he introduction of biological agents in recent years for the treatment and possible reversal of the progression of some serious chronic diseases was heralded as a breakthrough in therapy, in which the benefits seemed to outweigh the risks. Although carefully controlled clinical trials demonstrated several adverse effects, the benefits of these agents led to the Food and Drug Administration’s (FDA) approval. After several years on the market and with the widespread use of these biological agents throughout the world, some serious adversities have emerged. This article presents some of the potential problems associated with the long-term use of these agents.

BACKGROUND

Etanercept (Enbrel®, Immunex, marketed by Amgen) and infliximab (Remicade®, Centocor) are tumor necrosis factor (TNF) antibodies that are used to treat severe cases of rheumatoid arthritis (RA) and Crohn’s disease (CD).1-5

Infliximab is the first product that has been documented to reduce the number of open fistulas that burrow through the bowel wall into nearby organs or through the surface of the skin in patients with CD. On August 24, 1998, the FDA approved this product for marketing to treat moderately to severely active CD in patients who had responded inadequately to conventional therapy. Infliximab is also indicated for patients with fistulizing CD to reduce the number of draining enterocutaneous fistulas.6 Overproduction of TNF-α leads to inflammation in conditions such as CD, RA, and other autoimmune diseases.7 Infliximab seems to reduce intestinal inflammation in patients with CD by binding to and neutralizing TNF-α on cell membranes and in the blood.6

Seminal basic science work identified the importance of the proinflammatory cytokines (TNF-α and interleukin-1β (IL-1p)) by showing that they had an active role in the pathogenesis of RA.7 IL-1p is also a potent immunomodulator that mediates a wide range of immune and inflammatory responses, including the activation of B and T cells.7 These discoveries rapidly led to the development of biological agents that inhibited these cytokines and suppressed disease in patients with RA.

Etanercept is a soluble p75 TNF receptor that inhibits the action of TNF. Infliximab is a chimeric monoclonal antibody to TNF-α, approved for the treatment of severe RA.

Anti-interleukin-1β (anti-IL-1β) is a well-validated cytokine target in inflammatory disease with in vivo neutralization of IL-1β that suppresses the arthritic process and confers beneficial effects on joint erosion.8 Controlled clinical trials have demonstrated the efficacy of chronic administration of etanercept and infliximab with methotrexate in slowing the progression of disease activity and joint damage in patients with early RA, with emphasis on the importance of early treatment.9 Antibodies to pegylated IL-1β have the potential to complement anti–TNF-α treatment of RA, and one agent is currently under investigation (anti–IL-1β or CDP 484 [Cistron, Celltech]).10

Another agent, anakinra (Kineret™, Amgen), is a synthetic protein that is similar to a naturally occurring protein in the body called interleukin-1 receptor antagonist (IL-1Ra).11 In patients with RA, the body produces a high amount of IL-1Ra and other proteins that lead to joint damage. High concentrations of one of these proteins, IL-1, contribute to the pain, swelling, and stiffness associated with RA. Therapy with anakinra, which can block the action of IL-1, has been found to be safe and effective against RA.11 Etanercept has also received FDA approval for patients with ankylosing spondylitis (AS). This condition is characterized by inflammation of the spinal joints and causes painful stiffening of the spine, often leading to fusion of the vertebrae that can leave the back curved and inflexible. Treatment of AS with etanercept is safe and efficacious, with significant improvement noted in as early as two weeks and continuing for 24 weeks.12

The FDA has also approved etanercept for the improvement of physical function in patients with moderately to severely active RA. The approval was based on results from three placebo-controlled trials in which etanercept improved patients’ physical functioning and disability scores for up to four years.13 Adalimumab (Humira®, Abbott), previously known as D2E7, is the latest anti–TNF-α agent to be approved by the FDA for “reducing the signs and symptoms and inhibiting the progression of structural damage in adults with moderately to severely active RA who have had insufficient response” to one or more disease-modifying anti-rheumatic drugs (DMARDs).14

INFlixIMAB AND ETanERCEPT: MAJOR PROBLEMS WITH THERAPY

Infection

Controlled trials have shown no overall increase in the risk of serious sepsis in enrolled patients taking infliximab and etanercept.1,2,15 Such trials provide a comprehensive data set, but patients enrolled in trials are not always typical of those who receive these drugs in the real world. Indeed, postmarketing surveillance has identified an increased risk of reactivation of tuberculosis (TB) in patients taking infliximab and has led to additional FDA guidelines.16 However, recent experience in different treatment areas suggests that infection is usually an even greater cause for concern when these drugs are used in the general patient population.17

One of the striking features of sepsis is the rapidity of the onset of the infection.17 Four of the first 20 patients who received biological agents required admission to a hospital because of

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severe pneumonia and, in some circumstances, required ventilation. In another study, four of 88 adults receiving biological therapy for severe inflammatory arthritis experienced serious infections and required hospitalization; two of these patients died. In a different region, serious infections developed in four of the first 38 patients. Two of these were elderly patients with comorbidities who developed recurrent infections and ultimately died.

Infections associated with infliximab and etanercept use have been reported in England and Europe. The increased risk of infection in RA patients and its association with premature death are well documented. Many candidates for biological therapy are already taking corticosteroids and other immunosuppressive agents, both of which add to the risk of infection.

Serious infections are also associated with increased disability and comorbidity; the very features that one might expect to see in candidates for biological therapy. Currently, there seems little doubt that the risk of infection is an important safety issue in patients who are candidates for biological therapy. Patients receiving biological agents should have ready access to professional advice 24 hours a day, preferably from the center prescribing and administering their treatment.

Frequently disseminating or extrapulmonary TB at clinical presentation has been observed in patients receiving infliximab. All health care professionals should take the appropriate precautions when prescribing TNF inhibitors, including evaluating patients for latent tuberculosis with a tuberculin skin test, before initiating treatment with any immunosuppressive agent. Latent TB should be treated before infliximab therapy is begun.

Histoplasmosis, listeriosis, and pneumocystosis have been reported in both the clinical research and postmarketing surveillance settings. Some of these infections have been fatal. Invasive fungal infections and other opportunistic infections have been reported in patients taking infliximab. Adverse drug events (ADEs) involving rare cases of nervous system disorders, including demyelinating disorders such as multiple sclerosis, myelitis, and optic neuritis, have also been noted in patients with RA who have received etanercept therapy.

Cardiac Effects

Patients with CD and RA who have congestive heart failure should not use infliximab, which may cause additional adverse effects. Patients already receiving the agent should be closely monitored, but patients whose condition is worsening should discontinue infliximab.

The evaluation of data from the FDA's MedWatch program, including 47 patients who experienced heart failure while receiving long-term TNF antagonist therapy (with infliximab and etanercept), showed that 81% had never experienced heart failure before taking TNF antagonists. Half of the patients with new-onset heart failure had no identifiable risk factors for this condition, and 10 patients were younger than age 50.

The median interval from the first TNF antagonist dose to a diagnosis of new-onset heart failure or heart failure exacerbation was 3.5 months (range, 24 hours–24 months) and four months (range, 24 hours–20 months), respectively. Thus, it is clear that physicians must be aware that heart failure may occur in patients receiving TNF antagonists.

Lymphoma

Recently, there has been a disturbing association between the use of both infliximab and etanercept and the development of lymphoma. In one instance with each drug, lymphoma regression was observed when drug treatment was discontinued. Determining the etiologic mechanism associated with these anti-TNF drugs is complicated by the predisposition to lymphoma in patients with RA or CD. Most cases (81%) were non-Hodgkin’s lymphomas.

The time between the initiation of medication use and the development of lymphoma was short (median, eight weeks). In two instances, lymphoma regression was observed following discontinuation of anti-TNF treatment, without using any anti-lymphoma chemotherapy. Although patients with these conditions tend to be predisposed to the development of lymphoma, blocking TNF is an immunosuppressive activity and infections and tumors may therefore proliferate.

CONCLUSION

Before prescribing infliximab and etanercept, practitioners should carefully consider the benefits and risks associated with these agents for all patients. These new biologicals, discovered through scientific methods, are revolutionizing the treatment of CD and RA in a way that might alter the course of the diseases. These drugs have also changed the way we approach therapies for patients with older diseases. In the past, patients with RA simply coped with their symptoms by taking nonsteroidal anti-inflammatory drugs (NSAIDs) or DMARDs; now there are treatments that enable us to envision the possible eradication of this disease. The goals of treatment now focus on eliminating constitutional symptoms, bringing about the patient’s return to work, and minimizing the impact on activities of daily living.

Despite the intriguing findings for these biological response modifiers, there are drawbacks to using them. Anti-TNF therapies have been plagued with complications, such as infection, which accounts for as much as 22% of all reported ADEs. The development of lymphoma is a warning signal about the dangers of these agents for some patients, particularly those with congestive heart failure. Such problems only call attention to the need to observe these patients carefully when anti-TNF agents are prescribed.

REFERENCES

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