What Are the Risks of Biologic Therapy in Rheumatoid Arthritis? An Update on Safety

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ABSTRACT. The tumor necrosis factor-α (TNF-α) blockers infliximab and etanercept and the recombinant interleukin 1 (IL-1) receptor antagonist anakinra are effective in patients with active rheumatoid arthritis (RA). Here, information in the medical literature and public domain is used to consider the safety of these biologic agents. TNF-α inhibition with infliximab has been associated with reactivation of tuberculosis and possibly development of other opportunistic infections (histoplasmosis, listeriosis, and pneumocystis). Exacerbations of multiple sclerosis and other central nervous system events have been reported with etanercept and infliximab. Recently, a review of preliminary data from an ongoing phase II study suggests that infliximab may worsen congestive heart failure. On the basis of clinical trials, there appears to be a higher incidence of serious infections seen in anakinra patients compared with controls; the particular combination of anakinra and etanercept may be associated with a higher incidence of serious infections and clinically significant leukopenia. Additional data are needed to understand whether all these safety issues are unique to an individual biologic agent or representative of a class effect. At this time, treating physicians must carefully weigh the benefits of these new biologics against their risks, particularly in patients at risk of infection. (J Rheumatol 2002;29 Suppl 65:33–38)

Key Indexing Terms:
ANAKINRA TUMOR NECROSIS FACTOR-α ETANERCEPT
INFLIXIMAB RHEUMATOID ARTHRITIS SAFETY TUBERCULOSIS

Tumor necrosis factor-α (TNF-α) and interleukin 1 (IL-1) are believed to play major roles in the pathogenesis of rheumatoid arthritis (RA) and other autoimmune diseases, but these cytokines are also important in mechanisms of host defense and immune system regulation[1,2]. Two TNF-α blockers, infliximab, a chimeric murine-human anti-TNF-α monoclonal antibody, and etanercept, a recombinant soluble TNF receptor fusion protein, were effective in randomized controlled trials of patients with active RA[3-6] and are now available for use in RA. TNF agents have been shown to reduce the rate of radiographic progression, both in early onset, as well as established disease[3-6]. Infliximab is also approved for use in Crohn's disease[7]. Anakinra, a recombinant human IL-1 receptor antagonist, was also shown to improve clinical signs and symptoms of RA and slow radiographic disease progression[8,9].

Although the safety of these biologics has been evaluated as part of their respective clinical development programs, relatively rare and potentially serious adverse events may not have been detected among the several thousand patients participating in clinical trials. As use of these biologics increases in popularity, postmarketing surveillance becomes important in recognizing potential safety issues. The object of this paper is to review available information in the published medical literature and public domain about the safety of biologic therapy in RA.

PUBLISHED STUDIES OF TNF-α INHIBITORS

Tuberculosis Reactivation

In animal models, TNF-α plays an important role in the host response to tuberculosis (TB), particularly in granuloma formation and in containment of latent disease[10-12]. Moreover, in a murine model of latent infection, anti-TNF-α caused reactivation of TB[13], but in phase III clinical trials of infliximab, only one case of TB was reported[3]. However, as of May 29, 2001, postmarketing surveillance revealed 70 cases of TB after infliximab treatment, which were disclosed through the MedWatch Spontaneous Adverse Event Reporting System of the US Food and Drug Administration (FDA)[14]. Until that time, infliximab had been administered to about 147,000 patients worldwide, including 121,000 people in the United States. Of the US patients, 45,000 patients had RA and 76,000 patients had Crohn's disease.

Keane and colleagues identified an index patient in whom TB developed after infliximab was administered for Crohn's disease[14]. These investigators then reviewed adverse events from the MedWatch program[15] as well as reports from the manufacturer to identify other patients with a diagnosis of TB based on clinical, radiological, and labo-

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ratory findings. Of the 70 cases, which included the index case, 45 (64%) patients were women, and 47 (67%) patients were receiving infliximab for RA (Table 1). In the remaining cases, 18 (26%) patients received infliximab for Crohn's disease and 5 (7%) patients received it for other reasons. The median interval from the start of infliximab to onset of TB was 12 weeks (range 1 to 52), and the median number of infliximab doses until diagnosis was 3 (range 1 to 9). In most (79%) cases, patients received one or more concurrent medications that affect the immune system, generally corticosteroids alone or in combination with methotrexate. However, it should be noted that 9 of 11 US patients using corticosteroids did not receive a prednisone dose over 15 mg daily.

Among the 70 cases of TB, extrapulmonary TB was observed in 40 (57%) patients after infliximab therapy, including 17 (24%) patients with disseminated disease, 11 (16%) patients with lymph node disease, 4 (6%) patients with peritoneal disease, 2 (3%) patients with pleural disease, and one patient each with meningeal, enteric, paravertebral, bone, genital, or bladder disease. Of the remaining patients, 22 (31%) had pulmonary TB, whereas the manifestations of disease were not reported in 8 (11%) cases. Eight (11%) patients overall had a history of TB, and 2 (3%) patients reported possible recent exposure. Interestingly, most (91%) of the cases came from countries with a low incidence of TB (< 20 cases per 100,000 population per year), which included the US and several countries in western Europe.

On the basis of these spontaneous reports, the calculated rate (estimated) of TB occurring in patients receiving infliximab for RA in the US was 24.4 cases per 100,000 population for the previous year. In comparison, the background rate of TB in RA patients in the US is estimated to be 6.2 cases per 100,000 population per year[14]. Five (29%) of the 17 US patients were immigrants, but all 5 had lived in this country for more than 10 years. This is consistent with an analysis by the US Centers for Disease Control and Prevention that 44% of all cases of TB in the US occur in foreign-born persons. In the followup of the 70 cases of TB, 12 (17%) patients have died. In 4 cases, the cause of death was related directly to TB.

Table 1. Demographic and clinical characteristics of 70 patients developing tuberculosis after infliximab therapy. From Keane, et al [14], with permission.

Characteristic	Value
Age, yrs, median (range)	57 (18–83)
No. of infliximab doses, median (range)	3 (1–9)
Indication, n (%)	
Rheumatoid arthritis	47 (67)
Crohn's disease	18 (26)
Juvenile rheumatoid arthritis	2 (3)
Ankylosing spondylitis	2 (3)
Behçet's disease	1 (1)
Recent use of immunosuppressants, n (%)	
Corticosteroids alone	14 (20)
Methotrexate alone	6 (9)
Corticosteroids plus methotrexate	28 (40)
Corticostersoids plus azathioprine	3 (4)
Other immunosuppressants	4 (6)
Not reported	15 (21)
Country of report, n (%)	
United States	17 (24)
Spain	10 (14)
Italy	8 (11)
France	7 (10)
Other European countries	20 (29)
Other countries	8 (11)

According to the investigators of this study, the data strongly suggested that infliximab therapy was associated with the development of reactivation TB. This conclusion was supported by the large number of cases of TB reported in close temporal relationship to infliximab administration, the higher estimated rate of TB as compared to the background rate in RA patients in the US, and the laboratory evidence linking susceptibility to TB with decreases in TNF-α activity. Most patients appeared to have reactivation of disease. Importantly, there is concern that the pattern of TB reflects an immunosuppressive effect, inasmuch as more than half of all patients had disseminated disease.

At the time of the publication, etanercept had been administered to about 102,000 RA patients worldwide, but only 9 cases of TB were reported to the FDA[15]. The reason for the difference in rates of TB between infliximab and etanercept is unclear, but it may be related to the different ways in which each biologic binds to or neutralizes TNF-α. Alternatively, it may reflect that etanercept is used proportionately more often in the US than in European or other countries. Adalimumab, a humanized anti-TNF-α monoclonal antibody, has been administered to about 1200 patients in Europe and 1700 patients in the US[14]. Eight cases of reactivation TB were reported in Europe, whereas one case of primary TB was seen in the US. The association of adalimumab with TB was seen with higher but not lower doses of the antibody.

The study investigators postulated that the mechanism for reactivation of TB with anti-TNF-α therapy may reflect a failure of granulomas to compartmentalize the *Mycobacterium tuberculosis* organisms. This speculation is based, in part, on the importance of macrophage apoptosis as a primary feature of TB granuloma formation[16-18]. Because TNF-α is important in mediating apoptotic activity, the clinically significant reduction in TNF-α activity during infliximab and (possibly) adalimumab therapy may permit TB organisms to escape containment.

Central Nervous System (CNS) Disease

A recent report by Robinson and colleagues describes a number of cases involving demyelination and other CNS events occurring in patients receiving TNF-α blockers[19]. At least 9 cases of neurologic or demyelinating events were

reported in association with etanercept as of November 2000. These cases were divided into 4 general groups: exacerbation or worsening of preexisting muscular sclerosis (MS); new onset MS; acute changes in mental status with residual deficit or evidence of demyelination on biopsy; and findings consistent with neurologic disease but not diagnostic of MS. These cases varied greatly in clinical presentation, with many of those not diagnosed as MS having clinical or radiographic features consistent with possible MS. As of January 2001, 2 cases of neurologic events were associated with evidence on magnetic resonance imaging (MRI) of definite or possible demyelination in RA patients taking etanercept.

The exacerbation of MS appeared to occur as a result of neutralization of TNF-α rather than lymphotoxin. This association has been seen with a TNF receptor fusion protein (lenercept), which binds to TNF-α and lymphotoxin, as well as with infliximab, which specifically neutralizes TNF-α. These clinical studies of infliximab and lenercept in MS show an increase in disease activity with MRI evidence of disease worsening[20,21].

Why is this possible? On the basis of *in vitro* studies, animal models, and human disease, TNF-α overexpression appears associated with tissue injury in inflammatory arthritis, inflammatory bowel disease, and demyelinating disease[22]. The discordant activity of TNF-α blockers in RA and Crohn's disease relative to MS may reflect the inability of these drugs to enter the CNS. Complex molecules like infliximab, etanercept, and lenercept (in trials) are unable to cross the blood–brain barrier. In contrast, TNF-α blockers readily penetrate into inflamed synovial and bowel tissue of patients with RA and Crohn's disease, respectively.

Pathogenic T cells can induce tissue injury in the joint, bowel, and CNS by producing TNF-α. In RA, Crohn's disease, and other peripheral autoimmune disorders, TNF-α blockers neutralize local TNF-α activity, thereby preventing downstream tissue injury (Figure 1)[3,5,7]. In MS, however, the TNF-α blockers cannot penetrate the blood–brain barrier to neutralize TNF-α in the brain. Additionally, it is possible TNF-α blockers may exacerbate MS by increasing peripheral T cell autoreactivity. By blocking TNF-α peripherally, these drugs may alter the function of antigen-presenting cells, increase T cell receptor signaling, and decrease apoptosis of autoreactive T cells, some of which may be myelin-specific[23]. There is evidence that active MS is associated with increased entry of lymphocytes and other immune cells into the CNS. If TNF-α blockers enhance activation and survival of peripheral T cells, then these cells may enter the CNS and promote demyelination. In contrast, in RA and Crohn's disease, the very large local impact of TNF-α blockade on tissue destruction appears to outweigh the potential exacerbation caused by an increase in T cell autoreactivity. Thus, the heterogeneity of the role and mechanism of action of TNF-α in various autoimmune diseases may explain the observed discordant clinical effects, particularly when RA and Crohn's disease are compared with MS.

Anti-DNA Antibodies

In early clinical studies, 2 of 20 RA patients treated with infliximab developed antibodies to double-stranded DNA (anti-dsDNA), but developed no signs or symptoms of systemic lupus erythematosus (SLE)[24]. The incidence of anti-dsDNA development during infliximab treatment was assessed in 156 RA patients, who were treated with or without methotrexate in open label, randomized, placebo controlled trials[25]. Anti-dsDNA was evaluated by the *Crithidia luciliae* indirect immunofluorescence test (CLIFT), and then confirmed with a commercial Farr radioimmunoassay using mammalian DNA as the antigen source. Antinuclear antibody (ANA) frequency increased from 29% at baseline to 53% after infliximab therapy. Anti-dsDNA was not detected in any patient at baseline, but was found in 22 (14%) patients by the CLIFT assay following infliximab therapy. Of these, 8 patients had antibody levels

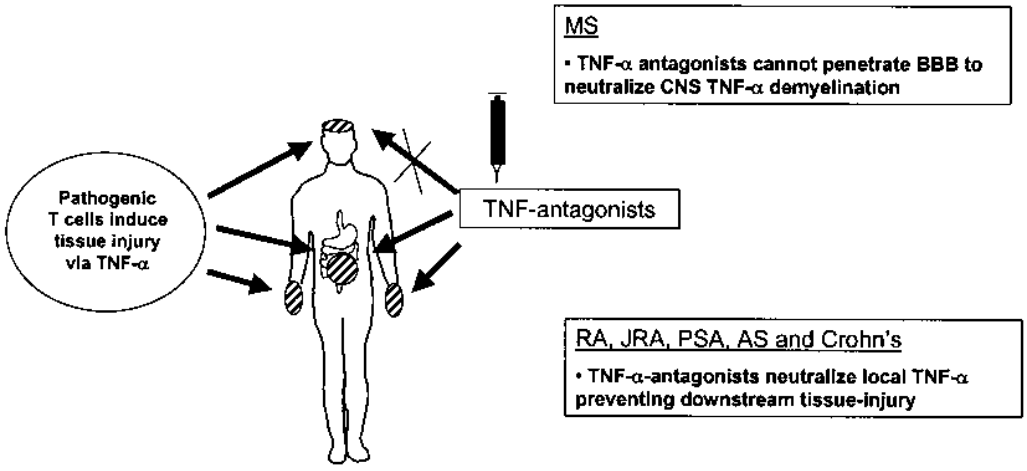

Figure 1. The protective effect of TNF-α antagonists against tissue injury in RA and Crohn's disease but not in multiple sclerosis. Adapted from Robinson, *et al*[19], with permission. BBB: blood-brain barrier.

> 25 units/ml and another 11 patients had levels > 10 units/ml when assessed by the Farr assay. The anti-dsDNA developed after a mean time of 6.3 weeks (range 4 to 10), and except for one case, it was of the IgM isotype. In that case, the patient developed a self-limiting clinical lupus syndrome with IgG, IgA, and IgM antibodies to dsDNA. This patient had seropositive erosive RA, which had been reduced in activity by treatment with infliximab 3 mg/kg every 4 weeks and methotrexate 7.5 mg weekly. Following the diagnosis of lupus, the patient began prednisone 17.5 mg daily, and within 8 weeks, symptoms and anti-dsDNA antibodies resolved. This study demonstrates that infliximab induces ANA and anti-dsDNA, but it appears to cause clinical lupus at a low frequency and by an unknown mechanism.

FDA PERSPECTIVE ON ANAKINRA AND TNF-α INHIBITORS

Anakinra

The FDA Arthritis Advisory Committee met in August 2001 to consider the safety of the recombinant IL-1 receptor antagonist, anakinra. The Anakinra Briefing Document Report[26] provided an overview of the safety database used by the advisory committee. Nineteen trials of anakinra have been completed, including 5 randomized, placebo controlled studies. Roughly 2500 patients received at least one dose of anakinra, and 345 patients received anakinra concomitantly with methotrexate. The incidence of serious adverse events was similar in anakinra and placebo treated patients, whereas mortality was identical in both groups of subjects (Figure 2). However, serious infectious episodes occurred more often with anakinra than placebo (1.8% vs 0.7%). Risk of infection appeared higher in corticosteroid treated patients and in those with a history of asthma or pneumonia. However, evidence of TB or other opportunistic infections was not seen.

The Anakinra Briefing Document Report[26] contained information about a 24 week, open label, single arm safety study of combination therapy with anakinra and etanercept. Fifty-eight patients were enrolled after receiving etanercept for an average of 1.2 years. Infections were reported in 48% of subjects as compared with 39% of those treated with anakinra in the 5 randomized, placebo controlled trials. Serious infections were reported in 6.9% of subjects treated with anakinra plus etanercept, but grade 3 or 4 neutropenia was not observed. According to the corporate sponsor, combination therapy with anakinra and etanercept may possibly increase the risk of infection compared to anakinra alone.

The briefing document prepared by the FDA[26] contained additional safety information. The briefing document agreed in general with the sponsor that there appears to be a higher incidence of serious infections seen in anakinra patients compared with controls. The document also noted this is more common in asthma patients and in those taking corticosteroids. The briefing document indicated there is limited information available on the safety of anakinra taken with other TNF agents, and it addressed the safety information from the above-mentioned 58 patient study. Serious infections were seen in 7% of the 58 patient combination study with etanercept. Leukopenia was seen more frequently, and 2 patients with neutrophil counts < 1000 developed subsequent serious infections. The briefing document noted this was a small study with no controls, but the study raises questions about whether the combination of anakinra and etanercept may be associated with a higher incidence of serious infections and clinically significant leukopenia. The package insert for anakinra now warns about the combination of anakinra with other anti-TNF agents.

TNF-α Inhibitors

The FDA briefing document[26] contained safety updates of the TNF-α blockers as of July 2001. The document discussed data from the MedWatch surveillance program, which normally raises a red flag when an adverse event is seen in close temporal relationship to drug administration or when an unexpected pattern of adverse events is seen in relationship to patient age or sex.

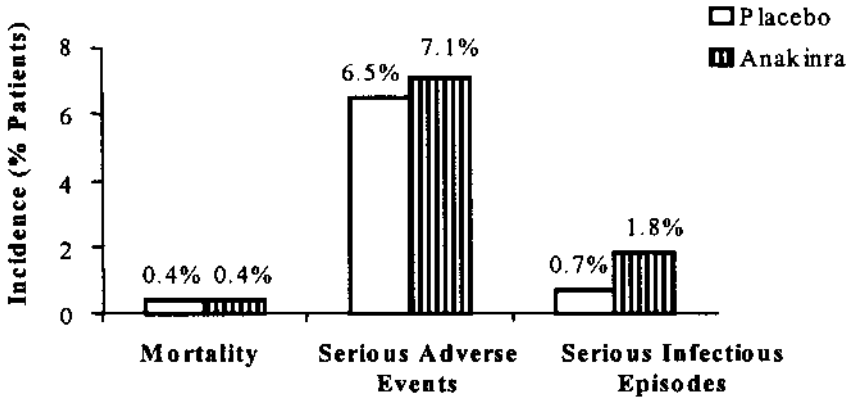

Figure 2. Safety of anakinra in clinical trials of 2531 subjects receiving at least one dose of drug.

It is important to recognize, however, that the MedWatch program has several limitations. First, associations between drug administration and adverse events are inevitably underreported, and the extent of this problem is difficult to measure. Second, temporal associations are often reported with limited information about potential causality of the drug. Third, adequate information about the number of patients treated with the drug is usually limited, making it difficult to accurately calculate reporting rates. Fourth, the diagnoses used in the reporting process are not standardized, and those that are unconfirmed often prove subsequently to be inaccurate. Finally, comparative information about exposure to the suspect drug as well as concomitant medications is often missing or lacking.

Despite these limitations, the FDA briefing document expressed major concerns about TNF-α inhibition with respect to serious infections (TB, histoplasmosis, listeriosis, and pneumocystis) and potential immune related and other adverse experiences [demyelinating and other neurological events, aplastic anemia and other hematological events, intestinal perforation, lymphoma, and congestive heart failure (CHF)]. As a result, the FDA recommended that several actions be taken regarding labeling of the TNF-α blockers. First, a black box warning was placed in the package insert to account for the higher reported incidence of TB with infliximab treatment relative to the background rate in RA patients. Second, the warning section was updated to account for the higher reporting rate of aplastic anemia with etanercept relative to incidence estimates. Third, because neurologic signs and symptoms suggestive of MS have occurred with etanercept, lenercept, and infliximab, a caution statement was added to the package insert. The FDA has suggested this is consistent with a "class" effect for all TNF-α blockers.

In October 2001, the manufacturer of infliximab issued "Dear Doctor" letters concerning the relationship of its drug with TB and CHF. As of June 30, 2001, 84 cases of TB were reported worldwide against a background of 170,000 patients treated with this agent. Although the majority of cases were pulmonary, one-third was disseminated. Moreover, 14 patients have died, including 10 due to TB. The letter notes that other serious opportunistic infections (histoplasmosis, listeriosis, and pneumocystis) have also been reported. Because of the association of infliximab and TB, a boxed warning has been added to product labeling indicating that patients should be evaluated and treated for latent TB before infliximab therapy is started.

According to the second "Dear Doctor" letter, a review of preliminary results from an ongoing phase II study of 150 patients with moderate to severe CHF found higher incidences of mortality and hospitalization for worsening heart failure in patients treated with infliximab, particularly those treated with the higher dose of 10 mg/kg. Accordingly, the manufacturer indicated that infliximab should not be given for RA or Crohn's disease in patients with CHF. Moreover, the letter indicated that infliximab treatment should be discontinued in patients whose CHF worsens, and treatment discontinuation should be considered in patients with stable CHF.

CONCLUSION

On the basis of information in published medical literature and in the public domain (FDA advisory committee documents and "Dear Doctor" letters), there appears to be appropriate concern about the relationship between systemic TNF-α inhibition and the development of TB and, possibly, other opportunistic infections. Most of this information has become available after the widespread use of these agents in the clinic setting. Analysis of the anakinra database from the clinical trial experience indicates the incidence of infections is increased in anakinra treated subjects relative to placebo and the incidence of serious infections associated with clinically significant leukopenia may be increased in patients taking this agent in combination with TNF-α inhibition. Therefore, the combination of biologic agents, especially those having the capability of causing widespread immune and antiinflammatory effects, remains a challenge for drug development. Additional data are needed to understand whether an observed safety concern is unique to an individual biologic agent or representative of a class effect. At this time, treating physicians must carefully weigh the risks and benefits of these new biologics in patients at risk of infection. Moreover, the apparent relationship of TNF-α inhibition and CHF is a new finding that may have important treatment implications yet to be determined.

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