Biologic Agents in the Treatment of Crohn’s Disease

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Abstract

• **Objective:** To review the role of the biologic agents in therapy for Crohn’s disease, with particular emphasis on efficacy, indications for use, and impact on disease outcomes.

• **Methods:** Qualitative review of the literature and expert opinion.

• **Results:** A number of biologic agents are showing great promise as therapeutics for Crohn’s disease. The best established are the anti–tumor necrosis factor-α compounds, of which infliximab is the prototype. Traditionally, these agents have been reserved for patients who have not responded adequately to “conventional” therapy, although there is increased interest in using these potent medications early, with a view to altering the natural history and the outcomes of this disease. Challenges remain, including identifying patients who are most likely to benefit from such agents and minimizing potential toxicity.

• **Conclusion:** Biologic agents will continue to expand the therapeutic options in Crohn’s disease and lead to improved patient outcomes.

The management of Crohn’s disease has evolved dramatically over the last decade with the advent of biologic therapies. These agents target specific components of the abnormal immune response that is characteristic of Crohn’s disease. In discussing these therapies, it is important to understand the underlying immune dysregulation and the natural history of the disease as well as limitations of traditional therapy. Despite the fact that biologic agents can be highly effective, there remains the occurrence of rare but serious adverse events. The potential for benefit must therefore be weighed against any risks posed to the patient.

**Background**

The precise cause of Crohn’s disease remains unknown. Etiologic theories postulate a complex interaction between genetic factors, environmental factors, and defects in the gut mucosal immune system. The incidence of Crohn’s disease has been rising steadily in the developed world for the last few decades, and more recently Crohn’s disease has also been emerging in developing countries. It can occur at any age, although it typically develops during adolescence and young adulthood and generally persists lifelong with a major impact on quality of life and quality of health of affected individuals. While the cause remains uncertain, most therapies “target” the activated immune system in order to minimize inflammation and subsequent tissue damage.

The gastrointestinal tract is the largest immune organ in the body, and in healthy individuals a remarkable state of “immune tolerance” to the resident gut flora is actively maintained. What appears to happen in Crohn’s disease is a loss of tolerance to the normal luminal antigens, with resultant uncontrolled inflammation. Much research has gone into understanding the abnormal immune response in Crohn’s disease. One factor in maintaining mucosal immune tolerance is the balance between pro- and anti-inflammatory cytokines. Crohn’s disease is associated with an excessive immune response, with activated immune cells secreting pro-inflammatory type 1 helper T (Th1) cytokines, including tumor necrosis factor-α (TNF-α) and interferon-γ (IFN-γ), driven by interleukin-12 (IL-12) [1] and perhaps also by the closely related cytokine IL-23. TNF-α plays a central role by inducing other inflammatory cytokines and enzymes involved in tissue destruction as well as up-regulating the expression of adhesion molecules, which facilitate the migration of further tissue-damaging immune cells into the gut.

Clinically, Crohn’s disease can affect any part of the gastrointestinal tract, from mouth to anus. It usually follows a relapsing, remitting course, with episodes of disease exacerbation followed by periods of remission induced by medication or surgery, or sometimes arising spontaneously. In the short term, inflammation may lead to diarrhea, abdominal pain, weight loss, bleeding, fever, anemia, or nutrient malabsorption. In the longer term, destructive complications develop, including intestinal obstruction, perforation, abscess development, or fistula formation, in which case surgery is usually required. In addition to the gut-related symptoms, individuals
with Crohn’s disease may experience various extraintestinal manifestations including joint, skin, liver, or eye problems.

For the purpose of clinical trials, the activity of Crohn’s disease is generally measured with the Crohn’s Disease Activity Index (CDAI), a complex scoring system that incorporates symptoms, examination findings, and laboratory results. While this index has been shown to correlate well with health-related quality of life, it does not clearly correlate with other clinically relevant outcomes, such as the need for hospitalization, need for surgery, and the ability to work. Indeed, while most of the emerging biologic therapies have demonstrated efficacy as measured by reducing CDAI score, it is important to acknowledge that very few agents have been assessed for their impact upon other, perhaps more relevant, disease outcomes. As a consequence, debate continues as to precisely where these agents fit in the armamentarium of medicines used to treat Crohn’s disease and how cost-effective they are.

It is important to note that although most patients with Crohn’s disease begin with an inflammatory phenotype, over time there is the progressive development of both structuring and penetrating complications. The risks of developing a penetrating complication at 5 and 20 years after diagnosis have been estimated at 40% and 70%, respectively [2]. Historically, at least 60% of patients with Crohn’s disease require surgery at some stage [3].

At present, Crohn’s disease is considered incurable, and the major therapeutic goal is the induction and maintenance of remission. Achieving this goal minimizes symptoms, disease complications, and the impact on quality of life. Of course, the medications used to achieve remission must display an acceptable side effect profile to be considered clinically useful. An emerging endpoint in the therapy of Crohn’s disease is healing of the mucosa, as this is considered the most accurate and objective measure of disease control. Induction of remission in moderate to severe Crohn’s disease is usually achieved with corticosteroids, with a short-term response rate of approximately 80% [4]. Despite this initial response, 28% of these patients are steroid-dependent at 1 year, with nearly 40% requiring surgery and leaving only 32% with a prolonged response. Corticosteroids do not effectively maintain remission and do not “heal” the mucosa, and their long-term use is limited by unacceptably high toxicity.

Immunomodulatory medications such as azathioprine, 6-mercaptopurine (6-MP), and methotrexate are important therapeutic options in Crohn’s disease. Both azathioprine and 6-MP have been proven effective in maintaining remission while allowing discontinuation or reduction in the use of prednisolone [5]. Methotrexate has been shown to decrease the rates of clinical relapse and allows remission in almost 65% of patients, with 39% corticosteroid-free [6]. There are, however, several limitations when using these drugs. There is a long delay in achieving therapeutic efficacy, with as much as 3 months of treatment required with azathioprine/6-MP before clinical effect. Side effects in the form of myelosuppression, hepatotoxicity, and pancreatitis also mandate regular monitoring and require discontinuation in a significant proportion of patients. There is also the risk of hepatic and pulmonary fibrosis with long-term methotrexate use. Methotrexate is teratogenic and contraindicated before conception and during pregnancy, an important consideration given that many women with Crohn’s disease are of child-bearing age.

**Biologic Agents**

The biologic agents used in Crohn’s disease target specific components of the inflammatory response. The major agents, either in routine clinical use or at various stages in the clinical trial process, can be broadly grouped into a simplistic classification system consisting of (1) agents that block inflammatory cytokines, (2) agents that block T-cell activation/proliferation, and (3) agents that block the recruitment of inflammatory cells into the inflamed bowel. Only the most developed of the biologic agents will be discussed further in this paper, but a more comprehensive Table is also offered, which includes a number of other compounds, often with incompletely defined mechanisms, that have been examined in Crohn’s disease.

**Biologic Agents That Block Inflammatory Cytokines**

Of the biologics that block inflammatory cytokines, the best-established are the anti-TNF-α compounds, such as infliximab, adalimumab, and certolizumab. More recently, other inflammatory cytokines have been targeted, with the most promising compounds seemingly those that inhibit the IL-12/IL-23 family, and perhaps those that inhibit IFN-γ.

**Infliximab**. Infliximab, the prototypic biologic agent in Crohn’s disease, is a chimeric monoclonal IgG1 antibody, composed of a 75% human sequence and 25% mouse sequence. Infliximab binds to both soluble and membrane-bound TNF-α. After binding to TNF-α-bearing cells, infliximab generates “inside-out” signalling and promotes complement fixation, leading to apoptosis of T cells and macrophages [7]. Induction of apoptosis, rather than simple neutralization of TNF-α, seems to account for much of the efficacy of infliximab in Crohn’s disease.

Infliximab has a rapid therapeutic benefit, with patients often reporting improvement within days of infusion. The dose used is typically 5 mg/kg given as an intravenous infusion, although some have reported improvement with a dose escalation to 10 mg/kg. Initial studies of a single infusion of infliximab in moderate to severe Crohn’s disease demonstrated an 81% response rate, with 48% of patients in
clinical remission, as defined by a CDAI less than 150 four weeks after infusion [8]. The benefit from a single infusion, however, is short-lived for many patients, with disease relapse often developing 8 to 12 weeks later; thus, regularly scheduled re-infusion is generally favored [9].

Infliximab is also effective in fistulizing Crohn’s disease, with 55% of patients having closure of all draining fistulas at 18 weeks following a 3-infusion induction regimen [10]. Longer-term studies have shown that regular infusion of infliximab every 8 weeks maintains response and remission in patients with fistulae [11]. Efficacy of infliximab has also been demonstrated in the therapy of a number of extra-intestinal manifestations of Crohn’s disease, particularly ankylosing spondylitis [12], pyoderma gangrenosum [13], uveitis [14], and metastatic Crohn’s disease [15].

Adalimumab. Adalimumab is a monoclonal antibody also directed against TNF-α; however, unlike infliximab it is a completely human peptide sequence and is given subcutaneously. A major limitation with infliximab use is the development of antibodies, which seem to arise, at least in part, due to its high (25%) murine component. These antibodies seemingly decrease clinical response and increase infusion reactions. There has been a low rate of antibodies to adalimumab in clinical trials, suggesting that long-term loss of response may be less common. Adalimumab is also a viable option in patients who have lost response or developed hypersensitivity reactions to infliximab [16], as the antibodies to infliximab (ATIs) do not cross-react.

The efficacy of adalimumab has been assessed in large clinical trials. The CLASSIC (Clinical Assessment of Adalimumab Safety and efficacy Studied as an Induction therapy in Crohn’s) I and II studies confirmed efficacy in the induction and maintenance of remission, respectively [17], while the CHARM (Crohn’s Trial of the Fully Human Antibody Adalimumab for Remission Maintenance) study also showed that adalimumab maintains remission in patients over 1 year of therapy [18].

Certolizumab. Certolizumab pegol is a pegylated humanized Fab’ fragment of an anti–TNF-α monoclonal antibody, given subcutaneously. The efficacy of certolizumab in patients with moderate to severe Crohn’s disease has been assessed in the PRECISE (Pegylated Antibody Fragment Evaluation in Crohn’s Disease: Safety and Efficacy) 1 and 2 trials. Certolizumab was shown to improve clinical symptoms in the short to intermediate term, but there was no significant benefit in clinical remission rates at 6 or 26 weeks [19]. However, the PRECISE 2 trial did show efficacy of certolizumab in maintaining remission at 26 weeks in 48% of the subgroup of patients that responded to initial induction dosing [20]. The modest efficacy of certolizumab may be related to the fact that, unlike infliximab and adalimumab, it does not induce apoptosis of activated immune cells. It

<table>
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<th>Table. Emerging Biologic Agents in Crohn’s Disease</th>
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<td><strong>Mechanism</strong></td>
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<tr>
<td>Inhibit proinflammatory pathways</td>
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<tr>
<td>IFN-γ blockade</td>
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<tr>
<td>IL-12/IL-23 blockade</td>
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<td>IL-6R blockade</td>
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<td>Stimulate anti-inflammatory pathways</td>
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<td>IL-11</td>
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<td>Disturb T-cell activation or proliferation</td>
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<td>Co-stimulation blockade</td>
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<td>Anti-α4β7 integrin</td>
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<td>Antisense ICAM-1</td>
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<td>Promote epithelial cell repair</td>
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EGF = epidermal growth factor; G-CSF = granulocyte colony-stimulating factor; GM-CSF = granulocyte monocyte colony-stimulating factor; ICAM = intercellular adhesion molecule; IFN = interferon; IL = interleukin; KGF = keratinocyte growth factor; MAPK = mitogen-activated protein kinase; TNF-α = tumor necrosis factor-α. (Adapted with permission from Brown SJ, Mayer L. The immune response in inflammatory bowel disease. Am J Gastroenterol 2007;102:2058–69.)

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does, however, display similar infectious complications and is associated with development of antinuclear antibodies and antibodies against the agent itself.

Anti–IL-12/anti–IL-23 compounds. IL-12 is the key Th1-inducing cytokine, and neutralizing it should reduce the inflammation seen in Crohn’s disease. Furthermore, IL-12 shares close structural homology to another cytokine, IL-23, which induces an alternative proinflammatory pathway known as Th17 that also plays a crucial role in Crohn’s disease. A number of emerging biologic agents neutralize IL-12/IL-23 and seem to offer great promise as therapeutic agents. The best established of these is the monoclonal antibody ABT-874, which when given as a weekly subcutaneous injection at 3 mg/kg for 7 weeks lead to a clinical response in 75% of patients, compared with 25% of those receiving placebo [22]. Further studies of this and a number of closely related compounds, including an orally administered small molecule inhibitor, are awaited.

Biologic Agents That Block T-cell Activation/ Proliferation

Modulating T-cell activation and proliferation is another strategy being examined in the treatment of inflammatory bowel disease. Visilizumab is a compound that targets the CD3 molecule expressed on T cells, leading to aberrant activation and subsequent cell death (apoptosis). Visilizumab was initially examined in the setting of severe, steroid-refractory ulcerative colitis, where it seemed to be an effective “salvage” therapy [23], although a larger phase 3 study in ulcerative colitis has recently been terminated early due to lack of efficacy. Emerging data suggest visilizumab may provide benefit in inflammatory Crohn’s disease [24], although no such benefit was seen in a small study in fistulizing Crohn’s disease.

CTLA4-Ig is another compound that interferes with T-cell activation by blocking the essential B7 “co-stimulatory” molecules on antigen-presenting cells. CTLA4-Ig, which is approved by the U.S. Food and Drug Administration for use in rheumatoid arthritis, is currently undergoing study in Crohn’s disease, with little efficacy data available to date.

Biologic Agents That Block Recruitment of Inflammatory Cells

A third strategy employed by some biologics used in Crohn’s disease involves blocking the recruitment of inflammatory cells into the bowel. Natalizumab is a compound that binds to the α4 integrins expressed on leukocytes. This binding prevents gut-homing T cells, which express α4β7, interacting with their ligand MAdCAM1 (mucosal addressin cell adhesion molecule-1) expressed on the endothelium of the gastrointestinal tract, thus preventing migration of these cells into the bowel. Natalizumab provides clinical benefit in Crohn’s disease, particularly in maintaining remission. In the ENACT-2 (Efficacy of Natalizumab in Active Crohn’s Therapy) study, patients who responded to natalizumab were then randomized to continued therapy with 300 mg every 4 weeks or placebo. Sixty-one percent of patients who continued on natalizumab maintained response, compared with 28% of those on placebo [25].

A non-integrin target for blocking recruitment of inflammatory cells to the bowel is utilized by Traficet-EN. This oral compound binds to CCR9, the chemokine receptor expressed by gut-homing T cells, and thus specifically blocks their ability to migrate into the inflamed gut along the CCL25 chemokine gradient. This agent is currently undergoing phase 3 study in Crohn’s disease.

Other Agents

A number of other compounds are under investigation with encouraging preliminary results, although large adequately controlled studies are lacking. One noteworthy exception is the innate immune system stimulant sargramostim (a granulocyte monocyte colony-stimulating factor), which seems effective in many patients with Crohn’s disease [26], although a recent large phase 3 study (“Novel 4”) failed to achieve its primary efficacy endpoint and the future role of this drug in the therapy of Crohn’s remains uncertain.

Impact of Biologic Therapy on Other Clinical Outcomes in Crohn’s Disease

With the exception of infliximab and more recently adalimumab, we know little about how the current biologic therapies may influence important clinical outcomes in Crohn’s disease. Post hoc analysis of the ACCENT (A Crohn’s Disease Clinical Trial Evaluating Infliximab in a New Long-Term Treatment Regimen) I study data [27] shows that regularly scheduled infusion of infliximab is associated with a significantly reduced need for Crohn’s-related surgeries (3.1% vs. 7.5%) and days in hospital compared with episodic “on-demand” infusions. Similar findings have also been demonstrated in patients with fistulizing Crohn’s disease treated within the ACCENT II study [28]. More recently, analysis of the CHARM study data has also shown similar results with adalimumab. The 56-week actuarial rates of Crohn’s-related hospitalization in patients who continued on regular adalimumab was 5.9%, compared with 13.9% in patients receiving placebo (relative risk reduction, 57%; P < 0.01). Reduction in the rates of Crohn’s-related surgery was also evident [29]. Mucosal healing, which is also more likely to be achieved with regular scheduled infusion, may be an important predictor of the need for hospitalization [30].
Limitations of Biologic Agents

There are several novel problems that have emerged with the clinical use of biologic agents. Their potent immunomodulatory properties predispose to unusual infections, immunologic disorders, and perhaps even malignant complications. Furthermore, immunogenicity, where the patient develops antibodies against the biologic agent, with subsequent loss of response and “allergic” type reactions, is also a concern.

Because of extensive postmarketing surveillance, the limitations and difficulties with biologic agents are best exemplified by infliximab, which was first used in Crohn’s disease almost 15 years ago. It is important to emphasize, however, that the scarcity of similar toxicity reports with the newer biologic agents does not indicate they are appreciably safer but simply that total exposure is not as extensive. Indeed, many of the side effects described with specific biologic agents are best considered “class effects,” meaning they apply equally to all related agents within the same class.

The major toxicity concern with the biologic agents used in Crohn’s disease is the risk of serious infection. TNF-α is important in the control of intracellular organisms such as tuberculosis (TB) and fungal infections including aspergillosis and histoplasmosis. All anti-TNF-α compounds used in Crohn’s disease increase the risk of primary infection or reactivation of latent infection with these organisms, potentially with fatal consequences. The development of less serious infections, such as upper respiratory or urinary tract infections, is also more common when using infliximab. In 1 of the largest published series in Crohn’s disease, 8.2% developed an infection attributed to infliximab, half of which were serious [31]. Due to the infectious risk, patients should be carefully assessed for infection before commencing anti-TNF-α compounds, including actively excluding latent TB infection through chest radiography, Mantoux test, and/or Quantiferon Gold assay. Infectious collections associated with Crohn’s disease such as perianal and intra-abdominal abscesses should also be screened for and treated before commencing biologic agents. Furthermore, the risk of reactivating latent chronic viral hepatitis, particularly hepatitis B, has increasingly been recognized and pretreatment screening and consideration of therapy should be undertaken in all patients [32].

The non–TNF-α targeting biologics used in Crohn’s disease also display a risk of specific infectious complications. There have been 3 cases of progressive multifocal leukoencephalopathy reported in patients receiving natalizumab [33–35]. This fatal neurologic condition is due to JC virus infection and may arise from a specific drug-induced decrease in immune surveillance of the central nervous system. These cases were identified in approximately 3000 patients exposed during trials, giving an estimated risk of approximately 1 in 1000. CTLA4-Ig increases the risk of pneumonia in rheumatoid arthritis patients [36]. It is also to be expected that anti–IL-12 agents would increase the risk of specific infections.

Noninfectious complications from biologics include a range of unusual immune-mediated inflammatory conditions and malignancies. There is an association with new-onset central nervous system demyelinating disorders such as multiple sclerosis [37]. Infliximab has been shown to increase the risk of death or hospitalization in patients with moderate to severe heart failure [38]. The risk of lymphoma also seems increased with the use of anti-TNF agents. This risk has been difficult to quantify given the seemingly higher baseline risk as a result of Crohn’s disease itself and the seemingly increased risk associated with immunomodulatory drug therapy [39]. A rare, aggressive hepatosplenic T-cell lymphoma has been reported in young patients with Crohn’s disease receiving both thiopurine immunomodulatory drugs and infliximab [40].

While the complications discussed above are serious, their occurrence remains reassuringly rare. The most comprehensive long-term safety data are provided by the TREAT (Crohn’s disease Therapy, Resource, Evaluation, and Assessment Tool) registry, which prospectively collects data on patients receiving infliximab [41,42]. The registry compares patients receiving infliximab with a control group of patients with Crohn’s disease on conventional therapy. With nearly 15,000 patient-years of follow-up, there was no overall increased risk of infectious complications found with infliximab. Multiple-regression analysis showed that the only subgroup of infliximab patients at risk for serious infections and mortality were those with concurrent use of corticosteroids or narcotic analgesics. One problem with analyzing safety data from biologic therapy is that patients with Crohn’s disease are unwell at baseline, with the majority of patients receiving biologic therapies having failed both corticosteroids or narcotic analgesics. One problem with analyzing safety data from biologic therapy is that patients with Crohn’s disease are unwell at baseline, with the majority of patients receiving biologic therapies having failed both corticosteroids or narcotic analgesics. One problem with analyzing safety data from biologic therapy is that patients with Crohn’s disease are unwell at baseline, with the majority of patients receiving biologic therapies having failed both corticosteroids or narcotic analgesics. One problem with analyzing safety data from biologic therapy is that patients with Crohn’s disease are unwell at baseline, with the majority of patients receiving biologic therapies having failed both corticosteroids or narcotic analgesics. 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In addition to the above side effects, immunogenicity is also a significant clinical problem. Patients receiving infliximab, and indeed any “non-self” protein, may “recognize” it as foreign antigenic material, leading to immune system activation and subsequent antibody formation. The development of ATIs occurs in up to 61% of patients and is associated with a decrease in clinical efficacy with a shortened duration of response [43]. In addition, patients who are ATI-positive are more likely to develop both acute and delayed infusion reactions [44]. Factors associated with a lower rate of antibody formation include regularly scheduled dosing, pretreatment with hydrocortisone, and concomitant treatment with corticosteroids or immunomodulators.
use of immunomodulators [9]. An episodic or on-demand treatment schedule is associated with ATI formation in more than 70% of patients treated with infliximab [43]. The newer-generation, fully human biologics such as adalimumab appear to be associated with less antibody formation but are still not immune from this problem.

How to Use Biologics

Despite the extensive clinical experience with infliximab, there remains great debate as to precisely how it should be used. A regular 8-weekly dosing schedule appears superior to on-demand infliximab for a number of reasons, but it is uncertain whether all patients really need this approach, particularly if they have not yet failed standard immunomodulatory therapy. Regularly scheduled maintenance therapy results in a greater improvement in mean CDAI scores, better quality of life scores, and a higher likelihood of complete mucosal healing after 54 weeks of therapy. Scheduled dosing also leads to fewer hospitalization days, fewer Crohn’s disease–related surgeries, and a lower incidence of neutralizing antibody formation [27]. Traditionally, it has been advised that infliximab should be administered with a concomitant immunomodulator to both improve efficacy and diminish immunogenicity; however, this paradigm is being challenged, primarily due to toxicity concerns (particularly the risk of lymphoma).

The treatment algorithm in Crohn’s disease has also been challenged by recent comparisons of conventional “step-up” therapeutic approaches, where increasingly potent drugs are added according to clinical need, and more aggressive “top-down” approaches, with the early use of biologic agents soon after diagnosis. The so-called top-down approach has been trialed with early use of infliximab and azathioprine as the first-line agents in treatment-naive patients. Preliminary data from a controlled study point to superior early disease control and increased rates of mucosal healing with the top-down approach [45]. Furthermore, a trend towards reduced need for Crohn’s disease–related surgery is seen with the top-down approach, raising the prospect that disease outcomes are truly altered by aggressive early therapy.

Despite the enthusiasm for earlier, more aggressive treatment with biologics, there is a need for caution to balance out the inherent risks with this course of action. The heterogeneity in the clinical course of Crohn’s disease means that many patients who would have otherwise had an uncomplicated disease course will be overtreated and exposed to potential toxicity from top-down strategies. Furthermore, it is unclear when these agents can actually be stopped once they are started. It has been clearly shown that regularly scheduled therapy with infliximab results in superior outcomes compared with on-demand therapy. That is, to be effective and not lose response, infliximab and seemingly other biologics may need to be continued long term. Follow-up data confirm these agents are relatively safe over the short term, provided that clinical vigilance is maintained; however, there remains a paucity of long-term safety data. Hopefully, with excellent monitoring in the form of treatment registries, any unexpected complications will be identified early.

Identifying patients with aggressive disease in whom biologic therapy from the outset would potentially lead to the greatest benefit remains a challenge. Unfortunately, there are only a few clinical features at diagnosis that allow identification of those who will experience complicated, aggressive disease. Clinically, patients with extensive small bowel disease, perforating complications at diagnosis, and perianal disease are more likely to follow an aggressive course and should be treated more aggressively from the outset. Serologic biomarkers may become more important in predicting disease behavior. The presence of anti-Saccharomyces cerevisiae antibodies is predictive of an internal perforating phenotype [46] and when used in combination with other serologies, it appears more accurate. Combinations of serologies and genetic polymorphisms have also been examined, with high specificity but low sensitivity for predicting complicated Crohn’s disease [47]. Currently, biomarkers play a small role in clinical decision making, although it seems important that the focus remains on finding better ways to predict disease outcome in an individual patient.

Conclusion

Biologic agents have already revolutionized the management of Crohn’s disease and with the emergence of a number of new agents in recent years, this “revolution” will only continue. However, there remains as many questions as there are answers. While efficacy, as measured by the CDAI score, is readily demonstrated, the impact of biologic agents upon other, more relevant disease outcomes is only just starting to be fully understood. These agents clearly provide benefit, but this benefit must be weighed against the risk of major side effects and the costs to the community at large.

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