Safety Update on TNF-α Antagonists: Infliximab and Etanercept

Contents

I. Purpose and Format of Safety Update

The purpose of the meeting is to update members of the Arthritis Advisory Committee (AAC) on recent changes made to package inserts of Remicade and Enbrel regarding new warnings, precautions, or adverse events added to the labels. In addition, CBER will update the committee on current data reported to the agency on malignancies in patients receiving these products.

The Center for Biologics Evaluation and Research periodically provides the AAC with updates on products both in development and marketed. This presentation, therefore, is one of a series of meetings intended to keep the committee informed of product development issues in the field of rheumatology. It is important to note that the agency's presentation to the committee is neither comprehensive of all new safety information available to the sponsors or agency on these products, nor is it primarily intended as a forum for directly comparing the risks and benefits of each agent to the other.

II. Limitations and Uses of Post-Licensure Safety Surveillance by the Food and Drug Administration.

Health care professionals and others may report an adverse clinical event associated with the use of an FDA-approved product to the product manufacturer or directly to the FDA under the agency's MedWatch post-licensure safety surveillance program (MedWatch). Manufacturers must forward reports they receive to the FDA, as required in Title 21, *Code of Federal Regulations* (21 CFR 600.80). Upon receipt at the FDA, the reported information is entered into the agency's Adverse Event Reporting System (AERS) database and is then available for review.

Like other passive surveillance systems, FDA's MedWatch Program is subject to many limitations. First, associations between a suspect medication and an adverse event are inevitably underreported, and underreported to an unknown extent. Second, temporal associations are reported with little information about potential causality. Third, adequate denominator information is not readily available to determine reporting rates. Fourth, reporting of unconfirmed diagnoses which often prove inaccurate is common. Fifth, comparative information about patients not exposed to the suspect drug is invariably lacking. Finally, the diagnoses used throughout the reporting process are not standardized.

Because of these limitations of passive surveillance and the MedWatch Program, it is typically not possible to determine causal associations between suspect drugs and adverse events. Signals of potential causal association include: (1) a close temporal relationship between dosing of a suspect drug and an observed adverse event, (2) unexpected patterns in patient age or gender, (3) substantial numbers of positive rechallenge or dechallenge reports, and (4) biological plausibility. The presence of pre-existing conditions,

medication usage, and other uncontrolled clinical variables should be carefully examined; an initial signal that suggests a causal association typically requires confirmation using a traditional epidemiologic or other study.

For TNF-α antagonists, infections and other immune-related adverse events remain as major concerns. Serious infections seen in post-licensure surveillance of TNF-α antagonists have included tuberculosis (TB), histoplasmosis, listeriosis, *Pneumocystis* pneumonia (PCP). Other concerns have included: (1) demyelination and other neurologic events, (2) aplastic anemia and other hematologic events, (3) intestinal perforation, (4) lymphoma, and (5) congestive heart failure. Small numbers of reports or complex medical conditions surrounding the reported events often compromise the ability to recognize important product-related complications. For some of the reported events, however, the reports and the relevant TNF literature taken together support a plausible pathogenetic association between product use and the observed adverse event.

III. Introduction

Tumor necrosis factor-alpha (TNF-α) is a central regulator of inflammation, and TNF-α antagonists may be effective in treating inflammatory disorders in which TNF-α plays an important pathogenetic role. To date, two TNF-α antagonists, infliximab and etanercept, are licensed in the United States (US) for clinical use. The major characteristics of these two TNF-α antagonists are shown in **Table 1**.

Infliximab (Infliximab™) is a chimeric mouse-human monoclonal IgG1 antibody directed against soluble and cell-associated TNF-α, which blocks the binding of TNF-α with its endogenous cell surface TNF-α receptor. The Food and Drug Administration (FDA) approved infliximab in October 1998 for use in moderate to severe or fistulizing Crohn's disease (CD) refractory to conventional therapies. The agency extended the indication for use in November 1999 to include adjunctive use with methotrexate in rheumatoid arthritis (RA) refractory to methotrexate therapy alone. As of March 2001, approximately 121,000 U.S. patients were treated with infliximab (manufacturer's communication; Centocor, Inc., Malvern, Pennsylvania).

Etanercept (Etanercept™), a TNF-α antagonist different from infliximab, is a recombinant protein consisting of the extracellular portion of the human TNF-α receptor fused to the Fc portion of human IgG1. Etanercept inhibits TNF-α activity by serving as a decoy TNF-α receptor. The FDA approved etanercept in November 1998 for use in RA only; approximately 96,500 patients had been treated with etanercept as of April 2001 (manufacturer's communication; Immunex Corporation, Seattle, Washington).

IV. Demyelinating Disease - Etanercept

A. Summary of Adverse Events

The original basis for the label change was 10 spontaneous reports to the sponsor, although more reports have been received subsequently. Two cases are consistent with new onset multiple sclerosis (MS).

Two cases are consistent with established MS with exacerbations after beginning etanercept.

Five additional cases were submitted. One case was characterized by a mental status change associated with demyelination by MRI and by brain biopsy. Although this may represent the initial presentation of MS, it is not a typical one. The patient was left with residual deficits. Of note, the patient had experienced a recurrence of the adverse event following an etanercept rechallenge, although the concomitant discontinuation of corticosteroids makes attribution of the patient's worsening difficult. Another case described a catastrophic neurologic event characterized by leukodystrophy involving the entire white matter. This patient experienced altered mental status, muscle rigidity, and eventual partial recovery. The other cases were suggestive of multiple sclerosis, but did fully meet diagnostic criteria for MS.

B. Review of the Literature

Considerable data suggested that TNFα plays an important pathogenic role in MS, which led to the conduct of clinical trials of TNF antagonists in patients with MS. A double-blind, randomized, placebo-controlled phase II study of 168 patients with MS was carried out with lenercept, a soluble form of the TNF receptor that has some similarity to etanercept (Neurology 1999;53:457-465). Contrary to expectation, a statistically significant increase in the proportion of subjects experiencing exacerbations of MS was observed with lenercept, as well as a shortening of time-to-flare. Neurologic deficits were also worsened in subjects receiving lenercept.

A second study examined the effects of cA2 (infliximab) in two subjects with MS (Neurology 1996;47:1531). Both patients had a transient increase in gadolinium-enhancing lesions on MRI after each treatment and an increase in CSF leukocyte counts and IgG. The authors conclude that further use of cA2 in MS is not warranted.

The incidence of MS in the US has been estimated as 8800 new cases annually, or approximately 4 per 100,000 person-years. The prevalence is about 250,000 to 350,000 Americans, or approximately 0.1% of the US population.

C. Conclusions

The case reports submitted demonstrate clear cases of neurologic syndromes temporally associated with the initiation of etanercept. Two of the cases appear to be new cases of MS. Two cases involve exacerbation of pre-existing MS. Five other cases are difficult to characterize, but two of them presented with severe neurologic syndromes with mental status changes and demyelination on MRI. Both of these cases had brain biopsy information as well: one showing spongiotic changes; the other showing demyelination.

Review of these cases alone cannot establish causality. However, the two reports from the literature suggest that TNF antagonists may exacerbate MS. Taken together, these data suggest that TNF antagonists, as a class, may worsen MS in some patients.

Caution is clearly warranted in treating patients with pre-existing demyelinating syndromes or in continuing etanercept therapy in patients who develop a demyelinating syndrome. However, it is not clear that therapy must be stopped in all cases as two subjects continued etanercept therapy without evidence of exacerbation of their neurologic condition. Another case worsened on reinstituting etanercept therapy (positive rechallenge), however the worsening in this patient coincides with the ending of a corticosteroid taper, confounding the interpretation of this observation.

D. Change to Package Insert

The following text was added to the etanercept package insert.

> **Neurologic Events**
>
> Treatment with ENBREL and other agents that inhibit TNF have been associated with rare cases of new onset or exacerbation of central nervous system demyelinating disorders, some presenting with mental status changes and some associated with permanent disability. Rare cases of transverse myelitis, optic neuritis, and new onset or exacerbation of seizure disorders have been observed in association with ENBREL therapy. The causal relationship to ENBREL therapy remains unclear. While no clinical trials have been performed evaluating ENBREL therapy in patients with multiple sclerosis, other TNF antagonists administered to patients with multiple sclerosis have been associated with increases in disease activity. Prescribers should exercise caution in considering the use of ENBREL in patients with preexisting or recent-onset central nervous system demyelinating disorders.

V. Demyelinating Disease - Infliximab

The attached manuscript (Mohan N, Edwards ET, Cupps TR, et al. Demyelination occurring during anti-TNFα therapy for inflammatory arthritides. *Arthritis and Rheumatism*, in press) describes two cases of demyelinating disease in patients receiving infliximab that are similar in character to those seen in patients receiving etanercept. In addition, a literature report (cited in the above manuscript) describes a prospective clinical trial of infliximab in patients with rapidly progressive MS, in which the first two treated subjects developed an increase in the number of gadolinium enhancing lesions on magnetic resonance imaging, CSF IgG index, and CSF lymphocyte count after each infusion, although there was no reported clinical worsening of disease.

A. Change to Package Insert

The following text was added to the infliximab package insert.

> **Warnings/Neurologic Events**
>
> Infliximab and other agents that inhibit TNF have been associated in rare cases with exacerbation of clinical symptoms and/or radiographic evidence of de-myelinating disease. Prescribers should exercise caution in considering the use of REMICADE in patients with pre-existing or recent onset of central nervous system de-myelinating disorders.

VI. Seizures - Etanercept

A. Summary of Adverse Events

The sponsor submitted 14 reports of seizures or convulsions from post-licensure adverse event reports on patients receiving etanercept. In two cases, the patients had a history of a seizure disorder which had been previously controlled but recurred in temporal association with etanercept. 10 cases are difficult to attribute to etanercept for a variety of reasons, including: history of seizures, concomitant illnesses, longer time after starting etanercept (>120 days). However, 4 cases occurred temporally associated with etanercept use in patients who had no prior seizures in whom no other explanation for seizure was discovered on investigation by the treating physician.

According to the sponsor, the age-adjusted incidence of seizures in the general population is 35 per 100,000 person-years. The mean age of all patients receiving etanercept is 52.

B. Conclusions

In several cases, seizure occurred early after starting etanercept in patients with no prior seizure history. Some of the patients may have been predisposed to seizures, as evidenced by an abnormal EEG. The reporting rate of seizures occurring with etanercept therapy was well below the expected incidence in the general population, and seizures were not observed during clinical trials. A preexisting seizure disorder does not appear to be a contraindication to etanercept therapy since only 2 patients with a seizure disorder had exacerbation on etanercept, and since some patients who experienced seizures continued etanercept without further seizures. However, given the expected underreporting and other limitations of passive surveillance, it is not possible to exclude an association between seizure and etanercept therapy.

C. Change to Package Insert

The following text was added to the etanercept package insert.

> Rare cases of transverse myelitis, optic neuritis, and new onset or exacerbation of seizure disorders have been observed in association with ETANERCEPT therapy. The causal relationship to ETANERCEPT therapy remains unclear.

Note: Seizures and Infliximab

In recent post-marketing reports seizures have been reported in patients receiving infliximab. Preliminary information suggests that these cases are similar in number and in character to the cases seen with etanercept. The agency is currently conducting a review of these cases and any appropriate actions, including labeling changes, that might be necessary. An update will be provided to the committee in the future.

VII. Aplastic Anemia and Pancytopenia - Etanercept

A. Summary of Adverse Events

The basis for changes to the package insert derived from 2 cases of aplastic anemia and 7 cases of pancytopenia.

Two definite cases of aplastic anemia were identified out of an estimated 96,000 patients treated with etanercept. Current estimates suggest that the incidence of aplastic anemia in the general population is approximately a few cases per million person-years. There are reports suggesting that the incidence may be increased up to 8-fold in patients with RA. The reporting rate in etanercept therapy, though rare, appears to be several fold higher than the incidence estimates. Although there are difficulties with estimating incidence based on the reporting rate (e.g., small numbers of patients and underreporting), including precautionary language in the **WARNINGS** section is warranted because of the

seriousness of aplastic anemia. Attribution of pancytopenia to etanercept use appears even less clear; all of these cases are confounded by other risk factors for bone marrow suppression. However, again in large part because of the seriousness of this adverse event and the need to inform physicians and patients, including pancytopenia in the **WARNINGS** section appears warranted.

B. Change to Package Insert

The following text was added to the package insert.

> **Warning/Hematologic Events**
>
> Rare reports of pancytopenia including aplastic anemia, some with a fatal outcome, have been reported in patients treated with ETANERCEPT. The causal relationship to ETANERCEPT therapy remains unclear. Although no high risk group has been identified, caution should be exercised in patients being treated with ETANERCEPT who have a previous history of significant hematologic abnormalities. All patients should be advised to seek immediate medical attention if they develop signs and symptoms suggestive of blood dyscrasias or infection (e.g., persistent fever, bruising, bleeding, pallor) while on ETANERCEPT. Discontinuation of ETANERCEPT therapy should be considered in patients with confirmed significant hematologic abnormalities.

Note: Aplastic Anemia and Pancytopenia in Infliximab Therapy

Cases of pancytopenia have been reported post-marketing associated with the use of infliximab. Many of these cases are complicated by the use of concomitant medications that are known to be associated with pancytopenia. Cases of aplastic anemia have not been reported with infliximab.

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VIII. Intestinal Perforation - Etanercept

A. Summary of Adverse Events

- The sponsor reported 13 cases of intestinal perforation (6 clinical trial and 7 post-licensure).

- In addition to the post-licensure reports, there have been 6 cases of perforated colon in clinical trials. Three of the patients were known to be on etanercept. The other 3 subjects were part of the CHF trial (2) and the psoriatic arthritis trial (1) and were still blinded at the time of the original submission. Since submission, these cases were unblinded: 2 were on placebo; 1 was receiving etanercept 25 mg biw in the CHF trial. Of the 4 cases that were on etanercept, 3 were men and 1 was a woman. The events

occurred more than 2 years after beginning etanercept in 3 subjects and after approximately 3 months in one case. All were receiving concomitant NSAIDs and corticosteroids.

The two subjects with perforation in the CHF trial who were receiving placebo had been on study for 3-7 (3, 4 and 7) months. Both were in their mid-70s and were men. Both patients died following surgery. The first patient presented with a perforated colon, underwent surgery with initially an uneventful post-operative course, then died suddenly. The second patient presented with a perforated sigmoid colon and appendicitis. He died after a protracted and complicated post-operative course. A systematic search of the AERS database did not identify additional cases of intestinal perforation associated with etanercept use.

B. Conclusions

In determining where in the label intestinal perforation should be discussed, it is necessary to evaluate: (1) whether the incidence of intestinal performation in etanercept therapy is higher than in the general population, and (2) the likelihood of a causal relationship between etanercept therapy and the occurrence of these serious adverse events. The evidence does not strongly indicate that etanercept use raises the incidence of intestinal perforation. No cases of intestinal perforation have been seen in randomized clinical trials of etanercept in RA. In the clinical trial in psoriatic arthritis involving 200 subjects, one case of intestinal perforation was observed. In two randomized controlled trials in congestive heart failure involving approximately 2000 patients, two subjects (both on placebo) developed perforation. Seven cases have been reported post-licensure out of over 70,000 patients who received etanercept therapy. Seven cases reported under passive surveillance are not inconsistent with estimates of the incidence in the general population, but underreporting remains a major concern.

Is there any evidence to suggest a causal association? There is some biologic plausibility to the association, since by inhibiting TNF-α, etanercept inhibits host defenses. One could hypothesize that in conditions like diverticulitis, an impairment in antibacterial host mechanisms could conceivably predispose patients to losing the integrity of the bowel wall leading to perforation. In some of these cases, there is an association in time between beginning etanercept and developing an intestinal perforation. Among the 7 post-licensure reports that state a duration on drug, 3 were in the first 10 days, one at 1 month, one at 4 months and one at 8 months. While some of these cases occurred shortly after beginning etanercept, this could be due a reporting bias. Indeed, in the clinical trial experience, 3 of the 4 cases occurred after more than 2 years on etanercept. Are there other predisposing factors that could explain these cases apart from the use of etanercept? Clearly there are. Among the patients not on clinical trials, a number of patients had a history of diverticulitis/diverticulosis, a number were on prednisone and one had severe Wegener's granulomatosis treated with cyclophosphamide. In addition, most of the patients are in the older age group, where diverticulitis and intestinal perforation are not rare occurrences.

In summary, although there is some data suggesting a possible association between intestinal perforation and etanercept use, the evidence is not strong. The reporting rate of intestinal perforation in etanercept therapy is not clearly elevated over that expected in this patient population. While including this adverse event in the Adverse Reaction section of the label is reasonable, a more prominent discussion of these events or a warning is not warranted at this time.

C. Change to Package Insert

The term intestinal perforation was added to the listing of adverse events by body system. The new listing under the Digestive body system reads as follows: Altered sense of taste, anorexia, diarrhea, dry mouth, intestinal perforation.

Note: Intestinal Perforation - Infliximab

Reports of intestinal perforation associated with use of infliximab were noted at the time of licensure of infliximab. A mention of the occurrence of intestinal perforation associated with the use of infliximab was incorporated in the original Remicade package insert

VIX. Cutaneous Lupus Rash - Etanercept

A. Summary of Adverse Events

The sponsor submitted four adverse event reports. Three of these reports represented cutaneous lupus-like skin rashes with positive autoantibodies temporally associated with starting etanercept. The other case presented with dramatic increases in acute phase reactants and platelets along with autoantibodies. None were associated with systemic features of SLE or with a definite diagnosis of SLE. Several cases had positive dechallenge and rechallenge, suggesting a causal association with etanercept use. These cases appear to be very uncommon or rare, as similar cases were not seen in the clinical trials.

B. Change to Package Insert

The following underlined text was added to the package insert.

PRECAUTIONS, autoantibodies

Treatment with ETANERCEPT may result in the formation of autoimmune antibodies (see ADVERSE REACTIONS, Autoantibodies). In post-marketing experience, rare spontaneous adverse event reports have described patients with rheumatoid factor positive RA who have developed additional autoantibodies in conjunction with rashes compatible with subacute cutaneous lupus and discoid lupus by clinical presentation and biopsy.

Note: Lupus-like illness - Infliximab

Cases of lupus-like illness were noted in clinical trials of infliximab associated with increases in autoantibodies. A discussion of lupus-like illness associated with the use of infliximab was included in the original Remicade label. Some additional cases of lupus-like illness have been reported post-marketing.

X. Tuberculosis and Other Opportunistic Infections with Infliximab and Etanercept: FDA Review of MedWatch Reports as of August 2000 Leading to Changes to Infliximab and Etanercept Package Inserts

Of an estimated 82,000 patients treated worldwide with etanercept through 8/31/2000, approximately 13,000 MedWatch reports were filed with the FDA. The large number of adverse event reports may have resulted for many reasons, including a large number of reports from consumers. 2,782 (21%) of all reports were infections. For infliximab, the numbers of post-licensure adverse event reports and patients treated were approximately 1100 and 80,000-150,000, respectively. 17,000 (11%) patients on infliximab were outside the US, while fewer than 10% of the etanercept patients were outside the US.

A similar proportion (20%) of the infliximab reports were infections. The data indicated that a variety of opportunistic infections were seen on etanercept, including herpes zoster, various fungal infections, herpes simplex, candida. Small numbers of cases of TB, PCP, aspergillosis and cryptococcosis were also seen. The proportion of total cases for these infections were generally similar between etanercept and infliximab, with certain exceptions. A higher proportion of reports were for Herpes zoster with etanercept, while Herpes simplex, TB, PCP and aspergillosis represented a higher proportion of reports with infliximab.

A. Tuberculosis - Infliximab: Interim Change to Package Insert

TB reports represented a considerably higher proportion of all reports for infliximab than for etanercept (7.5% versus < 0.1%). Of the 17 infliximab reports, 11 were from Europe and 6 from the US. Two of the 17 patients died. All the cases occurred within 2 to 4 months of starting infliximab. Many of the cases involved disseminated or miliary TB. In addition to the post-licensure reports, there was one death of disseminated TB in the clinical trials. Because of the large number of cases of TB with infliximab, the following language was added to the WARNING section of the infliximab package insert:

> **SERIOUS INFECTIONS, INCLUDING SEPSIS AND DISSEMINATED TUBERCULOSIS, HAVE BEEN REPORTED IN PATIENTS RECEIVING TNF-BLOCKING AGENTS, INCLUDING INFLIXIMAB. SOME OF THESE INFECTIONS HAVE BEEN FATAL.**
>
> **PATIENTS SHOULD BE EVALUATED FOR THE RISK OF TUBERCULOSIS, INCLUDING LATENT TUBERCULOSIS. TREATMENT**

FOR TUBERCULOSIS SHOULD BE INITIATED PRIOR TO TREATMENT WITH INFLIXIMAB.

B. Tuberculosis - Etanercept

To determine whether etanercept may predispose to TB, the MedWatch database was screened and 5 cases of TB were found associated with the use of etanercept, 3 in Europe, 1 in the US. There were no deaths. The time to presentation following the initiation of etanercept therapy was 3-4 months in 3 cases, 7 months in 1 case and 1 year in 1 other case.

No cases of TB were observed in either the US or the European trials of etanercept. 1197 patients were included in the US studies of RA and 827 patients have been treated in CHF studies. 612 patients were treated in the European trials of RA and 648 in the CHF studies. Two of the European studies did not specifically exclude patients with a history of TB: 70 patients enrolled in a pharmacokinetic/pharmacodynamic study and 559 patients in a placebo-controlled efficacy study.

Review of the European clinical trial experience revealed 14 subjects with a history of TB who were treated for a mean of approximately 2 years. None developed TB. Information is unavailable as to whether these patients had previously received anti-tuberculous therapy. Review of the US clinical trial experience revealed 5 patients with a past history of TB and 7 with a positive PPD. These 12 subjects received etanercept for a mean of 769 days. None developed TB. One subject developed a positive PPD while receiving etanercept and remained on etanercept while receiving anti-TB therapy.

Immunex reviewed post-licensure reports and found 6 cases with a prior history of TB who did not develop reactivation on etanercept. There were 2 other reports of exposure to active TB without the development of clinical TB and 2 reports of the discovery of a positive PPD while on etanercept without developing active TB.

Incidence estimates of TB in the US are 6.4 per 100,000 person-years for the general population and 8.2 per 100,000 person-years for the 45-64 year old age group. It should be noted that the incidence may be higher for RA patients receiving immunosuppressive agents, such as methotrexate and prednisone.

C. Opportunistic Infections with Etanercept

As of August 2000, the sponsor submitted 11 post-licensure reports of opportunistic infections. Review of these cases show that many of the patients had other risk factors, including underlying diseases, concomitant immunosuppressive medications. However, other cases are not associated with other risk factors and one case had a positive rechallenge. These factors suggest that in some cases the opportunistic infections may be caused by treatment with etanercept. It is important to take into account that RA is generally treated with immunosuppressive agents, which carry the risk of infections, including opportunistic infections. Therefore, the benefits of treatment with etanercept must be considered along with the possible increased risk of serious infections.

Rare cases of TB have been reported associated with the use of etanercept. Should all patients being considered for etanercept therapy be screened for latent TB and treated prophylactically? Such a recommendation would differ from current practice for US rheumatologists starting patients on other immunosuppressives such as methotrexate and prednisone; and may not be warranted by the data:

- The reporting rate does not exceed US TB incidence estimates.
- Three of the 5 cases come from Europe, where the incidence of TB is considerably higher than in US. Although etanercept may have played a role in the US cases, there are confounding factors: one of the US cases had been the caregiver for a sister who was suspected to have active TB, and the other US case involved foreign travel to areas where TB is endemic.
- There had been no fatal TB cases with etanercept.
- No cases of TB were observed among 2,024 patients treated in US trials and 1,260 in European trials
- There is evidence that patients with a positive PPD and with a history of TB have been treated safely with etanercept.
- These data support a recommendation of exercising caution in treating patient with etanercept and being alert to the possibility of developing TB.

D. Change to Etanercept Package Insert

Based on the reported clinical experience as of August 2000, the following underlined text was added to the package insert.

WARNINGS/INFECTIONS

IN POST-MARKETING REPORTS, SERIOUS INFECTIONS AND SEPSIS, INCLUDING FATALITIES, HAVE BEEN REPORTED WITH THE USE OF ETANERCEPT. MANY OF THESE SERIOUS EVENTS HAVE OCCURRED IN PATIENTS WITH UNDERLYING DISEASES THAT COULD PREDISPOSE THEM TO INFECTIONS. <u>RARE CASES OF TUBERCULOSIS (TB) HAVE BEEN OBSERVED IN PATIENTS TREATED WITH TNF ANTAGONISTS, INCLUDING ETANERCEPT</u>. PATIENTS WHO DEVELOP A NEW INFECTION WHILE UNDERGOING TREATMENT WITH ETANERCEPT SHOULD BE MONITORED CLOSELY. ADMINISTRATION OF ETANERCEPT SHOULD BE DISCONTINUED IF A PATIENT DEVELOPS A SERIOUS INFECTION OR SEPSIS. TREATMENT WITH ETANERCEPT SHOULD NOT BE INITIATED IN PATIENTS WITH ACTIVE INFECTIONS INCLUDING CHRONIC OR LOCALIZED INFECTIONS. PHYSICIANS SHOULD EXERCISE CAUTION WHEN CONSIDERING THE USE OF ETANERCEPT

IN PATIENTS WITH A HISTORY OF RECURRING INFECTIONS OR WITH UNDERLYING CONDITIONS WHICH MAY PREDISPOSE PATIENTS TO INFECTIONS, SUCH AS ADVANCED OR POORLY CONTROLLED DIABETES (see PRECAUTIONS and ADVERSE REACTIONS, Infections).

ADVERSE REACTIONS, Infections

In post-marketing experience, infections have been observed with various pathogens including viral, bacterial, fungal, and protozoal organisms. Infections have been noted in all organ systems and have been reported in patients receiving Enbrel alone or in combination with immunosuppressive agents.

XI. Tuberculosis and Other Opportunistic Infections with Infliximab and Etanercept: Updates to FDA Review of MedWatch Reports

A. Update on Tuberculosis with Infliximab as of May 2001

As of May 15, 2001, 70 patients were reported through MedWatch with TB following infliximab therapy. Their ages ranged from 18 to 83 years (median, 57 years). Forty-five patients were women. Forty-seven patients were taking the drug for RA, 18 patients for CD, and five patients for other types of arthritis. Fifty-four patients were reported to have received one or more other immunosuppressive medications, including corticosteroids (42 patients), methotrexate (35), azathioprine (5), and cyclosporine (1). Five patients were using anti-inflammatory agents, such as mesalamine and indomethacin, before the development of TB. The median time interval from beginning treatment with infliximab until development of TB was 12 weeks, with a range of 1 to 52 weeks.

The pattern of tuberculous disease was unusual. Most patients (56%) developed extrapulmonary TB, and 24% had disseminated disease, forms of TB associated with significant immunosuppression. In contrast, among human immunodeficiency virus (HIV) negative TB cases, approximately 18% present with extrapulmonary disease, and disseminated disease accounts for less than 2% of cases. Twenty-two other cases of extrapulmonary TB included lymph node (10 patients), peritoneal (4), pleural (2), meningeal (1), gastrointestinal tract (1), bone (1), genital (1), and bladder (1) involvement, as well as one case with paravertebral abscess. Thirty-two of the 70 patients underwent a biopsy to diagnose TB; biopsies were of lymph node (10), lung (12), enteric (2), peritoneum (3), pleura (1), bone marrow (1), liver (1), paravertebral mass (1) and bladder (1). This unusual presentation of TB may have contributed to diagnostic uncertainty (as reflected in the high numbers of invasive procedures that were required to establish the diagnoses), delayed diagnoses, and increased morbidity and mortality. Twelve patients reported with TB died; in four patients, patient death appeared to be related directly to TB. Remaining patients recovered with TB chemotherapy and discontinuation of infliximab. A possible recent exposure to TB was noted in 2 reports, and a prior history of TB infection or disease was noted in 8 reports. Of the 70 patients with TB on infliximab (23% US, 64% Europe, 11% other), most (91%) resided in countries with an estimated TB incidence of less than 20 cases per 100,000 person-years.

Reviewer comment: Although there is incomplete information about the tuberculous infection status of these patients prior to receiving infliximab, it is probable that the vast majority developed reactivation disease, in view of their older age (median age 53 years), the small number with reported recent exposure to TB and the currently low incidence of TB in their countries of origin.

According to a recent estimate, the incidence of TB in US RA patients is comparable to that of the US general population, approximately 6 cases per 100,000 person-years. Using MedWatch data, the reporting rate of TB in US RA patients receiving infliximab may be calculated as approximately 24 cases per 100,000 person-years in the first year after starting infliximab.

B. Update on Histoplasmosis with Infliximab or Etanercept as of June 2001

Life-threatening histoplasmosis has been observed in many immunocompromised states including HIV infection, cytotoxic therapies for malignancies, and immune suppression after organ transplantation. Incidence rates of histoplasmosis in RA and CD have not been estimated, and it is not known whether or not RA or CD is an independent risk factor for developing histoplasmosis. As of June 2001, 10 cases of histoplasmosis in patients treated with either infliximab (9 patients) or etanercept (1 patient) had been reported to the FDA.

- **Infliximab:** In the 9 cases with infliximab, the patients (5 with RA and 4 with CD) presented typically with fever, malaise, cough, dyspnea, and interstitial pneumonitis on chest X-ray (CXR) within 1 week to 6 months of receiving the first (or only) infliximab dose. All patients had preexisting immunosuppressive risk factors, typically the concomitant use of prednisone and/or methotrexate. The 9 patients resided in endemic histoplasmosis areas: Ohio (2 patients), Tennessee (2 patients), Alabama, Iowa, Kentucky, Louisiana, or Wisconsin. Eight patients required aggressive treatment in the intensive care unit; one patient was successfully managed as an outpatient. Definitive diagnosis of histoplasmosis was made by blood cultures or tissue biopsies of lung, liver, and/or bone marrow. Antifungal therapy (typically intravenous amphotericin B) resulted in recovery in 8 patients; one patient died. In all 9 patients, the primary disease (RA or CD) improved significantly with infliximab therapy.

- **Etanercept:** The single patient resided in a region known to be endemic for histoplasmosis (Indiana) and received concomitant immunosuppressive medications other than the TNF-α antagonist, including methotrexate and prednisone. The initial workup for pancytopenia included fungal serologies for overwhelming infection, which revealed elevated titers of antibodies to HC in blood and urine positive for HC antigen. The patient recovered with itraconazole therapy and is doing well as of June 2001 on etanercept, methotrexate, and prednisone. Etanercept has been effective in controlling previously refractory RA.

Reviewer Comment: The 10 cases described above suggest that histoplasmosis may be a life-threatening complication of TNF-α antagonist therapy in patients environmentally exposed to HC. The degree of patient immunosuppression, the HC dose to which a patient is exposed, the specific drug product and the amount given, and the time to recognition and treatment of histoplasmosis appear to influence clinical course and outcome. Atypical presentations of pulmonary, extrapulmonary, and disseminated histoplasmosis may mimick underlying RA or CD to result in delayed recognition and treatment. Early consideration may obviate invasive diagnostic procedures that have the potential for substantial patient morbidity. In the context of the existing literature on the pathogenesis of histoplasmosis, the current case series suggests that, until proven otherwise, immunotherapy using TNF-α antagonists should be regarded as a risk factor for developing histoplasmosis.

C. Update on Listeriosis with Infliximab or Etanercept as of June 2001

Infection by Listeria monocytogenes has been appreciated previously to occur in pregnancy, diabetes, malignancy, alcoholism, hepatic failure, and other conditions with compromised cell-mediated immunity. Elderly patients or those who ingest processed meats may also be at increased risk. Recent laboratory observations suggest that TNF-α plays a key role in host resistance against infection by Listeria and other bacteria. Mice given anti-TNF-α antibody failed to survive the typically sublethal infectious challenge with Listeria, provided that the antibody is given early in infection. As might be expected, cytokines other than TNF-α including interferon-γ, interleukin-1, interluekin-6, and macrophage colony stimulating factor also appear to be important. The specific mechanism by which TNF-α and other cytokines exert their effect against Listeria infection is not known. To date, 12 cases of listeriosis have been reported to the FDA in association with the use of either infliximab (11 patients) or etanercept (one patient).

- **Infliximab:** Typically, the patients were elderly (7 of 11 patients 60 or older), were on at least one other immunosuppressive medication besides infliximab or etanercept, and presented with fever, lethargy, and headache, and confusion within 4 to 290 days of receiving the first infliximab dose. Seven patients had RA and 4 had CD. Four of the 11 patients died from Listeria sepsis.

- **Etanercept:** A 72 year old man with RA on etanercept for one month presented with fever, chills, headache, dizziness. Listeria sepsis did not respond to antibiotic therapy; patient expired.

  Reviewer comment: Although the number of cases is small and the reported clinical setting consistent with that expected, the 12 clinical cases are consistent with previous experimental observations. Life-threatening listeriosis may prove to be a true complication of immunotherapy using TNF-α antagonists.

D. Update on PCP with Infliximab or Etanercept as of June 2001

PCP is a common complication of HIV infection and is seen also in many other disorders of immune dysfunction, including RA, Crohn's disease, ulcerative colitis, Wegener's

granulomatosis, systemic lupus erythematosus, and malignancy. PCP infection in HIV infection may have a more protracted and milder course with a lower mortality than in other immune compromised states. As of June 21, 2001, FDA had received 15 reports of PCP in TNF-α antagonist therapy worldwide, 10 with infliximab and 5 with etanercept.

- **Infliximab:** Of the 10 patients, 3 died (1 US), 6 were hospitalized, and 3 were from the US (7 reported as non-US or not reported). The ages ranged from 15 to 69 with a median of 57 (n=9). The male to female ratio was 3 to 6 with 1 unknown. The indications included RA(4 cases), CD (3 cases with 2 fistulizing), juvenile chronic polyarthritis (Still's Disease)(1 case), and acute fulminant ulcerative colitis (1 case). The time to onset from the start of infliximab to the diagnosis of PCP averaged 1 month (n=8) with a range of 5 days to 2.2 months. The number of doses of infliximab averaged 2 doses (n=9) with a range of 1 to 3 doses. Other suspect drugs reported with infliximab were methotrexate (5), 6-mercaptopurine (1) and prednisolone (1). Other concomitant immunosuppressive drugs were methotrexate (1), corticosteroids (4), Sandimmune/cyclosporine (1), 6-mercaptopurine (2), leflunomide (1), azathioprine (1) and mesalazine (1). Bronchoalveolar lavage was reported to diagnose PCP in 4 cases. Reported pulmonary or immunocompromised underlying medical conditions were bone marrow hypoplasia with Still's disease, lymphopenia with CD, CMV and TB co-infections with RA and Sjogren's syndrome, steroid-induced lung fibrosis with RA, and methotrexate lung toxicity and chronic steroid use with each of the fistulizing CD cases. Two cases reported a negative HIV status at the time of PCP diagnosis; the other 8 cases did not comment on the HIV status.

- **Etanercept:** Of the 5 cases, 3 died (all US) and 2 were hospitalized (both Swiss). The ages ranged from 23 to 67 with a median of 56 (n=3). Male to female ratio was 1 to 2 with 2 unknown. The indications included 4 RA and 1 hemangiosis. The time to onset from the start of etanercept to the diagnosis of PCP averaged 2 months (n=3) with a range of 1 week to 4 months. Other concomitant drugs were methotrexate and steroids (1) and steroids reported without methotrexate (1). Reported underlying medical conditions were Wegener's disease with positive serology for CMV, B-cell lymphoma, and anemia from gastrointestinal bleeding with glomerulonephritis. One case reported a negative HIV status at the time of PCP diagnosis and the other 4 cases did not comment on the HIV status.

  Reviewer comment: Based on these cases, reporting rates of PCP in TNF-α antagonist therapy may be calculated as 2.3 (infliximab) and 1.6 (etanercept) cases per 100,000 person-years in TNF-α antagonist therapy. In TNF-α antagonist therapy of RA, these figures reduce to 0.9 (infliximab) and 1.3 (etanercept) cases per 100,000 person years. In RA, the incidence of PCP has been estimated to be approximately 13 (outpatients) and 20 (hospitalized patients) per 100,000 person-years. Limitations of passive surveillance complicate a comparison of the observed reporting rates with previous incidence estimates. Pathogenetically, pulmonary alveolar macrophages, TNF-α, and cell-mediated immunity are known to be important in host defense against PCP.

E. Proposed Change to Infliximab Package Insert

Based on the MedWatch reports received as of June 2001, the manufacturer has proposed the following change to infliximab package insert.

Black Box Warning/RISK OF INFECTIONS

TUBERCULOSIS, FREQUENTLY DISSEMINATED OR EXTRAPULMONARY AT CLINICAL PRESENTATION, AND OTHER OPPORTUNISTIC INFECTIONS, INCLUDING LISTERIOSIS, HISTOPLASMOSIS AND OTHER INVASIVE FUNGAL INFECTIONS HAVE BEEN OBSERVED IN PATIENTS RECEIVING REMICADE. SOME OF THESE INFECTIONS HAVE BEEN FATAL (SEE *WARNINGS*).

PATIENTS SHOULD BE SCREENED FOR TUBERCULOSIS WITH A PPD SKIN TEST. PATIENTS SHOULD BE TREATED FOR LATENT TUBERCULOSIS INFECTION PRIOR TO THERAPY WITH REMICADE.

Warning/RISK OF INFECTIONS

CASES OF LIFE-THREATENING AND FATAL HISTOPLASMOSIS HAVE BEEN OBSERVED IN PATIENTS RECEIVING REMICADE. FOR PATIENTS WHO HAVE RESIDED IN REGIONS WHERE HISTOPLASMOSIS IS ENDEMIC, THE BENEFITS AND RISKS OF REMICADE TREATMENT SHOULD BE CAREFULLY CONSIDERED BEFORE INITIATION OF REMICADE THERAPY.

XII. Lymphoma in Etanercept or Infliximab Therapies

Lymphoproliferative disorders, especially non-Hodgkin's lymphoma, have been reported to occur in immune deficiency states and in disorders of immune regulation, either as a part of the natural history of the disease or as a result of the immunomodulatory medications used to treat the primary disease. The potential association between lymphoma and the use of a TNF-α antagonist is reviewed below.

A. Clinical Trials

Lymphoma had been observed with infliximab or etanercept use in previous clinical trials (5 reports in the literature). Of the approximately 2000 patients exposed to either agent, 7 developed lymphoma as follows: 4 with infliximab for RA, 2 with infliximab for CD, and 1 with etanercept for RA. The investigators did not consider the occurrence of lymphoma to be associated with the use of infliximab or etanercept.

B. Post-Licensure Reports

- **Etanercept:** Eighteen cases of lymphoma occurring after the initiation of etanercept therapy were reported to the Food and Drug Administration between May, 1999 and December, 2000. The symptoms that led to the diagnosis of lymphoma occurred within 2 and 52 weeks (median 8 weeks) of the first etanercept dose. The median patient age was 64 years. The majority of patients were female (61%), and the most common indication for use was RA (83%). Most patients on etanercept were reported to be currently on methotrexate or to have a history of methotrexate use (72%) or any immunosuppressive drug, including methotrexate (78%).

- **Infliximab:** Ten cases of lymphoma occurring after initiation of infliximab treatment were reported to the FDA between March 1999 and December 2000. The lymphomas occurred between 2 and 44 weeks of the first infliximab dose (median 3 weeks). The median age for infliximab cases was 62 years. The majority of the patients were male (60%), and the most common treatment indication was CD (60%).

  Reviewer comment: In patients with RA, estimated odds ratios for developing lymphoma range from 2 to 26. Active disease, advanced patient age, prolonged use of immunomodulatory drugs (most notably methotrexate), poor functional class, and widespread joint involvement may be associated with a greater odds ratio. For patients on either etanercept or infliximab therapy, the observed reporting rate of approximately 9 cases of lymphoma per 100,000 patient-years approximates the estimated incidence rate of lymphoma in the general population and is lower than that for patients with RA. However, underreporting is a major limitation of passive surveillance. The relationships among lymphoma, disorders of immune function including RA and CD, and immunomodulatory therapy including TNF-α antagonist therapy remain poorly defined.