Immunotherapy in Inflammatory Bowel Disease

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KEYWORDS

• Crohn disease • Ulcerative colitis
• Anti-tumor necrosis factor-α • Infliximab • Adalimumab
• Certolizumab • Anti-α_4-integrin therapy • Natalizumab
• Biologics

Key Points

- Inflammatory bowel disease (IBD) is one of the most prevalent gastrointestinal diseases.
- The dysregulation of the immune system with the increased expression of proinflammatory cytokines, such as tumor necrosis factor (TNF)-α, and increased mucosal expression of vascular adhesion molecules play an important role in the pathogenesis of IBD.
- The availability of anti-TNF-α agents has revolutionized the treatment of patients with IBD.
- Anti-TNF-α agents are effective in inducing and maintaining remission in patients with Crohn disease and ulcerative colitis.
- Loss of response to biologics is not uncommon and may be related to immunogenicity to the immunologic agent used for IBD treatment.
- Side effects include serious infections, reactivation of latent tuberculosis and fungal infections in the case of anti-TNF-α therapy, and an increased risk of progressive multifocal leukoencephalopathy in the case of natalizumab.
- Additional therapies are needed for the treatment of patients who are primary nonresponders and those who lose response during scheduled maintenance therapy.
- Based on the therapeutic efficacy of antibodies to cytokines, such as anti-interleukin (IL)-12 and IL-23, immunotherapy and biologic therapy hold a considerable promise in the treatment of IBD.

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INTRODUCTION

Inflammatory bowel disease (IBD), which includes Crohn disease (CD) and ulcerative colitis (UC), represents a group of chronic diseases that usually starts early in life, with 10% to 15% of the patients presenting with the disease later in life. Its incidence and prevalence seems to have increased, and it is considered to be one of the most prevalent gastrointestinal diseases.[1–3] Although the highest incidence and prevalence of IBD is reported to be in Europe, it is estimated that there are more than 1 million people with IBD in the United States.[3,4]

IBD is characterized by inflammation of the gastrointestinal tract and a relapsing and remitting or progressive clinical course resulting in significant morbidity and health care cost. Clinically, IBD is characterized by abdominal pain associated with diarrhea, rectal bleeding, and malnutrition. Although CD may affect any part of the gastrointestinal tract, UC is limited to the colon. IBD is also associated with an increased risk of colon cancer.[5]

Although the exact cause still remains unclear, IBD has been appreciated to have a genetic basis,[6] and environmental factors are thought to play a role in the pathogenesis of IBD as highlighted by the development of IBD in immigrants to high-prevalence areas[7] and discordance of IBD among monozygotic twins.[8] The importance of environmental factors is also underscored by a rising trend in the incidence and prevalence of IBD in countries undergoing rapid westernization.[9] In addition, the dysregulation of immune responses to intestinal bacterial antigens is hypothesized to play an important role in the development of IBD in genetically susceptible hosts.[10]

Standard nonsurgical treatment of IBD includes topical 5-aminosalicyclic acid agents, antimicrobials, steroids, and immunomodulators, such as azathioprine and 6-mercaptopurine. Patients with both CD and UC experience disease flares despite maintenance therapy with these agents used singly as monotherapy or in combination. Although these flares have been treated with short courses of corticosteroids, 20% to 40% of patients with IBD seem to become dependent on corticosteroids to maintain remission of the disease or become resistant to corticosteroids.[11–13] Of course, long-term use of corticosteroids is undesirable to avoid the known protean serious complications.

This article reviews the currently available immunologic agents for the treatment of patients with IBD and focuses on the efficacy of immunologic agents currently approved for the treatment of patients with CD and UC.

TUMOR NECROSIS FACTOR AND OTHER CYTOKINES IN IBD

Inflammation in UC and CD is regulated by increased secretion of proinflammatory cytokines.[14] Although an extensive review of cytokines involved in the development of IBD is beyond the scope of this article, it is noteworthy to mention that concentrations of cytokine tumor necrosis factor-α (TNF-α) are elevated in the blood,[15] mucosa,[16,17] and stool[18] of patients with IBD. In addition to TNF-α, the increased secretion of other proinflammatory cytokines in stools and rectal dialysates of patients with IBD was also seen in patients with both UC and CD.[19,20]

An increasing understanding of the involvement of the cytokines combined with the lack of adequate response and sustained remission of disease with standard medical treatment of IBD has allowed immunotherapy to emerge as an important modality in the treatment of patients with IBD. Several anti-TNF-α antibodies and other agents directed against cytokines or adhesion molecules involved in the pathogenesis of IBD have been developed and used in the treatment of IBD in clinical trials (**Table 1**). Thus far, 4 agents are approved for the treatment of IBD (see **Table 1**).