A SPECIAL ARTICLE

Immunospecific Therapy in IBD: Rationale and Practical Application

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Important scientific discoveries in the fields of immunology, genetics, and clinical medicine have changed our perception of chronic inflammatory diseases. Clinically diverse disorders, such as Crohn's disease, ulcerative colitis, rheumatoid arthritis, multiple sclerosis, psoriasis, and asthma to name a few, share striking pathophysiologic commonalities. Understanding the immunologic similarities between these disorders has led to their recent grouping under the term "immune-mediated inflammatory disorders." These conditions may respond favorably to tumor necrosis factor blocking therapies, including infliximab. This review examines clinical evidence supporting the theory that chronic inflammatory diseases share underlying pathologies and that many of them can be successfully treated with therapies that inhibit tumor necrosis factor. Case studies of Crohn's disease patients treated with infliximab are provided.

INTRODUCTION

In the 70 years since the clinical syndromes of inflammatory bowel disease (IBD) were first categorized, our basic understanding of these disorders has grown significantly. However, until recently, few experimental findings from the laboratory have had relevance in the clinical management of IBD patients. Ulcerative colitis (UC) and Crohn's disease (CD), affects about 1 million Americans (1), and as many as 75% of people with CD and up to 40% of those with UC eventually need surgery (2,3). Although there is symptomatic overlap between UC and CD, they are differentiated by a number of clinical and pathological factors. UC affects the colon and features chronic, superficial inflammation that always involves the distal portion and extends proximally; CD can affect the small and large intestine, features focal transmural inflammation, and may involve complica-

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tions such as abscesses, fistulae, and stenoses. As a result of the burden of their clinical symptoms, most patients with IBD have a significantly impaired quality of life. One study, using the Inflammatory Bowel Disease Questionnaire, showed that IBD patients had an impaired quality of life on all 6 categories assessed (4). The most frequent concerns of UC patients were having an ostomy bag, developing cancer, effects of medication, the uncertain nature of the disease, and having surgery; among CD patients, the most frequent disease-related concerns were the uncertain nature of the disease, energy level, effects of medication, having surgery, and having an ostomy bag (4,5). Other studies of CD patients have shown that rates of depression and anxiety rise significantly after their condition has been diagnosed (6).

Pharmacologic treatment of IBD has always been challenging, and every compound utilized in practice has strengths and limitations (Table 1) (7). Complicating factors in IBD pharmacotherapy include the unknown nature of the inciting agent(s), the chronicity and heterogeneity of inflammation, as well as the need to account for variation in pharmacokinetics of drugs related to individual patient characteristics, such as genetic composition, age, and severity of disease (8). However, advances in molecular medicine over the past decade have shown that IBD and many ostensibly unrelated diseases share a common pathophysiology: Immune-mediated inflammation. These immune-mediated inflammatory disorders, or I.M.I.D.s, all involve an inappropriate immune response that is associated with dysregulation of the body's normal cytokine milieu, and all ultimately result in end-organ specific chronic inflammatory injury (9). Identification of the shared underlying cytokine imbalance amongst I.M.I.D.s allows for the possibility that the most efficacious treatment for many of these conditions may turn out to be a single drug or group of drugs.

For patients with IBD, basic research describing key immune-mediated inflammatory pathways and the advent of anti-tumor necrosis factor (TNF) treatment strategies have signaled the onset of an era of specific immunotherapy. For the first time, therefore, clinicians caring for IBD patients need a basic understanding of immunologic mechanisms to fully appreciate the efficacy as well as the potential for adverse events of new biologic therapies. This article provides a brief review of IBD-related immunology, describes the rationale for and clinical use of anti-TNF therapies for IBD, and discusses the potential of anti-TNF agents in a variety of I.M.I.D.s.

MUCOSAL IMMUNITY IN IBD

As a simple but well-tested hypothesis for the etiology of inflammatory bowel disease, a combination of genetic and environmental factors initiate and perpetuate activation of the intestine's primary defense mechanism against attack by the external environment, the mucosal immune system. In a healthy mucosal immune system, pro- and anti-inflammatory events co-exist in delicate balance. The appropriate response of the mucosal immune system against an invading enteric pathogen such as *Salmonella* or *Shigella* is inflammation, which requires the production of inflammatory cytokines and the recruitment of inflammatory cells necessary to eradicate the pathogen. Yet, after it has served its purpose, the mucosal inflammatory response is rapidly downregulated in a process that can be thought of as "controlled inflammation." In people with IBD, on the other hand, perhaps an appropriately initiated inflammatory response is not downregulated, and chronic, uncontrolled intestinal inflammation ensues. Thus, in genetically susceptible individuals, an abnormal immune response to environmental stimuli, which may be innocuous under other circumstances, causes an excess of inflammatory (Th1) cells or a lack of an appropriate anti-inflammatory T regulatory response. Murine models of IBD best represent this immunologic hypothesis (10), but it may also have a strong human precedent in CD (11). Amongst the characteristics of this inflammatory Th1 response is the overproduction of the central cytokine TNF. To understand the rationale for new immunologic therapies in IBD, therefore, clinicians should first be familiar with the characteristics of TNF.

PATHOGENIC ROLE OF TNF IN INFLAMMATORY DISORDERS

TNF is an inflammatory cytokine produced by Th1 cells, but it also is abundantly expressed by cells involved in the first line of defense against pathogenic bacteria, macrophages. It is normally elaborated during the course of infection in humans, and it has a role in

Table 1
Characteristics of various therapies for CD and UC (7)

Compound (Brand)	*Typical Dosage*	*Authors' Comment*
Corticosteroids		
Prednisone (Orasone)	• 40 mg once daily	• Effective at inducing remission • Absolutely no role in maintenance or remission of CD or UC
"New" steroids		
Budesonide (Entocort EC)	• 9 mg daily for 8 weeks	• Effective for induction therapy for ileocolonic CD • No efficacy in maintaining remission • Better tolerated by patients over the short-term than conventional corticosteroids
5-ASAs		
Sulfasalazine (Azulfidine)	• Up to 6 g daily in 4 divided doses	• Effective for induction and maintenance of remission in UC • Data in CD are less convincing • Favorable side effect profile
"New" 5-ASAs		
For example, Mesalamine (Asacol)	• Up to 1600 mg 3 times daily	
Antibiotics		
Metronidazole (Flagyl)	• 15 to 20 mg/kg daily in divided doses	• Effective for reducing fistulae drainage in CD • May have primary anti-inflammatory effect in CD—very little data • No role in UC
Ciprofloxacin (Cipro)	• 500 mg twice daily	
Immunomodulatory drugs		
Azathioprine (Imuran)	• 2.5 mg/kg per day in divided doses	• Doses can exceed recommendations based on careful monitoring of white blood count and/or metabolite levels • Highly effective agents in maintaining remission in CD • May be effective in UC • Steroid-sparing
6-mercaptopurine (Purinethol)	• 1.5 mg/kg per day in divided doses	
Methotrexate (Trexall)	• 15- 25 mg weekly	• Pivotal studies demonstrate efficacy in induction and maintenance of remission in CD
Anti-TNF agents		
Infliximab (Remicade)	• 0.4 mg/mL to 4 mg/mL	• Steroid-sparing • Long-term efficacy in maintenance of remission and fistulae closure

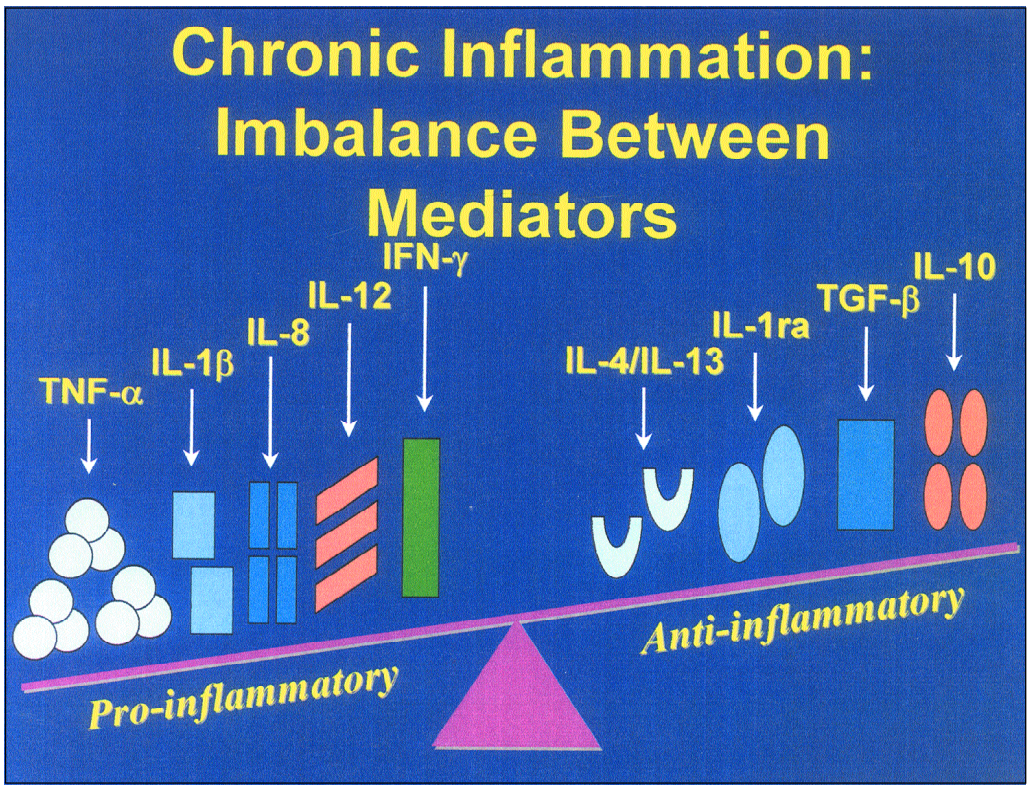

Figure 1. Numerous I.M.I.D.s may share the same immunologic mechanisms of cytokine imbalances. There may be an overabundance of pro-inflammatory cytokines, or conversely, a deficiency of anti-inflammatory cytokines.

containing and eradicating a range of infectious processes. The emerging view is that TNF is a major mediator of cell death (apoptosis), inflammation and immunity, and that it is a direct or indirect factor in the pathogenesis of a wide spectrum of health conditions: Inflammatory, infectious, as well as neoplastic.

As recently as a decade ago, few investigators believed that a specific receptor antagonist or inhibitor of a single mediator could significantly benefit patients with IBD. At that time, the cytokine cascade leading to chronic inflammation in IBD was thought to be redundant; that is, if one mediator were inhibited, others would be still abundantly available to yield identical pathologic consequences. Yet recent research and the success of anti-TNF therapies in IBD and other disorders indicate that the inflammatory cascade is characterized by a hierarchy, where some inflammatory mediators are more important than others (12) (Figure 1). In IBD, for example, TNF is a key molecule that acts on several master switches at or near the summit of the inflammatory cascade and has direct involvement in tissue damage and cell death in the intestinal mucosa (13). Several researchers have demonstrated that TNF-α is central to the development of mucosal inflammation seen in CD (12,14). Despite a range of basic experimental advances, however, recent clinical trials have yielded the most insight into the importance of cytokines in human IBD.

ANTI-TNF THERAPY IN IBD

Based on scientific rationale, the chimeric anti-TNF monoclonal antibody, infliximab, became the first-ever anti-inflammatory monoclonal antibody used for a clinical intervention. Some of the first trials using this agent were conducted in patients with rheumatoid arthritis (RA). In those trials, infliximab alleviated symptoms and significantly reduced the number of swollen and tender joints (15) and showed significant symptomatic improvement within two weeks (16). Although in a traditional interpretation RA and IBD differ significantly, investigators theorized that because of shared immunologic features—such as end organ damage characterized by overproduction of TNF and the presence of inflammatory Th1 cells—anti-TNF therapy might be effective in treating both diseases. The notion that similar immunopathologies could represent a new method of disease classification, as well as a new avenue of therapeutic opportunity, marked the beginning of the I.M.I.D. concept.

In CD patients, the efficacy and safety of infliximab were established in three well-controlled clinical

trials. In the first, subjects with treatment-refractory CD were given a single 5 mg/kg dose of infliximab, and 50% of subjects treated with infliximab achieved clinical remission versus 4% in the placebo group; 81% had decreases of 70 points or more on the CD activity index compared with 17% who took placebo (17). An additional clinical benefit seen in this study was that many infliximab-treated subjects were able to reduce or eliminate steroid use (17). In a second, longer-term study, infliximab subjects achieved a meaningful therapeutic response and maintained it, while the initial response among placebo-treated subjects faded (18). These investigators also observed significant improvement in clinical remission, health-related quality of life (HRQL), and C-reactive protein levels among infliximab-treated subjects (18). A third trial found that infliximab 5 mg/kg induced complete closure of fistulae in 55% of subjects compared with 13% for placebo, demonstrating conclusively that infliximab can heal enterocutaneous fistulae in CD (19).

The promising results seen with infliximab in RA and CD has prompted investigation of other anti-TNF agents that have shown effectiveness in treating chronic inflammatory conditions. Etanercept, for example, which is effective in treating patients with RA and psoriatic arthritis, was recently studied for the treatment of active CD (20). In the CD trials, with clinical response defined as a decrease in baseline Crohn's Disease Activity Index (CDAI) score of 7 0 points or an overall CDAI score <150, researchers found that etanercept 25 mg (subcutaneous, twice weekly) failed to induce a clinical response at four weeks in subjects with moderately to severely active CD. Specifically, only 39% of etanercept-treated patients had a meaningful response at four weeks compared with 45% of placebo-treated patients ($P = 0.763$), and the lack of efficacy extended to all secondary endpoints, including clinical response at weeks 2 or 8; clinical remission at weeks 2, 4, or 8; fistula improvement; and fistula closure (21). The authors suggested that etanercept's lack of efficacy in this trial may have been related to dosing, as subjects were given doses considered appropriate for RA. However, there may be fundamental differences in immunologic mechanism of action that explain why a TNF receptor fusion protein (etanercept) is ineffective in CD, while a chimeric antibody (infliximab) is highly effective. Furthermore, the discrepant findings with etanercept may suggest somewhat different immunologic etiologies in CD and RA. Adalimumab, a subcutaneous injectable anti-TNF antibody that has been used effectively for RA (22), is also currently undergoing assessment in clinical trials for patients with moderate to severe CD.

While further studies of biologic therapies in CD patients will clarify the initial results, two important principles have already emerged. First, all anti-TNF therapies are not alike; some work more effectively than others against certain I.M.I.D.s (e.g., CD). Second, an anti-TNF agent that is effective in treating one I.M.I.D. (e.g., RA) may be—but is not necessarily—effective in treating a second or third I.M.I.D.

PRACTICAL APPLICATION

In patients with IBD, infliximab is the only anti-TNF-α agent currently approved to reduce signs and symptoms, as well as induce and maintain clinical remission, in patients with moderately to severely active lumenal CD and patients with fistulizing CD. The recommended dose of infliximab is 5 mg/kg given as an induction regimen at 0, 2 and 6 weeks followed by a maintenance regimen of 5 mg/kg every 8 weeks thereafter. Consideration may be given to treating patients who respond and then lose their response with a 10 mg/kg dose. Patients who do not respond by week 14 should be discontinued, as they are unlikely to respond with continued dosing. Safety and efficacy data for the use of infliximab beyond the recommended duration in patients with fistulizing CD are insufficient.

Infliximab infusions can be safely prepared and administered via peripheral or central venous access device. The incidence of infusion reactions with infliximab during clinical trials was low, and those that did occur were manageable. During the infusion, monitor the patient for any changes in vital signs and watch for any manifestations of infusion reactions. The infusion site should also be observed for any signs of infiltration. In the event of an infusion reaction, such as headache or pruritus, the infusion may be slowed or stopped. Treatment for hypersensitivity reactions, such as acetaminophen, antihistamines, corticosteroids, and/or epinephrine, should be available for immediate use.

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Most adverse events with infliximab are mild or moderate, decrease over the course of therapy, and do not affect a patient's positive clinical response. The incidence of infusion reactions with infliximab during clinical trials was low, and those that did occur were manageable. Recent work in this area suggests that infliximab infusions are accompanied by acute infusion reactions in approximately 5% of infusions and that, using appropriate treatment protocols, the reactions can be effectively treated and prevented upon re-treatment in nearly all patients (20). Because TNF-α contains and kills Mycobacterium tuberculosis (MTb) and other intracellular pathogens, do a tuberculin skin test before treatment with infliximab to detect the presence of inactive MTb. Patients with a positive PPD (> 5 mm in duration) should not begin infliximab therapy until they have undergone a chest x-ray to rule out active TB and then begun a regimen for the treatment of latent TB. Careful evaluation, screening, and monitoring can minimize infusion-related reactions and adverse events.

Recently, it was reported that the development of antibodies to infliximab in CD patients may be associated with a decrease in therapeutic response and an increase in infusion reactions (23). In a practical sense, however, these findings should reinforce the need for a maintenance dosing regimen with infliximab; subjects in the study were treated "on demand," which increases the risk of antibody development. Moreover, when subjects in one- and two-year controlled studies of CD (16,24) were infused with infliximab once every 8 weeks, similar rates of clinical response and remission were seen whether they tested positive or negative for antibodies.

There have also been concerns over the use of infliximab in CD patients with concurrent hepatitis C infection. Some data has shown that infliximab therapy in the presence of active hepatitis C infection did not cause any worsening of liver function or viral load. However, more experience and research will help establish the risk in this patient subgroup (25).

CASE STUDIES

A 25-year-old white male was referred for management of Crohn's disease and ankylosing spondylitis. He was diagnosed with Crohn's involving both the small bowel and colon at the age of 19. He complained of 5 loose bowel movements per day, fecal urgency, and persisting left lower quadrant abdominal pain. He had short stature, severe kyphoscoliosis, and chronic back pain related to his ankylosing spondylitis. His medications at the time of presentation included mesalamine 800 mg three times a day, ibuprofen 800 mg two to three times a day, and loperamide as needed. The patient was started on methotrexate 25 mg intramuscularly per week and also received an infliximab 5 mg/kg infusion. After one to two weeks, the arthritic symptoms and the abdominal pain completely resolved. Subsequently, the frequency of bowel movements decreased to two to three per day. The patient maintained a good response for four months. He underwent repeat infliximab infusions and presently, the patient is doing well on a regimen of methotrexate and maintenance infliximab given every 8 weeks.

In this case, infliximab maintenance therapy of 5 mg/kg given every 8 weeks led to the control of symptoms from both CD and ankylosing spondylitis. Ankylosing spondylitis with or without IBD has been traditionally managed by treating symptoms as experience with anti-inflammatory therapy has been disappointing. Recently, infliximab was demonstrated to have significant clinical efficacy in ankylosing spondylitis and may be a front line therapy for this disease (26).

A 47-year-old white female with long standing Crohn's disease was hospitalized for abdominal pain and diarrhea. She was diagnosed with Crohn's disease 23 years ago and underwent ileocolonic resection 10 years ago. Since then, the patient required intermittent prednisone that resulted in a Cushingoid appearance, lower extremity edema, and hypertension. She had approximately 10 bowel movements per day, perirectal fistulae, and constant fatigue. As an inpatient, she received an infliximab 5 mg/kg infusion and soon after reported having formed stools for the first time in years. Two weeks after her first infliximab infusion, she developed a small bowel obstruction requiring re-hospitalization that resolved with conservative management. Three months later, cramping abdominal pain and diarrhea recurred. A three-dose induction regimen of 5 mg/kg infliximab at 0, 2, and 6 weeks and 6-mercaptopurine therapy resulted in a marked improvement. The patient had no abdominal pain and 2 semi-formed bowel movements daily, and was able to be tapered off steroids. Five weeks from the completion of induction therapy, the patient reported recurrent

mild abdominal discomfort and five bowel movements daily. The decision to initiate maintenance (5 mg/kg every 8 weeks) infliximab therapy was made. After the first maintenance dose, she experienced a transient and partial response lasting only for a week. Eight weeks later, infliximab was given at the dose of 10 mg/kg with an amelioration of all symptoms. Presently, the patient is doing well on a regimen of 6-mercaptopurine and maintenance infliximab at 10 mg/kg given every 8 weeks.

In this case, a patient who initially responded to infliximab developed an attenuated response while being treated with episodic, as opposed to maintenance, infusions. She was subsequently started on infliximab maintenance and required increasing the infliximab dose from 5 mg/kg to 10 mg/kg every 8 weeks to achieve an optimal outcome. In a recent study, CD patients treated episodically, 61% of patients developed antibodies to infliximab (ATI). ATIs correlated with a higher incidence of infusion reactions, which were manageable and preventable with prophylaxis. ATIs at high titers also correlated with decreased intervals until reinfusion (71 vs. 35 days), but patients who had an attenuated response to 5 mg/kg continued to do well when treated with 10 mg/kg infliximab. Based on this and other studies, the two strategies that should be adopted to prevent ATIs are maintenance versus episodic treatment and combination therapy with immunomodulators (6-MP, azathioprine, methotrexate) (23).

THE GROWTH THERAPEUTIC ROLE OF TNF

Increased appreciation of the pathogenic importance of TNF-α in I.M.I.D.s has widened the search and potential range of clinical applications for anti-TNF agents. Infliximab, in particular, has already shown effectiveness in patients with ankylosing spondylitis (27), and it may be effective in treating adult-onset Still's disease (28) and Behçet's disease (29,30). It is also being evaluated in IBD subtypes such as pediatric CD, and ulcerative colitis (31). Other researchers are studying infliximab for maintenance use in early RA, psoriatic arthritis, and psoriasis (32). Despite its inability to achieve positive results in patients with CD, etanercept has been effective in treating RA and psoriatic arthritis (33-35). Thalidomide, an orally bioavailable TNF-α production inhibitor, has been used off-label with some success to treat a number of dermatologic diseases, including several inflammatory skin conditions (36). Early work with this agent in CD showed limited efficacy and a prohibitive side effect profile (mainly peripheral neuropathy and increased sedation) (37,38), but derivative oral formulations have been developed that may have therapeutic potential. Success in the treatment of these disorders suggests that anti-TNF therapies may also be therapeutic in a vast number of other I.M.I.D.s in which TNF-α has been implicated, including Alzheimer's disease, asthma, cancer, diabetes, Felty's syndrome, organ transplant, Parkinson's disease, trauma, and uveitis. New therapies, such as the selective adhesion molecule (SAM) inhibitor natalizumab, has recently shown efficacy in MS (39) as well as CD (23,40). Anti-cytokine therapies not involving TNF-γ—including IL-1, IL-2, IL-6, IL-8, IL-12, and IFN-γ—may hold equal therapeutic promise. Future investigations will determine the breadth of application of anti-TNF and other therapies in the treatment of I.M.I.D.s.

CONCLUSIONS

Scientific and clinical understanding of the roles of TNF-α and other inflammatory cytokines in human biology and disease has grown considerably over the past century, especially in the last decade. We now know that TNF-α affects many physiologic processes and that TNF receptors are found on virtually all cell types. By studying how cytokines are involved in the pathophysiology of a variety of I.M.I.D.s, targeted anti-TNF-α therapies for RA and CD were developed. Many patients with CD, RA, psoriasis, and psoriatic arthritis are already benefiting from these treatments. However, despite strong evidence linking underlying pathologies and treatments for the range of diseases that constitute the I.M.I.D. group, providers have just recently become acquainted with the I.M.I.D. concept. As a wider audience of medical professionals comes to recognize the therapeutic importance of inflammatory cytokines like TNF-α in treating I.M.I.D.s safely and effectively, agents that modulate cytokine activity will surely become useful in further applications. ■

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