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Contemporary Issues in Crohn's Disease: Where Do the Data Lead Us? CME

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This activity is intended for gastroenterologists and other healthcare professionals, including internal medicine specialists and family practitioners/primary care physicians, conducting research and/or providing care for individuals with Crohn's disease.

Goal

The goal of this activity is to educate physicians on the latest advances in biologic therapy for the treatment of Crohn's disease, with a view toward how best to integrate current evidence-based recommendations into the care of patients.

Learning Objectives

Upon completion of this activity, participants will be able to:

1. Identify the barriers, challenges, and complexity of treating the patient who has Crohn's disease
2. Compare the overall efficacy of approved biologic therapies for Crohn's disease
3. Outline a plan for evidence-based integration of biologic therapies into the existing treatment paradigm to improve patient outcomes
4. Implement a patient-centered team approach involving gastroenterologists, colorectal surgeons, gastrointestinal pathologists, and gastrointestinal radiologists for treating a patient who has complex Crohn's disease

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Contents of this CME Activity

What Is the Window of Opportunity for Biologic Therapy in Crohn's Disease? CME

Remo Panaccione, MD, FRCPC

Expert Column

Introduction

Crohn's disease is a chronic inflammatory condition of the intestinal tract for which there is no medical cure. Thus, the current aim of treatment is focused on inducing and maintaining remission while maintaining the highest achievable quality of life and avoiding complications, hospitalizations, and surgeries. Evolving treatment goals include the concept of mucosal healing and biologic remission. The introduction of biologic agents, in the form of anti-tumor necrosis factor (TNF)-alpha therapy, has

significantly advanced the treatment of Crohn's disease and greatly expanded the range of options for patients and physicians. Infliximab, the chimeric monoclonal antibody directed against TNF-alpha, was first approved by the US Food and Drug Administration (FDA) in 1998 for the treatment of adult patients with moderate-to-severe Crohn's disease. Subsequently, infliximab has been approved for maintaining clinical remission in adult and pediatric patients with moderately to severely active disease who have had an inadequate response to conventional therapy, and for reducing the number of draining enterocut aneous and rectovaginal fistulas and maintaining fistula closure in adult patients with fistulizing disease.[1]

A decade's worth of experience as well as the approval of subsequent anti- TNF-alpha agents, the fully human IgG1 monoclonal antibody, adalimumab,[2] and the humanized antibody Fab' fragment, certolizumab pegol,[3] have firmly established this class of agents as an invaluable part of the current therapeutic armamentarium for Crohn's disease. In the United States, the anti-alpha-4 integrin agent, natalizumab, is another class of biologic; it is approved for the treatment of adult patients with moderate-to-severe Crohn's disease who have had an inadequate response to, or are unable to tolerate, conventional Crohn's disease therapies and inhibitors of TNF-alpha.[4]

However, questions remain: where should these biologic agents be positioned in the overall treatment paradigm, and is there a window of opportunity to maximize their benefit so that patients may experience the best possible outcomes?

Biologic Therapy for Crohn's Disease: The Evidence

The evidence for the use of biologic therapy comes from large-scale randomized clinical trials. The anti-TNF-alpha class of agents as a whole has demonstrated comparable efficacy in moderate-to-severe luminal Crohn's disease. Infliximab and adalimumab have solid evidence from phase 3 randomized controlled trials supporting their use for the induction of clinical response and remission in luminal Crohn's disease.[5,6] Certolizumab pegol has demonstrated efficacy in inducing response but not remission.[7] All 3 of these agents have demonstrated efficacy in maintaining response and remission in initial responders.[8-10] Additionally, the side effects and potential toxicity associated with the various anti-TNF-alpha agents are similar. These include an increase in the risk for minor infections, reactivation of latent tuberculosis and hepatitis B, other opportunistic infections, and infusion and injection site reactions. Rare side effects include worsening of congestive heart failure, demyelinating syndromes, hepatic and hematologic abnormalities, and rare cases of lymphoma. The safety of biologic therapy for Crohn's disease is reviewed in depth elsewhere.[11]

The use of natalizumab in patients with moderate-to-severe Crohn's disease with elevated C-reactive protein levels (indicative of inflammation), is equally supported by data from randomized controlled trials for inducing and maintaining clinical response and remission.[12,13] However, the long-term safety of maintenance treatment with natalizumab was questioned after 3 cases of JC virus-related progressive multifocal leukoencephalopathy (PML), a rare demyelinating disease, were reported.[14] In total, 75 cases of PML have been reported in patients treated with natalizumab for multiple sclerosis or Crohn's disease, with an estimated risk of 1:1000.[15-17] In the United States, natalizumab is available only to patients enrolled in a risk minimization plan called the TOUCH® (TYSABRI Outreach: Unified Commitment to Health) Prescribing Program for close monitoring for the occurrence of PML and other serious opportunistic infections. Natalizumab should not be used in combination with immunomodulators or inhibitors of TNF-alpha.[4] Large-scale, prospective clinical studies are currently under way to determine whether a new JC virus assay will help clinicians predict which patients are most at risk for PML. The new assay, which measures JC virus antibodies, is currently available in some medical laboratories and is currently in use.

The Current Treatment Paradigm for Moderate-to-Severe Luminal Crohn's Disease

The traditional treatment paradigm for Crohn's disease is based on a "step-up" approach, whereby agents with large "therapeutic windows" are used early in the course of the disease, with subsequent therapies then added when there is a lack of response or associated toxicity (intolerance). Indeed, most guidelines[18,19] advocate 5-aminosalicylate,* antimicrobials (antibiotics),* and more recently, oral corticosteroids with low systemic bioavailability in the form of budesonide, for short-term induction of response and remission in mild-to-moderate Crohn's disease. Systemic corticosteroids are used for induction of remission in patients with moderate-to-severe Crohn's disease, or in patients who fail to respond to therapy for mild-to-moderate Crohn's disease. Immunomodulators (azathioprine,* 6-mercaptopurine,* and methotrexate*) are reserved for those patients with corticosteroid-refractory or corticosteroid-dependent disease.[20,21] Only after these "conventional" agents have failed are patients considered for biologic therapy. This classical use of biologics in the overall treatment pyramid is consistent with the types of patients who were treated in the pivotal clinical trials -- but there is increasing concern that many patients are receiving biologic therapy too late in the disease course, at a time when many have already developed complications such as fibrostenosis or penetrating disease. The criticism is that current guidelines don't adequately take into account certain patient-specific parameters such as prognostic factors, burden or location of disease, previous exposure and response to medications, and surgical history, when assessing patients for treatment. In addition, the exact definition of "failure of conventional agents" is imprecise, and this may lead to futile cycling of conventional agents without considering other effective therapies soon enough. As a result, this treatment paradigm has come under increasing scrutiny over the past several years based on the experience gathered not only in clinical trials, but also by clinicians globally.

Positioning of Biologics in the Treatment of Crohn's Disease

There is mounting evidence that a strategy involving the earlier use of immunomodulators or biologic agents may be the optimal approach in appropriately selected patients. To understand this change in therapeutic thinking, it is important that one understands the concept of Crohn's disease as a chronic, relapsing and remitting, yet progressive disease. This was clearly demonstrated in a retrospective study including > 2000 patients with Crohn's disease in which the long-term evolution of disease behavior was studied.[22] Patients progressed in a stepwise fashion over time from an inflammatory phenotype (which likely would respond to conventional medical therapy), toward irreversible structural disease (development of a stricture [fibrostenosis] or penetrating complication). Much of the progression occurred early in the disease course, after diagnosis. In this context, the "window of opportunity" may well be limited if we are to exert maximal benefit with the most effective therapies. A direct analogy can be made with inflammatory joint disease, where irreversible structural damage occurs early and rapidly and may not necessarily be related to symptoms. Rheumatologists have long been using immunomodulator therapy very early in the course of rheumatoid arthritis and more recent data suggest that the early introduction of anti-TNF-alpha agents not only slows or even halts progression of structural damage, but may even allow for the eventual withdrawal of immunomodulators.[23,24]

In Crohn's disease, all 3 of the currently available anti-TNF-alpha agents are indicated as second-line therapy following the patient's failure to respond to conventional nonbiologic agents.[1-3] And as noted previously, natalizumab is indicated for those patients who have had an inadequate response to, or are unable to tolerate, conventional Crohn's disease therapies and inhibitors of TNF-alpha.[4] However, for the reasons previously outlined, there is a move to change the positioning of these biologic agents within the treatment paradigm, either in a more "accelerated step-up" approach or as the initial induction strategy to induce remission with anti-TNF-alpha agents, that is, the so called "top-down" strategy.[25] There are a number of lines of compelling evidence that serve as a rationale to substantiate this more aggressive approach.

The concept of top-down therapy was first introduced in a randomized, placebo-controlled trial of 6-mercaptopurine and prednisone* in pediatric patients with newly diagnosed Crohn's disease.[26] Pediatric patients with moderate-to-severe Crohn's disease were randomly assigned within 8 weeks of diagnosis to either 6-mercaptopurine 1.5 mg/kg/day plus a tapering course of prednisone or to placebo plus prednisone. Maintenance therapy with either 6-mercaptopurine or placebo was continued for 18 months. Remission was achieved in 89% of patients overall, but in patients maintained with 6-mercaptopurine, the 18-month relapse rate was only 9% as compared with 47% in those maintained with placebo (P = .007). Moreover, patients treated with 6-mercaptopurine were exposed to a lower cumulative dose of corticosteroids. Although in today's treatment paradigm, the initial use of an immunomodulator such as 6-mercaptopurine would not be considered a top-down approach, in the context of the time of this study, this represented a departure from traditional practice.

The next line of evidence supporting the rationale for a top-down approach comes from retrospective subgroup analyses of the large randomized controlled trials of the anti-TNF-alpha agents, adalimumab and certolizumab pegol. In a subanalysis of the CHARM (Crohn's Trial of the Fully Human Antibody Adalimumab for Remission Maintenance) trial, which evaluated the safety and efficacy of adalimumab for the maintenance of response and remission in patients with moderate-to-severe Crohn's disease, the relationship between duration of disease and response to adalimumab was assessed. The week-26, remission rate with adalimumab given 40 mg every other week was 56% in patients with a disease duration < 2 years, vs 35% in those with a disease duration of 2 to < 5 years, and 37% in those with disease > 5 years.[27] In PRECiSE (Pegylated Antibody Fragment Evaluation in Crohn's Disease: Safety and Efficacy) 2, which evaluated the efficacy and tolerability of certolizumab pegol in the maintenance of clinical response following successful induction therapy in patients with moderate-to-severe Crohn's disease, 62% of patients overall maintained response at week 26.[10] However, in those patients with an elevated C-reactive protein level and disease of < 2 years' duration, the maintenance of response was 90% (P = .02), suggesting that early use of an anti-TNF-alpha agent was more successful.[28] Furthermore, if one compares data from infliximab randomized controlled trails in adult and pediatric patients, differences also emerge. Insight can be gained through a comparison of the ACCENT (A Crohn's Disease Clinical Trial Evaluating Infliximab in a New Long-Term Treatment Regimen)-I trial, which assessed the benefit of maintenance infliximab therapy in adult patients with active Crohn's disease who responded to a single infusion of infliximab, and the REACH (A Randomized, Multicenter, Open-Label Study to Evaluate the Safety and Efficacy of Anti-TNF alpha Chimeric Monoclonal Antibody in Pediatric Subjects with Moderate to Severe Crohn's Disease) trial, which evaluated the safety and efficacy of infliximab in pediatric patients with active Crohn's disease.[8,29,30] The median disease duration in ACCENT-I was about 8 years, whereas in REACH, it was approximately 2 years. The week-10 and -54 response rates in REACH were 88.4% and 63.5% vs 68% and 43%, respectively, for the same timepoints in ACCENT-I. Therefore, both subgroup analyses of patients within trials and comparison between pediatric and adult trails would suggest that earlier treatment is associated with higher efficacy rates.

However, the most compelling data in support of the top-down strategy come from prospective studies of patients with newly diagnosed Crohn's disease naive to all therapy outside of 5-aminosalicylates or antibiotics (the "step-up vs top-down trial"), from patients with relatively newly diagnosed Crohn's disease naïve to biologic and immunomodulator therapy (SONIC [Study of Biologic and Immunomodulator Naive Patients in Crohn's Disease]), and from patients who have undergone ileocecal resection for Crohn's disease.[31-33]

The "step up vs top-down trial" was a randomized, controlled trial of patients with newly diagnosed Crohn's disease who were naïve to corticosteroids, immunomodulators, and anti-TNF-alpha agents.[31] Subjects were randomly assigned to either a top-down treatment approach, in which they received combined immunosupression with infliximab 5mg/kg at weeks 0, 2, and 6 in

addition to azathioprine 2.5 mg/kg/day, with infliximab being delivered subsequently on an episodic, as needed schedule; or a more traditional step-up treatment approach, in which they received corticosteroids followed in sequence by azathioprine upon relapse or corticosteroid dependence, and only then by infliximab if there was ongoing disease activity. The primary endpoints were the proportion of patients in clinical remission without corticosteroids and without need for surgical intervention at weeks 26 and 52. At weeks 26 and 52, 60% and 62%, of patients, respectively, treated with early combined immunosuppression (top-down approach) met this stringent endpoint vs 36% and 42%, of patients, respectively, in the step-up group. Moreover, this trial demonstrated that active Crohn's disease could theoretically be treated without using corticosteroids. At 104 weeks, there was no longer a difference between the 2 treatment groups in terms of clinical remission. However, in patients treated with early combined immunosuppression (the top-down approach), the rate of mucosal healing at 104 weeks was 71% vs only 30% in patients treated in a conventional step-up manner. In what is perhaps the most important finding of this trial, the achievement of mucosal healing at 2 years was a strong predictor of remission off corticosteroids, absence of subsequent relapse, and even need for further anti-TNF-alpha therapy out to a follow-up of 4 years, implying that early, aggressive therapy could have long-term benefits.[31,34] It is important to note that this is despite the fact that the trial design employed episodic use of infliximab rather than scheduled infliximab therapy, which is now advocated as more effective.

Although the SONIC trial[32] did not assess the "top-down" approach in the purest sense, it nevertheless provides some insight into the potential benefits of earlier introduction of anti-TNF-alpha agents into the treatment paradigm. In this randomized, double-blind trial, median disease duration was just over 2 years. Patients with active Crohn's disease who required corticosteroids and had not undergone previous immunomodulator or biologic therapy were randomly assigned to either azathioprine 2.5 mg/kg/day; infliximab 5 mg/kg at weeks 0, 2, 6, and then every 8 weeks; or to combination therapy with the 2 drugs. The primary study endpoint was corticosteroid-free clinical remission at week 26, but important secondary endpoints included the proportion of patients with mucosal healing at week 26 as well as pharmacokinetic data on infliximab levels and antibodies to infliximab. At 26 weeks, 30.0% of patients on azathioprine were in corticosteroid-free remission compared with 44.4% of patients on infliximab monotherapy, and 56.8% of patients who received combination therapy with both agents. Mucosal healing at week 26 occurred in 16.5% of patients on azathioprine alone, 30.1% of patients on infliximab monotherapy, and in 43.9% of patients on combination therapy.

In a sense, the ultimate top-down therapeutic strategy would be to initiate treatment before the development of disease. Although this is not possible at present, a general approximation of this model is represented by strategies to prevent postoperative recurrence in Crohn's disease after a curative resection. We now have some unique insight into the potential benefit of anti-TNF-alpha therapy in this setting as derived from a small, randomized-controlled trial involving 24 patients with Crohn's disease that evaluated whether administration of infliximab after ileocolonic resection prevented postoperative recurrence.[33] At 1 year, the rate of endoscopic recurrence was 9.1% in the infliximab group vs 84.6% in the placebo group. It is important to note that 53.8% of the placebo-treated patients were on immunomodulators during the trial.[33]

Taken together, these various lines of evidence demonstrate a number of key points. Intervention earlier in the course of disease with more aggressive therapy is likely to be more successful. Such a strategy of early intervention may decrease the likelihood of disease progression to more aggressive phenotypes that require surgical intervention. Anti-TNF-alpha agents appear to be more effective in patients with disease of shorter duration and, at least as seen with infliximab, are more effective than immunomodulators in inducing mucosal healing. Achieving early mucosal healing seems to have long-term benefits that, for the first time, may provide evidence of altering the natural history of Crohn's disease.

Redefining the Treatment Paradigm for Crohn's Disease: Challenges, Complexities, and Barriers

There are challenges, complexities, and barriers in redefining the treatment paradigm for Crohn's disease. The major challenge is to identify which patients would benefit from earlier, more aggressive intervention with biologic agents in order to optimize the benefit-to-risk ratio. If biologics are started early in the disease course, the additional challenge is to identify whether there is a timepoint when therapy can be stopped or when patients can be stepped down to nonbiologic therapy. The answer to this question remains largely undefined. Major barriers also surround patient and physician acceptance of biologic therapy/the top-down strategy, as well as economic issues associated with these higher-cost agents. From a health-economic perspective, the utility of a top-down approach was studied in a novel way using administrative claims data and findings were reported in abstract form.[35] In this study, Rubin and colleagues evaluated claims data for over 3000 patients with Crohn's disease who were exposed to biologic therapy to assess the "top-down" strategy in a real-world setting. Patients were categorized based on treatment path: a "step-up" approach was identified if biologic therapies were given after other therapies, and a "top-down" approach was identified when a biologic agent was initiated within 30 days of diagnosis of Crohn's disease. Patients who were treated with biologic agents earlier in their disease course were found to have a lower rate of Crohn's disease-related surgery. Although this study did not examine costs directly, the earlier use of biologics is likely to represent a less costly strategy.

Choosing Patients for Early Biologic Therapy

As the evidence mounts that early intervention with biologic therapy is associated with superior outcomes, we must develop strategies to identify patient populations that would most benefit from early use of these agents. Several types of patients who would benefit from early introduction of biologic therapy include those with prognostic factors of poorer outcomes, and patients with disease of undesirable location or burden.

There are several lines of evidence that have identified clinical, endoscopic, and serologic variables that place some patients at higher risk for poor prognosis and disease progression. A recent study from France identified young age at diagnosis (< 40 years), presence of perianal disease, and need for corticosteroids with first flare-up as predictors of poor prognosis.[36] The presence of any 2 or all 3 of these factors was particularly associated with a disabling disease course, which included chronic corticosteroid use, need for hospitalization or surgery, early need for immunomodulators, or chronically active disease. The presence of deep ulceration at colonoscopy has also been shown to be an independent factor associated with a high rate of surgery.[37] The study authors found that patients with severe endoscopic lesions, defined as deep ulcers in > 10% of the mucosal area of any colonic segment, was associated with increased need for surgery, with rates of 31%, 42%, and 62% reported at 1, 3, and 8 years, respectively. Patients without severe endoscopic lesions fared much better, with surgical rates of only 6%, 8%, and 18% over the same time points. These differences were statistically significant. Finally, the presence of multiple antibodies to gastrointestinal luminal flora (ASCA [anti-Saccharomyces cerevisiae antibodies], pANCA [protoplasmic-staining antineutrophil cytoplasmic antibodies], CBir [bacterial flagellin], Omp C [protein on the outer membrane of Escherichia coli]) has also been associated with an increased risk of developing complications such as fibrostenotic or penetrating disease and the need for surgery.[38]

Patients with a large burden of disease and those with disease in undesirable locations should be considered candidates for earlier use of biologic therapy. In particular, patients with extensive small bowel disease, patients with duodenal involvement, and those with anorectal involvement should be considered strong candidates to receive biologic therapy early in their disease course because surgery in these patient populations is associated with a high likelihood of post-surgical lifelong morbidity due to either the length of resection or the need for a stoma or diversion. Corticosteroid therapy is especially detrimental in the pediatric population because growth and development are already impeded in children with severe Crohn's disease and this is compounded by corticosteroid use. Therefore, these patients should be considered for early biologic therapy.

Conclusion

Current practice and many guidelines still focus on the conventional step-up approach to managing Crohn's disease. However, it is becoming clear that there is a window of opportunity in which biologic therapy should be used to maximize their benefit. Emerging data suggest that an updated consensus may be needed that reflects the growing body of evidence that suggests that the benefits of anti-TNF-alpha therapy extend beyond just the measure of clinical efficacy. Although it is too early to fully advocate a top-down approach, data suggest that earlier more aggressive treatment may have a disease-modifying effect similar to what has been shown in rheumatoid arthritis. Ultimately, the field will need to concentrate its efforts on strategies that identify those patients who would receive the most benefit from early intervention with biologic therapy and prove that early intervention indeed changes the natural history of the disease. What remains clear is that the management of inflammatory bowel disease in the 21st century will continue to evolve.

**The US Food and Drug Administration has not approved this medication for this use.*

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A 45-Year-Old Man With Crohn's Disease -- Achieving and Maintaining Deep Remission CME

Fernando S. Velayos, MD, MPH

Clinical Case

History of Present Illness

A 45-year-old man with an 8-year history of ileocolonic Crohn's disease presents to the clinic because of a flare in symptoms over the past 2 weeks. His baseline symptoms are 2-3 loose bowel movements per day with intermittent pain. He has been on full-dose azathioprine* for the past 6 years. His previous treatments included mesalamine (5-aminosalicylic acid),* budesonide, and corticosteroids.* He has been on a low dose of prednisone for at least 50% of the year. He has been hospitalized 4 times for his Crohn's disease since the time of diagnosis.

Evaluation

On physical examination, the patient appears nontoxic but fatigued. Abdominal examination reveals mild tenderness to palpation in the right lower quadrant without concern for guarding or rebound. Complete blood cell count reveals a white blood cell count of 9.6 cells/mm3, hematocrit of 34.6%, and C-reactive protein level is elevated at 16.6 mg/L. Azathioprine metabolite levels (6-thioguanine nucleotides) are in the therapeutic range. CT enterography shows thickening of the terminal ileum and right colon without abscess (Figure). Colonoscopy confirms moderate inflammation in the distal 5 cm of the ileum and right colon. Stool culture results are negative for infection, including *Clostridium difficile*. Biopsy specimens from colonoscopy show chronic ileitis and colitis and no evidence of Cytomegalovirus infection.

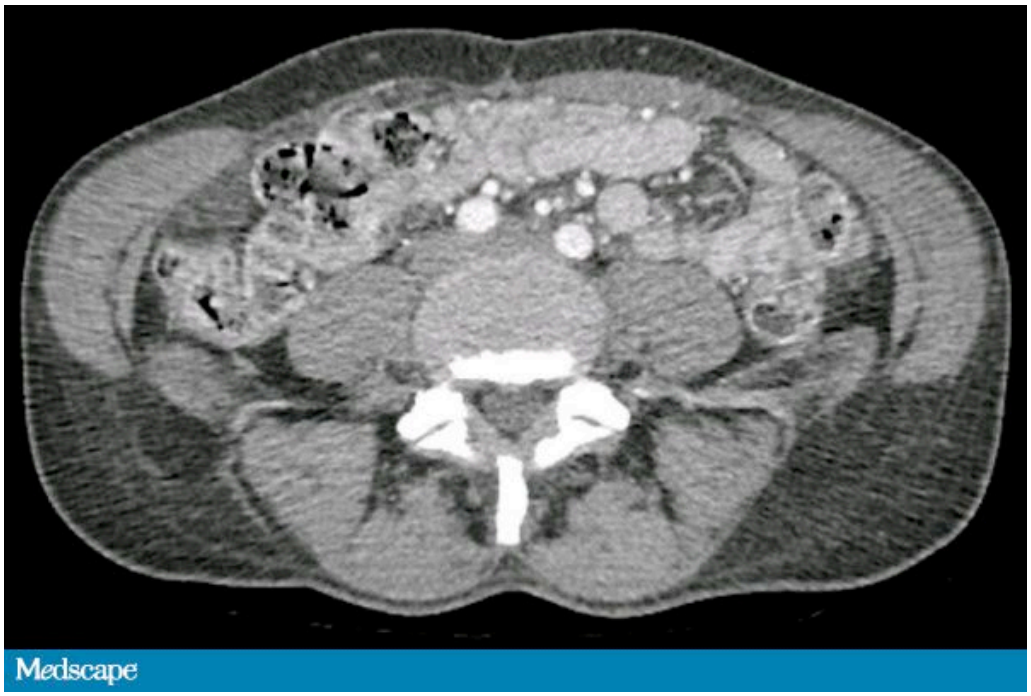

Figure. *CT enterography showing thickening of terminal ileum and right colon.*

In the setting of corticosteroid dependency and active flare despite the use of azathioprine, biologic therapy is anticipated. The patient is screened for the presence of latent tuberculosis and viral hepatitis because these can be reactivated by biologic therapy. You discuss the 3 antitumor necrosis factor (TNF)-alpha biologic agents currently approved for Crohn's disease: infliximab, adalimumab, and certolizumab pegol.

Which of the following therapeutic strategies do you recommend as superior with regard to efficacy in this situation?

- Stopping azathioprine and starting infliximab monotherapy
- Stopping azathioprine and starting adalimumab monotherapy
- Stopping azathioprine and starting certolizumab pegol monotherapy
- Continuing azathioprine and starting any of the above anti-TNF-alpha agents (combination therapy)
- None of the above individual strategies is superior to the other

Barriers, Challenges, and Complexities in Managing Crohn's Disease With Biologic Therapies

Crohn's disease is a lifelong chronic, inflammatory condition of the gastrointestinal tract. It most commonly affects teenagers and young adults. A major challenge in implementing evidence-based medicine in the clinical management of Crohn's disease is highlighted when trying to address the common clinical scenarios as presented in this case vignette. In each situation, physicians are trying to implement very granular clinical management decisions regarding initiation of biologic therapy. Unfortunately, clinical management decisions in Crohn's disease are rarely adequately addressed in 6- or 12-month pivotal clinical trials by virtue of their purpose, which is to obtain regulatory approval for clinical use by demonstrating superior efficacy compared with placebo. Therefore, the physician must apply the available data and speculate or await subgroup analyses of these trials to answer some of these clinically relevant questions.

Choice of Therapy

With regard to clinical challenge question 1, which addresses the relative efficacy of the 3 currently available anti-TNF-alpha agents, there are no head-to-head comparisons. Infliximab, is a chimeric IgG1 monoclonal antibody given intravenously; adalimumab is a fully human IgG1 monoclonal antibody administered subcutaneously; and certolizumab pegol is a humanized antibody Fab' fragment given subcutaneously.[1] Pivotal clinical trials for all 3 agents demonstrate superiority compared with placebo for the treatment of Crohn's disease. For example, response rates for induction at week 4 range from 21% to 48% for anti-TNF-alpha therapy compared with 4% to 12% for placebo.[2-5] Rates for maintenance of remission are approximately 60% for anti-TNF-alpha therapy vs 20% for placebo.[6-8] The choice of biologic agent is more often based on insurance coverage and patient preference and not clinical efficacy; these 3 anti-TNF-alpha agents appear to have comparable efficacy vs placebo.

Monotherapy vs Combination Therapy for Patients Who Have Failed to Respond to Immunomodulators

With regard to the relative efficacy of choosing monotherapy with a biologic agent vs combination therapy (biologic agent and an immunomodulator), for a patient who has failed to respond to immunomodulator therapy, the clinical approach has changed over the past decade due to the emergence of new data. All biologic agents are known to elicit immunogenicity -- the formation of anti-drug antibodies that can cause a secondary loss of response over time.[7,9,10] For a number of years, the strategy of combination therapy with an immunomodulator and a biologic agent was commonly used to optimize the efficacy of biologic therapy by reducing levels of anti-drug antibody.[11] However, when recent safety concerns were raised about the risk for lymphoma with combination therapy and when subgroup analyses of pivotal clinical trials[12-14] found similar efficacy among patients receiving combination therapy vs monotherapy with a biologic agent, the risk-benefit balance of this strategy among patients who had failed to respond to immunomodulators was questioned.

Similar results were seen in 2 more recent prospective trials.[15,16] The COMMIT (Combination of Maintenance Methotrexate-Infliximab Trial) trial randomly assigned patients with active Crohn's disease who were on corticosteroid therapy to receive either combination methotrexate* and infliximab vs infliximab alone.[15] At approximately 1 year (week 50), 55.6% of patients in the combination therapy group were in remission compared with 57.1% of patients in the monotherapy group (P = ns). The IMID (Infliximab Maintenance/Immunosuppression Discontinuation) trial enrolled patients in remission on combination therapy with infliximab and an immunomodulator for at least 6 months and then randomly assigned these patients to either continue the combination therapy regimen or discontinue the immunomodulator (azathioprine) and continue only on biologic (infliximab) monotherapy.[16] At 2 years, there was no significant difference in the proportion of patients who stopped infliximab therapy (28% of those in the combination therapy group vs 23% of those who discontinued immunomodulators [ie, on biologic monotherapy]) or need for change in infliximab dosing interval (55% in the group that discontinued immunomodulators [biologic monotherapy] vs 60% in the group that continued immunomodulators [combination therapy]). This was despite patients in the combination therapy group (ie, those continuing on immunomodulators) demonstrating lower rates of anti-infliximab antibodies (5% vs 12.5% in the biologic monotherapy group) as well as higher median levels of infliximab (P < .05). Thus, on the basis of the available data, none of the therapeutic strategies listed in clinical question 1 has been proven to be superior to the other.

Case

Following your discussion of his therapeutic options, the patient elects to initiate infliximab therapy and stops his azathioprine. Over time, he experiences a gradual clinical loss of response, with return of symptoms the week before his next scheduled infusion. You reduce the frequency of infusion first to 7 weeks, and then to 6 weeks. He is now reporting breakthrough symptoms at 5 weeks.

Based on currently available guidelines, what are acceptable strategies for managing this secondary loss of response?

- Continue to reduce infliximab dosing interval to match symptoms up to every 4 weeks
- Increase the dose of infliximab from 5 to 10 mg/kg
- Empirically switch to an alternate agent in the same class, either adalimumab or certolizumab pegol
- Empirically switch to an alternate agent in a different class, specifically the alpha-4 integrin inhibitor, natalizumab
- All of the above

Managing Secondary Loss of Response

Some patients may initially respond to anti-TNF-alpha therapy and then lose response or become intolerant to their initial anti-TNF-alpha agent over time. This is known as secondary loss of response. Secondary loss of response with biologic therapy occurs in about 30%-40% of patients, and is recognized by diminishing efficacy after a robust initial response.[17] Recent guidelines developed by the World Congress of Gastroenterology on Biological Therapy for IBD along with the European Crohn's and Colitis Organisation, endorsed all of the options listed in the answer choices for clinical challenge question 2 above as evidence-based strategies for managing loss of response based on the available clinical trial data.[17] For all of the anti-TNF-alpha agents, increasing the dose or reducing the dosing interval was the preferred first step before switching to another anti-TNF-alpha agent, as this is an efficacious strategy. For infliximab, increasing the dose to 10 mg/kg "recaptured" 86% of patients who had responded in the ACCENT (A Crohn's Disease Clinical Trial Evaluating Infliximab in a New Long- Term Treatment Regimen) I trial.[10] For adalimumab, shortening the dosing interval from every other week to every week reestablished response in about 75% of patients.[12,18] Switching to an alternate anti-TNF-alpha agent, although effective, is less efficacious than increasing the dose or shortening the dosing interval. In the GAIN (Gauging Adalimumab efficacy in Infliximab Nonresponders) study, switching to adalimumab because of lost response or intolerance to infliximab resulted in 21% of patients in the adalimumab group achieving remission compared with 7% in the placebo group.[19]

It is sometimes necessary to switch to an agent out of class because of loss of response. Natalizumab, an anti-alpha-4 integrin agent that blocks adhesion of leukocytes, is the fourth currently approved biologic therapy. It is approved for inducing and maintaining clinical response and remission in adult patients with moderately to severely active Crohn's disease with evidence of inflammation who have had an inadequate response to, or are unable to tolerate, conventional Crohn's disease therapies and inhibitors of TNF-alpha.[20,21] Natalizumab has been associated with progressive multifocal leukoencephalopathy (PML), a rare infectious demyelinating disease of the central nervous system. The rate of PML has been estimated as 1 in 1000.[22] As a result, natalizumab is limited to a second-line biologic agent, and its use is highly monitored and governed through the TOUCH® Prescribing Program (a risk management program).

Case (cont)

Over the next 18 months, your patient has periods of remission and relapse, but his disease progresses despite switching first to adalimumab (although certolizumab pegol would have been a reasonable option as well) and then natalizumab. You speak with your surgical colleagues and along with the patient, decide that he has failed to respond to the available medical therapy. He undergoes an ileocolic resection and is now currently in remission on certolizumab pegol for postoperative prophylaxis.

The patient tells you his brother has recently been diagnosed with Crohn's disease. He asks you if there are any strategies that might help minimize his brother's risk for recurrent hospitalizations, need for corticosteroids, and ultimately, surgery, as he personally had to experience. How do you answer?

- There are proven strategies
- There are no proven strategies
- There are promising strategies
- This topic has not yet been investigated

Step-up vs Top-Down and Strategies for Altering the Long-term Natural History of Crohn's Disease

The current medical management algorithm for moderate-to-severe Crohn's disease is commonly referred to as the step-up approach.[23] This strategy mimics the entry criteria of the original regulatory trials, when biologic agents were experimental a nd reserved for those who failed to respond to traditional therapies. However, now more than a decade after their initial approval, biologic agents are considered part of the medical armamentarium in the standard of care for the management of Crohn's disease. The question has been raised as to whether biologic therapy should be introduced earlier in the disease course (top-down approach). Recent subgroup analyses of regulatory clinical trials show that even in patients who fail to respond to immunomodulators, introduction of biologic agents at an early stage in the disease course, before the development of complications such as strictures and need for surgery, leads to significantly improved short-term outcomes.[12-14] In a subanalysis of CHARM (Crohn's Trial of the Fully Human Antibody Adalimumab for Remission Maintenance), adalimumab given at a dose of 40 mg weekly or every other week was found to be more effective than placebo in maintaining remission for 56 weeks in patients with active Crohn's disease. Patients with disease of < 2 years' duration had a remission rate of 51% at 56 weeks compared with 44% for those with disease of 2 to < 5 years' duration, and about 35% for those with disease > 5 years.[12]

At least 2 prospective clinical trials have demonstrated that early combined use of biologic therapy plus an immunomodulator (top-down approach) has superior short-term efficacy compared with the current step-up approach in patients who are naive to both therapies.[24,25] In the most recent trial, SONIC (Study of Biologic and Immunomodulator Naive Patients in Crohn's disease), 508 patients with moderate-to-severe Crohn's disease who were naive to both immunomodulator and biologic therapy and were either corticosteroid-dependent or being considered for a second course (or more) of prednisone within the past year were randomly assigned to receive azathioprine 2.5 mg/kg; infliximab 5 mg/kg at weeks 0, 2, 6, and then every 8 weeks; or combination therapy with both agents.[25] After 26 weeks (primary endpoint), 57% of patients in the combination therapy group were in corticosteroid-free remission vs 44% of those who received infliximab alone (P = .02) vs 30% of those who received azathioprine alone (P < .001 vs combination therapy and P = .006 vs infliximab). This trend persisted at week 50 as well. The occurrence of serious infections was comparable in all groups. It is important to clarify that the patient population in the SONIC study (naive to both immunomodulators and biologics) is different than the patient population discussed above (ie, those who failed to respond to immunomodulators and who were naive only to biologic therapy). In this latter population, combination therapy has not yet been shown to provide a significant benefit.

In addition to induction of corticosteroid-free clinical remission, early use of biologic agents alone or combined with immunomodulator therapy results in better rates of mucosal healing, a potentially independent predictor of reduced hospitalization, decreased need for surgery, and potentially, reduced rates of colorectal cancer.[26] In fact, mucosal healing is an important predictor of long-term "deep remission," an evolving combined endpoint of both clinical remission and endoscopically healed mucosa.[27] Therefore, to answer your patient's question, on the basis of short-term safety and efficacy data from clinical trials, 1 promising strategy to improve outcomes in moderate-to-severe Crohn's disease is the early introduction of biologic therapy alone or in combination with immunomodulators (azathioprine) in patients who are naive to both therapies.

Conclusion

It is clear that Crohn's disease is a disabling condition associated with high rates of hospitalizations and surgeries, and that biologic therapy can reduce the incidence of these important natural history endpoints. The day-to-day management of common clinical scenarios as presented in this case vignette can be challenging because the answers to important clinical management questions cannot be found in current clinical trials. Despite these gaps, it is evident that to change the natural history of Crohn's disease, and reduce the need for surgical intervention, hospitalizations, and achieve mucosal healing, a more proactive approach to management will be needed. What "shape" this proactive strategy will take is currently undergoing active debate.

**The US Food and Drug Administration has not approved this medication for this use.*
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A Patient-Centered Approach -- The Team Approach to Improving Outcomes in Crohn's Disease CME

Stephen B. Hanauer, MD

Expert Insight

Introduction

By its nature, Crohn's disease is an idiopathic, chronic immune-mediated inflammatory disorder with a spectrum of genetic and environmental underpinnings, clinical presentations, complications, and prognoses.[1,2] The diversity in presenting signs and symptoms and the absence of pathognomonic features create complexity in the diagnosis and differentiation from other enteric and systemic inflammatory and functional disorders.[3] Individual patients may present to primary care physicians (pediatricians, general practitioners, internists, gynecologists) or specialists (gastroenterologists, dermatologists, rheumatologists, or surgeons) at different ages or stages of the disease.[4] Furthermore, throughout the course of diagnostic studies and therapy, collaborative input to the treating physician and patient will be required from endoscopists, radiologists, pathologists, surgeons, as well as their "supporting casts" of nurses, enterostomal therapists, nutritionists/dieticians, social workers, physical therapists, and psychological/psychiatric consultants. Patients will also transition their care from pediatricians to adult gastroenterologists, gastroenterologists to surgeons, and back; and intervening or joint management of inflammatory bowel disease with obstetricians, geriatricians, rheumatologists, ophthalmologists, and dermatologists will commonly take place throughout the course of the patient's lifetime. The risk for systemic manifestations related to the disease and therapy also call into play endocrinologists and infectious disease experts.[5]

Therefore, the management of Crohn's disease will inherently require an individualized, patient-centered approach with a collaborative team of primary care providers, specialists, and their extended ancillary support to provide optimal outcomes in long-term disease management.

Diagnosis

The initial barrier/challenge is to confirm the diagnosis of Crohn's disease. The presentation varies with age, with younger children often diagnosed with more extensive colonic disease[6,7]; adolescents with growth or pubertal delay; young adults with pain, bleeding, weight loss, or diarrhea[8,9]; and, with the elderly presenting with more colonic disease, overlapping with diverticulitis.[10,11] Therefore, the differential diagnosis will depend on the presenting signs and symptoms that determine the initial evaluation strategy.

The differential diagnosis of Crohn's disease of the colon includes infections, vasculitis, drug-induced enterocolitis, ischemia, and, also, ulcerative colitis (eg, some cases of ulcerative colitis may show Crohn's disease-like features).[3] Up to 20% of patients may present with an indeterminate colitis (inflammatory bowel disease, undifferentiated) that cannot be classified as either ulcerative colitis or Crohn's disease.[12] In addition, infections, particularly *Clostridium difficile* and cytomegalovirus, can also mimic or complicate Crohn's disease.[3] Therefore, endoscopic-pathologic interpretation is an important collaborative determination when evaluating these patients.

Small-bowel Crohn's disease may present as mimicking appendicitis or with perianal complications (skin tags, fissures, fistulae, abscess) and may first be evaluated by surgeons or gynecologists.[13] Similarly, the presentation of rectal bleeding may be assessed by a nongastrointestinal specialist.

Diagnostic imaging requires collaborative interpretations with a radiologist to confirm the mucosal extent and severity of luminal disease as well as extraluminal complications (abscess or fistula). Identification of a fluid collection requires collaboration between gastroenterologists, surgeons, and interventional radiologists to determine the optimal route for drainage and subsequent plans pertaining to short- and long-term management.

Prognosis

In the past, the "step-up" management approach (where patients start with conventional agents such as 5-aminosalicylates,* antibiotics,* or corticosteroids,* and move up to immunomodulators/immunosuppressives*) allocated treatment according to the severity of symptoms (mild, moderate, or severe) as well as refractoriness to initial interventions. Subsequently, several factors have led to consideration of a "top-down" approach based on prognosis rather than presenting symptoms and signs (although aspects of the presentation do have an impact on prognosis).[14,15] The concept behind "top-down" or "early aggressive" strategies derives from the ability to modify disease behavior with early therapeutic intervention with biologic agents in rheumatoid arthritis, and the inadequacies of conventional therapies to alter the natural history of Crohn's disease to prevent hospitalizations and surgical resections.[16,17] Therefore, recognition that early presentations with extensive disease in children, transmural complications of fistulae and abscesses, early need for corticosteroids, deep mucosal ulcerations, cigarette smoking, and multiple or high

serologic titers against microflora (protoplasmic-staining antineutrophil cytoplasmic antibodies [pANCA], anti-Saccharomyces cerevisiae antibodies [ASCA], Omp C [protein on the outer membrane of Escherichia coli], Cbir1 [bacterial flagellin,] anti-glycans, etc), predict a poor outcome with conventional therapies, including immunomodulator agents. This has led to the proposal for earlier intervention with anti-tumor necrosis factor (TNF)-alpha biologic agents (infliximab, adalimumab, certolizumab pegol) in these patients.[18-22]

The prognosis of patients with Crohn's disease who require surgical resections is also determined by clinical presentation and the associated complications. Disease recurrence, predictably, follows the presurgical course related to disease extent and transmural complications.[23-25] The extent of recurrence has a direct correlation to the presurgical extent of disease, and patients typically re-present with similar complications that led to the initial surgical intervention (stricture, abscess, or fistula).[26] The selection of postoperative management can be based on the findings at surgery or by an endoscopic examination of the pre-anastomotic site within the first 6 months after a resection. The greater the degree of mucosal disease that is present, the higher the likelihood of a clinical recurrence.[25,27] Thus, postoperative management is based on the likelihood of disease recurrence and response to concomitant therapies, and involves input from surgeons, endoscopists, and radiologists.[28]

Management Options

Once the diagnosis and prognosis have been established, a personalized, long-term and integrative approach can be determined based on the individual, and in coordination with the family, primary care physician, and specialists. At this juncture it is common to also garner input from nurses, nurse practitioners, or physician's assistants who often assist with patient/family communications and education; dietary counselors or nutritionists regarding optimization of nutritional status to address or prevent complications; social workers and or psychological consultants to intervene with adaptive concerns or inappropriate family interactions, and, surgical consultants for patients with complications that are not amenable to medical interventions.

Because it has been recognized that the need for intervention with corticosteroids portends a poor prognosis,[29,30] and that most patients who start on corticosteroid therapy will require immunomodulators and/or biologic therapy for long-term disease management, it is important to prepare patients from the point of their diagnosis for the potential for immunosuppressing interventions.[31] Therefore, it is increasingly important to maintain vaccination schedules in conjunction with primary care physicians to reduce the likelihood of influenza, pneumococcal pneumonia, meningococcal infections, and human Papillomavirus in young women. Patients should be screened for opportunistic infections such as tuberculosis and viral hepatitis (B and C) before initiating immunomodulator or biologic therapies.[32] Individuals starting on such therapy require monitoring for infectious complications and will require early intervention for treatable complications, including infection with *Clostridium difficile*,[33] Cytomegalovirus, or herpes simplex or zoster.[34] In such settings, consultation with an infectious disease expert can assist in optimizing eradication and therapeutic dosing. Due to the risk for progressive multifocal leukoencephalopathy, patients who are initiating or continuing therapy with the alpha-4 integrin inhibitor, natalizumab, should be screened for neurologic complications and evaluated if any signs or symptoms arise.[35]

Long-term Considerations

Crohn's disease is currently a lifetime disease. Children will transition from the care of pediatricians to adult gastroenterologists.[36,37] Often this transition occurs at an emotionally vulnerable time for patients and their families as adolescents move out of their homes to more independent lifestyles and careers while continuing to deal with the challenges of their illness and necessary lifestyle adjustments. Crohn's disease is an embarrassing condition for both sexes because adapting to disrupted bowel activity, physical deformities (surgical scars, stomas, perianal manifestations), and dietary requirements, all have an impact on numerous aspects of socialization (intimacy, education, jobs, etc). Collaboration with primary care physicians, nurses, dieticians, and social workers are essential through these transitional times.

Another important transition occurs when patients wish to start a family/conceive.[25,38] It is important to maintain disease quiescence throughout pregnancy to assure optimal fetal outcomes. Discussions regarding family planning are best done in advance to decide on therapeutic strategies before pregnancy. Education regarding potential risks and benefits involving the patient, specialist, obstetrician, and neonatologist/pediatrician, and a mutually defined course of acceptable and nonacceptable strategies, is best accomplished before conception. Similarly, decisions regarding route of delivery (vaginal vs Cesarean) can be determined proactively.

Crohn's disease can be associated with systemic manifestations necessitating co-management with other specialists.[5,39] Disease-related complications including iritis/uveitis, complex arthropathies, and inflammatory dermatoses, benefit from co-management with ophthalmologic, rheumatologic, and dermatologic consultants. Therapy-related complications[40] are also common and include corticosteroid-related cataracts, osteoporosis and osteoporotic fractures, opportunistic infections in immunosuppressed patients, hepatobiliary complications (hepatitis and cholelithiasis), kidney disease (nephrolithiasis and nephritis), as well as neoplastic complications (cutaneous, adenocarcinomas, and lymphomas), that require a team approach to optimal management.[5]

Conclusion

Thus, from presentation through all ages and stages of Crohn's disease, a personalized approach involving input from a spectrum of practitioners, consultants, and their essential ancillary support staffs, is essential to optimize treatment strategies, manage complications and concomitant diseases, and to assist the patient in adapting to the physical and emotional sequelae of living with a chronic illness.

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