Adalimumab
Randomized Responders (n=499)



EOW = every other week; remission = CDAI < 150.
Adapted from Colombel JF, et al. DDW 2008, Abstract 999c.

CHARM: Serious Adverse Events
All Patients

Adverse Event	4-Week OL (n=854)	Post Randomization (Weeks 4–56) Placebo (n=261)	40 mg EOW (n=535)	40 mg Weekly (n=410)
Infections (n[%])	11 (1.3)	9 (3.4)	19 (3.6)	11 (2.7)
Abscess	5 (0.6)	3 (1.1)	3 (0.6)	4 (1.0)
Tuberculosis	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.2)
Other opportunistic infections	0 (0.0)	1 (0.4)	1 (0.2)	0 (0.0)
Wound infection/ septicemia	3 (0.4)	1 (0.4)	1 (0.2)	0 (0.0)
Pneumonia, chest infection	0 (0.0)	0 (0.0)	1 (0.2)	2 (0.5)
Cancer (n[%])	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)
Multiple sclerosis (n[%])	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)
Serum sickness (n[%])	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)
Death (n[%])	1 (0.1)*	0 (0.0)	0 (0.0)	0 (0.0)

*Pulmonary embolus.
EOW = every other week; OL = open label.
Adapted from Colombel JF, et al. Gastroenterology 2007.

PRECISE 1 & 2: Safety and Tolerability of Certolizumab Pegol in CD

	PRECISE 1		PRECISE 2	
Adverse Event (n[%])	Placebo (n=329)	Certolizumab (n=331)	Induction Certolizumab (n=908)	Placebo (n=212)	Maintenance Certolizumab (n=216)
Headache	54 (16.4)	60 (18.1)	64 (12.6)	14 (6.6)	15 (6.9)
Abdominal pain	37 (11.2)	37 (11.2)	27 (4.2)	10 (4.7)	10 (4.6)
Crohn's disease	37 (11.2)	33 (10.0)	36 (5.4)	25 (11.8)	9 (4.2)
Nasopharyngitis	27 (8.2)	44 (13.3)	25 (3.7)	8 (3.8)	12 (5.6)
Cough	8 (2.4)	9 (2.7)	5 (0.7)	2 (0.9)	12 (5.6)
Nausea	27 (8.2)	26 (7.9)	24 (3.63)	6 (2.8)	6 (2.8)
UTI	17 (5.2)	25 (7.6)	27 (4.2)	5 (2.4)	8 (3.7)
Pyrexia	22 (6.7)	21 (6.3)	16 (2.4)	7 (3.3)	10 (4.6)
Arthralgia	16 (4.9)	22 (6.6)	16 (2.4)	6 (2.8)	10 (4.6)
Injection site pain	23 (7.0)	4 (1.2)	8 (1.2)	11 (5.2)	1 (0.5)
Back pain	17 (5.2)	9 (2.7)	11 (1.6)	9 (4.2)	1 (0.5)
Vomiting	11 (3.3)	18 (5.4)	14 (2.1)	3 (1.4)	1 (0.5)

Adapted from Schreiber S, et al. DDW 2008, Abstract T1126.

For a free electronic download of these slides, please direct your browser to the following web address:
http://www.clinicaladvances.com/index.php/our_publications/gastro_hep-issue/gh_april_2009/

Notes

Utilizing Biologic Therapies in the Treatment of IBD: Maximizing Efficacy and Minimizing Risk in Moderate-to-Severe Crohn's Disease

CME Post-Test: *Circle the correct answer for each question below.*

1. According to the ACG guidelines, which classification of CD severity is correlated with a CDAI score between 220 and 450?

   a. Symptomatic remission
   b. Mild-to-moderate
   c. Moderate-to-severe
   d. Severe-to-fulminant

2. CD most frequently affects which of the following locations?

   a. Ileum/colon
   b. Small bowel
   c. Stomach
   d. Duodenum

3. Which of the following statements is FALSE regarding a recent 2-year study discussed by Dr. Lichtenstein, which compared the step-up and top-down approaches for CD treatment?

   a. Significantly more patients in the top-down arm (60.0%) achieved corticosteroid-free remission compared with the step-up arm (35.9%) at week 26.
   b. Significantly more patients in the top-down arm (61.5%) achieved corticosteroid-free remission compared with the step-up arm (42.2%) at week 52.
   c. Significantly more patients in the top-down arm experienced serious adverse events compared with the step-up arm.
   d. Although more patients in the top-down arm experienced serious adverse events, this difference was not significant.

4. In the SONIC study, discussed by Dr. Lichtenstein, the highest rate of remission at week 26 was experienced by which group of patients?

   a. Patients randomized to the infliximab in combination with azathioprine arm.
   b. Patients randomized to the infliximab alone arm.
   c. Patients randomized to the azathioprine alone arm.
   d. Patients randomized to the placebo arm.

5. Data from the CHARM study, discussed by Dr. Rubin, showed that adalimumab-induced remission occurred at a _____ rate in patients with a CD duration of ≥5 years compared with those with a CD duration of <2 years.

   a. higher
   b. lower
   c. equal
   d. slower

6. In the ACCENT I study, according to Dr. Rubin, _____ occurred at a much higher rate with an episodic regimen of adalimumab compared with a scheduled regimen.

   a. injection site reactions
   b. infusion reactions
   c. adverse events
   d. immunogenicity

7. In the GAIN study, what percentage of infliximab-refractory patients achieved a remission at 4 weeks with adalimumab therapy?

   a. 11%
   b. 21%
   c. 27%
   d. 34%

8. Because of an increased risk for TB, which CD patients are recommended to undergo screening for a latent TB infection prior to initiating biologic therapy?

   a. Only CD patients presenting with symptoms of TB
   b. Only CD patients considered at increased risk
   c. Only CD patients with a prior history of TB infection
   d. All CD patients

9. Although not specifically recommended, a(n) _____ _____ vaccination may be an appropriate strategy for women initiating a biologic therapy, as a recent clinical study found women with CD had an increased risk for having an abnormal Pap smear.

   a. pneumococcal
   b. influenza
   c. HBV
   d. HPV

10. In clinical studies, the incidence of injection-site reactions associated with infliximab is reported to be between _____.

    a. 1.2% and 3.4%
    b. 3.9% and 6.9%
    c. 5.7% and 7.2%
    d. 10.2% and 12.3%

Evaluation Form: Utilizing Biologic Therapies in the Treatment of IBD: Maximizing Efficacy and Minimizing Risk in Moderate-to-Severe Crohn's Disease

To assist us in evaluating the effectiveness of this activity and to make recommendations for future educational offerings, please take a few minutes to complete this evaluation form. You must complete this evaluation form to receive acknowledgment for completing this activity.

Please answer the following questions by circling the appropriate rating:
1 = Strongly Disagree 2 = Disagree 3 = Neutral 4 = Agree 5 = Strongly Agree

Extent to Which Program Activities Met the Identified Objectives

After completing this activity, I am now better able to:

1. Describe the current treatment guidelines including the therapeutic pyramid for moderate-to-severe Crohn's disease.	1 2 3 4 5
2. Cite data from recent studies of biologic and immunomodulatory agents in these patients.	1 2 3 4 5
3. Outline potential adjustments or revised algorithms, factoring the latest data on topics such as efficacy, safety, surgery, and quality-of-life outcomes associated with biologic therapies.	1 2 3 4 5

Overall Effectiveness of the Activity

The content presented:

Was timely and will influence how I practice	1 2 3 4 5
Enhanced my current knowledge base	1 2 3 4 5
Addressed my most pressing questions	1 2 3 4 5
Provided new ideas or information I expect to use	1 2 3 4 5
Addressed competencies identified by my specialty	1 2 3 4 5
Avoided commercial bias or influence	1 2 3 4 5

Impact of the Activity

Name one thing you intend to change in your practice as a result of completing this activity.

_____

Please list any topics you would like to see addressed in future educational activities.

_____

Additional comments about this activity. _____

_____

Follow-up

As part of our continuous quality improvement effort, we conduct postactivity follow-up surveys to assess the impact of our educational interventions on professional practice. Please indicate if you would be willing to participate in such a survey:

☐ Yes, I would be interested in participating in a follow-up survey. ☐ No, I'm not interested in participating in a follow-up survey.

If you wish to receive acknowledgment for completing for this activity, please complete the post-test by selecting the best answer to each question, complete this evaluation verification of participation, and fax to: (303) 790-4876.

Post-test Answer Key

1	2	3	4	5	6	7	8	9	10

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